Cancer and Oncogenes Literatures

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Abstract: Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries. This is a literature collection on cancer and oncogenes.
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1. Introduction

Cancer is the general name for a group of more than 100 diseases. Although there are many kinds of cancer, all cancers start because abnormal cells grow out of control. Untreated cancers can cause serious illness and death. The body is made up of trillions of living cells. Normal body cells grow, divide, and die in an orderly fashion. During the early years of a person's life, normal cells divide faster to allow the person to grow. After the person becomes an adult, most cells divide only to replace worn-out or dying cells or to repair injuries.

Literatures

Arvelo, F., M. Poupon, et al. (1993). "Heterogeneous expression of oncogenes in small-cell lung-cancer xenografts." Int J Oncol **2**(4): 621-5.

The analysis of oncogene expression may provide insights into the pathogenesis of small cell lung cancer (SCLC) and may help to predict clinical behavior. The expression of 8 oncogenes (c-myc, N-myc, L-myc, Ha-ras, Ki-ras, N-ras, erbB-2, v-sis) was evaluated in small cell lung cancer (SCLC) xenografts of tumor samples, recentlly transplanted, taken from 17 different patients. Eight of these 17 SCLC lines expressed the L-myc oncogene and 2 SCLC lines expressed the c-myc oncogene. One SCLC line (SCLC-63M) simultaneously expressed the L-myc and c-myc oncogenes. All SCLC lines examined had almost similar high RNA levels of the Ki-ras oncogene, while the expression of Ha- and N-ras oncogenes was not always observed. The N-myc and v-sis oncogenes were expressed in only one tumor and at a very weak level, and no transcript of the erbB-2 oncogene was observed in any of our 17 SCLC lines. These results indicate that oncogene expression in SCLC lines is heterogeneous, with the exception of the Ki-ras oncogene which is constantly overexpressed.

Asa, S. L. (2001). "How familial cancer genes and environmentally induced oncogenes have changed the endocrine landscape." Mod Pathol **14**(3): 246-53.

The gene responsible for MEN-2, the ret proto-ocogene, has elucidated mechanisms of endocrine tumorigenesis. Activating mutations of this transmembrane tyrosine kinase receptor represent the first known example of an inherited oncogene. This knowledge has altered our approach to affected patients by allowing in utero screening and prophylactic thyroidectomy rather than provocative testing and morphologic analysis of C cell hyperplasia--will it result in eradication of medullary carcinoma of thyroid? The lessons from Chernobyl taught us how radiation can induce chromosomal rearrangements that involve the same gene. This has led to a better understanding of papillary thyroid carcinoma and provides a novel immunohistochemical marker that widens our diagnostic armamentarium.

Aunoble, B., R. Sanches, et al. (2000). "Major oncogenes and tumor suppressor genes involved in epithelial ovarian cancer (review)." Int J Oncol **16**(3): 567-76.

Ovarian cancer remains the leading cause of death from gynecologic malignancy in Western countries. This cancer results from a succession of genetic alterations involving oncogenes and tumor suppressor genes which have a critical role in normal cell growth regulation. Mutations and/or overexpression of three oncogenes, HER-2/neu, c-myc and K-ras, and of the tumor suppressor gene p53, have frequently been observed in sporadic ovarian cancer. In the context of high risk families, the most frequently involved genes are BRCA1 and BRCA2.

We review the function of these different proteins, the incidence of mutations in their genes in carcinogenesis and as potential prognostic factors in sporadic and hereditary ovarian cancer.

Badawi, A. F. (1996). "Molecular and genetic events in schistosomiasis-associated human bladder cancer: role of oncogenes and tumor suppressor genes." Cancer Lett **105**(2): 123-38.

Carcinoma of the urinary bladder is the most common malignancy in many tropical and subtropical countries and is mainly due to endemic schistosomal infection. Schistosomiasis-associated bladder cancer defines a characteristic pathology and cellular and molecular biology that differs from urothelial carcinoma of non-schistosomal origin. N-Nitroso compounds are suspected etiologic agents in the process of bladder cancer induction during schistosomiasis. Elevated levels of DNA alkylation damage have been detected in schistosome-infected bladders and are accompanied by an inefficient capacity of DNA repair mechanisms. Consequently, high frequency of G --> A transition mutations were observed in the H-ras gene and at the CpG sequences of the p53 tumor suppressor gene. Genetic changes have also been detected in the c-erbB-1 and c-erbB-2 oncogenes and in the cdkn2 and Rb tumor suppressor genes. The potential application of these mutational patterns in providing a biological marker suitable for the biomonitoring and early detection of this neoplasm could indicate new avenues of approach that might alleviate the problem in the future. It can also assist in elucidating the mechanisms by which schistosomiasis augments human bladder cancers.

Barr, L. F., S. E. Campbell, et al. (1998). "The growth inhibitory effect of N1,N12-bis(ethyl)spermine in small cell lung cancer cells is maintained in cells expressing the c-myc and Ha-ras oncogenes." Clin Cancer Res **4**(6): 1557-61.

The N',N"-bis(ethyl) polyamine analogues demonstrate great potential as chemotherapeutic agents for lung cancer. This study examines how the expression of two oncogenes frequently associated with a worsened prognosis in lung cancer, c-myc and mutated ras, as well as the phenotypic transition induced by these genes, affects the sensitivity of small cell lung cancer (SCLC) cells to these polyamine analogues. Treatment with N1,N12-bis(ethyl)spermine (BE-Spm), a representative analogue, depresses polyamine levels and is cytostatic for the NCI H209 classic SCLC cell line. Both the overexpression of c-myc and the expression of oncogenic v-Ha-ras in these cells produce phenotypes that retain sensitivity to this growth inhibition. This sensitivity to BESpm is mediated by distinct pathways in these oncogene-expressing cells. c-myc overexpression markedly increases the expression of ornithine decarboxylase, which is then down-regulated by BESpm. In contrast, v-Ha-ras expression highly induces the polyamine catabolic enzyme spermidine/spermine N1-acetyltransferase. These findings suggest that the bis(ethyl)polyamine compounds may have broad utility for the treatment of both SCLC and non-SCLC, including those expressing oncogenic c-myc and ras.

Berchuck, A., M. F. Kohler, et al. (1992). "Oncogenes in ovarian cancer." Hematol Oncol Clin North Am **6**(4): 813-27.

The discovery of cancer-causing genes has provided us with the exciting opportunity to begin to understand the molecular pathology of ovarian cancer. Activation of several of these genes including HER-2/neu, myc, ras, and p53 has been described in some ovarian cancers (Table 2). In addition, some proto-oncogenes such as the EGF receptor (erbB) and the M-CSF receptor (fms) are expressed along with their respective ligands in some ovarian cancers. Finally, for every oncogene that has been studied in ovarian cancer, there are at least a half-dozen that remain unexplored. In the future, when we have a better understanding of the molecular pathology involved in the development of ovarian cancer, this may allow us to better diagnose and treat, and eventually prevent, ovarian cancer.

Bergh, J. C. (1990). "Gene amplification in human lung cancer. The myc family genes and other proto-oncogenes and growth factor genes." Am Rev Respir Dis **142**(6 Pt 2): S20-6.

The development of human lung cancer may require multiple genetic deletions affecting a number of chromosomes, e.g., 1, 3, 11, 13, and 17. These genetic aberrations may induce the activation of proto-oncogenes (c-jun, ras, c-raf1) and the loss of tumor suppressor genes (p53). Some of the activated proto-oncogenes and tumor suppressor genes are more selectively expressed or absent in small-cell lung cancer (L-myc, c-myb, c-scr, Rb gene) or non-small-cell lung cancer (c-erbB-2, c-sis, c-fes). These genes may thus be of importance for selection of differentiation pathway. The c-myc oncogene is frequently amplified in small-cell lung cancer cell lines in a much higher frequency than in vivo. This indicates that c-myc seems to be related to tumor progression and a relatively late event in the lung cancer development. The uncontrolled production of multiple growth factors has been identified in human lung cancer cell lines. These factors can promote and inhibit the proliferation via paracrine and autocrine loops via specific receptors. The products from some of the activated proto-oncogenes (c-sis, c-erbB-2) are

sequences homologous to a certain growth factor (PDGF) and a receptor (EGF) identified in lung cancer. The production and action of these growth factors may be of major importance for further activation of proto-oncogenes via intracellular signal transduction and specific oncogenic activation leading to further tumor progression.

Bommer, G. T., C. Jager, et al. (2005). "DRO1, a gene down-regulated by oncogenes, mediates growth inhibition in colon and pancreatic cancer cells." J Biol Chem **280**(9): 7962-75.

Neoplastic progression in human tissues appears to be paralleled by a series of genetic and epigenetic alterations. In human colorectal cancers, defect Wnt/beta-catenin/T-cell factor and RAS/RAF signaling pathways have a major contributing role in tumor initiation and progression. To date, much of the research on the consequences of beta-catenin activation has been focused on genes whose expression is believed to be activated by beta-catenin-associated T-cell factor-dependent transcription. Little is known about genes whose expression may be down-regulated secondary to beta-catenin activation. Using a subtractive suppression hybridization approach, we identified a gene with markedly decreased expression in rat RK3E epithelial cells neoplastically transformed by beta-catenin. Because expression of this gene was also down-regulated in RK3E transformed by several other oncogenes, the gene was named DRO1 for "down-regulated by oncogenes 1." Compared with corresponding normal tissues, DRO1 expression was found to be very reduced in colon and pancreatic cancer cell lines as well as in most colorectal cancer specimens. The predicted DRO1 protein contains three repetitive elements with significant similarity to the carboxyl-terminal regions of the predicted proteins from DRS/SRPX/ETX1 and SRPUL genes, suggesting the existence of a new protein family. Ectopic expression of DRO1 in neoplastically transformed RK3E or colorectal and pancreatic cancer cell lines lacking endogenous DRO1 expression resulted in substantial inhibition of growth properties. DRO1 was found to suppress anchorage independent growth and to sensitize cells to anoikis and CD95-induced apoptosis. Our findings suggest that inhibition of DRO1 expression may be an important event in the development of colorectal and pancreatic cancers.

Bover, L., M. Barrio, et al. (1998). "The human breast cancer cell line IIB-BR-G has amplified c-myc and c-fos oncogenes in vitro and is spontaneously metastatic in vivo." Cell Mol Biol (Noisy-le-grand) **44**(3): 493-504.

IIB-BR-G is an undifferentiated, highly heterogeneous, hormone receptor negative human breast cancer cell line previously established in our laboratory from a patient's primary tumor. An in vitro growing cell line (IIB-BR-G) and a xenotransplanted tumor growing in nude mice (IIB-BR-G(NUDE)) were derived. To further characterize these systems, immunocytochemical analysis was performed for differentiation antigens (PEM 200 kDa, CEA, NCA 90 kDa), blood-group related antigens (Le(x), sTn), oncogenes and tumor suppressor gene products (Her-2/neu protein, p53), metastasis-related cathepsin D and CD63/5.01 Ag, and the chemokine monocyte chemotactic protein 1 (MCP-1). Expression of markers was heterogeneous in these different systems. Previously reported karyotypic analysis has shown extensive chromosomal alterations including double min. Searching for oncogene amplification, we detected augmented copy number of c-myc and c-fos, the last one with two rearranged fragments. No amplification was found for c-erbB-2 in the cell line or in IIB-BR-G(NUDE), although this oncogene was amplified in the patient's primary tumor DNA. The differences observed between the patient's tumor, the cell line and the IIB-BR-G(NUDE) tumors are probably due to clonal expansion of cell variants not present in the original tumor. Electron microscopy of IIB-BR-G growing cells revealed epithelial characteristics with abundant dense granules, presumably secretory, distributed all over the cytoplasm and great nuclear pleomorphism. In vitro, IIB-BR-G cells showed a significant number of invading cells by Matrigel assay. After nearly 40 sequential subcutaneous passages of the original xenograft through nude mice, 80% of recipients developed spontaneous metastases, primarily to the lung and lymph nodes. Since this experimental model allowed to analyze changes produced in cancer cells from the primary tumor during adaptation to in vitro and in vivo growth, our results provide novel insights on the behaviour of hormone independent metastatic breast cancer.

Brahimi, F., Z. Rachid, et al. (2004). "Multiple mechanisms of action of ZR2002 in human breast cancer cells: a novel combi-molecule designed to block signaling mediated by the ERB family of oncogenes and to damage genomic DNA." Int J Cancer **112**(3): 484-91.

The mechanism of action of ZR2002, a chimeric amino quinazoline designed to possess mixed EGFR tyrosine kinase (TK) inhibitory and DNA targeting properties, was compared to those of ZR01, a reversible inhibitor of the same class and PD168393, a known irreversible inhibitor of EGFR. ZR2002 exhibited 4-fold stronger EGFR TK inhibitory activity than its structural homologue ZR01 but was approximately 3-fold less active than the 6-

acrylamidoquinazoline PD168393. It preferentially blocked EGF and TGFalpha-induced cell growth over PDGF and serum. It also inhibited signal transduction in heregulin-stimulated breast tumour cells, indicating that it does not only block EGFR but also its closely related erbB2 gene product. In contrast to its structural homologues, ZR2002 was capable of inducing significant levels of DNA strand breaks in MDA-MB-468 cells after a short 2 hr drug exposure at a concentration as low as 10 microM. Reversibility studies using whole cell autophosphorylation and growth assays in human breast cell lines showed that in contrast to its reversible inhibitor counterpart ZR01, ZR2002 induced irreversible inhibition of EGF-stimulated autophosphorylation in MDA-MB-468 cells and irreversible inhibition of cell growth. Moreover despite possessing a weaker binding affinity than PD168393, it induced a significantly more sustained antiproliferative effect than the latter after a pulse 2 hr exposure. More importantly, in contrast to ZR01 and PD168393, ZR2002 was capable of inducing significant levels of cell death by apoptosis in MDA-MB-468 cells. The results in toto suggest that the superior antiproliferative potency of ZR2002 may be due to its ability to induce a protracted blockade of receptor tyrosine kinase-mediated signaling while damaging cellular DNA, a combination of events that may trigger cell-killing by apoptosis.

Brandt, B., U. Vogt, et al. (1995). "Double-differential PCR for gene dosage estimation of erbB oncogenes in benign and cancer tissues and comparison to cellular DNA content." Gene **159**(1): 29-34.

Competitive and differential quantitative PCR methods circumvent the limiting factors of PCR which cause poor reproducibility. We describe the development and performance evaluation of another quantitative PCR method, double-differential PCR (ddPCR). The ddPCR method comprises the co-amplification of the single-copy gene HBB, the erbB-1, erbB-2 and erbB-3 oncogenes and the second single-copy reference gene SOD2 under equal reaction conditions. The ratio of band intensities of the PCR products in silver-stained polyacrylamide gels expresses the average gene copy number (AGCN) per cell of the erbB oncogenes. The coefficient of variability (CV) was less than 25% for an AGCN of 1. The PCR data were in correlation to the results from dot blotting. DNA image analysis did not reveal any correlation between DNA content and gene dosage deviation of the erbB oncogenes. The method was applied to normal breast tissue, benign breast diseases, breast cancer tissue and lymph node metastases. We suggest this method as being reproducible, low cost and rapid, and therefore suitable for clinical studies on erbB oncogene dosage estimation.

Brandt, B. H., A. Beckmann, et al. (1997). "Translational research studies of erbB oncogenes: selection strategies for breast cancer treatment." Cancer Lett **118**(2): 143-51.

Specific gene families, e.g. encoding members of signal transduction pathways, show a gene dosage sensitivity. We report on the determination of the gene dosages of egfr and c-erbB-2 in relation to the intratumoral concentration of the tyrosine kinase receptor protein EGFR and p185c-erbB-2 and the clinical outcome of breast cancer patients in a retrospective study. Prognostic unfavorable subgroups were determined in a life-table analysis by (a) an average gene copy number of egfr of less than 0.4 and greater than 1.6 and an intratumoral EGFR concentration of more than 56 fmol/mg, (b) an intratumoral p185c-erbB-2 concentration above 26 HNU/mg and (c) a quotient of egfr and c-erbB-2 average gene copy numbers of less than 0.15 and greater than 4.35.

Bronner, C., M. Achour, et al. (2007). "The UHRF family: oncogenes that are drugable targets for cancer therapy in the near future?" Pharmacol Ther **115**(3): 419-34.

In this paper, we review the current literature about the UHRF family that in particular includes the UHRF1 and UHRF2 genes. Its members play a fundamental role in cell proliferation through different structural domains. These domains include a ubiquitin-like domain (NIRF_N), a plant homeodomain (PHD) domain, a SRA domain and a RING domain. The SRA domain has only been observed in this family probably conferring unique properties to it. The unique enzymatic activity so far identified in this family involves the RING finger that contains a ubiquitin E3 ligase activity toward, for instance, histones. The physiological roles played by the UHRF family are most likely exerted during embryogenic development and when proliferation is required in adults. Interestingly, UHRF members are putative oncogenes regulated by tumor suppressor genes, but they exert also a feedback control on these latter. Finally, we propose some new roles for this family, including regulation and/or inheritance of the epigenetic code. Alteration of these regulatory mechanisms, such as those occurring in cancer cells, may be involved in carcinogenesis. The reasons why the UHRF family could be an interesting target for developing anticancer drugs is also developed.

Caesar, G. (1993). "Oncogenes, antioncogenes, and a hypothesis on cancer therapy, i.e. the origin of cancer, and the prevention of its activity." Med Hypotheses **40**(1): 15-8.

Existing data indicates there is a set of genes--oncogenes--whose increased or abnormal expression causes cancer. Another set of genes--antioncogenes--control oncogene expression. Implied is that cancer is neither infectious nor contagious, i.e. one cannot catch cancer, and cancers are fundamentally similar. Fetal cells can be used instead of immunosuppressing drugs, regulate antigen-antibody action-reaction, and may be in some instances genetically wholesome. They, therefore may be useful to compensate for the immunological breakdown or deficiency which results in active cancer.

Callahan, R. and D. S. Salomon (1993). "Oncogenes, tumour suppressor genes and growth factors in breast cancer: novel targets for diagnosis, prognosis and therapy." Cancer Surv **18**: 35-56.

The complexity of growth factors and growth factor receptors that are aberrantly expressed, as well as the mutational events that either directly cause or influence the expression of these and other gene products, should provide in the near future multiple diagnostic, prognostic indicators or targets for therapeutic intervention. It seems reasonable to expect that soon the search for aberrantly expressed gene products in breast cancer cells will merge with the search and characterization of somatic mutations that are selected during tumour progression. Clearly, the current rapid development of new molecular biological methodologies aimed at detecting and cloning of RNA sequences that are aberrantly expressed in breast tumour cells, as well as molecular probes and reagents to detect and physically map mutated genes on affected chromosomes, should accelerate the effort to identify targets for therapeutic intervention. We are at the beginning of this learning curve, but already several potential target gene products have been identified. A major challenge will be to sort out those approaches and reagents that appear efficacious on the basis of results from in vitro and in vivo model systems that will actually have an impact on the treatment of the disease in the clinic. Reagents that target some of these gene products are currently in clinical trials; however, there are others such as immunotherapy against the mutated TP53 protein and human CG treatment of high risk breast cancer patients that warrant testing in this context.

Campbell, C. T., U. Aich, et al. (2008). "Targeting pro-invasive oncogenes with short chain fatty acid-hexosamine analogues inhibits the mobility of metastatic MDA-MB-231 breast cancer cells." J Med Chem **51**(24): 8135-47.

Per-butanoylated N-acetyl-D-mannosamine (Bu(4)ManNAc), a SCFA-hexosamine cancer drug candidate with activity manifest through intact n-butyrate-carbohydrate linkages, reduced the invasion of metastatic MDA-MB-231 breast cancer cells unlike per-butanoylated-D-mannose (Bu(5)Man), a clinically tested compound that did not alter cell mobility. To gain molecular-level insight, therapeutic targets implicated in metastasis were investigated. The active compound Bu(4)ManNAc reduced both MUC1 expression and MMP-9 activity (via down-regulation of CXCR4 transcription), whereas "inactive" Bu(5)Man had counterbalancing effects on these oncogenes. This divergent impact on transcription was linked to interplay between HDACi activity (held by both Bu(4)ManNAc and Bu(5)Man) and NF-kappaB activity, which was selectively down-regulated by Bu(4)ManNAc. Overall, these results establish a new therapeutic end point (control of invasion) for SCFA-hexosamine hybrid molecules, define relative contributions of molecular players involved in cell mobility and demonstrate that Bu(4)ManNAc breaks the confounding link between beneficial HDACi activity and the simultaneous deleterious activation of NF-kappaB often found in epigenetic drug candidates.

Chen, Y., J. Dong, et al. (1995). "Quantitative detection of amplification of proto-oncogenes in breast cancer." Chin Med J (Engl) **108**(11): 849-54.

In the present study, dot-blot hybridization, serial dilution analysis and densitometric scanning were used to detect amplification of proto-oncogenes including c-erbB2, c-myc, int-2 and c-Ha-ras in 101 paraffin-embedded breast cancers. Expression of c-erbB2 was also examined by immunohistochemistry. Amplification of c-erbB2, c-myc and int-2 genes was found in 34.7%, 17.8% and 11.9% of breast cancers respectively. However amplification of c-Ha-ras was not detected in all cases. In 11.9% of cases co-amplification of two or more oncogenes was observed. Positive immunostaining of c-erbB2 was seen in 23.8% of the cases and it was significantly associated, but not always corresponding to the amplification of the gene. There was no difference between primary and metastatic breast cancer in the alterations of proto-oncogenes examined in this study, which suggested that the amplification and overexpression of these proto-oncogenes occurred prior to and maintained in the process of metastasis of breast cancer. Statistical analysis showed that high-scale of immunopositive staining of c-erbB2 and high-fold co-amplification of proto-oncogenes were significantly correlated with large size of the tumour and the number of involved lymph nodes. Our results indicate that the alterations of multiple oncogenes are involved in the development of breast cancer and some of them may have prognostic importance for breast cancer patients.

Chiao, P. J., F. Z. Bischoff, et al. (1990). "The current state of oncogenes and cancer: experimental approaches for analyzing oncogenetic events in human cancer." Cancer Metastasis Rev **9**(1): 63-80.

The development of cancer is a multistage process. The activation of proto-oncogenes and the inactivation of tumor suppressor genes play a critical role in the induction of tumors. Using human cell model systems of carcinogenesis, we have studied how oncogenes, tumor suppressor genes, and recessive cancer susceptibility genes participate in this multistep process. Normal human cells are resistant to the transforming potential of oncogenes, such as ras oncogenes, which are activated by specific point mutations. Since as many as 40% of some tumor types contain activated ras oncogenes, a preneoplastic transition in multistage carcinogenesis must involve changing from an oncogene-resistant stage to an oncogene-susceptible stage. The analysis of such critical steps in carcinogenesis using rodent systems has usually not represented the human disease with fidelity. In order to study this carcinogenic process, we have developed human cell, in vitro systems that represent some of the genetic changes that occur in cellular genes during human carcinogenesis. Using these systems, we have learned some of the functions of dominant activated-transforming oncogenes, tumor suppressor genes, and cellular immortalization genes and how they influence the carcinogenic process in human cells. Using our understanding of these processes, we are attempting to clone critical genes involved in the etiology of familial cancers. These investigations may help us to develop procedures that allow us to predict, in these cancer families, which individuals are at high risk for developing cancer.

Christensen, L. A., R. A. Finch, et al. (2006). "Targeting oncogenes to improve breast cancer chemotherapy." Cancer Res **66**(8): 4089-94.

Despite recent advances in treatment, breast cancer remains a serious health threat for women. Traditional chemotherapies are limited by a lack of specificity for tumor cells and the cell cycle dependence of many chemotherapeutic agents. Here we report a novel strategy to help overcome these limitations. Using triplex-forming oligonucleotides (TFOs) to direct DNA damage site-specifically to oncogenes overexpressed in human breast cancer cells, we show that the effectiveness of the anticancer nucleoside analogue gemcitabine can be improved significantly. TFOs targeted to the promoter region of c-myc directly inhibited gene expression by approximately 40%. When used in combination, specific TFOs increased the incorporation of gemcitabine at the targeted site approximately 4-fold, presumably due to induction of replication-independent DNA synthesis. Cells treated with TFOs and gemcitabine in combination showed a reduction in both cell survival and capacity for anchorage-independent growth (approximately 19% of untreated cells). This combination affected the tumorigenic potential of these cancer cells to a significantly greater extent than either treatment alone. This novel strategy may be used to increase the range of effectiveness of antitumor nucleosides in any tumor which overexpresses a targetable oncogene. Multifaceted chemotherapeutic approaches such as this, coupled with triplex-directed gene targeting, may lead to more than incremental improvements in nonsurgical treatment of breast tumors.

Ciotti, M., L. Giuliani, et al. (2006). "Detection and expression of human papillomavirus oncogenes in non-small cell lung cancer." Oncol Rep **16**(1): 183-9.

Human papillomavirus (HPV) has been found in lung cancer cases with variable frequency. In the present study, we analysed a series of 38 patients with non-small cell lung cancer (NSCLC) (21 paraffin-embedded archival samples and 17 fresh surgical specimens) for the presence of E6 and E7 oncogenes of HPV16, 18 and 31. Eight of the tumours were positive (21%): six HPV16, one HPV16+18, and one HPV31. The normal tissue surrounding the HPV-positive tumour was negative for the presence of the virus. Sequencing analysis of URR, of HPV16, which was the most frequently found HPV type in our cases, showed an adenosine deletion at nucleotide 7861 (E2-binding site) in four out of six patients. Sequencing of the entire E6 and E7 genes of HPV16 showed a T to G transition at nucleotide position 350 of E6, in all examined cases. This mutation is associated to the European variant of HPV16. Analysis of E6 and E7 transcripts was performed on the six fresh surgical specimens infected by HPV16. Our study showed that all of the tumours investigated, except one, contained E6 and E7 transcripts. Only in one case could we identify an unspliced form of the E6 transcript. Our results strengthen the relationship between HPV and NSCLC and support the hypothesis that HPV infection could play a role in bronchial carcinogenesis.

Cooper, G. M. (1992). "Oncogenes as markers for early detection of cancer." J Cell Biochem Suppl **16G**: 131-6.

Oncogenes are formed in human tumors as a result of mutations or DNA rearrangements leading to the abnormal expression or function of proto-oncogenes. Approximately 20 different oncogenes are reproducibly activated in malignancies of several types, including breast, colon, lung, pancreatic, and thyroid carcinomas, leukemias, and lymphomas. The potential utility of these oncogenes as markers for

early detection of cancer is dependent on the stage of tumor development at which they are activated, and on whether the mutated oncogenes are readily distinguished from the corresponding proto-oncogenes by assays that are sufficiently sensitive to detect precancerous lesions.

Cordon-Cardo, C. and J. Sheinfeld (1997). "Molecular and immunopathology studies of oncogenes and tumor-suppressor genes in bladder cancer." World J Urol **15**(2): 112-9.

Target genes implicated in cellular transformation and tumor progression have been divided into two categories: proto-oncogenes (that when activated become dominant events characterized by gain of function) and tumor-suppressor genes (recessive events characterized by the loss of function). Alterations in proto-oncogenes and tumor-suppressor genes seem equally prevalent among human cancers. Multiple mutations appear to be required to conform the malignant phenotype. It is therefore conceivable that cancer be viewed fundamentally as a genetic disease entailing inherited (also called germ-line) and/or acquired (also termed somatic) mutations of genes in these two categories. Molecular studies of bladder neoplasms have identified a series of nonrandom genetic alterations affecting a particular set of oncogenes and tumor-suppressor genes. Because the modality of therapy for patients with bladder neoplasms primarily depends on morphological evaluation and clinical staging, the diagnosis carries significant consequences. However, it is well known that morphologically similar tumors presenting in any assigned stage may behave in radically different fashions, which seriously hampers the physician's ability accurately to predict clinical behavior in a given case. Recent studies have shown that inactivation of certain tumor-suppressor genes, such as RB and TP53, occur in bladder tumors that have a more aggressive clinical outcome and poor prognosis. In the present paper we review the molecular abnormalities associated with these dominant and recessive genes in bladder cancer and discuss the potential clinical use of their detection. The implementation of objective predictive assays to identify these alterations in clinical material will enhance our ability to assess tumor biological activities and to design effective treatment regimens. The need now is to translate this newly developed scientific knowledge into diagnostic and therapeutic strategies, which in turn will enhance the quality of life and prolong the survival of patients with bladder cancer.

Dai, Z., W. G. Zhu, et al. (2003). "A comprehensive search for DNA amplification in lung cancer identifies inhibitors of apoptosis cIAP1 and cIAP2 as candidate oncogenes." Hum Mol Genet **12**(7): 791-801.

Amplification of oncogenes is an important mechanism that can cause gene overexpression and contributes to tumor development. The identification of amplified regions might have both prognostic and therapeutic significance. We used primary lung carcinomas and lung cancer cell lines for restriction landmark genomic scanning (RLGS) to identify novel amplified sequences. Enhanced RLGS fragments that indicate gene amplification were observed in primary tumors and lung cancer cell lines of both non-small cell lung cancer and small cell lung cancer. We identified one novel amplicon on chromosome 11q22, in addition to previously reported amplicons that include oncogenes MYCC, MYCL1 and previously identified amplification of chromosomal regions 6q21 and 3q26-27. Amplification of 11q22 has been reported in other types of cancer and was refined to an approximately 1.19 Mbp region for which the complete sequence is available. Based on a patient sample with a small region of low-level amplification we were able to further narrow this region to 0.92 Mbp. Genes localized in this region include two inhibitors of apoptosis (cIAP1 and cIAP2). Immunohistochemistry and western blot analysis identified cIAP1 and cIAP2 as potential oncogenes in this region as both are overexpressed in multiple lung cancers with or without higher copy numbers.

Diamandis, E. P. (1997). "Clinical applications of tumor suppressor genes and oncogenes in cancer." Clin Chim Acta **257**(2): 157-80.

In the search for new ways to better diagnose and monitor cancer, scientists have turned to oncogenes and tumor suppressor genes. These genes are involved in cell differentiation, communication and proliferation and their alteration is frequently associated with cancer. Such alterations include mutations, translocations, amplifications and deletions. In this review, I give examples of using the detection of such alterations for patient diagnosis and monitoring. The practical examples are restricted to a few cancer types, but the identification of new tumor suppressor genes, like BRCA-1 and BRCA-2, is creating new possibilities for determining cancer risk of individual family members. There is no doubt that the cloning of new genes which predispose to sporadic cancer will lead to the introduction of widespread testing to assess risk and to the application of preventive measures.

Duffy, M. J. (1993). "Cellular oncogenes and suppressor genes as prognostic markers in cancer." Clin Biochem **26**(6): 439-47.

Activation of cellular or c-oncogenes and loss of function of suppressor genes appears to be the key event in the formation of most human cancers. Altered forms of these genes or their protein products have the potential to provide a new generation of cancer markers. As cancer markers, the most useful application of c-oncogenes and suppressor genes so far, has been in providing prognostic information. The correlation of N-myc gene amplification with poor prognosis in neuroblastoma was one of the first examples of prognostic data supplied by a c-oncogene. Most, but not all investigators, find that either amplification or increased expression of c-erbB-2 gene correlates with poor prognosis in breast cancer. Other potential prognostic markers in breast cancer include amplification of the c-myc gene, and increased expression of both EGFR and p53 protein. Although c-oncogenes and suppressor genes have the potential to supply prognostic information in a broad range of cancers, many of the results are still preliminary with conflicting conclusions.

el-Deiry, W. S. (1997). "Role of oncogenes in resistance and killing by cancer therapeutic agents." Curr Opin Oncol **9**(1): 79-87.

Chemotherapeutic drug resistance is a major clinical problem and cause for failure in the therapy of human cancer. One of the goals of molecular oncology is to identify the underlying mechanisms, with the hope that more effective therapies can be developed. Several mechanisms have been suggested to contribute to chemoresistance: 1) amplification or overexpression of the P-glycoprotein family of membrane transporters (eg, MDR1, MRP, LRP) which decrease the intracellular accumulation of chemotherapy; 2) changes in cellular proteins involved in detoxification (eg, glutathione S-transferase pi, metallothioneins, human MutT homologue, bleomycin hydrolase, dihydrofolate reductase) or activation of the chemotherapeutic drugs (DT-diaphorase, nicotinamide adenine dinucleotide phosphate:cytochrome P-450 reductase); 3) changes in molecules involved in DNA repair (eg, O6-methylguanine-DNA methyltransferase, DNA topoisomerase II, hMLH1, p21WAF1/CIP1; 4) activation of oncogenes such as Her-2/neu, bcl-2, bcl-XL, c-myc, ras, c-jun, c-fos, MDM2, p210 BCR-abl, or mutant p53. An overview of these resistance mechanisms is presented, with a particular focus on the role of oncogenes. Some current strategies attempting to reverse their effects are discussed.

Elgendy, S., Q. Tahin, et al. (1995). "Coexpression of C-erbb2 and int-2 oncogenes in invasive breast-cancer." Int J Oncol **6**(5): 977-84.

Invasive breast carcinomas of 19 premenopausal and 49 postmenopausal women were studied by Southern blot analysis for detection of c-erbB2 and int-2 oncogenes, and quantitation of c-erbB2 protein, p185 by ELISA. The data were correlated with the histological grade of the tumor and the patient's clinical status. Seventeen tumors (25.0%) showed genomic alteration in one or both oncogenes. c-erbB2 and int-2 amplification were expressed by 10 (14.7%) and 7 (10.2%) of the tumors respectively. c-erbB2 overexpression was found in 15 out of 68 tumors (22.1%). All tumors exhibiting amplification of c-erbB2 also showed overexpression of p185 protein, however 5 out of 15 tumors (33.3%) showing c-erbB2 overexpression did not show amplification. Rearrangement of c-erbB2 and int-2 oncogenes was observed in 4 out of 68 tumors (5.9%) and 2 of these tumors presented rearrangement of both oncogenes. A significant positive correlation was found between c-erbB2 amplification and p185 protein overexpression, and c-erbB2 and int-2 amplification. Oncogene alterations were more frequently detected in tumors with high histological grade, but no correlation was found with patient's age, menopausal or lymph node status.

Ernberg, I. T. (1990). "Oncogenes and tumor growth factors in breast cancer. A minireview." Acta Oncol **29**(3): 331-4.

Five oncogenes have been implied as having a role in human breast tumorigenesis: int-2, c-erbB-2 (HER-2), c-myc, c-Ha-ras and the recessive Rb-1. As far as the function and biochemistry of these oncogenes have been studied, they act at different levels and have totally different functions in the cells. They are normally cellular genes, likely to have important functions in normal cell growth or differentiation. In the tumors their regulation or function is altered, due to a wide class of mutations. The oncogenes may cooperate to result in the malignant cell phenotype. However, different oncogenes are mutated in different tumors, so that the tumors show a variable pattern at the molecular level, underlining the individuality of these tumors already described as differences in histopathology, hormone receptor expression and clinical course. The main importance of the oncogene studies is still to reveal basic pathogenetic mechanisms. When appropriate it is important to test diagnostic or prognostic significance of the oncogene mutations.

Ewis, A. A., K. Kondo, et al. (2001). "Occupational cancer genetics: infrequent ras oncogenes point mutations in lung cancer samples from chromate workers." Am J Ind Med **40**(1): 92-7.

BACKGROUND: Chromium carcinogenicity and mutagenicity are no longer disputed. However, although chromium has various genetic effects that induce cancer, its mechanism of inducing lung cancer in humans is still not fully understood. p53, a tumor suppressor gene, was found to be infrequently mutated in samples of lung cancer in workers with long occupational exposure to chromium, suggesting other cancer-related genes to be targeted in such tumors. METHODS: To assess the contribution of the ras oncogenes in the pathogenesis of chromate-related lung cancer, we studied point mutations at the critical positions of codons 12, 13, and 61 of the Ha-ras and Ki-ras oncogenes in 38 lung cancer samples derived from Japanese patients who worked in the chromate industry for long periods. We used both radioactive isotope and non-radioisotope PCR-SSCP techniques. RESULTS: The results of this study demonstrated that activation of ras genes due to point mutations in chromate-related lung cancer is a rare event. CONCLUSIONS: Ras oncogenes activated by point mutations do not have a major role in the process of tumorigenesis of chromate-related lung cancer.

Felsher, D. W. (2003). "Cancer revoked: oncogenes as therapeutic targets." Nat Rev Cancer **3**(5): 375-80.

Recent findings show that even the brief inactivation of a single oncogene might be sufficient to result in the sustained loss of a neoplastic phenotype. It is therefore possible that the targeted inactivation of oncogenes could be a specific and effective treatment for cancer. So why does oncogene inactivation cause tumour regression and will this be a generally successful approach for the treatment of human neoplasia?

Fishleder, A. J. (1990). "Oncogenes and cancer: clinical applications." Cleve Clin J Med **57**(8): 721-6.

Oncogenes are aberrant forms of proto-oncogenes, which are normal cellular genes that participate in cell growth and development; proto-oncogenes contribute to tumor formation when mutations or chromosomal translocation cause them to escape normal controls. Anti-oncogenes, also involved in neoplasm development, normally participate in inhibition of cell growth and proliferation; they become tumorigenic when mutations alter their function. Oncogene or anti-oncogene abnormalities have been characterized for a variety of tumors, with resulting clinical applications. In some forms of leukemia, for example, determining the presence or absence of the bcr-abl gene rearrangement has both diagnostic and prognostic value. The best-studied anti-oncogene is that found in retinoblastoma. Molecular techniques can differentiate the hereditary from the nonhereditary form of this disease and, with hereditary retinoblastoma, predict disease likelihood in family members.

Garcia, M. J., J. C. Pole, et al. (2005). "A 1 Mb minimal amplicon at 8p11-12 in breast cancer identifies new candidate oncogenes." Oncogene **24**(33): 5235-45.

Amplification of 8p11-12 is a well-known alteration in human breast cancers but the driving oncogene has not been identified. We have developed a high-resolution comparative genomic hybridization array covering 8p11-12 and analysed 33 primary breast tumors, 20 primary ovarian tumors and 27 breast cancer cell lines. Expression analysis of the genes in the region was carried out by using real-time quantitative PCR and/or oligo-microarray profiling. In all, 24% (8/33) of the breast tumors, 5% (1/20) of the ovary tumors and 15% (4/27) of the cell lines showed 8p11-12 amplification. We identified a 1 Mb segment of common amplification that excludes previously proposed candidate genes. Some of the amplified genes did not show overexpression, whereas for others, overexpression was not specifically attributable to amplification. The genes FLJ14299, C8orf2, BRF2 and RAB11FIP, map within the 8p11-12 minimal amplicon, two have a putative function consistent with an oncogenic role, these four genes showed a strong correlation between amplification and overexpression and are therefore the best candidate driver oncogenes at 8p12.

Garraway, L. A. and W. R. Sellers (2006). "Lineage dependency and lineage-survival oncogenes in human cancer." Nat Rev Cancer **6**(8): 593-602.

Although cell-lineage and differentiation models dominate tumour classification and treatment, the recognition that cancer is also a genomic disease has prompted a reconfiguration of cancer taxonomies according to molecular criteria. Recent evidence indicates that a synthesis of lineage-based and genetic paradigms might offer new insights into crucial and therapeutically pliable tumour dependencies. For example, MITF (microphthalmia-associated transcription factor), which is a master regulator of the melanocyte lineage, might become a melanoma oncogene when deregulated in certain genetic contexts. MITF and other lineage-survival genes therefore implicate lineage dependency (or lineage addiction) as a newly recognized mechanism that is affected by tumour genetic alterations.

Giuriato, S., K. Rabin, et al. (2004). "Conditional animal models: a strategy to define when oncogenes will be effective targets to treat cancer." Semin Cancer Biol **14**(1): 3-11.

The ability to model cancer in the mouse has provided a robust methodology to dissect the molecular etiology of cancer. These models serve as potentially powerful platforms to preclinically evaluate novel therapeutics. In particular, the recent development of strategies to conditionally induce the or knockout the function of genes in a tissue specific manner has enabled investigators to engineer mice to demonstrate that the targeted inactivation of specific oncogenes can be effective in inducing sustained regression of tumors. Thus, these animal models will be useful to define the specific genes that will be therapeutically useful to target for the treatment of particular human cancers.

Goretzki, P. E., J. Lyons, et al. (1992). "Mutational activation of RAS and GSP oncogenes in differentiated thyroid cancer and their biological implications." World J Surg **16**(4): 576-81; discussion 581-2.

Activating mutations of ras-genes (Kirsten-ras, Harvey-ras, N-ras) and genes encoding for the alpha subunit of G-proteins (Gs, Gi2, Gi3, Go, Gz) were assessed in 32 differentiated thyroid cancer (DTC) tissues from German (n = 22) and American (n = 10) patients. Gs-protein (GSP) and/or ras mutations were found in 69% of all tissues with a heterogeneous distribution pattern. An increased prevalence could be demonstrated in metastatic (8 of 9 mutation positive) when compared to localized disease (13 of 23 mutation positive) (p less than 0.001) and in patients greater than 50 years of age (16 of 18 mutation positive), when compared to younger patients (6 of 14 mutation positive) (p less than 0.001). No activating mutations were found on H-ras and K-ras genes nor on genes encoding for the alpha subunits of Gi2, Gi3, Go, and Gz. Differentiated thyroid cancer tissue from German patients revealed a higher prevalence for GSP mutations (73%) than did DTC from American patients (20%) (p less than 0.001). We demonstrated a high frequency of ras and GSP mutations in DTC and suggest that these mutations may contribute to our basic understanding of this disease and might initiate a new search for more rational and individualized therapeutic approaches in patients with DTC.

Grander, D. (1998). "How do mutated oncogenes and tumor suppressor genes cause cancer?" Med Oncol **15**(1): 20-6.

In recent decades we have been given insight into the process that transforms a normal cell into a malignant cancer cell. It has been recognised that malignant transformation occurs through successive mutations in specific cellular genes, leading to the activation of oncogenes and inactivation of tumor suppressor genes. The further study of these genes has generated much of its excitement from the convergence of experiments addressing the genetic basis of cancer, together with cellular pathways that normally control important cellular regulatory programmes. In the present review the context in which oncogenes and tumor suppressor genes normally function as key regulators of physiological processes such as proliferation, cell death/apoptosis, differentiation and senescence will be described, as well as how these cellular programmes become deregulated in cancer due to mutations.

Griep, A. E. and P. F. Lambert (1994). "Role of papillomavirus oncogenes in human cervical cancer: transgenic animal studies." Proc Soc Exp Biol Med **206**(1): 24-34.

Human papillomaviruses are believed to be etiologic agents for the majority of human cervical carcinoma, a common cancer that is a leading cause of death by cancer among women worldwide. In cervical carcinoma, a subset of papillomaviral genes, namely E6 and E7, are expressed. In vitro tissue culture studies indicate that HPV E6 and E7 are oncogenes, and that their oncogenicity is due in part to their capacity to inactivate cellular tumor suppressor genes. The behavior of E6 and E7 in vitro and the genetic evidence from analysis of human cancers suggest that the E6 and E7 genes play a significant role in the development of cervical cancer. This hypothesis is now being tested using animal models. In this review, we summarize our current knowledge of the oncogenicity of papillomavirus genes that has been generated through their study in transgenic mice.

Gu, W., L. Putral, et al. (2006). "Inhibition of cervical cancer cell growth in vitro and in vivo with lentiviral-vector delivered short hairpin RNA targeting human papillomavirus E6 and E7 oncogenes." Cancer Gene Ther **13**(11): 1023-32.

In this study, we investigated the suppressive effect of a short hairpin RNA delivered by a lentiviral vector (LV-shRNA) against human papillomavirus (HPV) type 18 E6 on the expression of the oncogenes E6 and E7 in cervical cancer HeLa cells both in vitro and in vivo. The LV-shRNA effectively delivered the shRNA to HeLa cells and lead to a dose-dependent reduction of E7 protein and the stabilization of E6 target proteins, p53 and p21. Low-dose infection of HeLa cells with LV-shRNA caused reduced cell growth and the induction of senescence, whereas a high-dose infection resulted in specific cell death via apoptosis. Transplant of HeLa cells infected with a low dose of LV-shRNA into Rag-/- mice significantly reduced the tumor weight, whereas transplant of cells infected with a high dose resulted in a complete loss of tumor growth. Systemic delivery of LV-shRNA

into mice with established HeLa cell lung metastases led to a significant reduction in the number of tumor nodules. Our data collectively suggest that lentiviral delivery is an effective way to achieve stable suppression of E6/E7 oncogene expression and induce inhibition of tumor growth both in vitro and in vivo. These results encourage further investigation of this form of RNA interference as a promising treatment for cervical cancer.

Gullick, W. J. (1990). "Growth factors and oncogenes in breast cancer." Prog Growth Factor Res **2**(1): 1-13.

The growth of normal breast epithelial cells is regulated by a complex interacting system of polypeptide factors and by steroid hormones. The cells respond to these factors through receptors which generate mitogenic and other intracellular signals. These second messengers provoke complex responses which may ultimately result in DNA replication and cell division. A comparison of normal cells and tumour cells, either in culture or from primary tumour biopsies, has revealed differences in growth factor and growth factor receptor expression. Such changes may represent aspects of the process of malignant transformation. In addition some evidence suggests that changes in second messenger systems may also occur. Finally several changes in nuclear oncogenes have been observed in breast cancers. It has been proposed that changes in the nuclear oncogenes, perhaps involving the loss of function of tumour suppressor genes, may allow cells to enter the cell cycle. Changes in growth factors, their receptors or intracellular second messenger systems may stimulate unregulated growth. The combination of these events provide a model for the process of carcinogenesis.

Hall, E. J. (1991). "From chimney sweeps to oncogenes: the quest for the causes of cancer." Radiology **179**(2): 297-306.

Over the past 200 years, a bewildering array of chemical, physical, and viral agents has been identified that can cause cancer, but the mechanisms involved are only now becoming clear. In the leukemias and lymphomas, it appears that the activation of cellular oncogenes is important. The genes involved are present in all normal cells and are often associated with cell growth and regulation. When activated, they act in a dominant fashion to cause a cell to express the malignant phenotype. There is increasing evidence that in solid tumors, a more important mechanism may be the loss of a suppressor gene. The classic example is retinoblastoma, in which the retinoblastoma gene has been cloned and is also found to be associated with several other common cancers including sarcomas and small cell lung cancer. It is likely to be one of a family of such genes. It may well be that the activation of one or more oncogenes or the loss of one or more suppressor genes, or both, is required for a tumor to progress from initiation through promotion to a metastasizing malignancy.

Hall, J. M., P. J. Zuppan, et al. (1989). "Oncogenes and human breast cancer." Am J Hum Genet **44**(4): 577-84.

The role of oncogenes in breast tumorigenesis is unclear. Alterations and/or amplification of several oncogene sequences have been observed in primary human breast tumors, in breast tumor cell lines, and in mammary tumors in model systems. In principle, such alterations could be sites of primary lesions for human breast cancer, causes of tumor progression or metastasis, or simply secondary lesions of highly aberrant tumor genomes. The present study tested genetic linkage of breast cancer susceptibility to nine oncogenes in 12 extended families including 87 affected individuals. Lod scores for close linkage of each candidate sequence to breast cancer were -19.6 for HRAS, -12.3 for KRAS2, -1.0 for NRAS, -6.0 for MYC, -6.1 for MYB, -8.2 for ERBA2, -7.9 for INT2, and -5.1 for RAF1. Regions of chromosome 11p associated with tumor homozygosity and the region of 3p carrying the gene for Von Hippel-Lindau disease could also be excluded from linkage to human breast cancer. The 5-kb allele of the MOS oncogene, previously proposed to be associated with breast cancer, was absent in these families, suggesting that polymorphism at this locus is not associated with inherited susceptibility. These results strongly suggest that oncogenes are not the sites of primary alterations leading to breast cancer. On the other hand, alterations in one or more of these sequences may be associated with tumor progression.

Holt, J. A. (1993). "The glutathione cycle is the creative reaction of life and cancer. Cancer causes oncogenes and not vice versa." Med Hypotheses **40**(5): 262-6.

Life is definable as a chemical reaction which obeys exponential growth and dies if reversed. Such a reaction must be the commencement of all life so that every evolved form of it inherits these characteristics. As no single reaction known has these two features, life must be a combination of two or more reactions which whilst obeying all the classical laws of physics and chemistry assume an exponential form and effectively act as being irreversible. The reactions of glutathione--oxidation and reduction--when combined in sequence as a cyclical process fulfill these criteria. The cyclic changes of glutathione from reduced to oxidised to reduced forms must therefore be the reaction which creates life and is responsible for cancer's growth. 434 mHz electromagnetic radiation

stimulates cancer growth rate by forcing this cycle into activity. Proof of this hypothesis is the long-term control of cancer in 11 patients treated with oxidised glutathione and 434 mHz radiation. Genetic material does not contain any energy system with exponential form, neither is it self-replicating. Genetic material will only reproduce if placed within an immortal cell in which all controls of the glutathione system have been lost, as in a cancer cell. Oncogenes must be the product of cancer and not the reverse.

Hussain, S., Y. Zhang, et al. (2009). "DUBs and cancer: the role of deubiquitinating enzymes as oncogenes, non-oncogenes and tumor suppressors." Cell Cycle **8**(11): 1688-97.

It is increasingly apparent that ubiquitin (Ub) mediated events are critical in cell proliferation. With much attention placed on the ubiquitin-proteasome pathway as a target for pharmacologic intervention, we must consider the role of deubiquitinating enzymes (DUBs) as regulators of these processes. There is a growing recognition of DUBs that are mutated in human cancers suggesting their roles as oncogenes and tumor suppressors. There is also an expanding list of enzymes that play essential roles in pathways that contribute to, or support cellular adaptations required for, malignant transformation (non-oncogenes). (Luo J, Cell 2009) Here we review the association of DUBs with cancer beginning with those with known mutations in human disease and concluding with those with a clear role in regulating cancer-relevant pathways. The molecular mechanisms underlying the association with cancer are described along with data regarding altered expression in human diseases. Although few specific, cell permeable, inhibitors exist, DUBs as a class are eminently drugable targets making it important to better understand the sites at which such modulation may have useful effects therapeutically. Given the numbers of ubiquitin-dependent pathways where we do not yet understand the role of deubiquitination, it is certain that the list of cancer-related DUBs will grow in coming years.

Idelevich, E., M. Mozes, et al. (2003). "Oncogenes in male breast cancer." Am J Clin Oncol **26**(3): 259-61.

The objective of this study was to assess the degree of expression and prognostic significance of c-erbB-2, p53, and bcl-2 in male breast cancer (MBC). Thirty male patients with the diagnosis of adenocarcinoma of the breast were studied retrospectively. All patients underwent surgery; c-erbB-2, p53, and bcl-2 were immunohistochemically stained on sections from formalin-fixed, paraffin-embedded tissues. Seventeen (56.7%) of the 30 cases of MBC were bcl-2 positive. Few specimens were found positive for c-erbB-2 (6.7%) and p53 (6.7%). The 5-year survival rate was marginally better for those patients with tumors staining positively for bcl-2 ($p = 0.05$). It was impossible to estimate the association between survival rate and p53 and c-erbB-2 expression because of the small number of positively stained specimens. In this study, only bcl-2 showed marginal association to other tumor parameters and a trend toward a better 5-year survival rate. At present there is inadequate evidence to support the use of molecular markers as independent prognostic markers in MBC.

Irish, J. C. and A. Bernstein (1993). "Oncogenes in head and neck cancer." Laryngoscope **103**(1 Pt 1): 42-52.

Primary head and neck squamous cell carcinomas from 58 patients were analyzed for the presence of alterations in the K-ras, raf, and erb-B oncogenes. Analysis of 17 fresh tumor specimens using sequence analysis of target sequences amplified by the polymerase chain reaction showed no evidence of mutations in the K-ras oncogene. Thirty fresh tumor specimens were analyzed for the presence of raf gene activation using Southern blot analysis. Under these conditions, no mutations in the c-raf oncogene were detected. In this study, 6 (13%) of the 47 tumors studied displayed epidermal growth factor receptor (EGFR) gene amplification and/or gene rearrangement. Overexpression of the erb-B gene was observed in 18 (67%) of the 27 head and neck tumors studied. Those patients expressing high levels of EGFR or showing EGFR amplification had tumors that were clinically more advanced. These data suggest that amplification and over-expression of the EGFR gene may be a useful diagnostic and prognostic marker in head and neck squamous cell carcinomas.

Issing, W. J., T. P. Wustrow, et al. (1993). "Oncogenes related to head and neck cancer." Anticancer Res **13**(6B): 2541-51.

Cancer has been defined as a fundamental disorder of cellular growth control. Which arises in some cells through changes in genes (DNA-level: geneamplification, mutation and rearrangement) or their expression (RNA- and protein-level), and gives these cells a growth advantage in comparison to the surrounding cells. Since the last decade we know the identity of these genes and the nature of the changes they underwent in the cancer cell. Only a few of the known oncogenes play a role in head and neck cancer. These are the EGFR (epidermal growth factor receptor), c-myc, the ras gene family, int-2, hst- 1 and bcl- 1. In some clinical disorders, like childhood neuroblastoma and breast cancer, oncogenes play already an important role in tumor staging as well as a prognostic parameter. The aim for the future is the

therapeutic application of oncogenes better known as gene therapy.

Jiang, W., S. M. Kahn, et al. (1989). "Rapid detection of ras oncogenes in human tumors: applications to colon, esophageal, and gastric cancer." Oncogene **4**(7): 923-8.

We have developed a rapid, nonradioactive large scale method for the detection of ras oncogenes in human tumors. DNA is amplified by the polymerase chain reaction (PCR), and then digested with specific restriction enzymes to detect either endogenous or primer-mediated Restriction Fragment Length Polymorphisms (RFLPs). We report here that three of 15 colon tumors tested contain K-ras codon 12 aspartic acid mutations and one, along with the HCT 116 colon carcinoma cell line, contains a K-ras codon 13 aspartic acid mutation. On the other hand, we did not detect H- or K-ras codon 12 mutations or the K-ras codon 13 aspartic acid mutation in 25 esophageal and 27 gastric cardia tumors isolated from patients in Lin-xing County, China. By incorporating nucleotide substitutions in PCR primers, this method can be applied towards the rapid, non-radioactive screening of virtually any genetic disease caused by known point mutations.

Kalas, W., J. L. Yu, et al. (2005). "Oncogenes and Angiogenesis: down-regulation of thrombospondin-1 in normal fibroblasts exposed to factors from cancer cells harboring mutant ras." Cancer Res **65**(19): 8878-86.

The onset of angiogenesis in cancer often involves down-regulation of endogenous angiogenesis inhibitors, of which thrombospondin-1 (TSP-1) is a paradigm. As this effect is thought to occur under the influence of transforming genetic lesions (e.g., expression of the mutant ras oncogene), its nature is regarded as intrinsic to cancer cells themselves. Here, we show that ras-transformed cancer cells can also induce TSP-1 down-regulation in their adjacent nontransformed stromal fibroblasts, but not in endothelial cells, in a paracrine and distance-dependent manner. Indeed, several H-ras-expressing fibrosarcoma (528ras1, B6ras, and NIH3T3Ras) and carcinoma (DLD-1 and IEC18Ras3) cells were found to release soluble factors capable of suppressing TSP-1 protein, mRNA, and promoter activity in nontumorigenic, immortalized dermal fibroblastic cell lines in culture (e.g., in fibroblasts expressing enhanced green fluorescent protein/TSP-1 reporter). This effect was abrogated in Id1-/- fibroblasts. At least two low molecular weight (<3 kDa), heat-labile, and trypsin-resistant mediators of TSP-1 suppression were found to be released from 528ras1 cells. Their effects on normal fibroblasts were inhibited (albeit to different extents) by pertussis toxin and, in one case, by dimethylsphingosine, none of which affected TSP-1 expression by 528ras1 cells. Collectively, our study suggests that the effect of mutant ras on tumor neovascularization is not limited to changes in angiogenic properties of cancer cells themselves. Rather, mutant ras, through a different signaling mechanism, may modulate the properties of the adjacent normal stroma, thus eliciting a proangiogenic field effect.

Kaye, F. J., R. A. Kratzke, et al. (1990). "Recessive oncogenes in lung cancer." Am Rev Respir Dis **142**(6 Pt 2): S44-7.

The observation that carcinogen exposure is strongly associated with the probability of developing pulmonary neoplasms has suggested for many years that acquired somatic mutations play a key role in the genesis of these environmentally induced cancers. With the advent of new techniques in cytogenetics and in the molecular analysis of DNA extracted from lung tumors, it has now become possible to test this hypothesis and to search for candidate genes that may be targeted by the chronic exposure of these environmental insults. Early work in this field, studying lung tumors of different histologic types, appears to implicate several distinct chromosomal loci (at chromosomes 3p, 13q, 17p, and others), suggesting that sequential genetic events occur during the initiation and progression pathways to pulmonary tumorigenesis. Identifying the candidate gene products and understanding the chronology and stringency of mutational events at these loci will be an essential goal to understanding the cellular basis of lung tumors and for developing strategies for the next generation of diagnostic and therapeutic studies.

Kellar, K. A., M. V. Lorenzi, et al. (2006). "Constitutively active receptor tyrosine kinases as oncogenes in preclinical models for cancer therapeutics." Mol Cancer Ther **5**(6): 1571-6.

Receptor tyrosine kinases (RTK) remain an area of therapeutic interest because of their role in epithelial tumors, and experimental models specific to these targets are highly desirable. Chimeric receptors were prepared by in-frame fusion of the CD8 extracellular sequence with the cytoplasmic sequences of RTKs. A CD8HER2 fusion protein was shown to form disulfide-mediated homodimers and to transform fibroblasts and epithelial cells. CD8RTK fusion proteins transform rat kidney epithelial cells and impart phenotypes that may reflect signaling specificity inherent in the native receptors. Transgenic expression of CD8HER2 and CD8Met in mice resulted in the formation of salivary and mammary gland tumors. The transgenic tumors allow the

derivation of allograft tumors and cell lines that are sensitive to inhibition by small molecule kinase inhibitors. This approach provides excellent cell and tumor models for the characterization of signaling properties of diverse RTKs and for the evaluation of rationally designed antagonists targeting these kinases.

Kent, O. A. and J. T. Mendell (2006). "A small piece in the cancer puzzle: microRNAs as tumor suppressors and oncogenes." Oncogene **25**(46): 6188-96.

The known classes of genes that function as tumor suppressors and oncogenes have recently been expanded to include the microRNA (miRNA) family of regulatory molecules. miRNAs negatively regulate the stability and translation of target messenger RNAs (mRNA) and have been implicated in diverse processes such as cellular differentiation, cell-cycle control and apoptosis. Examination of tumor-specific miRNA expression profiles has revealed widespread dysregulation of these molecules in diverse cancers. Although studies addressing their role in cancer pathogenesis are at an early stage, it is apparent that loss- or gain-of-function of specific miRNAs contributes to cellular transformation and tumorigenesis. The available evidence clearly demonstrates that these molecules are intertwined with cellular pathways regulated by classical oncogenes and tumor suppressors such as MYC, RAS and p53. Incorporation of miRNA regulation into current models of molecular cancer pathogenesis will be essential to achieve a complete understanding of this group of diseases.

Kern, J. A. and A. E. Filderman (1993). "Oncogenes and growth factors in human lung cancer." Clin Chest Med **14**(1): 31-41.

We are only beginning to understand the importance of lung cancer tumor biology in relation to prognosis and response to therapy. Many of the biologic and genetic changes we have described are preliminary observations and require further confirmation before clinical use. However, information concerning three oncogenes may soon prove to be helpful in the clinical arena: the myc genes in SCLC, and the ras genes and c-erbB-2 in NSCLC. In general their presence identifies poor patient response to therapy and poor survival. These markers are currently being used in a clinical setting at some research centers, but are not recommended for general diagnostic or prognostic use without further confirmation of their utility. Incorporation of this information with that learned by standard staging procedures may result in improved understanding of patient prognosis and challenge current concepts of lung cancer treatment. For example, surgically resected stage I NSCLC patients may benefit from adjuvant therapy if found to have these adverse biologic factors, and require more stringent follow-up after therapy. Finally the understanding of the pathogenesis of lung cancer may enable the development of novel therapy directed against these growth pathways. Our ultimate goal is to derive a therapeutic and prognostic paradigm involving both molecular-genetic and clinical factors to arrive at an optimal staging model and treatment plan.

Kiefer, P. E., B. Wegmann, et al. (1990). "Different pattern of expression of cellular oncogenes in human non-small-cell lung cancer cell lines." J Cancer Res Clin Oncol **116**(1): 29-37.

Altered and deregulated cellular oncogenes were found in many human solid tumors. Except for a few types of tumors that consistently exhibited specific altered proto-oncogenes, the majority of tumors are associated with a number of transcriptionally activated cellular oncogenes. In the heterologous group of non-small-cell lung cancer (NSCLC), nothing about a specific pattern of proto-oncogene expression is known. Therefore, we investigated the expression of a panel of cellular oncogenes in NSCLC cell lines. DNA and RNA from 11 established NSCLC cell lines (4 adenocarcinoma cell lines, 3 squamous cell carcinoma cell lines, 3 large-cell carcinoma cell lines and 1 mesothelioma cell line) were isolated and analysed using the Southern, dot blot and Northern hybridization technique. c-myc RNA expression was found in all NSCLC cell line, L-myc expression only in 1 adenocarcinoma cell line, N-myc and c-myb expression in none of the 11 cell lines examined. No c-myc amplification could be detected in the DNAs. v-sis-related mRNA was observed in 5/11 cell lines without association to a specific NSCLC subtype. v-src-related mRNA, found in all tested cells, exhibited increased levels in 1 adenocarcinoma cell line (A-549) compared to the other cell lines. Binding sites for epidermal growth factor (EGF) had been described previously in NSCL, therefore we found erbB homologue transcripts coding for the EGF receptor in all NSCLC cell lines. Also, c-raf1-, N-ras-, Ki-ras-, and H-ras-related RNA expression was observed in all lines. We conclude that L-myc, N-myc, and c-myb expression does occur less frequently in NSCLC than in SCLC. Also amplification does not appear to be an important mechanism by which the c-myc proto-oncogene is activated in NSCLC. A specific pattern of oncogene expression could not be detected in NSCLC cells; each cell line examined showed its own pattern. However, transcriptional activation of a proto-oncogene like erbB, ras, raf, src, and c-myc, which are

all involved in the progression pathway of EGF, may be a common feature of NSCLC.

Kim, D. S., C. J. McCabe, et al. (2003). "Oncogenes in thyroid cancer." Clin Otolaryngol Allied Sci **28**(5): 386-95.

There have been significant advances in our understanding of carcinogenesis at the molecular level over the last 25 years. Oncogenes are of major interest as part of our search for knowledge surrounding the aetiology of cancer. There are several oncogenes associated with thyroid cancer. Detailed investigation of the nature and function of these tumour genes has provided important insights into both the tumour biology and the complex biochemical pathways of normal cellular functioning. Our knowledge of oncogene biology offers the hope of better diagnostic, therapeutic and prognostic modalities in our fight against this and other common cancers. Development of specific thyroid tumour markers and gene therapy is now a realistic prospect to supplement our present armamentarium of surgery and radiotherapy. This review aims to outline the pertinent information gained so far from studies of these oncogenes and provides both clinical relevance and fuel for further interest amongst the ENT thyroid community in this exciting area of research.

Klaes, R., S. M. Woerner, et al. (1999). "Detection of high-risk cervical intraepithelial neoplasia and cervical cancer by amplification of transcripts derived from integrated papillomavirus oncogenes." Cancer Res **59**(24): 6132-6.

Cervical cancer emerges from cervical intraepithelial neoplasia (CIN) induced by high-risk HPV (HR-HPV) infections. However, the vast majority of CIN lesions regresses spontaneously, and only a few lesions persist or progress to invasive carcinoma. On the basis of morphological criteria, it is not possible to differentiate high-grade lesions that will regress or persist from those that inevitably will progress to invasive cancers. In most cervical carcinomas, human papillomavirus (HPV) genomes are integrated into host cell chromosomes and transcribed into mRNAs encompassing viral and cellular sequences. In contrast, in early preneoplastic lesions, HPV genomes persist as episomes, and derived transcripts contain exclusively viral sequences. Thus, detection of HPV transcripts derived from integrated HPV genomes may specifically indicate both CIN lesions at high risk for progression as well as invasive cervical cancers. Here, we established a protocol for the amplification of papillomavirus oncogene transcripts (APOT) from cervical specimens that allows us to distinguish episome- from integrate-derived HPV mRNAs. Cervical swab and biopsy samples from 549 patients attending outpatient clinics for cervical dysplasia were screened for the presence of HPV DNA, and 155 samples that were positive for either HPV type 16 (n = 143) or 18 (n = 12) were subjected to the APOT assay. In samples derived from normal cervical epithelia (n = 19) or low-grade cervical lesions (CIN I, n = 10), no integrate-derived HPV transcripts were found. In contrast, in 1 (5%) of 22 samples derived from CIN II lesions, in 10 (16%) of 64 samples from patients with CIN III lesions, and in 35 (88%) of 40 samples from patients with cervical cancer, integrate-derived HPV transcripts were detected. Thus, detection of integrate-derived HPV transcripts in cervical swabs or biopsy specimens by the APOT assay points to advanced dysplasia or invasive cervical cancer.

Klein, N., J. M. Vignaud, et al. (1993). "Squamous metaplasia expression of proto-oncogenes and P 53 in lung cancer patients." Lab Invest **68**(1): 26-32.

BACKGROUND: The question of whether bronchial squamous metaplasia is a true preneoplasia is important and demonstrated in animal for several carcinogens. We have now approached this problem in humans and in vivo. EXPERIMENTAL DESIGN: Squamous metaplasia in the close vicinity of surgically resected lung tumors were evaluated for their mitotic index and screened for proto-oncogenes and P 53 protein expression by immunohistochemistry and/or in situ hybridization. RESULTS: Among 16 patients, 4 had squamous metaplasia positive for either myc messages and/or for P 53 protein accumulation. In the same patients (3/4), the autologous bronchial tumors were also positive for the same markers. Squamous metaplasia positivity was observed essentially in patients with advanced diseases and only in squamous cell carcinomas. In addition, when evaluated with 5 iodo-2'-deoxyuridine systemic infusion, all patients presented hyperproliferative basal squamous metaplasic cells. CONCLUSIONS: These results are reminiscent of the typical preneoplastic changes observed in familial colic adenomatosis, where genetic changes accumulate in hyperproliferative cells. They also suggest that bronchial squamous metaplasia could be an authentic preneoplasia in, at least, squamous cell carcinomas.

Knudson, A. G., Jr. (1989). "Nakahara memorial lecture. Hereditary cancer, oncogenes, and anti-oncogenes." Princess Takamatsu Symp **20**: 15-29.

Dominantly heritable predisposition to cancer is well known, even if rare. Such heritable cases are known for most cancers. Predisposition is usually to one or a few specific cancers, and the kinds of pedigrees that are found suggest the existence of an array of 50 or so such cancer genes. Penetrance is

usually high, as is the relative risk for a particular tumor. The inherited event is insufficient to cause cancer; at least one other (somatic) event must occur. For one tumor, retinoblastoma, the total number of necessary events seems to be two for both the hereditary and non-hereditary forms, and those events involve mutation or loss of the two copies of a tumor suppressor gene on chromosome 13. Analyses of tumors with polymorphic syntenic DNA probes and for abnormality of the gene itself have provided a picture of the kinds of first and second events that can occur. Several other tumors may follow the retinoblastoma scenario, including tumors associated with multiple endocrine neoplasia type 1 and with neurofibromatosis type 2, and identify the loci of several other putative anti-oncogenes. Still other hereditary cancer genes have been mapped, but evidence that they are suppressor genes is incomplete. It is possible that the inherited mutation may sometimes occur in an oncogene, although no such cases have been validated. In most, perhaps all, tumors, further genetic changes occur. In some instances these appear to be in oncogenes, and sometimes in anti-oncogenes. Some of these events appear to play a role similar to that of promotion in experimental carcinogenesis, whereas others are clearly important in progression. The process is particularly complicated in some of the common carcinomas, where changes in both oncogenes and anti-oncogenes are common.

Koffa, M. and D. A. Spandidos (1997). "Oncogenes and onco-suppressor genes in female genital cancer." Ann N Y Acad Sci **816**: 347-55.

Cancer is a multistep process resulting in the accumulation of genetic lesions in proto-oncogenes or tumor suppressor genes. In recent years, many biological studies have focused on the analysis of the genetic and molecular events occurring in genital tumors in order to identify genes involved in their initiation and progression. Understanding the genetic events that lead to initiation and progression of a disease remains an important challenge in gynecological research and ultimately may enable the development of better approaches for earlier diagnosis, in cases where current therapeutic strategies have a high cure rate.

Koster, A., S. Landgraf, et al. (1991). "Expression of oncogenes in human breast cancer specimens." Anticancer Res **11**(1): 193-201.

More than 60 breast cancer specimens were screened for their expression status of 25 different proto-oncogenes. The screening method is based on in vitro synthesis of a radioactive cDNA copied from the total cellular RNA of tumor tissue. This cDNA is hybridized to cloned oncogene probes which are immobilized to a GeneScreen membrane. Frequently multiple oncogenes were found expressed although expression levels were rather moderate. 25-30% of the analyzed tumors showed significant expression of either erbB, src, raf1, lck or H-ras. Although neu expression--an oncogene believed to be particular relevant as prognostic parameter for mamma carcinoma--was screened for most of the tumors with a heterologous gene probe, expression signals could be detected in about 20% cases. The only notable correlation with classical clinical parameters such as tumor size and proliferation stage, hormone receptor status and different DNA indices was the observation that tumors lacking the progesterone receptor frequently express multiple oncogenes. Advantages and limitations of the cDNA/dot-blot screening for oncogene expression are discussed.

Kratzke, R. A., E. Shimizu, et al. (1992). "Oncogenes in human lung cancer." Cancer Treat Res **63**: 61-85.

The rapid pace of research in the genetics of human cancer will predictably render any review of the topic out of date by the time of its publication. Prospects for the near future will likely include the identification of a chromosome 3p gene(s) linked with the development of familial renal cancer and, perhaps, also lung cancer. In addition, the availability from the Human Genome Project of an increasing number of well-characterized markers will accelerate the search for additional human recessive oncogenes. Many questions still remain about the etiology of lung cancer and how to apply this information for patient care. For example, identification of the cell of origin for small cell and non-small cell lung cancers will facilitate our understanding of the development of these tumors and improve the possibilities for future preventive strategies. In addition, we now realize that these cancers arise from the sequential accumulation of multiple genetic mutations (Table 3; Fig. 1). Therefore, a central question is which of these targets are essential for the process of carcinogenesis, and whether there is a critical temporal order for this process with a defined premalignant phase in a discrete field of bronchial tissue. In addition, are there genetically inherited susceptibilities to the development of lung cancer (either directly or via variabilities in carcinogen metabolism) that could be accurately identified in the general population? Finally, is there a rate-limiting mutation and will the genetic correction of this defect suffice to restore growth regulation, or will the replacement of multiple gene products be required for tumor suppression? We are already witnessing the beginnings of the use of molecular diagnostic markers as a research tool for assigning prognostic information. The expression of

neuroendocrine markers in non-small cell lung cancer has recently been applied as an indicator of the potential response to combination chemotherapy [15]. Similar methods are being applied to the expression of tumor suppressor genes or the presence of somatic mutations in dominant oncogenes such as the ras gene. However, the clinical benefit of this prognostic information with currently available treatment programs is still uncertain.(ABSTRACT TRUNCATED AT 400 WORDS)

Kretzschmar, J. L. (1990). "The role of oncogenes in cancer." Mil Med **155**(2): 83-6.

Researchers have accumulated evidence suggesting that most human cancers are the result of multiple events involving many genes functioning at various levels of expression over a long period of time. Recently, an important segment of cancer research has focused on oncogenes, a group of altered normal genes. The normal genes, known as proto-oncogenes, encode proteins necessary for the cell's structure, growth, and mitotic activity. Oncogenes have been found to be the activated forms of proto-oncogenes, which become activated as a result of point mutations, nucleotide deletions/insertions, or chromosomal translocations. Approximately 50 types of oncogenes have been discovered to date, and research had led us to believe that oncogenes are derived from normal genes that regulate growth and development. A general discussion of oncogenes will be presented in this review.

Lambert, P. F., H. Pan, et al. (1993). "Epidermal cancer associated with expression of human papillomavirus type 16 E6 and E7 oncogenes in the skin of transgenic mice." Proc Natl Acad Sci U S A **90**(12): 5583-7.

Certain "high-risk" anogenital human papillomaviruses (HPVs) have been associated with the majority of human cervical carcinomas. In these cancers, two papillomaviral genes, E6 and E7, are commonly expressed. In this study we provide evidence that expression of the E6 and E7 genes from the high-risk HPV-16 in the skin of transgenic mice potentiated the development of preneoplastic lesions, and a high percentage of these epidermal lesions subsequently developed into locally invasive cancers. High levels of E6/E7 expression were found in these tumors relative to the preneoplastic lesions, and expression was localized to the proliferating, poorly differentiated epidermal cells. Also, the p53 and Rb genes were found to be intact, not mutationally inactivated, in representative skin tumors. These findings demonstrate that the E6 and E7 genes from a papillomavirus etiologically associated with human cervical cancer can contribute to the development of epidermal cancers in an animal model.

Lemoine, N. R. and P. A. Hall (1990). "Growth factors and oncogenes in pancreatic cancer." Baillieres Clin Gastroenterol **4**(4): 815-32.

There are abnormalities in the structure and/or function of several oncogenes and growth factors in human pancreatic cancer, notably the EGF receptor and its ligand TGF alpha, c-erb B-2 proto-oncogene, Ki-ras oncogene and the tumour suppressor gene p53. The temporal sequence of their activation and the nature of the aetiological agents responsible for their activation are not yet clear. In vitro pancreatic culture systems and transgenic animal experiments are needed to reconstruct and define those molecular events that are necessary and sufficient for the neoplastic phenotype.

Lewis, B. C., D. S. Klimstra, et al. (2003). "The c-myc and PyMT oncogenes induce different tumor types in a somatic mouse model for pancreatic cancer." Genes Dev **17**(24): 3127-38.

We have generated a mouse model for pancreatic cancer through the somatic delivery of oncogene-bearing avian retroviruses to mice that express TVA, the receptor for avian leukosis sarcoma virus subgroup A (ALSV-A), under the control of the elastase promoter. Delivery of ALSV-A-based RCAS vectors encoding either mouse polyoma virus middle T antigen (PyMT) or c-Myc to elastase-tv-a transgenic, Ink4a/Arf null mice induced the formation of pancreatic tumors. RCAS-PyMT induced pancreatic tumors with the histologic features of acinar or ductal carcinomas. The induced pancreatic lesions express Pdx1, a marker for pancreas progenitor cells, and many tumors express markers for both exocrine and endocrine cell lineages, suggesting that the tumors may be derived from progenitor cells. In contrast, RCAS-c-myc induced endocrine tumors exclusively, as determined by histology and detection of differentiation markers. Thus, specific oncogenes can induce the formation of different pancreatic tumor types in a single transgenic line, most likely from one or more types of multipotential progenitor cells. Our model appears to be useful for elucidating the genetic alterations, target cells, and signaling pathways that are important in the genesis of different types of pancreatic cancer.

Lichtenstein, A., J. Berenson, et al. (1990). "Resistance of human ovarian cancer cells to tumor necrosis factor and lymphokine-activated killer cells: correlation with expression of HER2/neu oncogenes." Cancer Res **50**(22): 7364-70.

Since overexpression of HER2/neu oncogenes in breast cancer cells is associated with resistance to the cytotoxic effect of tumor necrosis factor (TNF), we investigated whether this correlation also existed for ovarian cancer targets. Nine continuously cultured human ovarian cancer lines were studied and compared to 3 breast cancer lines. Three of the ovarian and 1 breast cancer line demonstrated amplified HER2/neu genes by Southern analysis, increased HER2/neu RNA by Northern analysis, and marked immunoperoxidase staining for HER2/neu protein. The other 8 lines contained unamplified genes and undetectable RNA and protein. All 4 overexpressed lines were relatively resistant to the cytotoxic effects of TNF. Interestingly, they were also resistant to lymphokine-activated killer cells. In contrast, 7 of 8 nonexpressed lines showed sensitivity to TNF and all 8 were sensitive to lymphokine-activated killer cells. There was no difference in sensitivity to lysis by hydrogen peroxide or peptide defensins between over- and nonexpressed lines. These data indicate that expression of HER2/neu oncogenes may impart a proliferative advantage in tumor cells due to induction of resistance to several different cytotoxic mechanisms.

Liu, E. T. (1993). "Oncogenes, breast cancer, and chemoprevention." J Cell Biochem Suppl **17G**: 161-6.

Perturbations of oncogenes in breast carcinoma include amplifications of the HER-2/neu and PRAD1 genes, as well as p53 mutations. Some of these lesions frequently appear in early cancers such as ductal carcinoma in situ and are stable as the tumors become invasive and metastasize. Thus these findings suggest that oncogene mutations may define a point of origin for a given breast cancer, and are fixed lesions during tumor progression. Such germline abnormalities may occur at the BRCA1, H-RAS VNTR, and p53 loci. The rational use of genetics may be to identify women at high risk for the development of breast cancer so that they may be enrolled in future chemoprevention trials.

Machotka, S. V., C. T. Garrett, et al. (1989). "Amplification of the proto-oncogenes int-2, c-erb B-2 and c-myc in human breast cancer." Clin Chim Acta **184**(3): 207-17.

int-2 is a proto-oncogene that is partially homologous to angiogenesis-inducing fibroblast growth factor and is believed to play a role in mouse mammary carcinogenesis. Recent evidence has suggested that this proto-oncogene may also play a role in human breast cancer. In the present study, we used Southern hybridization analysis to examine DNA from 79 primary and 11 recurrent human breast cancers for evidence of activation of int-2 through either gene rearrangement or amplification. A similar analysis was performed for two other proto-oncogenes, c-erbB-2 and c-myc, also suspected of playing a role in the development of human breast cancer. Proto-oncogene status was correlated with estrogen (ER) and progesterone (PR) receptor status, patient age, and lymph node (LN) status at the time of surgery. Gene rearrangement was not a frequent occurrence with any of the proto-oncogenes. However, amplification of int-2 occurred at a significantly higher frequency in recurrent breast cancers than in primary cancers and in patients with primary cancers who were less than or equal to 50 years of age versus greater than 50 years of age at surgery. Although amplification of all three proto-oncogenes occurred at a greater frequency in primary tumors from patients with lymph node metastases than from those without lymph node metastases, a significant difference was noted only in the case of c-myc amplification. These findings confirm and extend earlier results of studies of int-2, c-erbB-2 and c-myc amplification in human breast cancers and point to a role for int-2 activation in certain cases of recurrent breast malignant neoplasia.

Mammas, I. N., A. Zafiropoulos, et al. (2004). "Transcriptional activation of H- and N-ras oncogenes in human cervical cancer." Gynecol Oncol **92**(3): 941-8.

OBJECTIVE: Overexpression of p21 protein has been detected in human cervical cancer. However, to date, there are no data on the differential activation of the three ras genes at the transcriptional level in cervical lesions. The purpose of this study was to evaluate the quantitative and qualitative changes of expression of the ras family genes in the development of human cervical cancer. METHODS: The expression of ras mRNA levels in 35 human cervical specimens [11 normal cervix, 15 cervical intraepithelial neoplasia (CIN), 9 cervical cancer] was examined using the RT-PCR technique. In addition, we studied the incidence of point mutations in codon 12 of each ras gene using RFLP analysis and human papilloma virus (HPV) status. RESULTS: The transcript levels for H-ras and N-ras were significantly higher in cancer cases compared to normal cervical tissues (P=0.0002 and P=0.001, respectively) and CIN lesions (P<0.0001 and P=0.002, respectively). The transcript levels for K-ras were similar in normal cervical tissue, CIN and cervical cancer. A strong positive correlation was found between H- and N-ras expression (P=0.001) and no correlation between H- and K- or N- and K-ras expression. Point mutations were detected only in three samples, located in codon 12 of K-ras gene. No relationship was found between expression levels of each ras gene and the presence of

HPV. CONCLUSION: Our findings indicate the expression pattern of the three ras genes in cervical tissue and the involvement of H- and N-ras up-regulation in the pathogenesis of cervical cancer independent of HPV infection.

Mano, H. (2008). "Non-solid oncogenes in solid tumors: EML4-ALK fusion genes in lung cancer." Cancer Sci **99**(12): 2349-55.

It is generally accepted that recurrent chromosome translocations play a major role in the molecular pathogenesis of hematological malignancies but not of solid tumors. However, chromosome translocations involving the e26 transformation-specific sequence transcription factor loci have been demonstrated recently in many prostate cancer cases. Furthermore, through a functional screening with retroviral cDNA expression libraries, we have discovered the fusion-type protein tyrosine kinase echinoderm microtubule-associated protein like-4 (EML4)-anaplastic lymphoma kinase (ALK) in non-small cell lung cancer (NSCLC) specimens. A recurrent chromosome translocation, inv(2)(p21p23), in NSCLC generates fused mRNA encoding the amino-terminal half of EML4 ligated to the intracellular region of the receptor-type protein tyrosine kinase ALK. EML4-ALK oligomerizes constitutively in cells through the coiled coil domain within the EML4 region, and becomes activated to exert a marked oncogenicity both in vitro and in vivo. Break and fusion points within the EML4 locus may diverge in NSCLC cells to generate various isoforms of EML4-ALK, which may constitute approximately 5% of NSCLC cases, at least in the Asian ethnic group. In the present review I summarize how detection of EML4-ALK cDNA may become a sensitive diagnostic means for NSCLC cases that are positive for the fusion gene, and discuss whether suppression of ALK enzymatic activity could be an effective treatment strategy against this intractable disorder.

Markowitz, S. D., L. Myeroff, et al. (1994). "A benign cultured colon adenoma bears three genetically altered colon cancer oncogenes, but progresses to tumorigenicity and transforming growth factor-beta independence without inactivating the p53 tumor suppressor gene." J Clin Invest **93**(3): 1005-13.

We describe the spontaneous progression of a colon adenoma cell line to tumorigenicity and growth factor independence. This system allows direct comparison of biologic stages of malignant progression with alterations of colon cancer suppressor genes and oncogenes. VACO-235, a human colon adenoma cell line, is at early passages nontumorigenic in the nude mouse, unable to grow in soft agar, growth stimulated by serum and EGF, and growth inhibited by TGF-beta. VACO-235 daughter passages 93 and higher have in culture spontaneously progressed to being weakly tumorigenic, but retain all other growth characteristics of VACO-235 early passages. A mouse xenograft from late passage VACO-235 was reestablished in culture as the granddaughter cell line, VACO-411. VACO-411 is highly tumorigenic, clones in soft agar, and is unresponsive to serum, EGF, and TGF-beta. Early passage VACO-235 bears a mutant K-ras allele, bears only mutant APC alleles, expresses no DCC transcripts, and expresses only wild type p53 transcripts. VACO-411 retains the identical genotype, still expressing only wild type p53. Colonic cells after ras mutation, APC mutation, and DCC inactivation remain nontumorigenic and growth factor dependent. Malignant progression involves at least two additional steps, and in VACO-411 can proceed by a novel pathway not requiring p53 inactivation.

Mayr, C. and D. P. Bartel (2009). "Widespread shortening of 3'UTRs by alternative cleavage and polyadenylation activates oncogenes in cancer cells." Cell **138**(4): 673-84.

In cancer cells, genetic alterations can activate proto-oncogenes, thereby contributing to tumorigenesis. However, the protein products of oncogenes are sometimes overexpressed without alteration of the proto-oncogene. Helping to explain this phenomenon, we found that when compared to similarly proliferating nontransformed cell lines, cancer cell lines often expressed substantial amounts of mRNA isoforms with shorter 3' untranslated regions (UTRs). These shorter isoforms usually resulted from alternative cleavage and polyadenylation (APA). The APA had functional consequences, with the shorter mRNA isoforms exhibiting increased stability and typically producing ten-fold more protein, in part through the loss of microRNA-mediated repression. Moreover, expression of the shorter mRNA isoform of the proto-oncogene IGF2BP1/IMP-1 led to far more oncogenic transformation than did expression of the full-length, annotated mRNA. The high incidence of APA in cancer cells, with consequent loss of 3'UTR repressive elements, suggests a pervasive role for APA in oncogene activation without genetic alteration.

McKenzie, S. J. (1991). "Diagnostic utility of oncogenes and their products in human cancer." Biochim Biophys Acta **1072**(2-3): 193-214.

The first clear cut association of an oncogene with a specific cancer is the c-abl translocation in chronic myelogenous leukemia and acute lymphocytic leukemia; it has been observed in 90% of CML cases

examined. This is the major contributing factor to its being the target of the first oncogene-based FDA-approved diagnostic test. Although the role of the abl translocation in the tumorigenic process is not yet understood, it is clear that somehow it must be causally related to the disease, and thus is an ideal target for a diagnostic test. The association of this oncogene with a specific cancer is the model on which all others may be based in the future. Second generation tests could easily include PCR on mRNA, and/or in situ hybridization, both of which could be performed using blood samples. Both methods would provide a faster means of testing a large number of cells, however, the methodologies must be improved through automation and computer-aided image analysis, respectively, in order to become useful routine tests. Both neu and epidermal growth factor receptor (EGFR) appear to have a close correlation between overexpression of the gene product and outcome of disease in breast cancer; valuable information for prognosis of the disease. And again, although the actual mechanism of action of these molecules and how this relates to the tumorigenic process is not yet known, it is believed from the very nature of the molecules that they must in some way contribute to the progression of the disease. In both cases, the protein products are overexpressed in tissue, and in the case of Neu, it appears as through at least some of the patients have a Neu-related protein in their serum. These molecules present relatively easy targets for the development of diagnostic/prognostic assays, as antibodies are easily made and can be incorporated into a variety of assay formats. Current assays available, an ELISA for Neu and a radio-ligand binding assay for EGFR, are highly sensitive, reproducible and relatively easy to perform. Only the ELISA is commercially available, however, and hence allows for easy comparison between laboratories. An abvious step towards the routine measurement of EGFR then is the development of a comparable commercially available test. An improvement for both types of assay would be the incorporation of an internal control to gauge the cellular component of the tissue samples that are tested. The outcome of the applications of myc and ras to cancer diagnostics is not so easily predictable, with a couple of exceptions.(ABSTRACT TRUNCATED AT 400 WORDS)

Medl, M., P. Sevelda, et al. (1995). "DNA amplification of HER-2/neu and INT-2 oncogenes in epithelial ovarian cancer." Gynecol Oncol **59**(3): 321-6.

OBJECTIVE: Oncogene alterations are thought to be prognostic indices in patients with breast cancer. The present study was carried out to investigate the amplification of the HER-2/neu and INT-2 oncogenes in ovarian cancer. METHODS: In a retrospective study of 196 patients with epithelial ovarian cancer, the amplification of the oncogenes HER-2/neu and INT-2 in the DNA of paraffin-embedded tumor cells was determined by quantitative PCR. The purpose of this study was to analyze whether the two oncogenes correlated with such predictive factors as FIGO stage, histological grade, ascites, postoperative residual tumor mass, hormone receptor content, and preoperative CA 125 serum levels. The effect of HER-2/neu and INT-2 amplification on patient survival was also studied. RESULTS: The only correlation found in this study was between INT-2 and preoperative CA 125 levels (P = 0.03). No correlations were demonstrable between HER-2/neu (log-rank test; P = 0.67) and INT-2 (log-rank test; P = 0.75) amplifications and overall survival. CONCLUSION: Unlike the established prognostic factors, neither HER-2/neu nor INT-2 appears to be predictive for survival in patients with ovarian cancer.

Miller, W. H., Jr., D. Moy, et al. (1990). "Retinoic acid induces down-regulation of several growth factors and proto-oncogenes in a human embryonal cancer cell line." Oncogene **5**(4): 511-7.

The human teratocarcinoma cell NTERA-2 cl. D1 (NT2/D1) is a cloned embryonal cancer cell line that differentiates into a neuronal phenotype and other cellular lineages after treatment with retinoic acid (RA). We examined the regulated expression of growth factors and proto-oncogenes in NT2/D1 cells. We studied RNA levels after six days of RA treatment to assess gene expression coincident with observed morphologic differentiation. Three growth factors were markedly down-regulated following RA treatment: Hst-1/kFGF and TGF-alpha expression became undetectable by Northern analysis and bFGF expression was substantially reduced. Minimal decline was seen for c-myc, N-myc, c-fos, and c-myb. Increased expression with differentiation was seen for the human homeotic genes Hox 2.1 and Hox 2.2. Assay of RNA levels daily after one to six days of RA treatment showed that the growth factor down-regulation inversely correlated with the homeotic gene up-regulation. Nuclear run-on studies showed low transcriptional rates for these homeotic genes, Hst-1/kFGF, and TGF-alpha that did not measurably change with RA treatment. To explore whether these regulated genes in NT2/D1 play a role in human testicular cancer, we examined RNA levels in a panel of human germ cell cancer lines. Hst-1/kFGF and bFGF are commonly expressed in five of seven male germ cell cancer lines. These data show that specific proto-oncogenes and growth factors are down-

regulated with RA treatment of the NT2/D1 cell and that some of these regulated genes are often expressed in human germ cell cancer lines.

Molis, T. M., L. L. Spriggs, et al. (1995). "Melatonin modulation of estrogen-regulated proteins, growth factors, and proto-oncogenes in human breast cancer." J Pineal Res **18**(2): 93-103.

The growth-inhibitory actions of the pineal hormone, melatonin, on human breast tumor cells and the possible association between this inhibition and melatonin's down-regulation of the estrogen receptor (ER) expression were examined in the ER-positive, estrogen-responsive MCF-7 human breast tumor cell line. As previously reported, melatonin dramatically inhibits the growth of these breast tumor cells and down-regulates ER levels in these cells, suggesting that the modulation of ER may be an important mechanism by which melatonin inhibits breast cancer cell growth. In the present studies, Northern blot analysis was used to examine the expression of estrogen-regulated transcripts known to be involved in estrogen's mitogenic actions. Melatonin, at a physiologic concentration (10(-9) M), rapidly, significantly, and, in some cases, transiently elevated the steady-state mRNA levels of growth stimulatory products such as TGF alpha, c-myc, and pS2, which are normally up-regulated in response to estrogen. Conversely, melatonin decreased the expression of other factors normally up-regulated by estrogen, such as progesterone receptor and c-fos. Significant stimulation of the expression of the growth-inhibitory factor TGF beta was seen with melatonin treatment, potentially supporting the concept that melatonin's growth-inhibitory activity is mediated through the breast tumor cells' estrogen-response pathway. The early regulation of many of these products by melatonin suggests that mechanisms more rapid than the down-regulation of ER are important in melatonin's modulation of their expression. However, the long-term modulation of these transcripts (12-48 hr) may be heavily influenced by melatonin's down-regulation of ER expression. These results clearly define the need for additional in depth studies to dissect the cellular events leading to melatonin-induced growth inhibition in breast tumor cells.

Mukhopadhyay, T. and J. A. Roth (1996). "Antisense regulation of oncogenes in human cancer." Crit Rev Oncog **7**(3-4): 151-90.

Gene transfer or manipulation of genes for the treatment of cancer is a rapidly expanding field. In recent years, much attention has been focused on manipulating cancer genes and applying antisense technology in therapeutic ways. Consequently, antisense RNA control is now recognized as a specific means of regulating gene expression at the posttranscriptional level. Defects in vital genes occur in many human diseases, including cancer, defects that may be due to an accumulation of mutations in the genes that leads to the production of faulty proteins. Although the biological significance of such mutant proteins still remains in question, recent experiments have demonstrated that genes overproducing faulty proteins are often associated with increased tumor cell growth. Moreover, using a stretch of antisense RNA to block the production of such defective proteins can effectively silence their genes; as a result, tumor cells stop dividing rapidly and revert to a more normal phenotype. Therefore, antisense RNA technology could have a significant impact on cancer gene therapy. Here, we have tried to give comprehensive coverage to some major cases of antisense RNA control of cancer-related genes highlighting the biological systems involved, the efficacy of the antisense RNA in altering target gene function, and how such antisense control affects the malignant phenotype. Furthermore, the therapeutic potential of the antisense technique depends on the in-depth understanding of the target gene function and its role in carcinogenesis.

Muller, W. J. (1991). "Expression of activated oncogenes in the murine mammary gland: transgenic models for human breast cancer." Cancer Metastasis Rev **10**(3): 217-27.

Breast cancer is the leading cause of death among non-smoking women and thus has been the focus of intensive research. It has been generally accepted that the deregulation of oncogenes or their regulators play a pivotal role in progression of this prevalent disease. For example, amplification and overexpression of a number of oncogenes has been observed in a proportion of primary breast cancer biopsies. More recently, there has also been reports of inactivation tumor suppressor genes in human breast cancer. While there is compelling evidence for a role of these genes in breast cancer tumor progression due to limitations inherent in these studies it is difficult to establish a direct causal association between expression of a certain oncogene and tumor progression. For this reason many groups have employed the transgenic mouse as a model system to directly study effects of oncogene expression in the murine mammary gland. This review will attempt to highlight some of the important lessons and potential applications that have emerged from the study of oncogene expression in the mammary epithelium of transgenic mice. The utility of the transgenic system to assess the transforming potential of oncogenes, to investigate the multi-step nature of malignant

progression, and to be used as models for therapeutic intervention will be discussed.

Murayama, Y., S. Kurata, et al. (1988). "Regulation of human estrogen receptor gene, epidermal growth factor receptor gene, and oncogenes by estrogen and antiestrogen in MCF-7 breast cancer cells." Cancer Detect Prev **13**(2): 103-7.

It is generally believed that estrogen may act either as an initiator or as a promoter in carcinogenesis of human breast cancer. This estrogenic action is generally dependent on the estrogen receptor. In the human estrogen receptor, cDNA has a homology to V-erb-A oncogene. Experiments using MCF-7 human breast cancer cells were carried out to study the regulatory effect of estrogen and antiestrogen on RNA activities of oncogenes, estrogen receptor gene, and epidermal growth factor (EGF) receptor gene. The effect of estradiol on activation of estrogen and EGF receptor genes and myc, ras, and fos oncogenes was positive in relation to the concentrations of supplemented estradiol. In addition, the effects of antiestrogen (tamoxifen) were investigated. Tamoxifen suppressed MCF-7 cell growth, and spot hybridization of the RNA of MCF-7 cells revealed that RNA activities of estrogen and EGF receptor genes and myc, ras, and fos oncogenes were suppressed by tamoxifen. These results suggest that the three oncogenes and two receptor genes are partly regulated by estrogen and antiestrogen (tamoxifen) in MCF-7 human breast cancer cells. This regulatory system may have a role in carcinogenesis and in the treatment of human breast cancer.

Nagasaka, T., H. Sasamoto, et al. (2004). "Colorectal cancer with mutation in BRAF, KRAS, and wild-type with respect to both oncogenes showing different patterns of DNA methylation." J Clin Oncol **22**(22): 4584-94.

PURPOSE: BRAF mutations are common in sporadic colorectal cancers (CRCs) with a DNA mismatch repair (MMR) deficiency that results from promoter methylation of hMLH1, whereas KRAS mutations are common in MMR proficient CRCs associated with promoter methylation of MGMT. The aim of this study was to further investigate the link between genetic alterations in the RAS/RAF/ERK pathway and an underlying epigenetic disorder. PATIENTS AND METHODS: Activating mutations of BRAF and KRAS were identified and correlated with promoter methylation of 11 loci, including MINT1, MINT2, MINT31, CACNA1G, p16(INK4a), p14(ARF), COX2, DAPK, MGMT, and the two regions in hMLH1 in 468 CRCs and matched normal mucosa. RESULTS: BRAF V599E mutations were identified in 21 (9%) of 234 CRCs, and KRAS mutations were identified in 72 (31%) of 234 CRCs. Mutations in BRAF and KRAS were never found in the same tumor. CRCs with BRAF mutations showed high-level promoter methylation in multiple loci, with a mean number of methylated loci of 7.2 (95% CI, 6.6 to 7.9) among 11 loci examined ($P < .0001$). Tumors with KRAS mutations showed low-level promoter methylation, and CRCs with neither mutation showed a weak association with promoter methylation, with an average number of methylated loci of 1.8 (95% CI, 1.5 to 2.1) and 1.0 (95% CI, 0.79 to 1.3), respectively. CONCLUSION: In CRC, the methylation status of multiple promoters can be predicted through knowledge of BRAF and, to a lesser extent, KRAS activating mutations, indicating that these mutations are closely associated with different patterns of DNA hypermethylation. These changes may be important events in colorectal tumorigenesis.

Nicolson, G. L. (1991). "Molecular mechanisms of cancer metastasis: tumor and host properties and the role of oncogenes and suppressor genes." Curr Opin Oncol **3**(1): 75-92.

The natural progression of benign tumors to malignancy and metastasis is characterized by their ability to circumvent microenvironmental controls on cellular proliferation, diversity, and positioning, and evolve into heterogeneous phenotypes, a process that probably involves qualitative and quantitative changes in gene expression. The oncogenes and suppressor genes that can effect tumor progression may control important points in the regulation of sets of genes that are ultimately responsible for the cellular alterations seen in highly metastatic cells. Because many cancers metastasize nonrandomly to particular distant sites, their colonization properties cannot be explained by mechanical considerations, such as arrest of tumor cells in the first microcirculatory network encountered. Metastatic cells that show a high propensity to metastasize to certain organs adhere at higher rates to microvessel endothelial cells isolated from their target sites, invade into target tissue at higher rates, and respond better to paracrine growth factors from the target site. These properties depend on multiple tumor cell, host cell, and stromal molecules that are differentially expressed by particular tumor and organ cells and by the organ extracellular matrix. Together these tumor and host factors appear to determine the organ metastatic properties of malignant cells.

Niederacher, D., H. X. An, et al. (1999). "Mutations and amplification of oncogenes in endometrial cancer." Oncology **56**(1): 59-65.

Alterations in oncogenes are critical steps in the development of endometrial cancer. To investigate

the potential clinical relevance of the amplification of the oncogenes c-erbB2, c-myc, and int-2 and the mutation of K-ras in endometrial cancer, 112 tumors were examined using PCR-based fluorescent DNA technology. Amplification of the three oncogenes and the mutation of K-ras were correlated with age, tumor size, lymph node status, metastases, stage, histological types, grade, steroid hormone receptor expression (estrogen receptor, ER; progesterone receptor, PgR), family history of cancer, previous history of cancer or precursor lesions, and previous history of hormone replacement therapy. Oncogene amplification of c-erbB2 was detected in 18.9%, of c-myc in 2.7% and of int-2 in 4.2%, and K-ras mutation in 11.6%. No significant correlations could be detected between amplification of c-erbB2 and any of the other parameters. Mutation of K-ras is associated with positive expression of PgR. This might indicate that mutation and activation of K-ras are involved in the development of hormonal independence in endometrial cancer.

Ortholan, C., M. P. Puissegur, et al. (2009). "MicroRNAs and lung cancer: new oncogenes and tumor suppressors, new prognostic factors and potential therapeutic targets." Curr Med Chem **16**(9): 1047-61.

MicroRNAs (miRNAs) are small non-protein-coding RNA that negatively control mRNA expression at a post-transcriptional level. They regulate various cellular functions and bioinformatic data suggest that they collectively control about 30% of human mRNAs. MiRNAs have been recently implicated in several carcinogenic processes, where they can act either as oncogenes or as tumor suppressors. This is the case in lung cancer, i.e. the leading cause of cancer deaths in Western countries, in which about 40-45 miRNAs have been found to be aberrantly expressed, thereby constituting a specific miRNA signature. Some of these miRNAs can play an important role in lung carcinogenesis. Indeed, some transcripts of the let-7 family that are significantly down-regulated in lung tumors have been identified as tumor suppressors through their ability to control several oncogenic pathways, including the RAS pathway. Identification of a growing number of other potential oncogenic or tumor suppressor miRNAs in lung cancers is in constant progress. Recent evidence supports the use of specific miRNA signatures to predict clinical outcome. This review aims to report the current knowledge about the role of miRNAs in lung cancer carcinogenesis, their potential for improving diagnosis and prognosis and their impact on future therapeutic strategies.

Osada, H. and T. Takahashi (2002). "Genetic alterations of multiple tumor suppressors and oncogenes in the carcinogenesis and progression of lung cancer." Oncogene **21**(48): 7421-34.

Lung cancer has become the leading cause of cancer death in many economically well-developed countries. Recent molecular biological studies have revealed that overt lung cancers frequently develop through sequential morphological steps, with the accumulation of multiple genetic and epigenetic alterations affecting both tumor suppressor genes and dominant oncogenes. Cell cycle progression needs to be properly regulated, while cells have built-in complex and minute mechanisms such as cell cycle checkpoints to maintain genomic integrity. Genes in the p16INK4A-RB and p14ARF-p53 pathways appear to be a major target for genetic alterations involved in the pathogenesis of lung cancer. Several oncogenes are also known to be altered in lung cancer, leading to the stimulation of autocrine/paracrine loops and activation of multiple signaling pathways. It is widely acknowledged that carcinogens in cigarette smoke are deeply involved in these multiple genetic alterations, mainly through the formation of DNA adducts. A current understanding of the molecular mechanisms of lung cancer pathogenesis and progression is presented in relation to cigarette smoking, an absolute major risk factor for lung cancer development, by reviewing genetic alterations of various tumor suppressor genes and oncogenes thus far identified in lung cancer, with brief summaries of their functions and regulation.

Osborne, C., P. Wilson, et al. (2004). "Oncogenes and tumor suppressor genes in breast cancer: potential diagnostic and therapeutic applications." Oncologist **9**(4): 361-77.

Carcinogenesis is a multistep process characterized by genetic alterations that influence key cellular pathways involved in growth and development. Oncogenes refer to those genes whose alterations cause gain-of-function effects, while tumor suppressor genes cause loss-of-function effects that contribute to the malignant phenotype. The effects of these alterations are complex due to the high number of changes in a typical case of breast cancer and the interactions of the biological pathways involved. This review focuses on the more common abnormalities in oncogenes and tumor suppressor genes in human breast cancer and their known associations with clinical outcome in terms of tumor classification, prognosis, and response to specific therapies. A better understanding of these relationships has led to new therapeutic applications. Agents that target oncogenes and their associated pathways are now in clinical use, with many more undergoing preclinical and clinical testing. The availability of antibodies, small synthetic

molecules, cyotokines, gene therapy techniques, and even natural compounds that are screened for specific biological properties has greatly increased the number of candidate drugs. Nevertheless, clinical successes have been limited because of the redundancy of many cancer-related pathways as well as the high degree of variability in genotype and phenotype among individual tumors. Likewise, strategies to replace tumor suppressor gene functions face numerous technical hurdles. This review summarizes the current achievements and future prospects for the therapeutic targeting of oncogenes and tumor suppressor genes and new technology to better classify tumors and accurately predict responses to standard and novel agents.

Pardal, R., A. V. Molofsky, et al. (2005). "Stem cell self-renewal and cancer cell proliferation are regulated by common networks that balance the activation of proto-oncogenes and tumor suppressors." Cold Spring Harb Symp Quant Biol **70**: 177-85.

Networks of proto-oncogenes and tumor suppressors that control cancer cell proliferation also regulate stem cell self-renewal and possibly stem cell aging. Proto-oncogenes promote regenerative capacity by promoting stem cell function but must be balanced with tumor suppressor activity to avoid neoplastic proliferation. Conversely, tumor suppressors inhibit regenerative capacity by promoting cell death or senescence in stem cells. For example, the polycomb family proto-oncogene, Bmi-1, is consistently required for the self-renewal of diverse adult stem cells, as well as for the proliferation of cancer cells in the same tissues. Bmi-1 promotes stem cell self-renewal partly by repressing the expression of Ink4a and Arf, tumor suppressor genes that are commonly deleted in cancer. Despite ongoing Bmi-1 expression, Ink4a expression increases with age, potentially reducing stem cell frequency and function. Increased tumor suppressor activity during aging therefore may partly account for age-related declines in stem cell function. Thus, networks of proto-oncogenes and tumor suppressors have evolved to coordinately regulate stem cell function throughout life. Imbalances within such networks cause cancer or premature declines in stem cell activity that resemble accelerated aging.

Peehl, D. M. (1993). "Oncogenes in prostate cancer. An update." Cancer **71**(3 Suppl): 1159-64.

Oncogenes have been implicated in the carcinogenic development of many diverse types of human malignancies. For some cancers, the expression of specific oncogenes has been shown to have diagnostic or prognostic value. By contrast currently, no oncogene has been correlated conclusively with the initiation or progression of prostate cancer. The ras oncogene has been investigated the most thoroughly for its involvement in prostate cancer, but ras does not appear to play a significant role in the development of this malignancy. Several years ago, limited studies hinted at the possibility of overexpression of the myc oncogene and aberrant expression of the sis oncogene in prostate cancer, but additional studies to clarify the involvement of these oncogenes have not been done. Oncogenic activity of growth factors or growth factor receptors in prostate cancer has been suggested but not amply demonstrated. Current dogma indicates that oncogenes exist in prostate cancer, but these will be identified only by more intensive investigation.

Peltomaki, P., O. Alfthan, et al. (1991). "Oncogenes in human testicular cancer: DNA and RNA studies." Br J Cancer **63**(6): 851-8.

Oncogene dosage and expression were studied in 16 testicular neoplasms, 14 of germ cell and two of non-germ cell origin. In comparison with normal DNA, tumour DNA of a total of eight patients (seven with germ cell neoplasm and one with testicular lymphoma) showed increased dosages of KRAS2, PDGFA, EGFR, MET and PDGFB. The most frequent (occurring in six tumours) and prominent (up to 3-4-fold) increases were detected in the dosages of KRAS2 (on chromosome 12p) and PDGFA (chromosome 7p), relative to a reference locus from chromosome 2. Importantly, there was a similar increase in 12p dosage in general in these tumours, suggesting the presence of the characteristic isochromosome 12p marker. On the contrary, possible 7p polysomy (assessed by molecular methods) did not explain the PDGFA (or EGFR) changes in all cases. NRAS, MYCN, CSFIR, MYB, MYC, ABL, HRASI, TP53, and ERBB2 did not reveal any consistent alterations in tumour DNA. In RNA dot blot assays the expression of KRAS2, PDGFA, EGFR, or MYC was generally not increased in the tumour samples when compared to that in normal testicular tissue of the same patients although there was interindividual variation in mRNA levels. It thus appears that while oncogene dosage changes occur in a proportion of testis cancers, they are often part of changes in large chromosomal regions or whole arms and are seldom accompanied by altered expression.

Pompetti, F., D. Pilla, et al. (2003). "Cancer therapy: switching off oncogenes." Bioessays **25**(2): 104-7.

Cancer derives from a cell clone that has accumulated genetic and epigenetic changes that influence its phenotype and finally enable it to escape from the normal controls of proliferation. A recent paper shows that, in myc-induced tumours, the

inactivation of this oncogene produces the regression of the tumours and the differentiation of the tumour cells into mature osteocytes.1 In addition, a further reactivation of myc in these cells does not restore the malignant phenotype but induces apoptosis. This discovery could lead to an innovative therapeutic strategy.

Putral, L. N., M. J. Bywater, et al. (2005). "RNA interference against human papillomavirus oncogenes in cervical cancer cells results in increased sensitivity to cisplatin." Mol Pharmacol **68**(5): 1311-9.

Targeted inhibition of oncogenes in tumor cells is a rational approach toward the development of cancer therapies based on RNA interference (RNAi). Tumors caused by human papillomavirus (HPV) infection are an ideal model system for RNAi-based cancer therapies because the oncogenes that cause cervical cancer, E6 and E7, are expressed only in cancerous cells. We investigated whether targeting HPV E6 and E7 oncogenes yields cancer cells more sensitive to chemotherapy by cisplatin, the chemotherapeutic agent currently used for the treatment of advanced cervical cancer. We have designed siRNAs directed against the HPV E6 oncogene that simultaneously targets both E6 and E7, which results in an 80% reduction in E7 protein and reactivation of the p53 pathway. The loss of E6 and E7 resulted in a reduction in cellular viability concurrent with the induction of cellular senescence. Interference was specific in that no effect on HPV-negative cells was observed. We demonstrate that RNAi against E6 and E7 oncogenes enhances the chemotherapeutic effect of cisplatin in HeLa cells. The IC50 for HeLa cells treated with cisplatin was 9.4 microM, but after the addition of a lentivirus-delivered shRNA against E6, the IC50 was reduced almost 4-fold to 2.4 microM. We also observed a decrease in E7 expression with a concurrent increase in p53 protein levels upon cotreatment with shRNA and cisplatin over that seen with individual treatment alone. Our results provide strong evidence that loss of E6 and E7 results in increased sensitivity to cisplatin, probably because of increased p53 levels.

Quaye, L., S. A. Gayther, et al. (2008). "The effects of common genetic variants in oncogenes on ovarian cancer survival." Clin Cancer Res **14**(18): 5833-9.

PURPOSE: The 5-year survival rate for invasive epithelial ovarian cancer is <35%. It has been suggested that common, germline genetic variation may influence survival after cancer diagnoses, which might enable the prediction of response to treatment and survival in the clinical setting. The aim of this study was to evaluate associations between common germline genetic variants in the oncogenes BRAF, ERBB2, KRAS, NMI, and PIK3CA, and survival after a diagnosis of epithelial ovarian cancer. EXPERIMENTAL DESIGN: We evaluated the association between 34 tagging single nucleotide polymorphisms and survival in 1,480 cases of invasive epithelial ovarian cancer cases from three different studies. Cox regression analysis, stratified by study, was used to estimate per rare allele hazard ratios (HR). RESULTS: The minor allele rs6944385 in BRAF was significantly associated with poor survival [HR, 1.19; 95% confidence intervals (95% CI), 1.02-1.39; P = 0.024]. The association remained after adjusting for prognostic factors (adjusted HR, 1.20; 95 CI, 1.03-1.40; P = 0.018). A haplotype of BRAF was also associated with poor survival (HR, 1.24; 95% CI, 1.02-1.51; P = 0.029) and was more significant after adjustment (HR, 1.44; 95% CI, 1.15-1.81; P = 0.001). We also found evidence of an association between a KRAS haplotype and poor survival in serous subtype (HR, 1.69; 95% CI, 1.21-2.38; P = 0.002), but this was no longer significant after adjustment. Finally, when analyses were restricted to the serous histologic subtype, the rare allele rs10842513 in KRAS, was associated with poor survival (HR, 1.40; 95% CI, 1.10-1.78; P = 0.007). CONCLUSION: Common genetic variants in the BRAF and KRAS oncogenes may be important in the prediction of survival in patients with invasive epithelial ovarian cancer.

Quaye, L., H. Song, et al. (2009). "Tagging single-nucleotide polymorphisms in candidate oncogenes and susceptibility to ovarian cancer." Br J Cancer **100**(6): 993-1001.

Low-moderate risk alleles that are relatively common in the population may explain a significant proportion of the excess familial risk of ovarian cancer (OC) not attributed to highly penetrant genes. In this study, we evaluated the risks of OC associated with common germline variants in five oncogenes (BRAF, ERBB2, KRAS, NMI and PIK3CA) known to be involved in OC development. Thirty-four tagging SNPs in these genes were genotyped in approximately 1800 invasive OC cases and 3000 controls from population-based studies in Denmark, the United Kingdom and the United States. We found no evidence of disease association for SNPs in BRAF, KRAS, ERBB2 and PIK3CA when OC was considered as a single disease phenotype; but after stratification by histological subtype, we found borderline evidence of association for SNPs in KRAS and BRAF with mucinous OC and in ERBB2 and PIK3CA with endometrioid OC. For NMI, we identified a SNP (rs11683487) that was associated with a decreased risk of OC (unadjusted P(dominant)=0.004). We then genotyped rs11683487 in another 1097 cases and 1792 controls from an

additional three case-control studies from the United States. The combined odds ratio was 0.89 (95% confidence interval (CI): 0.80-0.99) and remained statistically significant (P(dominant)=0.032). We also identified two haplotypes in ERBB2 associated with an increased OC risk (P(global)=0.034) and a haplotype in BRAF that had a protective effect (P(global)=0.005). In conclusion, these data provide borderline evidence of association for common allelic variation in the NMI with risk of epithelial OC.

Rak, J., J. L. Yu, et al. (2006). "Oncogenes, trousseau syndrome, and cancer-related changes in the coagulome of mice and humans." Cancer Res **66**(22): 10643-6.

Cancer is often associated with venous thrombosis, a phenomenon that was first described by Trousseau in 1865 (Trousseau syndrome). Recent studies have begun to explain how oncogenic events may deregulate the hemostatic system. For instance, activated oncogenes (K-ras, EGFR, PML-RARalpha, and MET) or inactivated tumor suppressors (e.g., 53 or PTEN) may increase the risk of thrombosis by inducing the expression of tissue factor, a potent procoagulant molecule, and plasminogen activator inhibitor-1, a fibrinolysis inhibitor. In a more complex clinical reality, transforming genes may often act in concert with numerous epigenetic factors, including hypoxia, inflammation, anticancer therapy, contact between blood and metastatic cancer cells, and emission of procoagulant vesicles from tumors and their stroma into the circulation. To add to mechanistic insights gained from mouse models, which may not fully phenocopy human Trousseau syndrome, we suggest that valuable clues to progression and thrombosis risk may be obtained by monitoring multiple hemostatic variables in cancer patients ("coagulomics").

Rhim, J. S. (1988). "Viruses, oncogenes, and cancer." Cancer Detect Prev **11**(3-6): 139-49.

Our current theories of virus-induced cellular transformation have changed with the emerging recognition that all normal cells contain proto-oncogenes which convert to oncogenes and induce transformation when activated and/or amplified. Cellular oncogenes have been identified by homology to the transforming genes of acute retroviruses and by the transforming activity of tumor cell DNA in transfection assays. More than two dozen cellular oncogenes identified to date constitute a heterogeneous group of genes which are remarkably conserved among highly diverse species. Expression of proto-oncogenes is linked to normal growth and development; whereas their expression as oncogenes due to gene mutation, rearrangement, amplification or other processes leading to altered or overexpression is associated with the development of tumors. Functions of oncogene proteins are being identified. These include unique protein kinase activity, growth factor/growth factor receptor properties, and the presence of DNA-binding polypeptides. It also appears that cooperation between several activated cellular oncogenes may be required in the multistep process of oncogenesis. Our recent in vitro experimental evidence supports that human cell carcinogenesis is indeed a multistep process. In addition, the involvement of the activated cellular transforming genes met and H-ras in chemically induced human cell carcinogenesis has been shown. Advancement in molecular biology of oncogenes and their products is likely to result in improvements in cancer diagnosis and cancer therapy.

Rigas, B. (1990). "Oncogenes and suppressor genes: their involvement in colon cancer." J Clin Gastroenterol **12**(5): 494-9.

Abnormalities in oncogenes, which are broadly classified into viral and cellular oncogenes, and suppressor genes appear critical for the development of colon cancer. Cellular oncogenes contribute to malignant transformation when they become activated by point mutation, translocation, amplification, or loss of regulator sequences. The properties of the oncoproteins, the proteins encoded by oncogenes which are essential for carcinogenesis, are unclear. Suppressor genes normally suppress the tumorigenic phenotype by keeping the growth of cells in check; it is their inactivation that contributes to malignant transformation. Development of colon cancer appears to take place by stepwise accumulation of multiple genetic alterations during the progression from normal colon to adenoma and carcinoma. Activation of ras, an early event in this sequence, is found in 50% of colon cancers; overexpression of c-myc is found in approximately 80%. Inactivation of suppressor genes, which occurs during later stages, is noted in greater than 70% of tumors. A current model of colonic tumorigenesis is presented.

Rodenhuis, S. and R. J. Slebos (1990). "The ras oncogenes in human lung cancer." Am Rev Respir Dis **142**(6 Pt 2): S27-30.

The three well-characterized genes of the ras gene family H-ras, K-ras, and N-ras, code for closely related 21-kD proteins that have a role in the transduction of growth signals. The ras proteins acquire transforming potential when a point mutation in the gene leads to replacement of an amino acid in one of the critical positions 12, 13, or 61. Overexpression of the normal protein, usually associated with gene amplification, can have similar

effects. The detection of mutationally activated ras genes has been facilitated by the development of oligonucleotide hybridization assays that allow the identification of each possible mutation at the critical sites. Employment of the polymerase chain reaction has greatly increased the sensitivity of these assays. Studies of human lung cancer have shown that adenocarcinoma is the only subtype associated with ras mutations. These occur in about 30% of primary tumors. In almost all cases, the mutation is present in codon 12 of the K-ras gene. No mutations have been observed to date in tumors of nonsmokers, suggesting that the mutation may result from exposure to carcinogenic ingredients of tobacco smoke. Amplifications of ras genes were shown to be very uncommon in clinically early stages of lung cancer. Analysis of the clinical data of patients who were operated on for adenocarcinoma of the lung shows that K-ras mutations are not associated with particular histologic characteristics of the tumors or with specific presenting features. Patients with K-ras mutations, however, had significantly worse survival than did those without an activation.

Rogers, S. J., K. J. Harrington, et al. (2005). "Biological significance of c-erbB family oncogenes in head and neck cancer." Cancer Metastasis Rev **24**(1): 47-69.

Squamous cell carcinoma of the head and neck (SCCHN) tends to run an aggressive course and the prognosis has remained virtually unchanged in recent decades. The development of novel therapeutic strategies to improve patient outcome centres on the biology of the disease, namely the pivotal c-erbB family of growth factor receptors. c-erbB1 (or epidermal growth factor receptor, EGFR), is key to the pathogenesis of SCCHN and plays a central role in a complex network of downstream integrated signalling pathways. EGFR overexpression, detected in up to 90% of SCCHN, correlates with an increased risk of locoregional tumour relapse following primary therapy and relative resistance to treatment. The biological sequelae of erbB receptor activation are not simply cell proliferation, but also inhibition of apoptosis, enhanced migration, invasion, angiogenesis and metastasis: the 'hallmarks of cancer' [1]. As EGFR overexpression is associated with a poor clinical outcome in SCCHN, this receptor is attractive as a therapeutic target and the successful development of targeted therapies represents a paradigm shift in the medical approach to head and neck cancer. However, the extensive cross talk between signalling pathways, the multiple molecular aberrations and genetic plasticity in SCCHN all contribute to inherent and acquired resistance to both conventional and novel therapies. Understanding the cancer cell biology, in particular the significance of co-expression of c-erbB (and other) receptors, and the cell survival stimuli from (for example) activation of the phosphoinositide 3-kinase (PI3-kinase) cascade is fundamental to overcome current limitations in biologically targeted therapies.

Rygaard, K., R. J. Slebos, et al. (1991). "Radiosensitivity of small-cell lung cancer xenografts compared with activity of c-myc, N-myc, L-myc, c-raf-1 and K-ras proto-oncogenes." Int J Cancer **49**(2): 279-84.

Oncogenes of the myc family c-raf-1 and K-ras have been reported to modulate radiosensitivity. We examined the possible relationship between in vivo radiosensitivity to single-dose irradiation with 3-10 Gy, and activity of these proto-oncogenes in 2 sets of small-cell lung cancer (SCLC) xenografts, the CPH and the GLC series. CPH-54A and CPH-54B are in vitro-derived subclones of a SCLC cell line, while the GLC tumours were established as cell lines from a patient during longitudinal follow-up. Both tumours were later transferred into nude mice. CPH-54A was more sensitive to single-dose irradiation than CPH-54B, while, with respect to the 3 GLC tumours examined, GLC-16 was most sensitive, followed by GLC-14 and GLC-19. The CPH tumours expressed similar amounts of c-myc and c-raf-1 mRNA, and neither expressed N-myc or L-myc. GLC-14 expressed N-myc and c-raf-1 mRNA but no c-myc. GLC-16 and GLC-19 expressed identical amounts of c-raf-1 and high levels of c-myc mRNA, but neither expressed N-myc or L-myc. None of the tumours was mutated at codon 12 or K-ras. Our results show that SCLC xenografts with different radiosensitivity may express identical amounts of some of the proto-oncogenes reported to modulate radiosensitivity. Thus, factors other than activation of the examined proto-oncogenes must be involved in causing the differences in radiosensitivity found in the SCLC xenografts. Possible long-term effects of irradiation on proto-oncogene expression was examined in xenografts of GLC-16, following regrowth after single-dose irradiation. No long-term difference in expression of c-raf-1 or c-myc mRNA was detected between control tumours and tumours irradiated with 5 or 10 Gy.

Sabichi, A. L. and M. J. Birrer (1996). "Regulation of nuclear oncogenes expressed in lung cancer cell lines." J Cell Biochem Suppl **24**: 218-27.

Lung cancer is a major cause of mortality in the United States and accounts for the majority of all cancer deaths in both men and women. It is hoped that through broadening our understanding of the mechanisms involved in transformation of bronchial

epithelial cells we will be able to improve methods of diagnosis and treatment of this disease, with the ultimate goal of reducing on lung cancer mortality. A knowledge of the molecular mechanisms involved in processes such as cell division and differentiation is paramount to this task, because it is known that aberrant responses to growth factors or cytokines found in the normal cellular milieu can lead to abnormal cell growth and/or transformation. Signals initiated at the cell membrane by tumor promoters, growth factors, or cytokines are transduced from the cell membrane to the nucleus and are, in part, mediated centrally by transcription factors encoded by nuclear protooncogenes. The transcription factors myc, jun, and fos have been characterized in both normal and transformed lung epithelial cells through detailed studies using cell lines. In this manuscript, we review what is known about the expression and regulation of these nuclear protooncogenes in normal and malignant epithelial cells of the lung, and their role in the development of lung cancer.

Sakorafas, G. H., A. Lazaris, et al. (1995). "Oncogenes in cancer of the pancreas." Eur J Surg Oncol **21**(3): 251-3.

A three-step immunoperoxidase staining technique was used in order to estimate the immunohistochemical expression of K-ras, c-fos, c-myc and c-erbB-2 oncoproteins, in paraffin sections of 20 patients, with histologically proven adenocarcinoma of the pancreas. The two oncogenes that were found to be associated with pancreatic adenocarcinoma were K-ras and c-erbB-2. in 15 patients (75%) and four patients (20%), respectively. Positive immunostaining was intense, cytoplasmic and was noted in a great percentage of cancer cells. The same model of expression was observed in the examined cases of metastatic tissue from liver and lymph node metastases. The expression of myc and fos oncogenes was nuclear, weak and was observed in a small number of patients.

Sakorafas, G. H., A. G. Tsiotou, et al. (2000). "Molecular biology of pancreatic cancer; oncogenes, tumour suppressor genes, growth factors, and their receptors from a clinical perspective." Cancer Treat Rev **26**(1): 29-52.

Pancreatic cancer represents the fourth leading cause of cancer death in men and the fifth in women. Prognosis remains dismal, mainly because the diagnosis is made late in the clinical course of the disease. The need to improve the diagnosis, detection, and treatment of pancreatic cancer is great. It is in this type of cancer, in which the mortality is so great and the clinical detection so difficult that the recent advances of molecular biology may have a significant impact. Genetic alterations can be detected at different levels. These alterations include oncogene mutations (most commonly, K-ras mutations, which occur in 75% to more than 95% of pancreatic cancer tissues), tumour suppressor genes alterations (mainly, p53, p16, DCC, etc.), overexpression of growth factors (such as EGF, TGF alpha, TGF beta 1-3, aFGF, bTGF, etc.) and their receptors (i.e., EGF receptor, TGF beta receptor I-III, etc.). Insights into the molecular genetics of pancreatic carcinogenesis are beginning to form a genetic model for pancreatic cancer and its precursors. These improvements in our understanding of the molecular biology of pancreatic cancer are not simply of research interest, but may have clinical implications, such as risk assessment, early diagnosis, treatment, and prognosis evaluation.

Saxena, S., A. K. Jain, et al. (1997). "Role of steroid hormone and growth factor receptors and proto-oncogenes in the behavior of human mammary epithelial cancer cells in vitro." Pathobiology **65**(2): 75-82.

The cultivation of cells from primary breast cancers is very unpredictable. The majority of breast-cancer-derived cell lines are of metastatic origin. To define the characteristics of tumor cells which govern their ability to grow in vitro as primary cultures as well as continuous or established culture cell lineages, human mammary epithelial cancer (HMEC) cells from 18 cases of unselected primary breast cancer were propagated in culture. Propagation of HMEC cells in vitro as monolayers in primary culture was successful in 10 out of 18 (55.5%) cases, which showed continous proliferation of tumor cells only up to 6-8 passages before they reached senescence. An investigation of the effects of phenotypic expression of estrogen receptors (ER), the progesterone receptors, c-erbB-2 oncoprotein and epidermal growth factor receptors (EGFR) on the capacity of HMEC cells to grow in vitro as monolayers showed that expression of ER and EGFR is required for controlling tumor proliferative activity in vitro. Expression of ER protein made the growth of HMEC cells more difficult, while expression of EGFR protein made their growth in vitro easier. Phenotypic characteristics of floating HMEC cells were found to be different from those grown on cover slips as adherent cultures, suggesting a selective growth of HMEC cells of a specific phenotype in culture. Cultured HMEC cells in subsequent passages showed a decrease in their proliferative capacity, alterations in phenotypic characteristics and development of morphologic features of terminal differentiation, resulting in senescence.

Scheerger, S. B. and J. Zempleni (2003). "Expression of oncogenes depends on biotin in human small cell lung cancer cells NCI-H69." Int J Vitam Nutr Res **73**(6): 461-7.

Oncogenes play important roles in cell proliferation and biotin status correlates with gene expression and proliferation rates in human cells. In this study we determined whether biotin supply affects biotin homeostasis, expression of oncogenes, and proliferation rates in NCI-H69 small cell lung cancer cells. NCI-H69 cells were cultured in media containing deficient (0.025 nmol/L), physiologic (0.25 nmol/L), or pharmacologic (10 nmol/L) concentrations of biotin for 3 weeks. Biotin concentrations in culture media correlated negatively with biotin transport rates, suggesting that cells responded to marginal biotin supply with increased expression of biotin transporters. Increased biotin uptake was not sufficient to prevent depletion of intracellular biotin in cells cultured in biotin-deficient medium, as judged by decreased activity of biotin-dependent propionyl-CoA carboxylase and decreased biotinylation of histones. The expression of oncogenes N-myc, c-myb, N-ras, and raf correlated with biotin supply in media: oncogene expression increased by up to 20% in cells cultured in pharmacologic medium compared to physiologic controls; oncogene expression decreased by up to 47% in cells cultured in deficient medium. This observation is consistent with a role for biotin in oncogene-dependent metabolic pathways. Cellular uptake of thymidine (marker for proliferation) was not affected by biotin supply, suggesting that effects of biotin-dependent expression of oncogenes on the growth of tumor cells are quantitatively minor. The clinical significance of effects of biotin supply on expression of oncogenes remains to be elaborated.

Schmitt, F. C. and J. S. Reis-Filho (2002). "Oncogenes, granules and breast cancer: what has c-myc to do with apocrine changes?" Breast **11**(6): 463-5.

This issue of The Breast includes an elegant study by Selim et al. on c-myc gene amplification and protein overexpression in apocrine metaplasia (APM) and apocrine adenosis (AA) of the breast using paraffin-embedded tissue. In their report, the authors observe that all cases of APM and AA harbored c-myc protein overexpression, but no definitive gene amplification was found. Most importantly, they observed that the percentage of cells expressing c-myc in APM and AA was significantly correlated with cell proliferation, as assessed by Ki-67 immunolabeling index. On the basis of their findings and of previously reported studies, the authors suggest that c-myc overexpression occurs in early stages of breast carcinogenesis, that c-myc gene amplification may be a late event, and that in APM and AA c-myc overexpression is related to cell proliferation. Selim et al. findings have brought to our attention two thorny but rather important issues regarding current concepts of apocrine changes and their association with breast carcinomas, and also the role of c-myc in breast carcinogenesis.

Schwab, M. (1998). "Amplification of oncogenes in human cancer cells." Bioessays **20**(6): 473-9.

Gene amplification refers to a genomic change that results in an increased dosage of the gene(s) affected. Amplification represents one of the major molecular pathways through which the oncogenic potential of proto-oncogenes is activated during tumorigenesis. The architecture of amplified genomic structures is simple in some tumor types, involving in the vast majority of cases only one gene, such as MYCN in neuroblastomas. On the other hand, it can be complex and discontinuous, involving several syntenic co-amplified genes, such as in the 11q13 amplification in breast cancer, although in many of these cases there may be a single target gene. The presence of different nonsyntenic amplified genes raises the possibility that cells of certain tumors are susceptible to independent amplification events. In general, the amplified genes do not undergo additional damage by mutations. The data indicate that it is the enhanced level of a wild-type protein that contributes to tumorigenesis.

Schwab, M. and L. C. Amler (1990). "Amplification of cellular oncogenes: a predictor of clinical outcome in human cancer." Genes Chromosomes Cancer **1**(3): 181-93.

Increased dosage of cellular oncogenes resulting from amplification of DNA is a frequent genetic abnormality of tumor cells and the study of oncogene amplification has been paradigmatic for the usefulness of molecular genetic research in clinical oncology. Certain types of human tumors carry an amplified cellular oncogene at frequencies of up to 50-60%. Human neuroblastoma has been prototypic for the importance of oncogene amplification in tumorigenesis, and evidence is emerging that amplification may be an early event involved in a more malignant form of this cancer. It is unclear at which stage amplification plays a role in other cancers. Amplification of cellular oncogenes is a good predictor of clinical outcome in some human malignancies.

Sherratt, J. A. and M. A. Nowak (1992). "Oncogenes, anti-oncogenes and the immune response to cancer: a

mathematical model." Proc Biol Sci **248**(1323): 261-71.

We develop a mathematical model for the initial growth of a tumour after a mutation in which either an oncogene is expressed or an anti-oncogene (i.e. tumour suppressor gene) is lost. Our model incorporates mitotic control by several biochemicals, with quite different regulatory characteristics, and we consider mutations affecting the cellular response to these control mechanisms. Our mathematical representation of these mutations reflects the current understanding of the roles of oncogenes and anti-oncogenes in controlling cell proliferation. Numerical solutions of our model, for biologically relevant parameter values, show that the different types of mutations have quite different effects. Mutations affecting the cell response to chemical regulators, or resulting in autonomy from such regulators, cause an advancing wave of tumour cells and a receding wave of normal cells. By contrast, mutations affecting the production of a mitotic regulator cause a slow localized increase in the numbers of both normal and mutant cells. We extend our model to investigate the possible effects of an immune response to cancer by including a first order removal of mutant cells. When this removal rate exceeds a critical value, the immune system can suppress tumour growth; we derive an expression for this critical value as a function of the parameters characterizing the mutation. Our results suggest that the effectiveness of the immune response after an oncogenic mutation depends crucially on the way in which the mutation affects the biochemical control of cell division.

Shi, X. H., Z. Y. Liang, et al. (2009). "Combined silencing of K-ras and Akt2 oncogenes achieves synergistic effects in inhibiting pancreatic cancer cell growth in vitro and in vivo." Cancer Gene Ther **16**(3): 227-36.

Cancer is a complex disease involving multiple oncogenes with diverse actions. Inhibiting only one oncogene is unlikely to eliminate the malignancy of cancer cells. The goal of this study was to investigate whether synergistic effects can be achieved by combined silencing of two oncogenes, K-ras and Akt2, which are key players in the Ras/MAPK and PI3K/Akt signaling pathways. The pancreatic cancer cell line, Panc-1, was selected for these studies as it has elevated expression of K-ras and Akt2. Compared with inhibiting each oncogene alone, simultaneously silencing the two oncogenes with RNA interference (RNAi) more effectively inhibited Panc-1 cell proliferation and colony formation, induced a significantly higher percentage of apoptosis and resulted in greater inhibition of c-myc expression in vitro. Furthermore, when delivered by polyethyleneimine into Panc-1 tumors in nude mice, RNAi simultaneously targeting K-ras and Akt2 inhibited tumor growth more efficiently than RNAi targeting the individual oncogenes. Therefore, RNAi simultaneously silencing the oncogenes K-ras and Akt2 may offer potential opportunities for pancreatic cancer gene therapy.

Sidransky, D. and E. Messing (1992). "Molecular genetics and biochemical mechanisms in bladder cancer. Oncogenes, tumor suppressor genes, and growth factors." Urol Clin North Am **19**(4): 629-39.

Transitional-cell carcinoma of the bladder is believed to arise through a series of genetic changes affecting cell growth and proliferation. Two basic types of such genes have been described: protooncogenes and tumor suppressor genes. The former have not been studied extensively in bladder cancer, although there is evidence that c-erb B-2/neu is overexpressed. Loss of specific chromosomal regions, which is common in bladder tumors, may inactivate tumor suppressor genes, of which p53 has received the most attention. Work also has been done on epidermal growth factor and its receptor, yielding evidence that malignant and normal urothelium have different sensitivities to its action. Although several advances must be made before genetic changes come to the clinical forefront, the information now being gained with such speed holds considerable promise for diagnosis and treatment.

Singh, J., G. Kelloff, et al. (1997). "Modulation of alterations in p53 tumor suppressor gene and its association with activation of ras proto-oncogenes during chemoprevention of colon cancer." Int J Oncol **10**(3): 449-56.

Previously, we reported (Carcinogenesis 15: 1317-1323, 1994) a high rate of activating point mutations in I ns proto-oncogenes in azoxymethane (AOM)-induced colon tumors, and a significant suppression of these mutations by dietary administration of chemopreventive agents, D,L-alpha-difluoromethylornithine (DFMO) and piroxicam. To understand the role of p53 tumor suppressor gene in chemoprevention of colon cancer and to study the association of p53 gene alterations with activation of ras genes, we determined point mutations in conserved regions (exons 5-9) of p53 gene and analyzed the occurrence of double event of ms activation acid p53 mutation. Groups of male F344 rats were fed the modified AIN-76A diet containing 0, 4000 ppm DFMO, or 150 ppm piroxicam and administered s.c. AOM at a dose rate of 15 mg/kg body wt, once weekly, for 4 weeks. Vehicle controls received s.c. equal volume of normal saline. Animals were sacrificed 32 weeks after the last AOM or saline

injection and their grossly visible colon tumors were analyzed to determine p53 mutations by PCR amplification based single strand conformation polymorphism (SSCP) and direct DNA sequencing. Our results demonstrate that about 57% tumors from animals fed the control diet contained predominantly missense but also nonsense mutations, whereas only 30% tumors from animals on piroxicam diet, and none (0%) from animals fed the DFMO diet had similar mutations. Analysis of data revealed that about half of the tumors from animals on control diet possessed both ms and p53 mutations together, only 27% of colon tumors from animals on piroxicam diet and none of the tumors from animals on DFMO diet exhibited both ms and p53 mutations. These results indicate that the administration of piroxicam, a non-steroidal anti-inflammatory drug, and DFMO, a irreversible inhibitor of ornithine decarboxylase, may inhibit selective proliferation of initiated cells containing activated las and/or mutant p53. Dietary DFMO exerted more pronounced inhibition of selective amplification of initiated cells containing mutated ras and/or p53.

Sinkovics, J. G. (1989). "Oncogenes-antioncogenes and virus therapy of cancer." Anticancer Res **9**(5): 1281-90.

Viruses can render services to mankind. 1. Retroviruses pinpoint and transduce cellular oncogenes. 2. Retroviral vectors can introduce antioncogenes (the RB gene) into malignant cells thus rendering the recipient cells nonmalignant. 3. Oncolytic viruses lyse tumor cells. 4. Parvoviruses replicate only in dividing cells and exert lysis and antioncogene effect in tumor cells without affecting resting normal cells. 5. Myxo- and paramyxoviruses (and other viruses) upgrade the immunogenicity of cell surface antigens thus eliciting rejection type host immunity against these cells which is operational against not virus-infected cells of the same type (post-oncolytic antitumor immunity). 6. Viruses or virally infected cells (including tumor cells) induce the production of lymphokines and cytokines (interferons, interleukins and tumor necrosis factor) and activate NK cells and specific immune T cells cytotoxic to virus-infected cells (including tumor cells). 7. Measles virus may activate suppressor cells and both directly (by infecting lymphoma cells) and indirectly (by inducing molecular mediators of suppressor mononuclear cells inhibitory to the growth of neoplastic lymphoid and hematopoietic cells) induce remissions of lympho- and hematopoietic malignancies. 8. Retroviral vectors deliver genes into tumor cells for encoding new surface antigens that render the tumor cells highly antigenic and more vulnerable to rejection type immune reactions of the host. Examples illustrate each statement. Immunotherapy of tumors with active tumor-specific immunization after the induction of suppressor cells by fetal antigens and the elimination of the proliferating suppressor clones by cyclophosphamide will again be proposed.

Smith, I. M., C. A. Glazer, et al. (2009). "Coordinated activation of candidate proto-oncogenes and cancer testes antigens via promoter demethylation in head and neck cancer and lung cancer." PLoS One **4**(3): e4961.

BACKGROUND: Epigenetic alterations have been implicated in the pathogenesis of solid tumors, however, proto-oncogenes activated by promoter demethylation have been sporadically reported. We used an integrative method to analyze expression in primary head and neck squamous cell carcinoma (HNSCC) and pharmacologically demethylated cell lines to identify aberrantly demethylated and expressed candidate proto-oncogenes and cancer testes antigens in HNSCC. METHODOLOGY/PRINCIPAL FINDINGS: We noted coordinated promoter demethylation and simultaneous transcriptional upregulation of proto-oncogene candidates with promoter homology, and phylogenetic footprinting of these promoters demonstrated potential recognition sites for the transcription factor BORIS. Aberrant BORIS expression correlated with upregulation of candidate proto-oncogenes in multiple human malignancies including primary non-small cell lung cancers and HNSCC, induced coordinated proto-oncogene specific promoter demethylation and expression in non-tumorigenic cells, and transformed NIH3T3 cells. CONCLUSIONS/SIGNIFICANCE: Coordinated, epigenetic unmasking of multiple genes with growth promoting activity occurs in aerodigestive cancers, and BORIS is implicated in the coordinated promoter demethylation and reactivation of epigenetically silenced genes in human cancers.

Soh, L. T., D. Heng, et al. (2002). "The relevance of oncogenes as prognostic markers in cervical cancer." Int J Gynecol Cancer **12**(5): 465-74.

To study the prevalence of the oncogenes c-myc, IFN-alpha; c-erbB2; H-ras codon 12, 13, and 61; c-fos; and E6/E7 oncogenes of human papillomavirus (HPV) 16 in patients with invasive carcinoma of the cervix and their prognostic significance, genomic DNA and RNA were isolated from tissues of 275 patients in Singapore with nonmetastatic cervical cancer and 32 patients with normal cervix. The levels of expression of the various oncogenes were quantified by PCR using the respective primers. When the PCR data on the DNA were analyzed by the log-

rank test, IFN gamma (P = 0.02) and H-ras codon 12 and 13 (P = 0.02) were found to be prognostic. In the multivariate analysis, a statistically significant trend for increasing risk with higher quartiles was found for c-myc (P = 0.007) and c-erbB2 (P = 0.03). After adjusting for age and stage, a correlation appears between the amplification of the oncogenes c-myc, c-erbB2, and H-ras codon 12, 13, and 61 and the development of recurrent cervical cancer. Further adjustment to include the parameters of treatment and histology type did not change the outcome of the correlation observed.

Spandidos, D. A. and M. L. Anderson (1989). "Oncogenes and onco-suppressor genes: their involvement in cancer." J Pathol **157**(1): 1-10.

We review the involvement of two groups of genes, oncogenes and onco-suppressor genes, in malignant transformation. Approximately 40 oncogenes have been described mainly through studies on retroviruses and by in vitro functional analyses such as transfection of transforming genes into 'normal' cells. Because they are more difficult to identify, only a handful of onco-suppressor genes have been described so far, but potentially they could number as many as oncogenes. Where these genes have been isolated and sequenced, they have been shown to be highly conserved among species, suggesting that these genes play an essential role in the normal cell. Although some of properties of oncogenes have been identified, we do not know in detail the role these genes play in normal cells or how genetic damage contributes to malignancy. The effect of oncogene expression on a cell depends both on the cell type and on the oncogene, and in some circumstances oncogenes act as onco-suppressor genes and vice versa. The elucidation of the mechanism of action of oncogenes and onco-suppressor genes will not only increase our understanding of these important genes but might also provide the framework for a biological approach to the treatment of cancer.

Stemmermann, G., S. C. Heffelfinger, et al. (1994). "The molecular biology of esophageal and gastric cancer and their precursors: oncogenes, tumor suppressor genes, and growth factors." Hum Pathol **25**(10): 968-81.

The evolution of sequential histological changes from normal cells through invasive cancer affords the cancer biologist the opportunity to identify separate molecular steps involved in cancer progression. As one studies the development of human carcinoma, it becomes apparent that multiple genetic alterations affecting both cellular proto-oncogenes and tumor suppressor genes are involved during the development and progression of both esophageal and gastric cancers. The different histological forms of both esophageal and gastric carcinomas as well as their differing etiologies result in the possibility that a spectrum of genetic changes is involved in different tumor types. p53 abnormalities occur frequently in tumors arising in both organs, and in both sites p53 abnormalities can be observed in precancerous lesions as well as in overt cancer. Subsequent abnormalities affecting other genes (eg, epithelial growth factor receptors [EGFRs]) potentially enhance the growth potential of tumors. This review focuses on abnormalities of oncogenes, tumor suppressor genes, and growth factors commonly found in cancers of the esophagus and stomach.

Stephen, A. L., C. H. Thompson, et al. (2000). "Analysis of mutations in the URR and E6/E7 oncogenes of HPV 16 cervical cancer isolates from central China." Int J Cancer **86**(5): 695-701.

High rates of cervical cancer have been reported from parts of China and this may reflect a predominance of cervical infection with particularly aggressive human papillomavirus (HPV) variants. This PCR-based investigation of cervical tumours from Sichuan province in central China demonstrated an HPV positivity rate of 88%. HPV 16 was most common (21/34, 61%), followed by HPV 18 (3/34, 9%), while types 33, 45, 58 and 59 were each identified in one specimen. Sequencing of up to 1349 bases of the 21 HPV 16-positive isolates, encompassing the enhancer/promoter of the upstream regulatory region (URR) and the E6 and E7 genes, revealed distinct patterns of genomic stability and variability. An overall mutation rate of 5% was seen in the URR. One isolate had a large deletion of 436 bases in the enhancer; while varying combinations of 21 point mutations were identified in the remainder, impacting several YY1, NF1, TEF-1 and Oct-1 sites. More sequence variations were found in E6 compared to E7 (81% vs. 52% of isolates showing at least one mutation), some of which resulted in changes to the translated amino acids. Since the E6/E7 genes encode the oncogenic proteins essential for malignant transformation, and as their expression is controlled by the URR, it is possible that some of the identified mutations altered the oncogenicity of the virus: either directly by changing amino acid sequences of the E6 or E7 oncoproteins, or indirectly through alterations to transcription factor binding sites in the URR.

Stopera, S. A., M. Ray, et al. (1990). "Variant Philadelphia translocations in chronic myeloid leukemia: correlation with cancer breakpoints, fragile sites and oncogenes." Cancer Lett **55**(3): 249-53.

Four cases of variant Philadelphia (Ph1) translocations were found in 72 patients (5.5%) with Ph1-positive chronic myeloid leukemia (CML). One previously unreported case was a simple variant translocation, namely, 46,XY,t(11;17)(q13;p13),t(17;22)(q25;q22); 46,XY,t(1;21)(q32;q11),t(11;17)(q13;p13), t(17;22)(q25;q11). Complex variant translocations were observed in three cases, namely, 46,XY,t(5;9;22)(q31;q34;q11),46,XX,t(8;9;22) (q22;q34;q11) and 46,XX,t(9;15;22) (q34;q15;q11). The chromosomal breakpoints in the cases of variant Ph1 translocations were the following: 1q32, 5q31, 8q22, 11q13, 15q15, 17p13, 17q25 and 21q11. Eight of the eight (100%) breakpoints were located in Giemsa-negative bands. Furthermore, seven of the eight (87%) variant Ph1 breakpoints correspond to the breakpoints present in consistent cancer arrangements. Three of the eight (38%) correspond to fragile sites and four of the eight (50%) correspond to oncogenes.

Sukumar, S. (1990). "An experimental analysis of cancer: role of ras oncogenes in multistep carcinogenesis." Cancer Cells **2**(7): 199-204.

Carcinogen-induced animal tumor models are invaluable resources for studies aimed at understanding the participation of ras oncogenes in multistep carcinogenesis. Mutationally activated ras oncogenes are frequently detected in chemically induced animal tumors. The nature of the mutations in ras oncogenes reflects the chemical specificity of the carcinogen, implying that the carcinogen interacts with ras sequences. In chemically induced rat mammary tumor models, ras activation is the earliest detectable change in the mammary gland cells following administration of the chemical. Further, expression of the tumorigenic phenotype of cells containing activated ras requires the cooperation of normal physiological factors that are active during puberty.

Suzuki, H., S. Aida, et al. (1994). "State of adenomatous polyposis coli gene and ras oncogenes in Japanese prostate cancer." Jpn J Cancer Res **85**(8): 847-52.

Genetic alterations of ras oncogenes (K-, H- and N-ras) and adenomatous polyposis coli (APC) gene in tissues of prostate cancer from Japanese patients were examined using PCR-SSCP (polymerase chain reaction-single strand conformation polymorphism) analysis and direct sequencing. Tissues from 8 cases of untreated stage B prostate cancer surgically removed and from 10 cases of endocrine therapy-resistant metastatic disease obtained at autopsy were used in the present study. In four out of 18 cases (22%), ras point mutations were found, two in either codon 12 or 61 of K-ras and two in either 13 or 61 of H-ras. These point mutations were detected in one of the stage B cases (13%) and in three of the autopsy cases (30%). All these cases were poorly differentiated adenocarcinoma. In autopsy cases showing ras mutation in cancerous prostate, the same alteration was observed in metastatic tissues. No APC gene mutation was detected in any sample, although polymorphism was found in some cases. These results indicate that ras oncogene mutations are related to the progression of prostate cancer, whereas APC gene alteration is not involved in tumorigenesis and development of this cancer.

Tadokoro, K., M. Ueda, et al. (1989). "Activation of oncogenes in human oral cancer cells: a novel codon 13 mutation of c-H-ras-1 and concurrent amplifications of c-erbB-1 and c-myc." Oncogene **4**(4): 499-505.

By NIH3T3 transfection assay in conjunction with in vitro transient neomycin selection, activated c-H-ras-1 oncogenes were detected in two squamous cell carcinoma cell lines, ZA and HOC-313, newly established from human oral cancer patients. ZA had a point mutational activation at the 13th codon, this activation of c-H-ras-1 being novel in human cancer cells, while HOC-313 appeared to have an activation at the 12th codon. In ZA, 16- to 32-fold amplification of the EGF receptor gene, c-erbB-1 and a few-fold amplification of c-myc were detected. The significance of these findings is discussed in relation to multistep carcinogenesis in human cells.

Thompson, T. C. (1990). "Growth factors and oncogenes in prostate cancer." Cancer Cells **2**(11): 345-54.

Prostatic cancer is an increasing medical problem. Investigations of the biology of the prostate and the development of prostate cancer have shown that the prostate gland contains high levels of polypeptide growth factors, especially members of the fibroblast growth factor (FGF) and transforming growth factor (TGF)-beta family. Activated oncogenes and elevated proto-oncogene activities including ras and myc have been detected in human prostate cancer tissues, but there is no consensus as to the predominant genetic alterations involved in the progression of this disease. In vivo animal models have shown that relevant growth factors and oncogenes can induce both premalignant and malignant changes in prostate tissue. Additional experimental and clinical studies are needed to present a clearer molecular profile of this important malignancy.

Tormanen, V. T. and G. P. Pfeifer (1992). "Mapping of UV photoproducts within ras proto-oncogenes in UV-irradiated cells: correlation with mutations in human skin cancer." Oncogene **7**(9): 1729-36.

Mutations in ras proto-oncogenes have been found in human skin cancers. Since ultraviolet light is implicated in the development of skin cancers, we have investigated the formation of UV-induced photoproducts along exons 1 and 2 of the three ras proto-oncogenes, H-ras, K-ras, and N-ras, in UV-irradiated human cells. The two major types of DNA photoproducts, cyclobutane pyrimidine dimers and pyrimidine (6-4) pyrimidone photoproducts [(6-4) photoproducts], were mapped at the DNA sequence level by ligation-mediated polymerase chain reaction (LMPCR). No significant differences were seen between irradiated purified DNA and irradiated cells, implying that local chromatin structure does not influence the distribution of photoproducts along exons 1 and 2 of the three ras genes. We find that the transcribed strand near codon 61 in H-ras, K-ras and N-ras shows a high frequency of potentially mutagenic cyclobutane dimers and (6-4) photoproducts. Codon 12 of H-ras, K-ras and N-ras displays only barely detectable photoproducts at a CpC dinucleotide. In human skin cancers, mutations were most frequently detected at codon 12 of H-ras and K-ras. These results imply that the initial frequency distribution of a mutagenic DNA adduct may not correlate with mutation spectra in human tumors.

Torry, D. S. and G. M. Cooper (1991). "Proto-oncogenes in development and cancer." Am J Reprod Immunol **25**(3): 129-32.

Although analogies are often made comparing development to cancer, there is of course a major difference. Normal development requires complex patterns of rigidly controlled cell proliferation and differentiation. In contrast, cancer represents the pathological condition that results when normal cell growth patterns are uncoupled from their regulatory influences. Genetic studies of RNA tumor viruses have provided insights into the relationships and differences of the genes responsible for normal development and cancer. The presence of discrete genes (oncogenes) within the genome of oncogenic retroviruses is responsible for their tumorigenic potential. Molecular genetic studies have found that normal eukaryotic cells possess genes that are quite homologous to the retroviral oncogenes. These normal cellular genes (proto-oncogenes) are involved in the regulation of proliferation and differentiation. However, if mutated, proto-oncogenes have the potential for inducing neoplastic transformation. The conversion of a proto-oncogene to an oncogene is called activation. Proto-oncogenes can become activated by a variety of genetic mechanisms including transduction, insertional mutagenesis, amplification, point mutations, and chromosomal translocations. In each instance the genetic aberration results in a proto-oncogene that is now free of its normal regulatory constraints. Such deregulation of function imparts a distinct growth advantage to the cell.

Tsuchiya, T., Y. Ueyama, et al. (1989). "Co-amplification of c-myc and c-erbB-2 oncogenes in a poorly differentiated human gastric cancer." Jpn J Cancer Res **80**(10): 920-3.

c-erbB-2 oncogene has been reported to be frequently amplified in differentiated, tubular type of gastric cancer. Here we report a human gastric cancer which bore co-amplified c-myc and c-erbB-2 oncogenes: a portion of the amplified c-erbB-2 oncogene was found to be rearranged. Furthermore, c-myc and c-erbB-2 oncogenes were over-expressed in the tumor cells. In contrast to the previous reports, this gastric adenocarcinoma was classified as a poorly differentiated type, and was highly tumorigenic in nude mice. These results might suggest that activated c-myc and c-erbB-2 oncogenes co-operate and influence the malignant state of some gastric carcinomas.

Tsuda, H., S. Hirohashi, et al. (1991). "Alterations in copy number of c-erbB-2 and c-myc proto-oncogenes in advanced stage of human breast cancer." Acta Pathol Jpn **41**(1): 19-23.

In our previous study, amplification of c-erb B-2 and c-myc proto-oncogenes in DNA of human breast cancer occurred in 16% and 4% of cases, respectively, and increased copy number of these genes is suggested to be associated with aggressive primary tumors. We examined change in the copy number of c-erb B-2 and c-myc proto-oncogenes between primary and multiple metastatic tumors in 10 patients with breast cancer, who underwent breast surgery and were later autopsied, by using DNAs isolated from formalin-fixed paraffin-embedded tissues and the dot blot-hybridization method. In primary tumors, amplification of c-erb B-2 and c-myc was detected in three and two cases, whereas at the stage with systemic metastasis, it was detected in four and three cases, respectively. In all four cases with amplified c-erb B-2 gene and in one of the three with amplified c-myc gene, the copy number was clearly increased in the metastatic tumors in comparison with the primary. Microscopically, more than five mitotic figures per high power field were detected in metastatic tumors of five cases including three with amplified c-erb B-2, but in only two primary. These

results suggested that the aggressive nature of breast cancer is frequently enhanced in accordance with cancer metastasis.

Turner, D. P. and D. K. Watson (2008). "ETS transcription factors: oncogenes and tumor suppressor genes as therapeutic targets for prostate cancer." Expert Rev Anticancer Ther **8**(1): 33-42.

ETS factors represent one of the largest families of transcriptional regulators and have known functional roles in many biological processes. Significantly, ETS factors have oncogenic and suppressive activity and their aberrant expression is associated with many of the processes that lead to prostate cancer progression. The targeting of transcription for therapeutic gain has met with some success. Therefore, better understanding the mechanisms that regulate ETS factor activity during both normal and aberrant transcription provides a novel means to identify processes that may be targeted in order to re-establish the normal ETS regulatory networks that are perturbed in cancer. Specific examples of altered ETS factor expression are highlighted, and therapeutic technologies that may be used to target ETS factors and their cofactors and downstream target genes in prostate cancer are discussed.

Urbain, J. L. (1999). "Oncogenes, cancer and imaging." J Nucl Med **40**(3): 498-504.

At the dawn of the 21st century, nuclear oncology is undergoing a formidable and rapid mutagenesis. The progress in radiochemistry, radiopharmacy and, foremost, the advances in molecular oncology are the determinant mutagenic factors. Mutation, amplification, deletion or translocation of deoxyribonucleic acid segments in proto-oncogenes and tumor suppressor genes also called anti-oncogenes account for the uncontrolled cell growth and proliferation resulting in cancer. The astonishing developments in peptide and nucleic acid chemistry have opened the door for the development of new, highly specific probes such as antisense, aptamer and peptidomimetic molecules to image the oncogenes and anti-oncogenes transcriptional (messenger ribonucleic acid) and translational (protein) products involved in carcinogenesis. In this article, I shall review the basic molecular mechanisms of carcinogenesis and describe the molecular probes that are currently being developed.

van Leenders, G. J., D. Dukers, et al. (2007). "Polycomb-group oncogenes EZH2, BMI1, and RING1 are overexpressed in prostate cancer with adverse pathologic and clinical features." Eur Urol **52**(2): 455-63.

OBJECTIVES: Polycomb group (PcG) proteins are involved in maintenance of cell identity and proliferation. The protein EZH2 is overexpressed in disseminated prostate cancer, implicating a role of PcG complexes in tumor progression. In this study, we evaluated the expression of eight members of both PcG complexes in clinicopathologically defined prostate cancer. METHODS: Components of both PcG protein complexes PRC2 (EZH2, EED, YY1) and PRC1 (BMI1, RING1, HPH1, HPC1, HPC2) were immunohistochemically identified in tissue microarrays of 114 prostate cancer patients. Protein expression was semi-quantitatively scored and correlated with pathologic parameters and recurrence of prostate-specific antigen (PSA). RESULTS: Whereas BMI1, RING1, HPC1 and HPH1 were all abundantly present in normal and malignant prostate epithelium, expression of EZH2 occurred in only <10% of cells. Expression of EZH2, BMI1 and RING1 were all significantly enhanced in tumours with Gleason score (GS) > or = 8, extraprostatic extension, positive surgical margins, and PSA recurrence. When only the subgroup of GS < or = 6 was considered, representing the tumour grade in the majority of needle biopsies, EZH2 and BMI1 were also predictive for PSA recurrence. In a multivariable analysis, BMI1 was the only PcG protein with an independent prognostic value. CONCLUSIONS: PcG proteins EZH2, BMI1, and RING1 are associated with adverse pathologic features and clinical PSA recurrence of prostate cancer. Whereas BMI1 and RING1 are abundantly present in prostate cancer, EZH2 is expressed at relatively low levels, making it a less obvious target for therapy.

Van Tine, B. A., J. C. Kappes, et al. (2004). "Clonal selection for transcriptionally active viral oncogenes during progression to cancer." J Virol **78**(20): 11172-86.

Primary keratinocytes immortalized by human papillomaviruses (HPVs), along with HPV-induced cervical carcinoma cell lines, are excellent models for investigating neoplastic progression to cancer. By simultaneously visualizing viral DNA and nascent viral transcripts in interphase nuclei, we demonstrated for the first time a selection for a single dominant papillomavirus transcription center or domain (PVTD) independent of integrated viral DNA copy numbers or loci. The PVTD did not associate with several known subnuclear addresses but was almost always perinucleolar. Silent copies of the viral genome were activated by growth in the DNA methylation inhibitor 5-azacytidine. HPV-immortalized keratinocytes supertransduced with HPV oncogenes and selected for marker gene coexpression underwent crisis, and the surviving cells transcribed

only the newly introduced genes. Thus, transcriptional selection in response to environmental changes is a dynamic process to achieve optimal gene expression for cell survival. This phenomenon may be critical in clonal selection during carcinogenesis. Examination of HPV-associated cancers supports this hypothesis.

Van Zandwijk, N. and L. J. Van 't Veer (1998). "The role of prognostic factors and oncogenes in the detection and management of non-small-cell lung cancer." Oncology (Williston Park) **12**(1 Suppl 2): 55-9.

Like other epithelial tumors, non-small-cell lung cancer (NSCLC) is a result of a series of genetic and epigenetic changes that eventually progress to invasive cancer. The order and timing of these changes, involving specific chromosomal locations, oncogenes, and tumor-suppressor genes, have become important areas of translational research. It is hoped that this research will lead to "very early" diagnosis and "very early" treatment of non-small-cell lung cancer, and to the identification of patients with poor prognostic tumor characteristics who may be helped by additional treatment. The recognition of persons with inherited predisposition to lung cancer is also on the horizon, and, together with the molecular characterization of lung cancer, brings with it a promise of improved treatment results.

Vasquez, H. and H. Strobel (1996). "Effect of cytochrome P450 inducers on expression of oncogenes and a tumor suppressor gene in human colon cancer cells." Int J Oncol **9**(3): 427-31.

To examine the possibility that chemical inducers of cytochrome P450 may have effects on the expression of oncogenes and a tumor suppressor gene, human colon LS174T cells were treated with different cytochrome P450 inducers such as benzanthracene (Ba), pyrazole (Pyr) and phenobarbital-hydrocortisone (Pb-Hc). Three forms of cytochrome P450 (CYP1A1, CYP1A2 and CYP2E1) were detected in the colon cell line and all of them were induced following chemical treatments. Altered expression of c-fos, c-myc, c-jun, was observed following the treatments. c-src, K-ras and p53 were not significantly affected by any of the treatments at the time-point selected. Interestingly, c-fos expression was the most dramatically altered by different treatments, showing repression with all of the treatments. These data show that some oncogenes are responsive to inducers of cytochrome P450, the enzyme system by which many carcinogens are activated.

Vecchio, G. and M. Santoro (2000). "Oncogenes and thyroid cancer." Clin Chem Lab Med **38**(2): 113-6.

Human thyroid tumors can be derived either from epithelial follicular cells or from parafollicular C-cells. Follicular cell-derived tumors represent a wide spectrum of lesions, ranging from benign adenomas through differentiated (follicular and papillary) and undifferentiated (anaplastic) carcinomas, thus providing a good model for finding a correlation between specific genetic lesions and histologic phenotype. Follicular adenomas and carcinomas show frequently the presence of mutations in one of the three ras genes. Papillary carcinomas show frequently a specific gene rearrangement which gives rise to the formation of several types of so-called RET/PTC chimeric genes. This lesions occur in almost 50% of papillary cancers and consist in the juxtaposition of the 3' or tyrosine kinase domain of the RET gene (which codes for a receptor protein not normally expressed in follicular thyroid cells) with the 5' domain of ubiquitously expressed genes, which provide the promoter and dimerization functions, necessary for the constitutive activation of RET/PTC proteins. Anaplastic carcinomas are frequently associated with mutations of the p53 tumor suppressor. Finally, point mutations of the RET gene are found in familial endocrine syndromes (FMTC; MEN2A and MEN2B), a common feature of which is the medullary thyroid carcinoma, a malignant tumor derived from parafollicular C-cells.

Viallet, J. and J. D. Minna (1990). "Dominant oncogenes and tumor suppressor genes in the pathogenesis of lung cancer." Am J Respir Cell Mol Biol **2**(3): 225-32.

An understanding of the molecular pathogenesis of lung cancer has evolved from classic cytogenetic studies and the use of restriction fragment length polymorphisms to encompass the definition of specific genetic abnormalities associated with this disease. Activation of the dominant class of oncogenes is frequent, with involvement of the ras and myc families of genes being the best defined. Several examples of inactivation at specific loci exist and have been related to the presence of tumor suppressor genes, most notably the retinoblastoma gene, p53, and a putative gene located on the short arm of chromosome 3. As our understanding of the nature and interactions between these numerous genetic events evolves, new opportunities for early diagnosis, prevention, and treatment will arise.

Vias, M., A. Ramos-Montoya, et al. (2008). "Terminal and progenitor lineage-survival oncogenes as cancer markers." Trends Mol Med **14**(11): 486-94.

Tumour classification has traditionally focused on differentiation and cellular morphology, and latterly on the application of genomic approaches.

By combining chromatin immunoprecipitation with expression array, it has been possible to identify direct gene targets for transcription factors for nuclear hormone receptors. At the same time, there have been great strides in deriving stem and progenitor cells from tissues. It is therefore timely to propose that pairing the isolation of these cell subpopulations from tissues and tumours with these genomics approaches will reveal conserved gene targets for transcription factors. By focusing on transcription factors (lineage-survival oncogenes) with roles in both organogenesis and tumourigenesis at multiple organ sites, we suggest that this comparative genomics approach will enable developmental biology to be used more fully in relation to understanding tumour progression and will reveal new cancer markers. We focus here on neurogenesis and neuroendocrine differentiation in tumours.

von Knebel Doeberitz, M., D. Spitkovsky, et al. (1997). "Interactions between steroid hormones and viral oncogenes in the pathogenesis of cervical cancer." Verh Dtsch Ges Pathol **81**: 233-9.

Steroid hormones are frequently prescribed as anticontraceptive drugs to young women. Persistent papillomavirus infections particularly with high risk virus types are very common in younger women and were shown to be the strongest risk factor for the later development of cervical cancer. Steroid hormones interfere with persistent papillomavirus infections on various levels. They enhance the expression level of two viral genes, E6 and E7, which are required for the oncogenic activities of high risk papillomaviruses. In addition, they interfere with cellular gene functions involved in cell cycle regulation and programmed cell death, for example through inhibition of p53-mediated transcriptional transactivation of genes involved in cell cycle arrest and apoptosis. Furthermore, steroids inhibit the immunologically mediated resolution of minor HPV-induced cervical lesions, particularly through inhibition of major histocompatibility class I and class II antigen expression. These observations point to potent cocarcinogenic effects of steroid hormones in persistently papillomavirus infected individuals by enhancing the transforming activities of viral oncogenes and interfering with the efficient resolution of virus infected lesions. The clinical significance of these experimental observations requires careful analysis in prospective trials.

Wang, Y. Z. and Y. C. Wong (1997). "Oncogenes and tumor suppressor genes in prostate cancer: a review." Urol Oncol **3**(2): 41-6.

The activation of oncogenes and inactivation of tumor suppressor genes (TSGs) have been implicated in the development of many human and animal malignancies. Changes in certain specific genes have been shown to be of potential value for diagnosis and prognosis, as well as treatment, of some cancers. By contrast, no oncogene has been correlated conclusively at the DNA level with the initiation and progression of prostate cancer, although though there are alterations in expression of a number of oncogenes (i.e., ras, c-sis, c-fos, and neu) in messenger RNA and/or protein level. It is also thought that alterations of certain known TSGs, such as p53, KAII, and E-cadherin, may be important in prostate carcinogenesis; alterations of KAII (known as a metastasis suppressor gene) and p53 are more likely to be associated with the late events in the development of prostate cancers. Other TSGs, such as Rb, nm23, and PACI, require more studies to further define their role. The possible presence of TSGs in frequently altered regions on chromosomes 6q14-21, 8q, 10p, 10q, 13q, and 17p have been actively studied. Moreover, further studies on other frequently altered regions on chromosomes 2q, 5q, 15q, 16q, l7q, and 18q may provide further insight into the mechanism of prostate cancer progression. Future studies should be targeted on these putative oncogenes and TSGs and to determine whether assessment of specific gains or losses may have prognostic value in the diagnosis and treatment of prostate cancer.

Werner, H., M. Shalita-Chesner, et al. (2000). "Regulation of the insulin-like growth factor-I receptor gene by oncogenes and antioncogenes: implications in human cancer." Mol Genet Metab **71**(1-2): 315-20.

The insulin-like growth factor-I receptor (IGF-I-R) has a central role in normal cellular proliferation as well as in transformation processes. Transcription of the IGF-I receptor gene is controlled by a number of tumor suppressors, including WT1, p53, and BRCA1. It has been demonstrated that, in their wild-type form, these transcription factors can suppress the activity of the IGF-I-R promoter, with ensuing reduction in the levels of cell-surface IGF binding. On the other hand, a number of oncogenes, including mutant p53 and c-myb, and the fusion protein EWS-WT1 significantly stimulate promoter activity. Interactions between stimulatory and inhibitory transcription factors may determine the level of expression of the IGF-I-R gene and, consequently, the proliferative status of the cell.

Wu, Y., Y. Chen, et al. (2006). "Analysis of mutations in the E6/E7 oncogenes and L1 gene of human papillomavirus 16 cervical cancer isolates from China." J Gen Virol **87**(Pt 5): 1181-8.

Human papillomavirus type 16 (HPV16) has a number of intratypic variants; each has a different

geographical distribution and some are associated with enhanced oncogenic potential. Cervical samples were collected from 223 cervical cancer patients and from 196 age-matched control subjects in China. DNA samples were amplified by using primers specific for the E6, E7 and partial L1 regions. Products were sequenced and analysed. It was found by using a PCR-sequence-based typing method that HPV infection rates in China were 92.8 % in cervical cancer patients and 15.8 % in healthy controls. HPV16 was detected in 70.4 % of cervical cancer patients and in 6.1 % of controls. In HPV16-positive cervical cancers, 23.6 % belonged to the prototype, 65.5 % were of the Asian variant, 5.5 % were of African type 1 and 3.6 % were European variants, whilst only one was a new variant that differed from any variant published so far. Prevalences of HPV16 E6 D25E and E113D variants were 67.3 and 9 %, respectively. In addition to D25E and E113D, the following E6 variations were found in this study: R129K, E89Q, S138C, H78Y, L83V and F69L. The results also showed that the prevalences of three hot spots of E7 nucleotide variation, N29S, S63F and a silent variation, nt T846C, were 70.2 % (33/47), 51.1 % (24/47) and 61.7 % (29/47), respectively. The following L1 variations were found in this study: S377A, K387E, E378D, K382E and T379P. It was also found that the average age of Asian variant-positive cervical cancer patients (42.98+/-10.43 years) was 7.56 years lower than that of prototype-positive patients (50.54+/-10.91). It is suggested that the high frequency of HPV16 Asian variants might contribute to the high incidence of cervical cancer in China.

Yamamoto, M., R. Metoki, et al. (2004). "Systematic multiplex polymerase chain reaction and reverse transcription-polymerase chain reaction analyses of changes in copy number and expression of proto-oncogenes and tumor suppressor genes in cancer tissues and cell lines." Electrophoresis **25**(20): 3349-56.

Systematic multiplex reverse transcription-polymerase chain reaction (SM RT-PCR) is distinguishable from other multiplex RT-PCR methods by (i) utilization of primers that amplify sequences that fall within a single exon of the genes, (ii) utilization of genomic DNA as a calibration standard, and (iii) optimized PCR conditions that allow amplification of bands of similar intensity using genomic DNA template. We previously developed the human experimental systems of 68 glycosyltransferase genes, 39 Hox genes, and 26 integrin subunit genes, and analyzed the expression of those genes in human adult tissues. Here we report the establishment of an SM RT-PCR system of proto-oncogenes and tumor suppressor genes and the analysis of gene expression in human cancer tissues and cell lines. We also demonstrate that the SM RT-PCR system, which was developed for cDNA expression analysis, could also be used successfully for more exquisite analysis of copy number changes in genomic DNA. We observed a decrease in band intensity of HRAS, TP73, CDKN2A, and CDKN2B genes in most of the breast and prostate cancer cell lines examined. The decrease in copy number of HRAS proto-oncogene leads us to suspect the presence of tumor suppressor genes in the vicinity of this gene on chromosome 11p15.5.

Yamashita, H., S. Kobayashi, et al. (1993). "Analysis of oncogenes and tumor suppressor genes in human breast cancer." Jpn J Cancer Res **84**(8): 871-8.

Oncogenes (c-erbB-2, c-myc, and some genes linked to the 11q13 lesion), tumor suppressor genes (retinoblastoma gene, p53) and an antimetastatic gene (nm23/nucleoside diphosphate kinase) play important roles in breast cancer progression. Amplification of c-erbB-2, c-myc, and int-2, and expression of RB, p53(mutant), and NDP kinase were determined in 77 primary breast cancer specimens. nm23-H1 allelic loss was also studied. c-erbB-2 and c-myc amplification, loss of RB expression, p53(mutant) expression, and nm23-H1 allelic loss were also found in non-invasive carcinoma. int-2 amplification was significantly correlated with lymph node status ($P = 0.02$) and a significant association was found between p53(mutant) expression and tumor size ($P = 0.04$). c-erbB-2 amplification was strongly associated with disease-free and overall survival in multivariate analysis ($P = 0.002$). All of the c-erbB-2 amplified cases and all but one of the int-2 amplified cases in node-positive patients had relapsed within 2 years post resection. The cancer cells may acquire new proliferative pathways sequentially as a result of multiple genetic alterations which enable them to bypass the estrogen-dependent proliferation.

Yang, Z. Q., K. L. Streicher, et al. (2006). "Multiple interacting oncogenes on the 8p11-p12 amplicon in human breast cancer." Cancer Res **66**(24): 11632-43.

The 8p11-p12 genomic region is amplified in 15% of breast cancers and harbors several candidate oncogenes. However, functional evidence for a transforming role for these genes is lacking. We identified 21 genes from this region as potential oncogenes based on statistical association between copy number and expression. We further showed that three of these genes (LSM1, BAG4, and C8orf4) induce transformed phenotypes when overexpressed in MCF-10A cells, and overexpression of these genes in combination influences the growth factor independence phenotype and the ability of the cells to grow under anchorage-independent conditions. Thus,

LSM1, BAG4, and C8orf4 are breast cancer oncogenes that can work in combination to influence the transformed phenotype in human mammary epithelial cells.

Yarbro, J. W. (1992). "Oncogenes and cancer suppressor genes." Semin Oncol Nurs **8**(1): 30-9.

Cancer is caused by the malfunction of genes that regulate cell proliferation. Two kinds of regulatory genes have been discovered in the search for cancer genes: those that promote growth, called oncogenes, and those that suppress growth, called anti-oncogenes or cancer suppressor genes. The retroviruses that cause animal cancers contain oncogenes coding for growth-promoting signals. These retroviruses rarely cause human cancer but study of their oncogenes has allowed identification of many human cancer genes. These genes code for growth factors, growth factor receptors, cytoplasmic proteins, and nuclear proteins. The complete sequence of cellular growth control begins when a growth factor binds to its receptor and acts directly or indirectly through a G protein and second messenger to induce phosphorylation (activation) of an intracellular protein that ultimately alters the expression of the genes necessary to initiate cell division. At each step in the complex sequence that up-regulates cell division, there is an opposite down-regulating activity produced by the protein products of anti-oncogenes or cancer suppressor genes. These proteins do this by binding to and inactivating transcription factors that initiate DNA synthesis or by directly inactivating the molecules activated by the oncogene products. When this carefully orchestrated and regulated cell control process goes awry because one or more of the proteins in the sequence has been altered by a mutated gene, the cell divides in an uncontrolled manner and malignancy results. It is thought that most human cancers result from a combination of genetic changes that must include both the absence of the protein products of cancer suppressor genes and the presence of abnormal products of oncogenes. The work of Volgelstein and coworkers at Johns Hopkins University has provided the best insight so far into the complex pathogenesis of a common tumor, colon cancer. Carcinogenesis in colon cancer requires a sequence of events that involves more than five genes. Understanding of these pathogenic mechanisms should improve cancer diagnosis and treatment.

Yokota, J., M. Wada, et al. (1988). "Heterogeneity of lung cancer cells with respect to the amplification and rearrangement of myc family oncogenes." Oncogene **2**(6): 607-11.

Seventy lung tumors from 53 patients were analysed for alterations of myc family oncogenes, c-myc, N-myc and L-myc, to evaluate when activation of these genes occurs during tumor development. The 53 cases were 17 small cell carcinomas (SCCs), 18 adenocarcinomas, 12 squamous cell carcinomas (SqCs), 4 large cell carcinomas and 2 adenosquamous carcinomas. Either N-myc or L-myc was amplified in 4 of the 17 (one N-myc and 3 L-myc) SCCs (24%), while c-myc was amplified in 3 of the 12 SqCs (25%). In one SCC, amplification of N-myc was found in the primary tumor, a pulmonary hilar lymph node metastasis and a pleural metastasis, but not in a liver metastasis or a para-aortic lymph node metastasis. In one SqC, c-myc was amplified in a pleural metastasis and a lymph node metastasis, but not in the primary tumor. In 2 cases of SCCs, amplification or rearrangement of c-myc was detected only in the cell lines, but not in the original tumors taken from the same individuals. These results indicate that tumor cells were heterogeneous for amplification and rearrangement of myc family oncogenes, and suggest that activation of these oncogenes in SCCs and SqCs occurs not at the time of malignant transformation but during tumor progression.

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