Cancer and Physiology

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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 paper collects some literatures on cancer and physiology.
[Smith MH. **Cancer and Physiology.** *Cancer Biology* 2011;1(3):131-142]. (ISSN: 2150-1041). http://www.cancerbio.net. 6

Keywords: cancer; biology; research; life; disease; physiology

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

Asaka, M., A. R. Sepulveda, et al. (2001). "Gastric Cancer."

Nearly 20 years have elapsed since the discovery of Helicobacter pylori (168). Due to the progress of research during this period, a causal link between H. pylori and gastric mucosal lesions seems almost certain. Experimental ingestion of H. pylori demonstrated that it caused gastritis in humans, with the inflammation being cured by eradication of the organism (103, 109). Furthermore, H. pylori infection is one of the major causes of recurrent peptic ulcer disease (124, 164). Accordingly, patients with peptic ulcer disease are advised to undergo H. pylori eradication therapy. Gastric cancer is one of the most common malignancies in the world, although the incidence and mortality rate have been decreasing in recent decades. The association between H. pylori and gastric cancer has attracted great interest worldwide because the International Agency for Research on Cancer (IARC), a subordinate organization of the World Health Organization (WHO), identified H. pylori as a "group 1 (definite carcinogen)" in 1994 (1). That is, the IARC concluded that H. pylori was certainly linked to carcinogenesis on the basis of the results of epidemiologic studies. The association between H. pylori and gastric cancer may be explained by two possible mechanisms: one is based on a carcinogenesis-promoting effect of H. pylori itself and the other is based on the establishment of a carcinogenic environment due to long-term infection with H. pylori. In the second case, although H. pylori may have no carcinogenesis-promoting effect itself, infection causes inflammation of the gastric mucosa and chronic infection causes mucosal atrophy, resulting in intestinal metaplasia. These latter changes are considered precursors of gastric cancer. Research concerning the association between gastric cancer and H. pylori has achieved enormous progress over time, leading to the recognition of this relationship by the WHO. One of the greatest concerns is to ascertain whether ultimately H. pylori-induced gastritis may lead to gastric cancer. The onset of gastric cancer can be explained as being caused not only by H. pylori infection, but also by a combination of various factors such as food and the environment. However, the possibility that the occurrence of gastric cancer, like the recurrence of peptic ulcer disease, can be prevented by eradication of H. pylori has also been suggested. Further progress in epidemiologic research is needed to resolve this issue.

Brown, J. M. and A. J. Giaccia (1998). "The unique physiology of solid tumors: opportunities (and problems) for cancer therapy." Cancer Res **58**(7): 1408-16.

The physiology of solid tumors differs from that of normal tissues in a number of important aspects, the majority of which stem from differences between the two vasculatures. Compared with the regular, ordered vasculature of normal tissues, blood vessels in tumors are often highly abnormal, distended capillaries with leaky walls and sluggish flow. Tumor

growth also requires continuous new vessel growth, or angiogenesis. These physiological differences can be problems for cancer treatment; for example, hypoxia in solid tumors leads to resistance to radiotherapy and to some anticancer drugs. However, these differences can also be exploited for selective cancer treatment. Here we review four such areas that are under active investigation: (a) hypoxia-selective cytotoxins take advantage of the unique low oxygen tension in the majority of human solid tumors. Tirapazamine, a drug in the final stages of clinical trials, is one of the more promising of these agents; (b) leaky tumor blood vessels can be exploited using liposomes that have been sterically stabilized to have a long intravascular half-life, allowing them to selectively accumulate in solid tumors; (c) the tumor microenvironment is a stimulus to angiogenenesis, and inhibition of angiogenesis can be a powerful anticancer therapy not susceptible to acquired drug resistance; and (d) we discuss attempts to use gene therapy activated either by the low oxygen environment or by necrotic regions of tumors.

Brunelli, A. and M. Salati (2008). "Preoperative evaluation of lung cancer: predicting the impact of surgery on physiology and quality of life." Curr Opin Pulm Med **14**(4): 275-81.

PURPOSE OF REVIEW: To summarize the best clinical evidence published in the last year and regarding the functional evaluation and the residual quality of life after lung resection in patients with lung cancer. RECENT FINDINGS: Recent evidences have shown that predicted postoperative forced expiratory volume in 1 s is not a reliable predictor of complications in patients with obstructive pulmonary disease and that carbon monoxide lung diffusion capacity predicts complications even in patients with normal forced expiratory volume in 1 s. Maximal stair-climbing test appears to discriminate better between complicated and noncomplicated patients compared with traditional split-lung function measures. Patients unable to climb 12 m have 2.5-fold and 13-fold higher complications and mortality rates compared with those able to climb 22 m. Quality of life has been shown to decrease in the first month but to return to preoperative values after 3 months in most of the patients after lung resection. SUMMARY: Carbon monoxide lung diffusion capacity and stair-climbing test should be performed routinely in all lung-resection candidates. In those with poor exercise tolerance in stair-climbing test or exercise oxygen desaturation, or candidates to pneumonectomy, the measurement of VO2max is recommended. Quality of life should always be assessed through specific instruments and not inferred by traditional functional tests.

Carpenter, J. S. (2005). "State of the science: hot flashes and cancer. Part 1: definition, scope, impact, physiology, and measurement." Oncol Nurs Forum **32**(5): 959-68.

PURPOSE/OBJECTIVES: To critically evaluate and synthesize multidisciplinary research related to hot flashes in the context of cancer. Topics include the definition, scope, and impact of hot flashes; physiologic mechanisms; and measurement issues. DATA SOURCES: Published, peer-reviewed articles and textbooks; editorials; unpublished data; and computerized databases. DATA SYNTHESIS: Hot flashes can affect a diverse group of men and women diagnosed with or at high risk for certain cancers with a resulting negative impact on quality of life. Although the exact physiologic mechanisms underlying hot flashes remain unclear, a complex interplay of thermoregulatory, gluconeuroendocrine, genetic, and behavioral factors appears to be involved. Measurement of hot flashes should be considered carefully because they can be operationalized objectively and subjectively. CONCLUSIONS: The large and diverse evidence base and current national attention on measurement of hot flashes highlight the importance of the symptom to healthcare professionals, including oncology nurses. IMPLICATIONS FOR NURSING: Careful attention to assessment and measurement of hot flashes in patients with cancer is needed.

Chang, L., C. F. Horng, et al. (2006). "Prognostic accuracy of Acute Physiology and Chronic Health Evaluation II scores in critically ill cancer patients." Am J Crit Care **15**(1): 47-53.

BACKGROUND: The predictive accuracy of scores on the Acute Physiology and Chronic Health Evaluation II (APACHE II) for in-hospital mortality among critically ill cancer patients varies. OBJECTIVE: To evaluate the predictive accuracy of APACHE II scores for severity of illness in critically ill cancer patients and to find clinical indicators to improve the accuracy. METHODS: Actual hospital mortality rates were compared with predicted rates. Data were collected prospectively from 1263 cancer patients admitted to the intensive care unit during a 5-year period in a cancer center in Taiwan. The APACHE II score for each patient was calculated at admission. Stepwise logistic regression was used to identify clinical predictors associated with increased mortality. RESULTS: The scores ranged from 2 to 54. The mortality rates were 19% overall, 45% for medical patients, and 1% for surgical patients. The fit of the scores was good for the medical patients (Hosmer-Lemeshow statistic 8.2, P = .41). The estimated odds ratios for mortality of presence of

metastasis and respiratory failure were 4.18 (95% CI 2.65-6.59) and 2.03 (95% CI 1.22-3.38), respectively. When metastasis and respiratory failure were incorporated into the APACHE II model, the area under the receiver operating characteristic curve for medical patients increased from 0.82 to 0.86. The fit of the modified model was excellent (Hosmer and Lemeshow statistic 6.57, P=.58). CONCLUSIONS: APACHE II scores are predictive of hospital mortality in critically ill cancer patients. The presence of metastasis and respiratory failure at admission are also associated with outcome.

Dauchy, E. M., R. T. Dauchy, et al. (2006). "Human cancer xenograft perfusion in situ in rats: a new perfusion system that minimizes delivery time and maintains normal tissue physiology and responsiveness to growth-inhibitory agents." J Am Assoc Lab Anim Sci **45**(3): 38-44.

We developed an artificial lung and catheter system for perfusing tissue-isolated tumors in situ that dramatically minimizes perfusate delivery time. Our investigations demonstrated that the circadian neurohormone melatonin (MLT), eicosapentaenoic acid (EPA), and conjugated linoleic acid (CLA) inhibit growth and metabolism in several rodent and human tumors. These anticancer agents function in a receptor-mediated manner to suppress tumor uptake of linoleic acid (LA), the principal tumor growth-promoting fatty acid, and its conversion to the mitogenic agent 13-hydroxyoctadecadienoic acid (13-HODE). Using this perfusion system and MCF-7 human breast xenografts, we examined the efficacy and timing of perfusate delivery to tumors. Tumors were perfused with rat donor blood to establish baseline LA uptake values; after 36 min of perfusion, we supplemented the perfusate with MLT, EPA, or CLA and collected arteriovenous whole-blood samples over 5-min intervals for a total perfusion period of 70 min. Arterial blood pH, pO2, and pCO2 (mean+/-33.7+/-1.9, and 59.8+/-1.9 mm Hg, respectively; none of these values varied during the perfusions. Tumor LA uptake and 13-HODE production were 1.06+/-0.28 microg/min/g and 1.38+/-0.02 ng/min/g, respectively, and were completely suppressed within 5 min after delivery of anticancer agents to the tissue. This new system provides rapid perfusate delivery for use with both normal and neoplastic tissues while maintaining normal physiologic tissue parameters.

Dorward, A., S. Sweet, et al. (1997). "Mitochondrial contributions to cancer cell physiology: redox balance, cell cycle, and drug resistance." J Bioenerg Biomembr **29**(4): 385-92.

Alterations in the biochemistry of mitochondria have been associated with cell transformation and the acquisition of drug resistance to certain chemotherapeutic agents, suggesting that mitochondria may play a supportive role for the cancer cell phenotype. Mitochondria are multifunctional organelles that contribute to the cellular adenosine triphosphate (ATP) pool and cellular redox balance through the production of reactive oxygen intermediates (ROI). Our laboratory has focused on these mitochondrial functions in the context of cancer cell physiology to evaluate the potential role of mitochondria as controllers of tumour cell proliferation. Low concentrations of ROI have been implicated as messengers in intracellular signal transduction mechanisms; thus an imbalance of ROI production from the mitochondria may support cancer cell growth. In addition, suppression of mitochondrial ATP production can halt cell cycle progression at two energetic checkpoints, suggesting that the use of tumor-selective agents to reduce ATP production may offer a therapeutic target for cancer growth control.

Dougall, W. C. (2007). "RANKL signaling in bone physiology and cancer." Curr Opin Support Palliat Care **1**(4): 317-22.

PURPOSE OF REVIEW: Increased osteoclast activity plays an operative role in the pathophysiology of skeletal complications of malignancy. This review focuses on the critical roles of a triad of molecules - receptor activator of nuclear factor kappa beta ligand and its two receptors, receptor activator of nuclear factor kappa beta and osteoprotegerin - in the regulation of osteoclastogenesis across a broad spectrum of cancer-induced bone diseases. RECENT FINDINGS: While it is well established that osteoclastic bone resorption plays an operative role in the skeletal complications of 'osteolytic' bone metastasis, recent evidence has described osteoclasts in osteoblastic prostate cancer metastases and increases in serum markers of bone resorption in these patients. In addition to its essential role in osteoclastogenesis, receptor activator of nuclear factor kappa beta ligand has also been recently shown to increase migration and invasive properties of receptor activator of nuclear factor kappa beta-positive tumor cells, and potentially may play a direct role in the bone tropism of those tumors. SUMMARY: The critical role of receptor activator of nuclear factor kappa beta ligand signaling in regulating osteoclast activity is described in detail in this review, as is its role in cancer-mediated bone destruction, and the potential of receptor activator of nuclear factor kappa beta ligand inhibition as a novel treatment in tumor-induced bone disease.

Engstrom, C. A. and C. E. Kasper (2007). "Physiology and endocrinology of hot flashes in prostate cancer." Am J Mens Health **1**(1): 8-17.

The purpose of this article is to integrate the physiology of the male reproductive system and the role of hormones in the pathophysiology and treatment of prostate cancer. The primary focus is to review hormonal changes associated with androgen ablation treatment and to integrate the available hormonal data into a hypothesis. This review used a systematic search of Medline references from 1990 to 2006. All sources were critically evaluated to arrive at an understanding of androgen deprivation symptoms, such as hot flushes/flashes, and to identify research needed in this area. Research is needed to explore the physiological mechanisms of hot flashes to develop better therapeutic treatment options to ameliorate side effects of hormonal treatment. Studies are needed to investigate all aspects of hot flashes in populations other than those with breast cancer, such as men with prostate cancer, carcinoid tumors, medullary thyroid tumors, pancreatic islet-cell tumors, renal cell carcinoma, and phenochromocytoma.

Fahrmann, M. (2008). "Targeting protein kinase C (PKC) in physiology and cancer of the gastric cell system." Curr Med Chem **15**(12): 1175-91.

Protein kinase C (PKC) family members are multifunctional kinases that have been implicated in many cell biological and physiological tasks including acid, pepsinogen, and mucous production. Through the use of small-molecule PKC modulators, PKC has been found to be involved in gene expression, the control of cytoskeleton, membrane and secretagogue-dependent signal transduction for secretion of acid. Gastric carcinoma and adenocarcinoma cells often show dysregulated PKC-dependent cell signal transduction compared to normal gastric cells. Moreover, PKC was the first known target of tumor promoting phorbol esters. These findings support PKC as a potential chemotherapy target in gastric cancer. Various approaches have been launched in directly targeting PKC for chemotherapy of gastric cancer. The macrocyclic lactone bryostatin-1 is a promising agent that acts as a modulator of PKC activity, and enhances the effect of chemotherapeutic agents such as paclitaxel. This article provides an overview of the findings to date regarding the physiological role of PKC in the gastric cell system by various pharmacological approaches and examines PKC as a target in gastric (adeno-)carcinoma chemotherapy.

Giese-Davis, J., A. Conrad, et al. (2008). "Exploring Emotion-Regulation and Autonomic Physiology in Metastatic Breast Cancer Patients: Repression, Suppression, and Restraint of Hostility." Pers Individ Dif **44**(1): 226-237.

We examined relationships between three emotion-regulation constructs and autonomic physiology in metastatic breast cancer patients (N = 31). Autonomic measures are not often studied in breast cancer patients and may provide evidence of an increase in allostatic load. Patients included participated as part of a larger clinical trial of supportive-expressive group therapy. Systolic and diastolic blood pressure and heart rate were assessed at a semi-annual follow-up. We averaged 3 resting assessments and used measures of Repression, Suppression, Restraint of Hostility, and Body Mass Index as predictors of autonomic response. We found that higher repression was significantly associated with higher diastolic blood pressure, while higher restraint of hostility was significantly associated with higher systolic blood pressure. A repressive emotion regulation style may be a risk factor for higher sympathetic activation possibly increasing allostatic load, while restraint of hostility may be a protective factor for women with metastatic breast cancer.

Giordano, A., M. Calvani, et al. (2003). "Skeletal muscle metabolism in physiology and in cancer disease." J Cell Biochem **90**(1): 170-86.

Skeletal muscle is a tissue of high demand and it accounts for most of daily energy consumption. The classical concept of energy metabolism in skeletal muscle has been profoundly modified on the basis of studies showing the influence of additional factors (i.e., uncoupling proteins (UCPs) and peroxisome proliferator activated receptors (PPARs)) controlling parameters, such as substrate availability, cellular enzymes, carrier proteins, and proton leak, able to affect glycolysis, nutrient oxidation, and protein degradation. This extremely balanced system is greatly altered by cancer disease that can induce muscle cachexia with significant deleterious consequences and results in muscle wasting and weakness, delaying or preventing ambulation, and rehabilitation in catabolic patients.

Hunter, G. J., L. M. Hamberg, et al. (1998). "Dynamic T1-weighted magnetic resonance imaging and positron emission tomography in patients with lung cancer: correlating vascular physiology with glucose metabolism." Clin Cancer Res **4**(4): 949-55.

The management of primary lung cancer relies on sophisticated imaging methods to assist in the diagnosis, staging, and evaluation of tumor regression during treatment. The information provided is generally anatomical in nature, except for that provided by positron emission tomography with [18F]fluorodeoxyglucose, a modality that yields

physiological data that have been shown to be useful in identifying neoplasia, based on an elevated glucose metabolic rate. Because the metabolism of malignant tissue depends intimately on neovascularization to provide oxygen and glucose in sufficient quantities to allow tumor growth, the characterization of tumor vascular physiology could be an important tool for assessing and predicting the likely effectiveness of treatment. Our goal was to show the feasibility and practical value of parameters of tumor vascular physiology obtained using dynamic T1-weighted magnetic resonance imaging (MRI), to correlate them with glucose metabolism and to demonstrate changes in these parameters during and after treatment in patients with lung cancer. Parameters of vascular physiology [permeability-surface area (PS) product and extracellular contrast agent distribution volume] and glucose metabolism were assessed in 14 patients with lung cancer. Glucose metabolism was measured by using [18F]fluorodeoxyglucose-positron emission tomography. Vascular physiology was assessed by dynamic T1-weighted, contrast-enhanced MRI. The mean PS product in tumor was 0.0015 +/- 0.0002 s(-1) (n = 13) before, 0.0023 +/- 0.0003 s(-1) (n = 3, P = 0.053) midway through, and 0.00075 +/- 0.0002 s(-1) (n = 5, P < 0.03) 2 weeks after treatment. Values for the extracellular contrast distribution space were 0.321 +/- 0.03 before, 0.289 +/- 0.02 midway through, and 0.195 +/- 0.02 (P < 0.01) 2 weeks after therapy. The glucose metabolic rate was significantly correlated with the PS product (P < 0.01) but not with the extracellular contrast distribution space. Our results demonstrate that tumor PS product correlates with glucose metabolism, that chemo- and radiotherapy induce observable and quantifiable changes in these parameters, and that such changes can be measured by in vivo dynamic MRI. Quantitative dynamic T1-weighted MRI of tumor vascular physiology may have a useful role in the clinical management of lung cancer.

Kreidl, E., D. Ozturk, et al. (2009). "Activins and follistatins: Emerging roles in liver physiology and cancer." World J Hepatol **1**(1): 17-27.

Activins are secreted proteins belonging to the TGF-beta family of signaling molecules. Activin signals are crucial for differentiation and regulation of cell proliferation and apoptosis in multiple tissues. Signal transduction by activins relies mainly on the Smad pathway, although the importance of crosstalk with additional pathways is increasingly being recognized. Activin signals are kept in balance by antagonists at multiple levels of the signaling cascade. Among these, follistatin and FLRG, two members of the emerging family of follistatin-like proteins, can bind secreted activins with high affinity, thereby blocking their access to cell surface-anchored activin receptors. In the liver, activin A is a major negative regulator of hepatocyte proliferation and can induce apoptosis. The functions of other activins expressed by hepatocytes have yet to be more clearly defined. Deregulated expression of activins and follistatin has been implicated in hepatic diseases including inflammation, fibrosis, liver failure and primary cancer. In particular, increased follistatin levels have been found in the circulation and in the tumor tissue of patients suffering from hepatocellular carcinoma as well as in animal models of liver cancer. It has been argued that up-regulation of follistatin protects neoplastic hepatocytes from activin-mediated growth inhibition and apoptosis. The use of follistatin as biomarker for liver tumor development is impeded, however, due to the presence of elevated follistatin levels already during preceding stages of liver disease. The current article summarizes our evolving understanding of the multi-faceted activities of activins and follistatins in liver physiology and cancer.

Laking, G. R., C. West, et al. (2006). "Imaging vascular physiology to monitor cancer treatment." Crit Rev Oncol Hematol **58**(2): 95-113.

The primary physiological function of the vasculature is to support perfusion, the nutritive flow of blood through the tissues. Vascular physiology can be studied non-invasively in human subjects using imaging methods such as positron emission tomography (PET), magnetic resonance imaging (MRI), X-ray computed tomography (CT), and Doppler ultrasound (DU). We describe the physiological rationale for imaging vascular physiology with these methods. We review the published data on repeatability. We review the literature on 'before-and-after' studies using these methods to monitor response to treatment in human subjects, in five broad clinical settings: (1) antiangiogenic agents, (2) vascular disruptive agents, (3) conventional cytotoxic drugs, (4) radiation treatment, and (5) agents affecting drug delivery. We argue that imaging of vascular physiology offers an attractive 'functional endpoint' for clinical trials of anticancer treatment. More conventional measures of tumour response, such as size criteria and the uptake of fluorodeoxyglucose, may be insensitive to therapeutically important changes in vascular function.

Lucia, A., C. Earnest, et al. (2003). "Cancer-related fatigue: can exercise physiology assist oncologists?" Lancet Oncol **4**(10): 616-25.

Most patients with cancer experience fatigue, a severe activity-limiting symptom with a multifactorial origin. To avoid cancer-related fatigue,

patients are frequently advised to seek periods of rest and to reduce their amount of physical activity. This advice is reminiscent of that formerly given to patients with heart disease. However, such recommendations can paradoxically compound symptoms of fatigue, since sedentary habits induce muscle catabolism and thus cause a further decrease in functional capacity. By contrast, there is scientific evidence that an exercise programme of low to moderate intensity can substantially reduce cancer-related fatigue and improve the quality of life of these patients. Current knowledge, combined with findings soon to be published, could launch new opportunities for patients with cancer. In this new century, exercise physiology could soon prove to be very useful for oncologists.

McDonald, P. C., A. B. Fielding, et al. (2008). "Integrin-linked kinase--essential roles in physiology and cancer biology." J Cell Sci **121**(Pt 19): 3121-32.

Integrin-linked kinase (ILK) is a multifunctional intracellular effector of cell-matrix interactions and regulates many cellular processes, including growth, proliferation, survival, differentiation, migration, invasion and angiogenesis. The use of recently developed Cre-lox-driven recombination and RNA-interference technologies has enabled the evaluation of the physiological roles of ILK in several major organ systems. Significant developmental and tissue-homeostasis defects occur when the gene that encodes ILK is deleted, whereas the expression of ILK is often elevated in human malignancies. Although the cause(s) of ILK overexpression remain to be fully elucidated, accumulating evidence suggests that its oncogenic capacity derives from its regulation of several downstream targets that provide cells with signals that promote proliferation, survival and migration, supporting the concept that ILK is a relevant therapeutic target in human cancer. Furthermore, a global analysis of the ILK 'interactome' has yielded several novel interactions, and has revealed exciting and unexpected cellular functions of ILK that might have important implications for the development of effective therapeutic agents.

Mitsiades, C. S. and M. Koutsilieris (2001). "Molecular biology and cellular physiology of refractoriness to androgen ablation therapy in advanced prostate cancer." Expert Opin Investig Drugs **10**(6): 1099-115.

We review the extensive body of data on the molecular aetiology of hormone refractory disease in metastatic prostate cancer patients. Particular emphasis is placed on the crucial role of the bone micro-environment, especially the intercellular interactions of metastatic prostate cancer cells and osteoblasts in promoting the establishment of hormone refractory disease. Resistance of tumour cells to anticancer therapies is generally viewed as a phenomenon almost exclusively determined by chromosomal defects and/or gene mutations. However, it is now well-documented that the local milieu of the bone metastases can also protect tumour cells from anticancer therapy- induced apoptosis, either independently or synergistically with resistance-related genetic alterations. A key determinant of this protection is the urokinase/plasmin cascade which modulates the local concentration of survival factors, such as insulin-like growth factor (IGF-1). The molecular pathways whereby this major growth and survival factor for prostate cancer cells exerts its anti-apoptotic effect on prostate cancer cells are discussed.

Nam, R. K., J. Trachtenberg, et al. (2005). "Serum insulin-like growth factor-I levels and prostatic intraepithelial neoplasia: a clue to the relationship between IGF-I physiology and prostate cancer risk." Cancer Epidemiol Biomarkers Prev **14**(5): 1270-3.

Serum insulin-like growth factor-I (IGF-I) levels at the higher end of the reference range have been associated with increased risk for the future development of prostate cancer. We determined whether high serum IGF-I levels are associated with precancerous lesions of the prostate. We conducted a case-control study to determine whether high serum IGF-I levels were associated with the presence of high-grade prostatic intraepithelial neoplasia (HGPIN) among patients who presented for prostate biopsy because of an abnormal serum prostate-specific antigen level or digital rectal exam. We measured serum IGF-I and insulin-like growth factor binding protein-3 (IGFBP-3) prior to prostate biopsy and compared them between 103 men with HGPIN (cases) and 205 men with normal prostate histology (controls). The mean IGF-I level in patients with HGPIN (130.2 ng/mL) was significantly higher compared with controls (118.8 ng/mL, P = 0.01). The mean IGFBP-3 level in patients with HGPIN (2,393.9 ng/mL) was also higher compared with controls (2,276.0 ng/mL, P = 0.06). After adjusting for age, prostate-specific antigen, digital rectal examination, and ethnic background, the odds ratio for a HGPIN diagnosis among men in the highest relative to the lowest quartile of serum IGF-I level was 1.94 (95% confidence interval, 1.0-3.7; P = 0.04). The potential association between a high serum IGF-I level and the presence of HGPIN may represent an important clue to understanding the basis for the relationship between IGF-I physiology and prostate cancer risk. Larger studies will be required to confirm this relationship.

Nishibori, M., S. Mori, et al. (2005). "Physiology and pathophysiology of proteinase-activated receptors (PARs): PAR-2-mediated proliferation of colon cancer cell." J Pharmacol Sci **97**(1): 25-30.

Proteinase-activated receptor-2 (PAR-2) has been demonstrated to be highly expressed in the gastrointestinal tract. In the present minireview, we summarize the effects of PAR-1 and PAR-2 stimulation using their activating peptides and agonist proteinases on the calcium signaling and the cell proliferation in DLD-1 cell, a human colon cancer cell line. PAR-2 but not PAR-1 stimulation induced the enhancement of cell proliferation, whereas both PAR-1 and PAR-2 stimulation induced the transient increase in [Ca(2+)](i). PAR-2 stimulation induced the phosphorylation of MEK1/2 and ERK1/2, but PAR-1 stimulation did not. The inhibition of MEK1/2 by PD98059 completely abolished the proliferative response to PAR-2 stimulation. Thus, MEK-ERK activation plays major role in the PAR-2-mediated proliferative response. The coupling of PARs to calcium signaling and MEK-ERK activation may be independent, and varied dependent on cell types.

Ntziachristos, V. and B. Chance (2001). "Probing physiology and molecular function using optical imaging: applications to breast cancer." Breast Cancer Res **3**(1): 41-6.

The present review addresses the capacity of optical imaging to resolve functional and molecular characteristics of breast cancer. We focus on recent developments in optical imaging that allow three-dimensional reconstruction of optical signatures in the human breast using diffuse optical tomography (DOT). These technologic advances allow the noninvasive, in vivo imaging and quantification of oxygenated and deoxygenated hemoglobin and of contrast agents that target the physiologic and molecular functions of tumors. Hence, malignancy differentiation can be based on a novel set of functional features that are complementary to current radiologic imaging methods. These features could enhance diagnostic accuracy, lower the current state-of-the-art detection limits, and play a vital role in therapeutic strategy and monitoring.

Pain, S. J., R. W. Barber, et al. (2005). "Short-term effects of axillary lymph node clearance surgery on lymphatic physiology of the arm in breast cancer." J Appl Physiol **99**(6): 2345-51.

It is not known why some women develop breast cancer-related lymphedema (BCRL) of the arm, whereas others having similar treatment do not. We speculated that increased uptake of protein into local blood may protect against BCRL. Sixteen women were given bilateral subcutaneous hand webspace injections of polyclonal immunoglobulin (HIgG), (99m)Tc-HIgG on one side and (111)In-HIgG on the other, before and 3 mo after axillary clearance surgery. The rates of clearance of activity from the depot (k) and accumulation in central blood (b(contra)) were measured using a scintillation probe and bilateral antecubital vein blood sampling, respectively. Activity accumulating in blood ipsilateral to the injected side, in excess of central blood activity (b(ipsi)) was also calculated as a measure of local vascular uptake. The k correlated with b(contra), but neither changed in response to surgery. However, b(ipsi) for injections of (99m)Tc-HIgG into the affected arm increased in all seven patients in whom data were available (0.018 +/- 0.006 to 0.038 +/- 0.007%/min; $P < 0.05$); indeed, in five of these seven, b(ipsi) paradoxically exceeded b(contra), and none developed BCRL at 3-yr follow-up. We conclude that uptake of protein into local blood and/or proteolysis increases after axillary surgery and may protect against BCRL.

Pampalakis, G. and G. Sotiropoulou (2007). "Tissue kallikrein proteolytic cascade pathways in normal physiology and cancer." Biochim Biophys Acta **1776**(1): 22-31.

Human tissue kallikreins (KLKs or kallikrein-related peptidases) are a subgroup of extracellular serine proteases that act on a wide variety of physiological substrates, while they display aberrant expression patterns in certain types of cancer. Differential expression patterns lead to the exploitation of these proteins as new cancer biomarkers for hormone-dependent malignancies, in particular. The prostate-specific antigen or kallikrein-related peptidase 3 (PSA/KLK3) is an established tumor marker for the diagnosis and monitoring of prostate cancer. It is well documented that specific KLK genes are co-expressed in tissues and in various pathologies suggesting their participation in complex proteolytic cascades. Here, we review the currently established knowledge on the involvement of KLK proteolytic cascades in the regulation of physiological and pathological processes in prostate tissue and in skin. It is well established that the activity of KLKs is often regulated by auto-activation and subsequent autolytic internal cleavage leading to enzymatic inactivation, as well as by inhibitory serpins or by allosteric inhibition by zinc ions. Redistribution of zinc ions and alterations in their concentration due to physiological or pathological reasons activates specific KLKs initiating the kallikrein cascade(s). Recent studies on kallikrein substrate specificity allowed for the construction of a kallikrein interaction network involved in semen liquefaction and prostate cancer, as well as in skin pathologies, such as skin

desquamation, psoriasis and cancer. Furthermore, we discuss the crosstalks between known proteolytic pathways and the kallikrein cascades, with emphasis on the activation of plasmin and its implications in prostate cancer. These findings may have clinical implications for the underlying molecular mechanism and management of cancer and other disorders in which KLK activity is elevated.

Payne, R. (1987). "Anatomy, physiology, and neuropharmacology of cancer pain." Med Clin North Am **71**(2): 153-67.

The anatomy, physiology, and pharmacology of nociception and its modification by analgesic drugs have been studied extensively in the past decade. Although the neural mechanisms of nociceptors and the stimuli that activate them are much better understood, it must be emphasized that the perception of pain, as well as the meaning of pain to the individual, is a complex behavioral phenomenon and involves psychologic and emotional processes in addition to activation of nociceptive pathways. Pain related to malignant disease can be classified as somatic, visceral, and deafferentation in type. Somatic pain and visceral pain involve direct activation of nociceptors and are often a complication of tumor infiltration of tissues or injury of tissues as a consequence of cancer therapy. The management of this type of pain is typically accomplished by treating the tumor (with surgery, chemotherapy, and/or radiation therapy) and by using the appropriate non-narcotic, narcotic, and adjuvant analgesic agents. Neuroablative therapies may be helpful in specific circumstances. For example, cordotomy may be helpful for unilateral pain below the waist in patients with somatic and visceral pain. This procedure may also be helpful for early deafferentiation pain (i.e., lumbosacral plexopathy) in which peripheral nerves are compressed but not infiltrated or destroyed by metastatic tumor growth. Deafferentiation pain may be a complication of tumor infiltration of peripheral nerve or of cancer therapy that injures neural tissue. This type of pain is often poorly tolerated and difficult to control, particularly if not treated early and aggressively. Although incompletely understood, the pathophysiology of deafferentation pain appears to be different from that of somatic or visceral pain, and the treatment approaches may be different. Management approaches to deafferentation pain usually emphasize treatment of the pain, because injury to the nervous system may be difficult to reverse, even if one can successfully treat the underlying malignancy, and many deafferentation pain syndromes occur as a complication of cancer therapy. The role of narcotic analgesics in the management of deafferentation pain is not clear, although the published experience suggests that they are less useful than in somatic or visceral pain.

Payne, R. (1989). "Cancer pain. Anatomy, physiology, and pharmacology." Cancer **63**(11 Suppl): 2266-74.

Cancer pain can be divided into three classes: somatic, visceral, and deafferentation. Somatic and visceral pain result from activation of nociceptors by tumor infiltration of tissues and from secondary inflammatory changes with release of algesic chemicals that act to sensitize nociceptors. Pain may be experienced locally (somatic and visceral) or referred to remote cutaneous sites (visceral). Deafferentation pain results from injury to the nervous system due to tumor infiltration or cancer therapy and may persist even after the cause of the injury has been removed. Somatic, visceral, and deafferentation pain may be complicated by sympathetically maintained pain, in which efferent sympathetic activity promotes persistent pain, hyperpathia, and vasomotor and sudomotor changes after tissue injury from cancer or its therapy. The neurobiology of cancer pain is complex and incompletely understood. This article summarizes current knowledge in this area and briefly discusses approaches to cancer pain management that are based on this knowledge.

Pollak, M. (1998). "IGF-I physiology and breast cancer." Recent Results Cancer Res **152**: 63-70.

Recent studies imply that IGF-I levels vary greatly between normal women, and that premenopausal breast cancer risk is increased among women with higher IGF-I levels. It is known that tamoxifen lowers IGF-I levels, but further research is needed to determine whether antiestrogens will be of particular value in risk reduction for women with high IGF-I levels, and also to determine if IGF-I levels can indeed be used as an intermediate endpoint in risk reduction interventions. With respect to adjuvant therapy, we currently have convincing data that antiestrogens have moderate IGF-I lowering actions, but it remains unclear to what extent these contribute to the therapeutic effect of these compounds. Ongoing trials are addressing this question, as well as the hypothesis that interventions that increase IGF-I suppression will be associated with reduced relapse rates.

Pollak, M. (2000). "Insulin-like growth factor physiology and cancer risk." Eur J Cancer **36**(10): 1224-8.

In the past few years, both laboratory investigations and population studies have provided strong circumstantial evidence that insulin-like growth factor (IGF) physiology influences cancer risk. In contrast to the influence of germ line mutations that

are rare but are associated with very high risks, the impact of inter-individual variability in IGF physiology on risk appears to be modest but to effect a relatively high percentage of the population. Although this field of investigation is young, attention is already being given to the possibility that it may be relevant to clinical assessment of risk and/or to the identification of novel prevention strategies and intermediate endpoints. This review summarises key results in this field and provides a hypothesis concerning the mechanism by which IGF physiology influences risk of common epithelial cancers including those of breast, prostate, lung and colon.

Potter, J. D. (1993). "Colon cancer--do the nutritional epidemiology, the gut physiology and the molecular biology tell the same story?" J Nutr **123**(2 Suppl): 418-23.

Colon carcinogenesis models exist at epidemiologic, physiologic and molecular biologic levels. Thinking about the coherence of such models is useful both to inform colon cancer research and because the reasoning process may be generalizable. The consistent epidemiologic risk factors are low vegetable/fiber and high fat/meat/protein intakes. Others include physical activity, alcohol and reproduction. These epidemiologic risk factors appear to map to physiologic variables that provide mechanistic explanations for the associations: higher bile acids, fiber fermentation and effects of specific anticarcinogens found in vegetables. The possibility that the meat/fat association is due to carcinogens or promoters produced in cooked foods adds complexity to the physiologic model. As a link across genetics, physiology and epidemiology, the role of acetylator status is considered. Finally, whether relationships might exist between the epidemiologic/physiologic risk factors and the recently described molecular genetic changes and other colon cancer molecular mechanisms is considered.

Preston, T. J., A. Abadi, et al. (2001). "Mitochondrial contributions to cancer cell physiology: potential for drug development." Adv Drug Deliv Rev **49**(1-2): 45-61.

Mitochondria make an integral contribution to the regulation of several aspects of cell biology such as energy production, molecular metabolism, redox status, calcium signalling and programmed cell death. In accordance with an endosymbiotic origin, mitochondria rely upon the nucleus for synthesis and function. In addition, these organelles can respond to intra- and extracellular cues independently, and there exists a highly coordinated "cross talk" between mitochondrial and nuclear signals that can greatly influence cell behaviour. This review focuses upon the putative roles of altered mitochondrial physiology in the process of cellular transformation. Discussed are: mitochondria as targets of drug-induced cytotoxicity or cancer promotion, as regulators of apoptosis, as sources of cell signalling through reactive oxygen species, and mitochondrial control of specific nuclear responses.

Sapi, E. (2004). "The role of CSF-1 in normal physiology of mammary gland and breast cancer: an update." Exp Biol Med (Maywood) **229**(1): 1-11.

Colony stimulating factor (CSF-1) and its receptor (CSF-1R, product of c-fms proto-oncogene) were initially implicated as essential for normal monocyte development as well as for trophoblastic implantation. However, studies have demonstrated that CSF-1 and CSF-1R have additional roles in mammary gland development during pregnancy and lactation. This apparent role for CSF-1/CSF-1R in normal mammary gland development is very intriguing because this receptor/ligand pair has also been found to be important in the biology of breast cancer in which abnormal expression of CSF-1 and its receptor correlates with tumor cell invasiveness and adverse clinical prognosis. Recent findings also implicate tumor-produced CSF-1 in promotion of bone metastasis in breast cancer, and a certain membrane-associated form of CSF-1 appears to induce immunity against tumors. This review aims to summarize recent findings on the role of CSF-1 and its receptor in normal and neoplastic mammary development that may elucidate potential relationships of growth factor-induced biological changes in the breast during pregnancy and tumor progression.

Sebti, S. M. (2005). "Protein farnesylation: implications for normal physiology, malignant transformation, and cancer therapy." Cancer Cell **7**(4): 297-300.

Protein farnesylation is a lipid posttranslational modification required for the cancer-causing activity of proteins such as the GTPase Ras. Although farnesyltransferase inhibitors (FTIs) are in clinical trials, their mechanism of action and the role of protein farnesylation in normal physiology are ill understood. In this issue of Cancer Cell, two articles shed light on these important issues. Protein farnesylation was found to be essential for early embryogenesis, dispensable for adult homeostasis, and critical for progression but not initiation of tumorigenesis. Furthermore, Rab geranylgeranyltransferase was identified as a target for some FTIs. This minireview discusses the implications of these findings on normal physiology, malignant transformation, and cancer therapy.

Shafik, A. (1986). "A new concept of the anatomy of the anal sphincter mechanism and the physiology of defecation. Reversion to normal defecation after combined excision operation and end colostomy for rectal cancer." Am J Surg **151**(2): 278-84.

Twenty-one patients with combined excision operation for rectal cancer were subjected to electromyographic study of the levator ani muscle, the puborectalis muscle, and the external anal sphincter. Myoelectric activity of the puborectalis and levator ani muscles was detected in 12 patients, 6 of whom had normal activity of both muscles. Of the remaining six patients, there was reduced activity of the levator ani muscle in four and of the puborectalis muscle in all six. These patients underwent training and electric stimulation of these muscles. To verify the myoelectric findings, 15 specimens removed at combined excision operation were examined grossly and microscopically for the muscles removed at operation. Eight specimens were found to be free of the levator and puborectalis muscles, which indicated that these muscles were not excised. The 12 patients with myoelectrically active levator and puborectalis muscles were operated on to restore defecation by way of the normal perineal route. The technique comprises freeing of the colostomy and mobilization of the entire left side of the colon. The perineal scar is then excised and the colonic end fixed to the perineal skin and thus is controlled by the levator and puborectalis muscles. Full fecal control was achieved in seven patients and incomplete control in five. It is concluded that excision of the levator ani muscle, the puborectalis muscle, and the external anal sphincter should not be considered a standard part of the radical operation for cancer of the lower or middle third of the rectum, and that a combined excision operation has no place in the treatment of rectal cancer.

Stefano, G. B., R. M. Kream, et al. (2008). "Endogenous morphine/nitric oxide-coupled regulation of cellular physiology and gene expression: implications for cancer biology." Semin Cancer Biol **18**(3): 199-210.

Cancer is a simplistic, yet complicated, process that promotes uncontrolled growth. In this regard, this unconstrained proliferation may represent primitive phenomena whereby cellular regulation is suspended or compromised. Given the new empirical evidence for a morphinergic presence and its profound modulatory actions on several cellular processes it is not an overstatement to hypothesize that morphine may represent a key chemical messenger in the process of modulating proliferation of diverse cells. This has been recently demonstrated by the finding of a novel opiate-alkaloid selective receptor subtype in human multilineage progenitor cells (MLPC). Adding to the significance of morphinergic signaling are the findings of its presence in plant, invertebrate and vertebrate cells, which also have been shown to synthesize this messenger as well. Interestingly, we and others have shown that some cancerous tissues contain morphine. Furthermore, in medullary histolytic reticulosis, which is exemplified by cells having hyperactivity, the mu3 (mu3) opiate select receptor was not present. Thus, it would appear that morphinergic signaling has inserted itself in many processes taking a long time to evolve, including those regulating the proliferation of cells across diverse phyla.

Vainer, G. W., E. Pikarsky, et al. (2008). "Contradictory functions of NF-kappaB in liver physiology and cancer." Cancer Lett **267**(2): 182-8.

Rudolf Virchow (1821-1902), one of the founding fathers of modern pathology, hypothesized that cancer and inflammatory processes are linked, due to the presence of leukocytes in the tumor tissue. Today, chronic inflammation is believed to be one of the major causes for cancer development, accounting for nearly 20% of cancer cases worldwide. Hepatocellular carcinoma (HCC) is the third leading cause of cancer mortality throughout the world, and its incidence is increasing in the United States. HCC is widely accepted to be the outcome of continuous injury and chronic inflammation, and thus provides a good model to gain insight into inflammatory related cancer processes. Nuclear Factor- kappa B (NF-kappaB) was first identified as an enhancer protein of the kappa light-chain gene in B lymphocytes. Later it was realized that there are five NF-kappaB transcription factors with important roles in inflammation, innate immunity, cancer and apoptosis aborting. Consequently, NF-kappaB was shown to link inflammation and cancer, but recent reports have revealed it to play a much more complex role, where in some disease processes it promotes cancer and in others it impedes carcinogenesis. In this review, we will focus on the seemingly contradictory role of NF-kappaB in liver homeostasis, as well as in liver cancer.

Yasuda, H. (2008). "Solid tumor physiology and hypoxia-induced chemo/radio-resistance: novel strategy for cancer therapy: nitric oxide donor as a therapeutic enhancer." Nitric Oxide **19**(2): 205-16.

Hypoxia exists in solid tumor tissues due to abnormal vasculature, vascular insufficiency, treatment or malignancy related anemia, and low intratumor blood flow. Hypoxic status in solid tumor promotes accumulation of hypoxia-inducible factor-1 alpha which is promptly degraded by proteasomal ubiquitination under normoxic conditions. However, under hypoxic conditions, the ubiquitination system

for HIF-1 alpha is inhibited by inactivation of prolyl hydroxylase which is responsible for hydroxylation of proline in the oxygen-dependent degradation domain of HIF-1 alpha. HIF-1 alpha is an important transcriptional factor that codes for hundreds of genes involved in erythropoiesis, angiogenesis, induction of glycolytic enzymes in tumor tissues, modulation of cancer cell cycle, cancer proliferation, and cancer metastasis. Hypoxia and accumulation of HIF-1 alpha in solid tumor tissues have been reported to associate with resistance to chemotherapy, radiotherapy, and immunotherapy and poor prognosis. Production of vascular endothelial growth factor (VEGF) in cancer cells is regulated by the activated HIF-1 mediated system. An increase in VEGF levels subsequently induces HIF-1 alpha accumulation and promotes tumor metastasis by angiogenesis. Recently, angiogenesis targeting therapy using humanized VEGF antibody and VEGF receptor tyrosine kinase inhibitors have been used in solid cancer therapy. Nitric oxide (NO) is a unique chemical gaseous molecule that plays a role as a chemical messenger involved in vasodilator, neurotransmitter, and anti-platelet aggregation. In vivo, NO is produced and released from three different isoforms of NO synthase (NOS) and from exogenously administered NO donors. In cancer science, NO has been mainly discussed as an oncogenic molecule over the past decades. However, NO has recently been noted in cancer biology associated with cancer cell apoptosis, cancer cell cycle, cancer progression and metastasis, cancer angiogenesis, cancer chemoprevention, and modulator for chemo/radio/immuno-therapy. The presence and activities of all the three isoforms of NOS and were detected in cancer tissue components such as cancer cells, tumor-associated macrophages, and vascular endothelium. Overexpression of iNOS in cancer tissues has been reported to associate with poor prognosis in patients with cancers. On the other hand, NO donors such as nitroglycerin have been demonstrated to improve the effects of cancer therapy in solid cancers. Nitroglycerin has been used safely for a long time as a potent vasodilator for the treatment of ischemic heart diseases or heart failure. Therefore, we think highly of clinical use of nitroglycerin as a novel cancer therapy in combination with anticancer drugs for improvement of cancer therapeutic levels. In this review article, we demonstrate the unique physiological characteristics of malignant solid tumors, several factors in solid tumors resulting in resistance for cancer therapies, and the effects of NO from NOS or exogenous NO-donating drugs on malignant cells. Furthermore, we refer to promising therapeutic roles of NO and NO-donating drugs for novel treatments in solid tumors.

References

1. Asaka, M., A. R. Sepulveda, et al. (2001). "Gastric Cancer."
2. Brown, J. M. and A. J. Giaccia (1998). "The unique physiology of solid tumors: opportunities (and problems) for cancer therapy." Cancer Res **58**(7): 1408-16.
3. Brunelli, A. and M. Salati (2008). "Preoperative evaluation of lung cancer: predicting the impact of surgery on physiology and quality of life." Curr Opin Pulm Med **14**(4): 275-81.
4. Carpenter, J. S. (2005). "State of the science: hot flashes and cancer. Part 1: definition, scope, impact, physiology, and measurement." Oncol Nurs Forum **32**(5): 959-68.
5. Chang, L., C. F. Horng, et al. (2006). "Prognostic accuracy of Acute Physiology and Chronic Health Evaluation II scores in critically ill cancer patients." Am J Crit Care **15**(1): 47-53.
6. Dauchy, E. M., R. T. Dauchy, et al. (2006). "Human cancer xenograft perfusion in situ in rats: a new perfusion system that minimizes delivery time and maintains normal tissue physiology and responsiveness to growth-inhibitory agents." J Am Assoc Lab Anim Sci **45**(3): 38-44.
7. Dorward, A., S. Sweet, et al. (1997). "Mitochondrial contributions to cancer cell physiology: redox balance, cell cycle, and drug resistance." J Bioenerg Biomembr **29**(4): 385-92.
8. Dougall, W. C. (2007). "RANKL signaling in bone physiology and cancer." Curr Opin Support Palliat Care **1**(4): 317-22.
9. Engstrom, C. A. and C. E. Kasper (2007). "Physiology and endocrinology of hot flashes in prostate cancer." Am J Mens Health **1**(1): 8-17.
10. Fahrmann, M. (2008). "Targeting protein kinase C (PKC) in physiology and cancer of the gastric cell system." Curr Med Chem **15**(12): 1175-91.
11. Giese-Davis, J., A. Conrad, et al. (2008). "Exploring Emotion-Regulation and Autonomic Physiology in Metastatic Breast Cancer Patients: Repression, Suppression, and Restraint of Hostility." Pers Individ Dif **44**(1): 226-237.
12. Giordano, A., M. Calvani, et al. (2003). "Skeletal muscle metabolism in physiology and in cancer disease." J Cell Biochem **90**(1): 170-86.
13. Hunter, G. J., L. M. Hamberg, et al. (1998). "Dynamic T1-weighted magnetic resonance imaging and positron emission tomography in patients with lung cancer: correlating vascular physiology with glucose metabolism." Clin Cancer Res **4**(4): 949-55.
14. Kreidl, E., D. Ozturk, et al. (2009). "Activins and follistatins: Emerging roles in liver physiology and cancer." World J Hepatol **1**(1): 17-27.

15. Laking, G. R., C. West, et al. (2006). "Imaging vascular physiology to monitor cancer treatment." Crit Rev Oncol Hematol **58**(2): 95-113.
16. Lucia, A., C. Earnest, et al. (2003). "Cancer-related fatigue: can exercise physiology assist oncologists?" Lancet Oncol **4**(10): 616-25.
17. McDonald, P. C., A. B. Fielding, et al. (2008). "Integrin-linked kinase--essential roles in physiology and cancer biology." J Cell Sci **121**(Pt 19): 3121-32.
18. Mitsiades, C. S. and M. Koutsilieris (2001). "Molecular biology and cellular physiology of refractoriness to androgen ablation therapy in advanced prostate cancer." Expert Opin Investig Drugs **10**(6): 1099-115.
19. Nam, R. K., J. Trachtenberg, et al. (2005). "Serum insulin-like growth factor-I levels and prostatic intraepithelial neoplasia: a clue to the relationship between IGF-I physiology and prostate cancer risk." Cancer Epidemiol Biomarkers Prev **14**(5): 1270-3.
20. Nishibori, M., S. Mori, et al. (2005). "Physiology and pathophysiology of proteinase-activated receptors (PARs): PAR-2-mediated proliferation of colon cancer cell." J Pharmacol Sci **97**(1): 25-30.
21. Ntziachristos, V. and B. Chance (2001). "Probing physiology and molecular function using optical imaging: applications to breast cancer." Breast Cancer Res **3**(1): 41-6.
22. Pain, S. J., R. W. Barber, et al. (2005). "Short-term effects of axillary lymph node clearance surgery on lymphatic physiology of the arm in breast cancer." J Appl Physiol **99**(6): 2345-51.
23. Pampalakis, G. and G. Sotiropoulou (2007). "Tissue kallikrein proteolytic cascade pathways in normal physiology and cancer." Biochim Biophys Acta **1776**(1): 22-31.
24. Payne, R. (1987). "Anatomy, physiology, and neuropharmacology of cancer pain." Med Clin North Am **71**(2): 153-67.
25. Payne, R. (1989). "Cancer pain. Anatomy, physiology, and pharmacology." Cancer **63**(11 Suppl): 2266-74.
26. Pollak, M. (1998). "IGF-I physiology and breast cancer." Recent Results Cancer Res **152**: 63-70.
27. Pollak, M. (2000). "Insulin-like growth factor physiology and cancer risk." Eur J Cancer **36**(10): 1224-8.
28. Potter, J. D. (1993). "Colon cancer--do the nutritional epidemiology, the gut physiology and the molecular biology tell the same story?" J Nutr **123**(2 Suppl): 418-23.
29. Preston, T. J., A. Abadi, et al. (2001). "Mitochondrial contributions to cancer cell physiology: potential for drug development." Adv Drug Deliv Rev **49**(1-2): 45-61.
30. Sapi, E. (2004). "The role of CSF-1 in normal physiology of mammary gland and breast cancer: an update." Exp Biol Med (Maywood) **229**(1): 1-11.
31. Sebti, S. M. (2005). "Protein farnesylation: implications for normal physiology, malignant transformation, and cancer therapy." Cancer Cell **7**(4): 297-300.
32. Shafik, A. (1986). "A new concept of the anatomy of the anal sphincter mechanism and the physiology of defecation. Reversion to normal defecation after combined excision operation and end colostomy for rectal cancer." Am J Surg **151**(2): 278-84.
33. Stefano, G. B., R. M. Kream, et al. (2008). "Endogenous morphine/nitric oxide-coupled regulation of cellular physiology and gene expression: implications for cancer biology." Semin Cancer Biol **18**(3): 199-210.
34. Vainer, G. W., E. Pikarsky, et al. (2008). "Contradictory functions of NF-kappaB in liver physiology and cancer." Cancer Lett **267**(2): 182-8.
35. Yasuda, H. (2008). "Solid tumor physiology and hypoxia-induced chemo/radio-resistance: novel strategy for cancer therapy: nitric oxide donor as a therapeutic enhancer." Nitric Oxide **19**(2): 205-16.
36. PubMed (2011). http://www.ncbi.nlm.nih.gov/pubmed.
37. Cancer. Wikipedia. (2010) http://en.wikipedia.org/wiki/Cancer.

1/7/2011