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Immortality and Cancer Biology Research 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 article introduces recent research reports as references in the immortality and cancer biology studies.
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Key words: cancer; life; research; literature; cell

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.

The following introduces recent reports as references in the immortality and cancer biology studies.

Abolhassani, H., et al. (2021). "Hallmarks of Cancers: Primary Antibody Deficiency Versus Other Inborn Errors of Immunity." Front Immunol **12**: 720025.

Inborn Errors of Immunity (IEI) comprise more than 450 inherited diseases, from which selected patients manifest a frequent and early incidence of malignancies, mainly lymphoma and leukemia. Primary antibody deficiency (PAD) is the most common form of IEI with the highest proportion of malignant cases. In this review, we aimed to compare the oncologic hallmarks and the molecular defects underlying PAD with other IEI entities to dissect the impact of avoiding immune destruction, genome instability, and mutation, enabling replicative immortality, tumor-promoting inflammation, resisting cell death, sustaining proliferative signaling, evading growth suppressors, deregulating cellular energetics, inducing angiogenesis, and activating invasion and metastasis in these groups of patients. Moreover, some of the most promising approaches that could be clinically tested in both PAD and IEI patients were discussed.

Ahmad, M. F. (2020). "Ganoderma lucidum: A rational pharmacological approach to surmount cancer." J Ethnopharmacol **260**: 113047.

ETHNOPHARMACOLOGICAL RELEVANCE: Ganoderma lucidum (G. lucidum) has been broadly used for health endorsement as well as longevity for over 2000 years in Asian countries. It is an example of an ancient remedy and known as immortality mushroom. It has been employed as a health promoting agent owing to its broad pharmacological and therapeutical approaches. It has been confirmed that G. lucidum exhibits significant potency to prevent and treat different types of cancers such as breast, prostate, colon, lung and cervical. AIM OF THE STUDY: To explore anticancer effects of various pharmacologically active compounds obtained from G. lucidum and their possible mechanism of action. MATERIALS AND METHODS: A literature search was conducted using PubMed, Goggle Scholar, Saudi Digital Library and Cochrane Library until October 11, 2019. Search was made by using keywords such as anticancer evidence, mechanism of action, pharmacology, antioxidant, toxicity, chemotherapy, triterpenoids and polysaccharides of G. lucidum. RESULTS: Various chemical compounds from G. lucidum exhibit anticancer properties mainly through diverse mechanism such as cytotoxic properties, host immunomodulators, metabolizing enzymes induction, prohibit the expression of urokinase plasminogen activator (uPA) and urokinase plasminogen activator

receptor (uPAR) in cancer cells. Among the various compounds of G. lucidum triterpenoids and polysaccharides are under the major consideration of studies due to their several evidence of preclinical and clinical studies against cancer. CONCLUSION: Natural alternatives associated with mild side effects are the basic human need of present therapy to eradicate the new emerging disorders. This review is an attempt to compile pharmacologically active compounds of G. lucidum those exhibit anti cancer effects either alone or along with chemotherapy and anticancer mechanisms against various cancer cells, clinical trials, chemotherapy induced toxicity challenges with limitations. It acts as a possible substitute to combat cancer growth with advance and conventional combination therapies as natural alternatives.

Akter, J. and T. Kamijo (2021). "How Do Telomere Abnormalities Regulate the Biology of Neuroblastoma?" Biomolecules **11**(8).

Telomere maintenance plays important roles in genome stability and cell proliferation. Tumor cells acquire replicative immortality by activating a telomere-maintenance mechanism (TMM), either telomerase, a reverse transcriptase, or the alternative lengthening of telomeres (ALT) mechanism. Recent advances in the genetic and molecular characterization of TMM revealed that telomerase activation and ALT define distinct neuroblastoma (NB) subgroups with adverse outcomes, and represent promising therapeutic targets in high-risk neuroblastoma (HRNB), an aggressive childhood solid tumor that accounts for 15% of all pediatric-cancer deaths. Patients with HRNB frequently present with widely metastatic disease, with tumors harboring recurrent genetic aberrations (MYCN amplification, TERT rearrangements, and ATRX mutations), which are mutually exclusive and capable of promoting TMM. This review provides recent insights into our understanding of TMM in NB tumors, and highlights emerging therapeutic strategies as potential treatments for telomerase- and ALT-positive tumors.

Amen, A. M., et al. (2021). "Cancer-specific loss of TERT activation sensitizes glioblastoma to DNA damage." Proc Natl Acad Sci U S A **118**(13).

Most glioblastomas (GBMs) achieve cellular immortality by acquiring a mutation in the telomerase reverse transcriptase (TERT) promoter. TERT promoter mutations create a binding site for a GA binding protein (GABP) transcription factor complex, whose assembly at the promoter is associated with TERT reactivation and telomere maintenance. Here, we demonstrate increased binding of a specific GABPB1L-isoform-containing complex to the mutant TERT promoter. Furthermore, we find that TERT promoter mutant GBM cells, unlike wild-type cells, exhibit a critical near-term dependence on GABPB1L for proliferation, notably also posttumor establishment in vivo. Up-regulation of the protein paralogue GABPB2, which is normally expressed at very low levels, can rescue this dependence. More importantly, when combined with frontline temozolomide (TMZ) chemotherapy, inducible GABPB1L knockdown and the associated TERT reduction led to an impaired DNA damage response that resulted in profoundly reduced growth of intracranial GBM tumors. Together, these findings provide insights into the mechanism of cancer-specific TERT regulation, uncover rapid effects of GABPB1L-mediated TERT suppression in GBM maintenance, and establish GABPB1L inhibition in combination with chemotherapy as a therapeutic strategy for TERT promoter mutant GBM.

Berei, J., et al. (2020). "Potential Telomere-Related Pharmacological Targets." Curr Top Med Chem **20**(6): 458-484.

Telomeres function as protective caps at the terminal portion of chromosomes, containing non-coding nucleotide sequence repeats. As part of their protective function, telomeres preserve genomic integrity and minimize chromosomal exposure, thus limiting DNA damage responses. With continued mitotic divisions in normal cells, telomeres progressively shorten until they reach a threshold at a point where they activate senescence or cell death pathways. However, the presence of the enzyme telomerase can provide functional immortality to the cells that have reached or progressed past senescence. In senescent cells that amass several oncogenic mutations, cancer formation can occur due to genomic instability and the induction of telomerase activity. Telomerase has been found to be expressed in over 85% of human tumors and is labeled as a near-universal marker for cancer. Due to this feature being present in a majority of tumors but absent in most somatic cells, telomerase and telomeres have become promising targets for the development of new and effective anticancer therapeutics. In this review, we evaluate novel anticancer targets in development which aim to alter telomerase or telomere function. Additionally, we analyze the progress that has been made, including preclinical studies and clinical trials, with therapeutics directed at telomere-related targets. Furthermore, we review the potential telomere-related therapeutics that are used in combination therapy with more traditional cancer treatments. Throughout the review, topics related to medicinal chemistry are discussed, including drug bioavailability and delivery, chemical structure-activity relationships of select therapies, and the development of a unique telomere

assay to analyze compounds affecting telomere elongation.

Berrino, E., et al. (2020). "Azidothymidine "Clicked" into 1,2,3-Triazoles: First Report on Carbonic Anhydrase-Telomerase Dual-Hybrid Inhibitors." J Med Chem **63**(13): 7392-7409.

Cancer cells rely on the enzyme telomerase (EC 2.7.7.49) to promote cellular immortality. Telomerase inhibitors (i.e., azidothymidine) can represent promising antitumor agents, although showing high toxicity when administered alone. Better outcomes were observed within a multipharmacological approach instead. In this context, we exploited the validated antitumor targets carbonic anhydrases (CAs; EC 4.2.1.1) IX and XII to attain the first proof of concept on CA-telomerase dual-hybrid inhibitors. Compounds 1b, 7b, 8b, and 11b showed good in vitro inhibition potency against the CAs IX and XII, with KI values in the low nanomolar range, and strong antitelomerase activity in PC-3 and HT-29 cells (IC50 values ranging from 5.2 to 9.1 muM). High-resolution X-ray crystallography on selected derivatives in the adduct with hCA II as a model study allowed to determine their binding modes and thus to set the structural determinants necessary for further development of compounds selectively targeting the tumoral cells.

Bilsland, A. E., et al. (2019). "A Novel Pyrazolopyrimidine Ligand of Human PGK1 and Stress Sensor DJ1 Modulates the Shelterin Complex and Telomere Length Regulation." Neoplasia **21**(9): 893-907.

Telomere signaling and metabolic dysfunction are hallmarks of cell aging. New agents targeting these processes might provide therapeutic opportunities, including chemoprevention strategies against cancer predisposition. We report identification and characterization of a pyrazolopyrimidine compound series identified from screens focused on cell immortality and whose targets are glycolytic kinase PGK1 and oxidative stress sensor DJ1. We performed structure-activity studies on the series to develop a photoaffinity probe to deconvolute the cellular targets. In vitro binding and structural analyses confirmed these targets, suggesting that PGK1/DJ1 interact, which we confirmed by immunoprecipitation. Glucose homeostasis and oxidative stress are linked to telomere signaling and exemplar compound CRT0063465 blocked hypoglycemic telomere shortening. Intriguingly, PGK1 and DJ1 bind to TRF2 and telomeric DNA. Compound treatment modulates these interactions and also affects Shelterin complex composition, while conferring cellular protection from cytotoxicity due to bleomycin and desferroxamine. These results demonstrate therapeutic potential of the compound series.

Blagosklonny, M. V. (2019). "Rapamycin for longevity: opinion article." Aging (Albany NY) **11**(19): 8048-8067.

From the dawn of civilization, humanity has dreamed of immortality. So why didn't the discovery of the anti-aging properties of mTOR inhibitors change the world forever? I will discuss several reasons, including fear of the actual and fictional side effects of rapamycin, everolimus and other clinically-approved drugs, arguing that no real side effects preclude their use as anti-aging drugs today. Furthermore, the alternative to the reversible (and avoidable) side effects of rapamycin/everolimus are the irreversible (and inevitable) effects of aging: cancer, stroke, infarction, blindness and premature death. I will also discuss why it is more dangerous not to use anti-aging drugs than to use them and how rapamycin-based drug combinations have already been implemented for potential life extension in humans. If you read this article from the very beginning to its end, you may realize that the time is now.

Causin, R. L., et al. (2021). "A Systematic Review of MicroRNAs Involved in Cervical Cancer Progression." Cells **10**(3).

To obtain a better understanding on the role of microRNAs in the progression of cervical cancer, a systematic review was performed to analyze cervical cancer microRNA studies. We provide an overview of the studies investigating microRNA expression in relation to cervical cancer (CC) progression, highlighting their common outcomes and target gene interactions according to the regulatory pathways. To achieve this, we systematically searched through PubMed MEDLINE, EMBASE, and Google Scholar for all articles between April 2010 and April 2020, in accordance with the PICO acronym (participants, interventions, comparisons, outcomes). From 27 published reports, totaling 1721 cases and 1361 noncancerous control tissue samples, 26 differentially expressed microRNAs (DEmiRNAs) were identified in different International Federation of Gynecology and Obstetrics (FIGO) stages of cervical cancer development. It was identified that some of the dysregulated microRNAs were associated with specific stages of cervical cancer development. The results indicated that DEmiRNAs in different stages of cervical cancer were functionally involved in several key hallmarks of cancer, such as evading growth suppressors, enabling replicative immortality, activation of invasion and metastasis, resisting cell death, and sustained proliferative signaling. These dysregulated microRNAs could play an important role

in cervical cancer's development. Some of the stage-specific microRNAs can also be used as biomarkers for cancer classification and monitoring the progression of cervical cancer.

Chang, H. L. and J. C. Lin (2019). "SRSF1 and RBM4 differentially modulate the oncogenic effect of HIF-1alpha in lung cancer cells through alternative splicing mechanism." Biochim Biophys Acta Mol Cell Res **1866**(12): 118550.

Alternative splicing (AS) constitutes a pivotal mechanism for expanding the transcriptome and proteome diversity in higher eukaryotes. In contrast, misregulated AS events are relevant to carcinogenic signatures, including migration, angiogenesis, immortality, and drug resistance of cancer cells. Using a transcriptome analysis, discriminative splicing profiles of hypoxia-inducible factor (HIF)-1alpha transcripts were identified in tumorous tissues compared to adjacent normal tissues of lung cancer (LC) patients. In cancerous tissues or LC-derived cells, relatively high levels of HIF-1alpha(-ex14) transcripts encoding the HIF-1alphaS isoform were noted compared to adjacent normal tissues and non-cancerous cells. The HIF-1alphaS isoform exhibited a more-prominent effect than that of the HIF-1alphaL isoform translated from HIF-1alpha(+ex14) transcripts on enhancing promoter activities of the vascular endothelial growth factor receptor 2 (VEGFR2), serine/arginine splicing factor 1 (SRSF1), and c13orf25 genes. An increase in the SRSF1 protein facilitated the generation of HIF-1alpha(-ex14) transcripts, whereas overexpression of RNA-binding motif protein 4 (RBM4) enhanced the expression of HIF-1alpha(+ex14) transcripts in the A549 cells. Results of splicing reporter assays demonstrated the differential impacts of RBM4 and SRSF1 on the utilization of HIF-1alpha exon 14 in a CU element-dependent manner. In addition to transcriptional regulation, overexpression of the HIF-1alphaS and HIF-1alphaL isoforms differentially enhanced the metastatic signatures of A549 cells. Taken together, SRSF1 and RBM4 constitute an antagonistic mechanism on regulating the splicing profiles of HIF-1alpha gene, which is relevant to the oncogenic signatures of LC cells.

Claude, E. and A. Decottignies (2020). "Telomere maintenance mechanisms in cancer: telomerase, ALT or lack thereof." Curr Opin Genet Dev **60**: 1-8.

Cancer cells acquire replicative immortality by activating a telomere maintenance mechanism (TMM), either the telomerase or the Alternative Lengthening of Telomeres (ALT) mechanism. ALT is frequently activated in tumors derived from mesenchymal cells, which are more frequent in childhood cancers. Recent studies showed that, occasionally, cancer cells can arise without any TMM activation. Here, we discuss the challenge in assessing which TMM is activated in tumors. We also evaluate the prevalence of ALT mechanism in pediatric cancers and review the associated survival prognosis in different tumor types. Finally, we discuss about possible anti-TMM therapies for new emerging cancer treatments.

Eckburg, A., et al. (2020). "Oligonucleotides and microRNAs Targeting Telomerase Subunits in Cancer Therapy." Cancers (Basel) **12**(9).

Telomerase provides cancer cells with replicative immortality, and its overexpression serves as a near-universal marker of cancer. Anti-cancer therapeutics targeting telomerase have garnered interest as possible alternatives to chemotherapy and radiotherapy. Oligonucleotide-based therapies that inhibit telomerase through direct or indirect modulation of its subunits, human telomerase reverse transcriptase (hTERT) and human telomerase RNA gene (hTERC), are a unique and diverse subclass of telomerase inhibitors which hold clinical promise. MicroRNAs that play a role in the upregulation or downregulation of hTERT and respective progression or attenuation of cancer development have been effectively targeted to reduce telomerase activity in various cancer types. Tumor suppressor miRNAs, such as miRNA-512-5p, miRNA-138, and miRNA-128, and oncogenic miRNAs, such as miRNA-19b, miRNA-346, and miRNA-21, have displayed preclinical promise as potential hTERT-based therapeutic targets. Antisense oligonucleotides like GRN163L and T-oligos have also been shown to uniquely target the telomerase subunits and have become popular in the design of novel cancer therapies. Finally, studies suggest that G-quadruplex stabilizers, such as Telomestatin, preserve telomeric oligonucleotide architecture, thus inhibiting hTERC binding to the telomere. This review aims to provide an adept understanding of the conceptual foundation and current state of therapeutics utilizing oligonucleotides to target the telomerase subunits, including the advantages and drawbacks of each of these approaches.

Edwardson, D. W., et al. (2019). "Chemotherapy and Inflammatory Cytokine Signalling in Cancer Cells and the Tumour Microenvironment." Adv Exp Med Biol **1152**: 173-215.

Cancer is the result of a cell's acquisition of a variety of biological capabilities or 'hallmarks' as outlined by Hanahan and Weinberg. These include sustained proliferative signalling, the ability to evade growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and the ability to invade other tissue and metastasize. More recently, the ability to escape immune destruction has

been recognized as another important hallmark of tumours. It is suggested that genome instability and inflammation accelerates the acquisition of a variety of the above hallmarks. Inflammation, is a product of the body's response to tissue damage or pathogen invasion. It is required for tissue repair and host defense, but prolonged inflammation can often be the cause for disease. In a cancer patient, it is often unclear whether inflammation plays a protective or deleterious role in disease progression. Chemotherapy drugs can suppress tumour growth but also induce pathways in tumour cells that have been shown experimentally to support tumour progression or, in other cases, encourage an anti-tumour immune response. Thus, with the goal of better understanding the context under which each of these possible outcomes occurs, recent progress exploring chemotherapy-induced inflammatory cytokine production and the effects of cytokines on drug efficacy in the tumour microenvironment will be reviewed. The implications of chemotherapy on host and tumour cytokine pathways and their effect on the treatment of cancer patients will also be discussed.

Fresques, T., et al. (2019). "Breast Tissue Biology Expands the Possibilities for Prevention of Age-Related Breast Cancers." Front Cell Dev Biol **7**: 174.

Preventing breast cancer before it is able to form is an ideal way to stop breast cancer. However, there are limited existing options for prevention of breast cancer. Changes in the breast tissue resulting from the aging process contribute to breast cancer susceptibility and progression and may therefore provide promising targets for prevention. Here, we describe new potential targets, immortalization and inflammaging, that may be useful for prevention of age-related breast cancers. We also summarize existing studies of warfarin and metformin, current drugs used for non-cancerous diseases, that also may be repurposed for breast cancer prevention.

Frost, F. G., et al. (2020). "Pan-cancer RNA-seq data stratifies tumours by some hallmarks of cancer." J Cell Mol Med **24**(1): 418-430.

Numerous genetic and epigenetic alterations cause functional changes in cell biology underlying cancer. These hallmark functional changes constitute potentially tissue-independent anticancer therapeutic targets. We hypothesized that RNA-Seq identifies gene expression changes that underly those hallmarks, and thereby defines relevant therapeutic targets. To test this hypothesis, we analysed the publicly available TCGA-TARGET-GTEx gene expression data set from the University of California Santa CruzToil recompute project using WGCNA to delineate co-correlated 'modules' from tumour gene expression profiles and functional enrichment of these modules to hierarchically cluster tumours. This stratified tumours according to T cell activation, NK-cell activation, complement cascade, ATM, Rb, angiogenic, MAPK, ECM receptor and histone modification signalling. These correspond to the cancer hallmarks of avoiding immune destruction, tumour-promoting inflammation, evading growth suppressors, inducing angiogenesis, sustained proliferative signalling, activating invasion and metastasis, and genome instability and mutation. This approach did not detect pathways corresponding to the cancer enabling replicative immortality, resisting cell death or deregulating cellular energetics hallmarks. We conclude that RNA-Seq stratifies tumours along some, but not all, hallmarks of cancer and, therefore, could be used in conjunction with other analyses collectively to inform precision therapy.

Ghareghomi, S., et al. (2021). "Fundamental insights into the interaction between telomerase/TERT and intracellular signaling pathways." Biochimie **181**: 12-24.

Telomerase activity is critical for cancer cells to provide unrestricted proliferation and cellular immortality through maintaining telomeres. Telomerase enzymatic activity is regulatable at the level of DNA, mRNA, post translational modifications, cellular transport and enzyme assembly. More recent studies confirm the interaction of the telomerase with various intracellular signaling pathways including PI3K/AKT/mTOR, NF-kappaB and Wnt/beta-catenin which mainly participating in inflammation, epithelial to mesenchymal transition (EMT) and tumor cell invasion and metastasis. Furthermore, hTERT protein has been detected in non-nuclear sites such as the mitochondria and cytoplasm in cells. Mitochondrial TERT indicates various non-telomere-related functions such as decreasing reactive oxygen species (ROS) generation, boosting the respiration rate, protecting mtDNA by direct binding, interacting with mitochondrial tRNAs and increasing mitochondrial membrane potential which can lead to higher chemoresistance rate in cancer cells during therapies. Understanding the molecular mechanisms of the TERT function and depended interactions in tumor cells can suggest novel therapeutic approaches. Hence, in this review we will explain the telomerase activity regulation in translational and post translational levels besides the established correlations with various cell signaling pathways with possible pathways for therapeutic targeting.

Girotti, M. R., et al. (2020). "Sweetening the hallmarks of cancer: Galectins as multifunctional mediators of tumor progression." J Exp Med **217**(2).

Hanahan and Weinberg have proposed 10 organizing principles that enable growth and metastatic

dissemination of cancer cells. These distinctive and complementary capabilities, defined as the "hallmarks of cancer," include the ability of tumor cells and their microenvironment to sustain proliferative signaling, evade growth suppressors, resist cell death, promote replicative immortality, induce angiogenesis, support invasion and metastasis, reprogram energy metabolism, induce genomic instability and inflammation, and trigger evasion of immune responses. These common features are hierarchically regulated through different mechanisms, including those involving glycosylation-dependent programs that influence the biological and clinical impact of each hallmark. Galectins, an evolutionarily conserved family of glycan-binding proteins, have broad influence in tumor progression by rewiring intracellular and extracellular circuits either in cancer or stromal cells, including immune cells, endothelial cells, and fibroblasts. In this review, we dissect the role of galectins in shaping cellular circuitries governing each hallmark of tumors, illustrating relevant examples and highlighting novel opportunities for treating human cancer.

Guterres, A. N. and J. Villanueva (2020). "Targeting telomerase for cancer therapy." Oncogene **39**(36): 5811-5824.

Telomere maintenance via telomerase reactivation is a nearly universal hallmark of cancer cells which enables replicative immortality. In contrast, telomerase activity is silenced in most adult somatic cells. Thus, telomerase represents an attractive target for highly selective cancer therapeutics. However, development of telomerase inhibitors has been challenging and thus far there are no clinically approved strategies exploiting this cancer target. The discovery of prevalent mutations in the TERT promoter region in many cancers and recent advances in telomerase biology has led to a renewed interest in targeting this enzyme. Here we discuss recent efforts targeting telomerase, including immunotherapies and direct telomerase inhibitors, as well as emerging approaches such as targeting TERT gene expression driven by TERT promoter mutations. We also address some of the challenges to telomerase-directed therapies including potential therapeutic resistance and considerations for future therapeutic applications and translation into the clinical setting. Although much work remains to be done, effective strategies targeting telomerase will have a transformative impact for cancer therapy and the prospect of clinically effective drugs is boosted by recent advances in structural models of human telomerase.

Houston, T. J. and R. Ghosh (2020). "Untangling the association between environmental endocrine disruptive chemicals and the etiology of male genitourinary cancers." Biochem Pharmacol **172**: 113743.

Endocrine disrupting chemicals disrupt normal physiological function of endogenous hormones, their receptors, and signaling pathways of the endocrine system. Most endocrine disrupting chemicals exhibit estrogen/androgen agonistic and antagonistic activities that impinge upon hormone receptors and related pathways. Humans are exposed to endocrine disrupting chemicals through food, water and air, affecting the synthesis, release, transport, metabolism, binding, function and elimination of naturally occurring hormones. The urogenital organs function as sources of steroid hormones, are targeted end organs, and participate within systemic feedback loops within the endocrine system. The effects of endocrine disruptors can ultimately alter cellular homeostasis leading to a broad range of health effects, including malignancy. Human cancer is characterized by uncontrolled cell proliferation, mechanisms opposing cell-death, development of immortality, induction of angiogenesis, and promotion of invasion/metastasis. While hormonal malignancies of the male genitourinary organs are the second most common types of cancer, the molecular effects of endocrine disrupting chemicals in hormone-driven cancers has yet to be fully explored. In this commentary, we examine the molecular evidence for the involvement of endocrine disrupting chemicals in the genesis and progression of hormone-driven cancers in the prostate, testes, and bladder. We also report on challenges that have to be overcome to drive our understanding of these chemicals and explore the potential avenues of discovery that could ultimately allow the development of tools to prevent cancer in populations where exposure is inevitable.

Kent, T., et al. (2019). "Alternative Lengthening of Telomeres in Pediatric Cancer: Mechanisms to Therapies." Front Oncol **9**: 1518.

Achieving replicative immortality is a crucial step in tumorigenesis and requires both bypassing cell cycle checkpoints and the extension of telomeres, sequences that protect the distal ends of chromosomes during replication. In the majority of cancers this is achieved through the enzyme telomerase, however a subset of cancers instead utilize a telomerase-independent mechanism of telomere elongation-the Alternative Lengthening of Telomeres (ALT) pathway. Recent work has aimed to decipher the exact mechanism that underlies this pathway. To this end, this pathway has now been shown to extend telomeres through exploitation of DNA repair machinery in a unique process that may present a number of druggable targets. The identification of such targets, and the subsequent development or repurposing of therapies to

these targets may be crucial to improving the prognosis for many ALT-positive cancers, wherein mean survival is lower than non-ALT counterparts and the cancers themselves are particularly unresponsive to standard of care therapies. In this review we summarize the recent identification of many aspects of the ALT pathway, and the therapies that may be employed to exploit these new targets.

Kontomanolis, E. N., et al. (2020). "Role of Oncogenes and Tumor-suppressor Genes in Carcinogenesis: A Review." Anticancer Res **40**(11): 6009-6015.

Cancer is a medical condition which has a molecular basis. Proto-oncogenes are the first regulatory factors of this biological process. They act in transmitting signals, resulting as growth factors. Modifications of these genes, called oncogenes, lead to the appearance of cancer cells. The activation process leading to proto-oncogenes are chromosomal translocation, point mutation, and gene amplification. Concerning the clonal theory of oncogenesis, it is believed that a tumor starts from a cell. Furthermore, there is close association between tumor development and inhibition of apoptosis or programmed cell death, providing cell immortality. Angiogenesis and angiogenic factors found to be expressed in tumors and may play a key role in tumor formation and development. Tumor-suppressor genes block the growth of cancer and contribute to the normal development of cells. This article highlights the evidence that neoplasms develop as the after-effect of the increase of acquired and physical genetic variations in proto-oncogenes and tumor-suppressor genes; these form a target group in the cells of neoplasms. Tumor formation and development are characterized by individual processes, working synergistically, and an understanding of each individual process may provide a better basis for further anticancer research.

Korshavn, K. J., et al. (2020). "A redox switch regulates the structure and function of anti-apoptotic BFL-1." Nat Struct Mol Biol **27**(9): 781-789.

Apoptosis is regulated by BCL-2 family proteins. Anti-apoptotic members suppress cell death by deploying a surface groove to capture the critical BH3 alpha-helix of pro-apoptotic members. Cancer cells hijack this mechanism by overexpressing anti-apoptotic BCL-2 family proteins to enforce cellular immortality. We previously identified and harnessed a unique cysteine (C55) in the groove of anti-apoptotic BFL-1 to selectively neutralize its oncogenic activity using a covalent stapled-peptide inhibitor. Here, we find that disulfide bonding between a native cysteine pair at the groove (C55) and C-terminal alpha9 helix (C175) of BFL-1 operates as a redox switch to control the accessibility of the anti-apoptotic pocket. Reducing the C55-C175 disulfide triggers alpha9 release, which promotes mitochondrial translocation, groove exposure for BH3 interaction and inhibition of mitochondrial permeabilization by pro-apoptotic BAX. C55-C175 disulfide formation in an oxidative cellular environment abrogates the ability of BFL-1 to bind BH3 domains. Thus, we identify a mechanism of conformational control of BFL-1 by an intramolecular redox switch.

Lee, D. D., et al. (2020). "DNA methylation of the TERT promoter and its impact on human cancer." Curr Opin Genet Dev **60**: 17-24.

Telomere maintenance is a hallmark of human cancer that enables replicative immortality. Most cancer cells acquire telomere maintenance by telomerase activation through expression of telomerase reverse transcriptase (TERT), a rate-limiting component of the telomerase holoenzyme. Although multiple cancer-specific genetic alterations such as gain of TERT copy number and recurrent TERT promoter mutations (TPM) have been identified, the majority of cancers still express TERT via unknown mechanisms. In the last decade, DNA methylation of the TERT promoter emerged as a putative epigenetic regulatory mechanism of telomerase activation in cancer. Here, we comparatively discuss studies that investigated the DNA methylation landscape of the TERT promoter. We further review the biological and clinical impacts of TERT promoter hypermethylation in cancer and provide insight into future applications of this phenomenon.

Lee, W. L. and P. H. Wang (2020). "Aberrant sialylation in ovarian cancers." J Chin Med Assoc **83**(4): 337-344.

Sialylation (the covalent addition of sialic acid to the terminal end of glycoproteins or glycans), tightly regulated cell- and microenvironment-specific process and orchestrated by sialyltransferases and sialidases (neuraminidases) family, is one of the posttranslational modifications, which plays an important biological role in the maintenance of normal physiology and involves many pathological dysfunctions. Glycans have roles in all the cancer hallmarks, referring to capabilities acquired during all steps of cancer development to initiate malignant transformation (a driver of a malignant genotype), enable cancer cells to survive, proliferate, and metastasize (a consequence of a malignant phenotype), which includes sustaining proliferative signaling, evading growth suppressor, resisting cell apoptosis, enabling replicative immortality, inducing angiogenesis, reprogramming of energy metabolism, evading tumor destruction, accumulating inflammatory microenvironment, and activating invasion and accelerating metastases.

Regarding the important role of altered sialylation of cancers, further knowledge about the initiation and the consequences of altered sialylation pattern in tumor cells is needed, because all may offer a better chance for developing novel therapeutic strategy. In this review, we would like to update alteration of sialylation in ovarian cancers.

Lippert, T. P., et al. (2021). "Oncogenic herpesvirus KSHV triggers hallmarks of alternative lengthening of telomeres." Nat Commun **12**(1): 512.

To achieve replicative immortality, cancer cells must activate telomere maintenance mechanisms to prevent telomere shortening. ~85% of cancers circumvent telomeric attrition by re-expressing telomerase, while the remaining ~15% of cancers induce alternative lengthening of telomeres (ALT), which relies on break-induced replication (BIR) and telomere recombination. Although ALT tumours were first reported over 20 years ago, the mechanism of ALT induction remains unclear and no study to date has described a cell-based model that permits the induction of ALT. Here, we demonstrate that infection with Kaposi's sarcoma herpesvirus (KSHV) induces sustained acquisition of ALT-like features in previously non-ALT cell lines. KSHV-infected cells acquire hallmarks of ALT activity that are also observed in KSHV-associated tumour biopsies. Down-regulating BIR impairs KSHV latency, suggesting that KSHV co-opts ALT for viral functionality. This study uncovers KSHV infection as a means to study telomere maintenance by ALT and reveals features of ALT in KSHV-associated tumours.

LS, D. E. H., et al. (2019). "Characterization of Telomerase (hTERT) in Solid and Hematopoietic Cancer Cell Lines Reveals Different Expression Patterns." Anticancer Res **39**(9): 4743-4748.

BACKGROUND/AIM: Overexpression of human telomerase reverse transcriptase (hTERT) allows disordered proliferation and immortality of malignant cells, which has been of interest for the development of targeted therapies. The present study aimed to characterize hTERT gene expression in a series of cancer cell lines. MATERIALS AND METHODS: Leukemia cell lines K-562, its vincristine-resistant derivative K-562-Lucena1 and daunorubicin-resistant derivative FEPS; gastric adenocarcinoma lines AGP01, ACP02 and ACP03; melanoma SK-Mel-103 cells; and MN01 and MRC5, two non-neoplastic cell lines were analyzed by real-time polymerase chain reaction in order to evaluate hTERT gene expression. RESULTS: In leukemia cells, hTERT gene expression was significantly increased only in K-562 ($p<0.05$) and K-562-Lucena1 ($p<0.001$) when compared to the calibrator MRC5. For solid tumor types, only ACP03 presented a significant hTERT gene expression when compared to ACP02 ($p<0.05$). hTERT gene expression in K-562 and K-562-L ucena was significantly increased ($p<0.05$ to $p<0.001$) compared to all other cell lines except ACP03. CONCLUSION: In leukemia cell lines, hTERT gene overexpression was shown to be a potential target for pharmacological assays for drugs aiming to inhibit telomerase activity and control cell proliferation in oncohematological diseases.

Mangosh, T. L., et al. (2021). "SLX4IP Promotes Telomere Maintenance in Androgen Receptor-Independent Castration-Resistant Prostate Cancer through ALT-like Telomeric PML Localization." Mol Cancer Res **19**(2): 301-316.

In advanced prostate cancer, resistance to androgen deprivation therapy is achieved through numerous mechanisms, including loss of the androgen receptor (AR) allowing for AR-independent growth. Therapeutic options are limited for AR-independent castration-resistant prostate cancer (CRPC), and defining mechanisms critical for survival is of utmost importance for targeting this lethal disease. Our studies focus on identifying telomere maintenance mechanism (TMM) hallmarks adopted by CRPC to promote survival. TMMs are responsible for telomere elongation to instill replicative immortality and prevent senescence, with the two TMM pathways available being telomerase and alternative lengthening of telomeres (ALT). Here, we show that AR-independent CRPC demonstrates an atypical ALT-like phenotype with variable telomerase expression and activity, whereas AR-dependent models lack discernible ALT hallmarks. In addition, AR-independent CRPC cells exhibited elevated levels of SLX4IP, a protein implicated in promoting ALT. SLX4IP overexpression in AR-dependent C4-2B cells promoted an ALT-like phenotype and telomere maintenance. SLX4IP knockdown in AR-independent DU145 and PC-3 cells led to ALT-like hallmark reduction, telomere shortening, and induction of senescence. In PC-3 xenografts, this effect translated to reduced tumor volume. Using an in vitro model of AR-independent progression, loss of AR in AR-dependent C4-2B cells promoted an atypical ALT-like phenotype in an SLX4IP-dependent manner. Insufficient SLX4IP expression diminished ALT-like hallmarks and resulted in accelerated telomere loss and senescence. IMPLICATIONS: This study demonstrates a unique reliance of AR-independent CRPC on SLX4IP-mediated ALT-like hallmarks and loss of these hallmarks induces telomere shortening and senescence, thereby impairing replicative immortality.

Mason-Osann, E., et al. (2020). "RAD54 promotes alternative lengthening of telomeres by mediating branch migration." EMBO Rep **21**(6): e49495.

Cancer cells can activate the alternative lengthening of telomeres (ALT) pathway to promote replicative immortality. The ALT pathway promotes telomere elongation through a homologous recombination pathway known as break-induced replication (BIR), which is often engaged to repair single-ended double-stranded breaks (DSBs). Single-ended DSBs are resected to promote strand invasion and facilitate the formation of a local displacement loop (D-loop), which can trigger DNA synthesis, and ultimately promote telomere elongation. However, the exact proteins involved in the maturation, migration, and resolution of D-loops at ALT telomeres are unclear. In vitro, the DNA translocase RAD54 both binds D-loops and promotes branch migration suggesting that RAD54 may function to promote ALT activity. Here, we demonstrate that RAD54 is enriched at ALT telomeres and promotes telomeric DNA synthesis through its ATPase-dependent branch migration activity. Loss of RAD54 leads to the formation of unresolved recombination intermediates at telomeres that form ultra-fine anaphase bridges in mitosis. These data demonstrate an important role for RAD54 in promoting ALT-mediated telomere synthesis.

Moloudizargari, M., et al. (2022). "Targeting Hippo signaling pathway by phytochemicals in cancer therapy." Semin Cancer Biol **80**: 183-194.

The current era of cancer research has been continuously advancing upon identifying novel aspects of tumorigenesis and the principal mechanisms behind the unleashed proliferation, invasion, drug resistance and immortality of cancer cells in hopes of exploiting these findings to achieve a more effective treatment for cancer. In pursuit of this goal, the identification of the first components of an extremely important regulatory pathway in Drosophila melanogaster that largely determines cell fate during the developmental stages, ended up in the discovery of the highly sophisticated Hippo signaling cascade. Soon after, it was revealed that deregulation of the components of this pathway either via mutations or through epigenetic alterations can be observed in a vast variety of tumors and these alterations greatly contribute to the neoplastic transformation of cells, their survival, growth and resistance to therapy. As more hidden aspects of this pathway such as its widespread entanglement with other major cellular signaling pathways are continuously being uncovered, many researchers have sought over the past decade to find ways of therapeutic interventions targeting the major components of the Hippo cascade. To date, various approaches such as the use of exogenous targeting miRNAs and different molecular inhibitors have been recruited herein, among which naturally occurring compounds have shown a great promise. On such a basis, in the present work we review the current understanding of Hippo pathway and the most recent evidence on targeting its components using natural plant-derived phytochemicals.

Mungan, I., et al. (2020). "Correction to: Does the preoperative platelet-tolymphocyte ratio and neutrophil-tolymphocyte ratio predict morbidity after gastrectomy for gastric cancer?" Mil Med Res **7**(1): 12.

In the original publication of this article [1] there are two garbled codes in the second sentence, the fourth paragraph of the Background section. The correct sentence should be: Tumor growth leads to the increased production of inflammatory cytokines and growth factors (mainly IL-1, IL-3, IL-6, IL-11, IL-23, and TNF-), and this perpetual process ensures immortality. These promoting factors are also important for angiogenesis and hematopoiesis, which explains the increase in blood cell types in cancerous diseases. The original publication has been corrected.

Nagy, A., et al. (2021). "Pancancer survival analysis of cancer hallmark genes." Sci Rep **11**(1): 6047.

Cancer hallmark genes are responsible for the most essential phenotypic characteristics of malignant transformation and progression. In this study, our aim was to estimate the prognostic effect of the established cancer hallmark genes in multiple distinct cancer types. RNA-seq HTSeq counts and survival data from 26 different tumor types were acquired from the TCGA repository. DESeq was used for normalization. Correlations between gene expression and survival were computed using the Cox proportional hazards regression and by plotting Kaplan-Meier survival plots. The false discovery rate was calculated to correct for multiple hypothesis testing. Signatures based on genes involved in genome instability and invasion reached significance in most individual cancer types. Thyroid and glioblastoma were independent of hallmark genes (61 and 54 genes significant, respectively), while renal clear cell cancer and low grade gliomas harbored the most prognostic changes (403 and 419 genes significant, respectively). The eight genes with the highest significance included BRCA1 (genome instability, HR 4.26, $p < 1E-16$), RUNX1 (sustaining proliferative signaling, HR 2.96, $p = 3.1E-10$) and SERPINE1 (inducing angiogenesis, HR 3.36, $p = 1.5E-12$) in low grade glioma, CDK1 (cell death resistance, HR = 5.67, $p = 2.1E-10$) in kidney papillary carcinoma, E2F1 (tumor suppressor, HR 0.38, $p = 2.4E-05$) and EREG (enabling replicative immortality, HR 3.23, $p = 2.1E-07$) in cervical cancer, FBP1 (deregulation of cellular energetics, HR 0.45, $p = 2.8E-07$) in kidney renal clear cell carcinoma and MYC (invasion and

metastasis, HR 1.81, p = 5.8E-05) in bladder cancer. We observed unexpected heterogeneity and tissue specificity when correlating cancer hallmark genes and survival. These results will help to prioritize future targeted therapy development in different types of solid tumors.

Nersisyan, L., et al. (2019). "Telomere Length Maintenance and Its Transcriptional Regulation in Lynch Syndrome and Sporadic Colorectal Carcinoma." Front Oncol **9**: 1172.

Background: Activation of telomere maintenance mechanisms (TMMs) is a hallmark of most cancers, and is required to prevent genome instability and to establish cellular immortality through reconstitution of capping of chromosome ends. TMM depends on the cancer type. Comparative studies linking tumor biology and TMM have potential impact for evaluating cancer onset and development. Methods: We have studied alterations of telomere length, their sequence composition and transcriptional regulation in mismatch repair deficient colorectal cancers arising in Lynch syndrome (LS-CRC) and microsatellite instable (MSI) sporadic CRC (MSI s-CRC), and for comparison, in microsatellite stable (MSS) s-CRC and in benign colon mucosa. Our study applied bioinformatics analysis of whole genome DNA and RNA sequencing data and a pathway model to study telomere length alterations and the potential effect of the "classical" telomerase (TEL-) and alternative (ALT-) TMM using transcriptomic signatures. Results: We have found progressive decrease of mean telomere length in all cancer subtypes compared with reference systems. Our results support the view that telomere attrition is an early event in tumorigenesis. TMM gets activated in all tumors studied due to concerted overexpression of a large fraction of genes with direct relation to telomere function, where only a very small fraction of them showed recurrent mutations. TEL-related transcriptional state was dominating in all CRC subtypes, showing, however, subtype-specific activation patterns; while contribution of the ALT-TMM was slightly more prominent in the hypermutated MSI s-CRC and LS-CRC. TEL-TMM is mainly activated by over-expression of DKC1 and/or TERT genes and their interaction partners, where DKC1 is more prominent in MSS than in MSI s-CRC and can serve as a transcriptomic marker of TMM activity. Conclusions: Our results suggest that transcriptional patterns are indicative for TMM pathway activation with subtle differences between TEL and ALT mechanisms in a CRC subtype-specific fashion. Sequencing data potentially provide a suited measure to study alterations of telomere length and of underlying transcriptional regulation. Further studies are needed to improve this method.

Nguyen, N. H., et al. (2021). "Triterpenoids from the genus Gynostemma: Chemistry and pharmacological activities." J Ethnopharmacol **268**: 113574.

ETHNOPHARMACOLOGICAL RELEVANCE: G. pentaphyllum, also known as Jiao-Gu-Lan, has been used traditionally as folk remedies for many diseases, including diabetes mellitus, metabolic syndrome, aging, and neurodegenerative diseases in China and some countries in East and Southeast Asia. It is considered as an "immortality herb" in Guizhou Province, because it was consumed regularly by the elderly native inhabitants. Other species of the same genus Gynostemma such as G. longipes and G. laxum have been used as alternatives to G. pentaphyllum in ethno-medicine in Vietnam and other Asian countries. AIM OF THE REVIEW: The review aims to summarize up-to-date study results on Gynostemma species, including traditional usage, phytochemical profile, pharmacological activities, and toxicological studies, in order to suggest future research orientation and therapeutic applications on acute and chronic diseases. MATERIALS AND METHODS: The relevant literature on the genus Gynostemma was gathered from secondary databases (Web of Science and PubMed), books, and official websites. The latest literature cited in this review was published in February 2020. RESULTS: The genus Gynostemma has been widely used in traditional medicine, mainly for treatment of diabetes, hypertension, obesity, and hepatosteatosis. To date, 328 dammarane-type saponins were isolated and structurally elucidated from Gynostemma species. Crude extracts, saponin-rich fractions (gypenosides), and pure compounds were reported to show a wide range of pharmacological activities in both in vitro and in vivo experiments. The most notable pharmacological effects were anti-cancer, cardioprotective, hepatoprotective, neuroprotective, anti-diabetic, anti-obesity, and anti-inflammatory activities. Toxicological studies were conducted only on G. pentaphyllum, showing that the plant extracts were relatively safe in both acute and long-term toxicity experiments at the given dosage while no toxicological studies were reported for the other species. CONCLUSIONS: The review summarizes current studies on traditional uses, phytochemistry, biological properties, and toxicology of medicinal Gynostemma species. Till now, the majority of publications still focused only on G. pentaphyllum. However, the promising preliminary data of other Gynostemma species indicated the research potential of this genus, both in phytochemical and pharmacological aspects. Furthermore, clinical data are required to evaluate the efficacy and undesired effects of crude extracts, standard saponin fractions, and pure compounds prepared from Gynostemma medicinal plants.

Pandkar, M. R., et al. (2021). "Oxygen gradient and tumor heterogeneity: The chronicle of a toxic relationship." Biochim Biophys Acta Rev Cancer **1876**(1): 188553.

The commencement of cancer is attributed to one or a few cells that become rogue and attain the property of immortality. The inception of distinct cancer cell clones during the hyperplastic and dysplastic stages of cancer progression is the utimate consequence of the dysregulated cellular pathways and the proliferative potential itself. Furthermore, a critical factor that adds a layer of complexity to this pre-existent intra-tumoral heterogeneity (ITH) is the foundation of an oxygen gradient, that is established due to the improper architecture of the tumor vasculature. Therefore, as a resultant effect, the poorly oxygenated regions thus formed and characterized as hypoxic, promote the emergence of aggressive and treatment-resistant cancer cell clones. The extraordinary property of the hypoxic cancer cells to exist harmoniously with cancerous and non-cancerous cells in the tumor microenvironment (TME) further increases the intricacies of ITH. Here in this review, the pivotal influence of differential oxygen concentrations in shaping the ITH is thoroughly discussed. We also emphasize on the vitality of the interacting networks that govern the overall fate of oxygen gradient-dependent origin of tumor heterogeneity. Additionally, the implications of less-appreciated reverse Warburg effect, a symbiotic metabolic coupling, and the associated epigenetic regulation of rewiring of cancer metabolism in response to oxygen gradients, have been highlighted as critical influencers of ITH.

Reda, A., et al. (2019). "Next-generation nanotheranostics targeting cancer stem cells." Nanomedicine (Lond) **14**(18): 2487-2514.

Cancer is depicted as the most aggressive malignancy and is one the major causes of death worldwide. It originates from immortal tumor-initiating cells called 'cancer stem cells' (CSCs). This devastating subpopulation exhibit potent self-renewal, proliferation and differentiation characteristics. Dynamic DNA repair mechanisms can sustain the immortality phenotype of cancer to evade all treatment strategies. To date, current conventional chemo- and radio-therapeutic strategies adopted against cancer fail in tackling CSCs. However, new advances in nanotechnology have paved the way for creating next-generation nanotheranostics as multifunctional smart 'all-in-one' nanoparticles. These particles integrate diagnostic, therapeutic and targeting agents into one single biocompatible and biodegradable carrier, opening up new avenues for breakthroughs in early detection, diagnosis and treatment of cancer through efficient targeting of CSCs.

Seimiya, H. (2020). "Crossroads of telomere biology and anticancer drug discovery." Cancer Sci **111**(9): 3089-3099.

The telomere is the specialized nucleoprotein complex at the end of the chromosome. Its highly conserved 5'-TTAGGG-3' repeats and shelterin protein complexes form a protective loop structure to maintain the integrity and stability of linear chromosomes. Although human somatic cells gradually shorten telomeres to undergo senescence or crisis, cancer cells activate telomerase, or the recombination-based mechanism to maintain telomeres and exhibit immortality. As the most frequent non-coding mutations in cancer, gain-of-function mutations in the promoter region of the telomerase catalytic subunit, TERT, trigger telomerase activation. Promoter methylation and copy number gain are also associated with the enhanced TERT expression. Although telomerase inhibitors were pioneered from telomere-directed therapeutics, their efficacies are limited to cancer with short telomeres and some hematological malignancies. Other therapeutic approaches include a nucleoside analog incorporated to telomeres and TERT promoter-driven oncolytic adenoviruses. Tankyrase poly(ADP-ribose) polymerase, a positive regulator of telomerase, has been rediscovered as a target for Wnt-driven cancer. Meanwhile, telomeric nucleic acids form a higher-order structure called a G-quadruplex (G4). G4s are formed genome-wide and their dynamics affect various events, including replication, transcription, and translation. G4-stabilizing compounds (G4 ligands) exert anticancer effects and are in clinical investigations. Collectively, telomere biology has provided clues for deeper understanding of cancer, which expands opportunities to discover innovative anticancer drugs.

Slusher, A. L., et al. (2020). "The Role of Alternative RNA Splicing in the Regulation of hTERT, Telomerase, and Telomeres: Implications for Cancer Therapeutics." Cancers (Basel) **12**(6).

Alternative RNA splicing impacts the majority (>90%) of eukaryotic multi-exon genes, expanding the coding capacity and regulating the abundance of gene isoforms. Telomerase (hTERT) is a key example of a gene that is alternatively spliced during human fetal development and becomes dysregulated in nearly all cancers. Approximately 90% of human tumors use telomerase to synthesize de novo telomere repeats and obtain telomere-dependent cellular immortality. Paradigm shifting data indicates that hTERT alternative splicing, in addition to transcription, plays an important role in the regulation of active telomerase in cells. Our group and others are pursuing the basic science studies to progress this emerging area of telomerase biology. Recent evidence demonstrates that switching splicing of hTERT from

the telomerase activity producing full-length hTERT isoform to alternatively spliced, non-coding isoforms may be a novel telomerase inhibition strategy to prevent cancer growth and survival. Thus, the goals of this review are to detail the general roles of telomerase in cancer development, explore the emerging regulatory mechanisms of alternative RNA splicing of the hTERT gene in various somatic and cancer cell types, define the known and potential roles of hTERT splice isoforms in cancer cell biology, and provide insight into new treatment strategies targeting hTERT in telomerase-positive cancers.

Stern, J. L., et al. (2020). "Mesenchymal and MAPK Expression Signatures Associate with Telomerase Promoter Mutations in Multiple Cancers." Mol Cancer Res **18**(7): 1050-1062.

In a substantial fraction of cancers TERT promoter (TERTp) mutations drive expression of the catalytic subunit of telomerase, contributing to their proliferative immortality. We conducted a pan-cancer analysis of cell lines and find a TERTp mutation expression signature dominated by epithelial-to-mesenchymal transition and MAPK signaling. These data indicate that TERTp mutants are likely to generate distinctive tumor microenvironments and intercellular interactions. Analysis of high-throughput screening tests of 546 small molecules on cell line growth indicated that TERTp mutants displayed heightened sensitivity to specific drugs, including RAS pathway inhibitors, and we found that inhibition of MEK1 and 2, key RAS/MAPK pathway effectors, inhibited TERT mRNA expression. Consistent with an enrichment of mesenchymal states in TERTp mutants, cell lines and some patient tumors displayed low expression of the central adherens junction protein E-cadherin, and we provide evidence that its expression in these cells is regulated by MEK1/2. Several mesenchymal transcription factors displayed elevated expression in TERTp mutants including ZEB1 and 2, TWIST1 and 2, and SNAI1. Of note, the developmental transcription factor SNAI2/SLUG was conspicuously elevated in a significant majority of TERTp-mutant cell lines, and knock-down experiments suggest that it promotes TERT expression. IMPLICATIONS: Cancers harboring TERT promoter mutations are often more lethal, but the basis for this higher mortality remains unknown. Our study identifies that TERTp mutants, as a class, associate with a distinct gene and protein expression signature likely to impact their biological and clinical behavior and provide new directions for investigating treatment approaches for these cancers.

Sun, Y., et al. (2020). "Near-infrared-traceable DNA nano-hydrolase: specific eradication of telomeric G-overhang in vivo." Nucleic Acids Res **48**(17): 9986-9994.

Telomeric DNA, whose length homeostasis is closely correlated with immortality of cancer cells, is regarded as a molecular clock for cellular lifespan. Regarding the capacity in forming G-quadruplex, G-rich 3'-overhang (G-overhang) has been considered as an attractive anticancer target. However, it is still challenging to precisely target telomeric G-overhang with current ligands because of the polymorphism of G-quadruplexes in cells. Herein, we construct a telomeric G-overhang-specific near-infrared-traceable DNA nano-hydrolase, which is composed of four parts: (i) dexamethasone for targeting cell nuclei; (ii) complementary DNA for hybridizing with G-overhang; (iii) multinuclear Ce(IV) complexes for hydrolyzing G-overhang; and (iv) upconversion nanoparticles for real-time tracking. The multivalent targeted DNA nano-hydrolase can be traced to precisely digest telomeric G-overhang, which contributes to telomeric DNA shortening and thereby causes cell aging and apoptosis. The anticancer treatment is further proved by in vivo studies. In this way, this design provides a telomeric G-overhang-specific eradication strategy based on a non-G-quadruplex targeting manner.

Takakura, M., et al. (2020). "A Novel Liquid Biopsy Strategy to Detect Small Amounts of Cancer Cells Using Cancer-Specific Replication Adenoviruses." J Clin Med **9**(12).

Circulating tumor cells (CTCs) are a promising source of clinical and biological cancer information and can be a material for liquid biopsy. However, detecting and capturing these cells remains a challenge. Various biological factors (e.g., cell surface proteins, cell size, deformability, or dielectrophoresis) have been applied to detect CTCs. Cancer cells dramatically change their characteristics during tumorigenesis and metastasis. Hence, defining a cell as malignant using such a parameter is difficult. Moreover, immortality is an essential characteristic of cancer cells. Telomerase elongates telomeres and plays a critical role in cellular immortality and is specifically activated in cancer cells. Thus, the activation of telomerase can be a good fingerprint for cancer cells. Telomerase cannot be recognized by antibodies in living cells because it is a nuclear enzyme. Therefore, telomerase-specific replication adenovirus, which expresses the green fluorescent protein, has been applied to detect CTCs. This review explores the overview of this novel technology and its application in gynecological cancers.

Tatit, N. S. and P. Kevin (2019). "All-trans retinoic acid (atra) inhibits telomerase expression of BeWo choriocarcinoma cell (ATCC CCL-98)." Med J Malaysia **74**(6): 504-508.

INTRODUCTION: Choriocarcinoma is malignant cancer originating from placental trophoblast. The incidence of this cancer is estimated at

0.57-1.1 per 1000 births in the United States of America, Australia, Europe, and New Zealand. The rate is much higher in South East Asia and Japan with two occurrences per a thousand births. Telomerase activity is an important part of the apoptotic process. Increased telomerase activity will result in cellular immortality and poor prognosis in cancer. Vitamin A possess an essential role in cell proliferation and differentiation. One of the active metabolites of vitamin A is All-Trans Retinoic Acid (ATRA). METHODS: In this study, we examined the role of ATRA against telomerase activity in choriocarcinoma cell. This cell was derived from BeWo cell line (ATCC CCL-98) and were given different doses of ATRA. RESULTS: From this study, Choriocarcinoma cell that was given ATRA in dosage of 50mug/ml inhibit telomerase activity by extending the cycle time of 39.51+/-0.09, compared to the control group with a cycle time of 37.62+/-0.43. Cycle length change consistently with higher dose of ATRA. CONCLUSION: This study has proven that ATRA could inhibit telomerase activity by lengthening the cycle. Changes in the increase of ATRA doses in this experimental test need to be studied further on experimental animals, either administered as a single agent or as an addition to standard treatment of trophoblastic disease.

Trivedi, P., et al. (2021). "When Viruses Cross Developmental Pathways." Front Cell Dev Biol **9**: 691644.

Aberrant regulation of developmental pathways plays a key role in tumorigenesis. Tumor cells differ from normal cells in their sustained proliferation, replicative immortality, resistance to cell death and growth inhibition, angiogenesis, and metastatic behavior. Often they acquire these features as a consequence of dysregulated Hedgehog, Notch, or WNT signaling pathways. Human tumor viruses affect the cancer cell hallmarks by encoding oncogenic proteins, and/or by modifying the microenvironment, as well as by conveying genomic instability to accelerate cancer development. In addition, viral immune evasion mechanisms may compromise developmental pathways to accelerate tumor growth. Viruses achieve this by influencing both coding and non-coding gene regulatory pathways. Elucidating how oncogenic viruses intersect with and modulate developmental pathways is crucial to understanding viral tumorigenesis. Many currently available antiviral therapies target viral lytic cycle replication but with low efficacy and severe side effects. A greater understanding of the cross-signaling between oncogenic viruses and developmental pathways will improve the efficacy of next-generation inhibitors and pave the way to more targeted antiviral therapies.

Vahidi, S., et al. (2020). "DNA Methylation Profiling of hTERT Gene Alongside with the Telomere Performance in Gastric Adenocarcinoma." J Gastrointest Cancer **51**(3): 788-799.

PURPOSE: Epigenetic modification including of DNA methylation, histone acetylation, histone methylation, histon phosphorylation and non-coding RNA can impress the gene expression and genomic stability and cause different types of malignancies and also main human disorder. Conspicuously, the epigenetic alteration special DNA methylation controls telomere length, telomerase activity and also function of different genes particularly hTERT expression. Telomeres are important in increasing the lifespan, health, aging, and the development and progression of some diseases like cancer. METHODS: This review provides an assessment of the epigenetic alterations of telomeres, telomerase and repression of its catalytic subunit, hTERT and function of long non-coding RNAs such as telomeric-repeat containing RNA (TERRA) in carcinogenesis and tumorgenesis of gastric cancer. RESULTS: hTERT expression is essential and indispensable in telomerase activation through immortality and malignancies and also plays an important role in maintaining telomere length. Telomeres and telomerase have been implicated in regulating epigenetic factors influencing certain gene expression. Correspondingly, these changes in the sub telomere and telomere regions are affected by the shortening of telomere length and increased telomerase activity and hTERT gene expression have been observed in many cancers, remarkably in gastric cancer. CONCLUSION: Epigenetic alteration and regulation of hTERT gene expression are critical in controlling telomerase activity and its expression. Graphical Abstract.

Veeramachaneni, R., et al. (2019). "Analysis of head and neck carcinoma progression reveals novel and relevant stage-specific changes associated with immortalisation and malignancy." Sci Rep **9**(1): 11992.

We report changes in the genomic landscape in the development of head and neck squamous cell carcinomas HNSCC from potentially premalignant lesions (PPOLS) to malignancy and lymph node metastases. Likely pathological mutations predominantly involved a relatively small set of genes reported previously (TP53, KMT2D, CDKN2A, PIK3CA, NOTCH1 and FAT1) but also other predicted cancer drivers (MGA, PABPC3, NR4A2, NCOR1 and MACF1). Notably, all these mutations arise early and are present in PPOLs. The most frequent genetic changes, which follow acquisition of immortality and loss of senescence, are of consistent somatic copy number alterations (SCNAs) involving chromosomal regions enriched for genes in known and previously unreported cancer-related pathways. We mapped the evolution of SCNAs in HNSCC progression. One of the earliest SCNAs involved deletions of CSMD1

(8p23.2). CSMD1 deletions or promoter hypermethylation were present in all of the immortal PPOLs and occurred at high frequency in the immortal HNSCC cell lines. Modulation of CSMD1 in cell lines revealed significant suppression of proliferation and invasion by forced expression, and significant stimulation of invasion by knockdown of expression. Known cancer drivers NOTCH1, PPP6C, RAC1, EIF4G1, PIK3CA showed significant increase in frequency of SCNA in transition from PPOLs to HNSCC that correlated with their expression. In the later stages of progression, HNSCC with and without nodal metastases showed some clear differences including high copy number gains of CCND1, hsa-miR-548k and TP63 in the metastases group.

Veisi, A., et al. (2020). "Role of crocin in several cancer cell lines: An updated review." Iran J Basic Med Sci **23**(1): 3-12.

Cancer is a major public health problem worldwide. The most important considerable features of cancer cells are uncontrolled proliferation, up-regulated differentiation, and immortality. Crocin, as a bioactive compound of saffron and as a water-soluble carotenoid has radical scavenging, anti-hyperlipidemia, memory improving, and inhibition of tumor growth effects. The present review was designed to evaluate molecular mechanisms underlying crocin effects against cancer cell lines. Data of this review have been collected from the scientific articles published in databases such as Science Direct, Scopus, PubMed, and Scientific Information Database from 1982 to 2019. According to various literature, crocin inhibits tumor growth, and its spread in several types of cancer including colorectal, pancreatic, breast, and prostate, as well as chronic myelogenous and leukemia. It inhibits telomerase activity, microtubule polymerization, cyclin D1, nuclear factor kappa B (NF-kB), multidrug resistance-associated protein (MRP1), and MRP2 overexpression. Crocin can induce apoptosis through activation of caspase 8, up-regulation of p53 expression, Bax/Bcl-2 ratio, and down-regulation expression of Bcl-2, survivin, and cyclin D1. It also down-regulates matrix metalloproteinase 2 and 9 (MMP2 and MMP9), N-cadherin, and beta-catenin expression, which are involved in tumor invasion and metastasis. Tumor invasion was also inhibited by crocin through increasing E-cadherin expression, cell cycle suppression at G1, G0/G1, S, and G2/M phases. Crocin has therapeutic and preventive effects on cancer cells line. Therefore, it has been suggested that this agent can be administered in patients that suffer from this problem.

Wagner, N. and K. D. Wagner (2020). "PPAR Beta/Delta and the Hallmarks of Cancer." Cells **9**(5).

Peroxisome proliferator-activated receptors (PPARs) belong to the nuclear hormone receptor family. Three different isoforms, PPAR alpha, PPAR beta/delta and PPAR gamma have been identified. They all form heterodimers with retinoic X receptors to activate or repress downstream target genes dependent on the presence/absence of ligands and coactivators or corepressors. PPARs differ in their tissue expression profile, ligands and specific agonists and antagonists. PPARs attract attention as potential therapeutic targets for a variety of diseases. PPAR alpha and gamma agonists are in clinical use for the treatment of dyslipidemias and diabetes. For both receptors, several clinical trials as potential therapeutic targets for cancer are ongoing. In contrast, PPAR beta/delta has been suggested as a therapeutic target for metabolic syndrome. However, potential risks in the settings of cancer are less clear. A variety of studies have investigated PPAR beta/delta expression or activation/inhibition in different cancer cell models in vitro, but the relevance for cancer growth in vivo is less well documented and controversial. In this review, we summarize critically the knowledge of PPAR beta/delta functions for the different hallmarks of cancer biological capabilities, which interplay to determine cancer growth.

Wen, L., et al. (2020). "CRISPR/Cas9-Mediated TERT Disruption in Cancer Cells." Int J Mol Sci **21**(2).

Mammalian telomere lengths are primarily regulated by telomerase, a ribonucleoprotein consisting of a reverse transcriptase (TERT) and an RNA subunit (TERC). TERC is constitutively expressed in all cells, whereas TERT expression is temporally and spatially regulated, such that in most adult somatic cells, TERT is inactivated and telomerase activity is undetectable. Most tumor cells activate TERT as a mechanism for preventing progressive telomere attrition to achieve proliferative immortality. Therefore, inactivating TERT has been considered to be a promising means of cancer therapy. Here we applied the CRISPR/Cas9 gene editing system to target the TERT gene in cancer cells. We report that disruption of TERT severely compromises cancer cell survival in vitro and in vivo. Haploinsufficiency of TERT in tumor cells is sufficient to result in telomere attrition and growth retardation in vitro. In vivo, TERT haploinsufficient tumor cells failed to form xenograft after transplantation to nude mice. Our work demonstrates that gene editing-mediated TERT knockout is a potential therapeutic option for treating cancer.

Wu, L., et al. (2020). "Telomerase: Key regulator of inflammation and cancer." Pharmacol Res **155**: 104726.

The telomerase holoenzyme, which has a highly conserved role in maintaining telomere length, has long been regarded as a high-profile target in cancer therapy due to the high dependency of the majority of cancer cells on constitutive and elevated

telomerase activity for sustained proliferation and immortality. In this review, we present the salient findings in the telomerase field with special focus on the association of telomerase with inflammation and cancer. The elucidation of extra-telomeric roles of telomerase in inflammation, reactive oxygen species (ROS) generation, and cancer development further complicated the design of anti-telomerase therapy. Of note, the discovery of the unique mechanism that underlies reactivation of the dormant telomerase reverse transcriptase TERT promoter in somatic cells not only enhanced our understanding of the critical role of TERT in carcinogenesis but also opens up new intervention ideas that enable the differential targeting of cancer cells only. Despite significant effort invested in developing telomerase-targeted therapeutics, devising efficacious cancer-specific telomerase/TERT inhibitors remains an uphill task. The latest discoveries of the telomere-independent functionalities of telomerase in inflammation and cancer can help illuminate the path of developing specific anti-telomerase/TERT therapeutics against cancer cells.

Yu, S., et al. (2020). "MCMs in Cancer: Prognostic Potential and Mechanisms." Anal Cell Pathol (Amst) **2020**: 3750294.

Enabling replicative immortality and uncontrolled cell cycle are hallmarks of cancer cells. Minichromosome maintenance proteins (MCMs) exhibit helicase activity in replication initiation and play vital roles in controlling replication times within a cell cycle. Overexpressed MCMs are detected in various cancerous tissues and cancer cell lines. Previous studies have proposed MCMs as promising proliferation markers in cancers, while the prognostic values remain controversial and the underlying mechanisms remain unascertained. This review provides an overview of the significant findings regarding the cellular and tumorigenic functions of the MCM family. Besides, current evidence of the prognostic roles of MCMs is retrospectively reviewed. This work also offers insight into the mechanisms of MCMs prompting carcinogenesis and adverse prognosis, providing information for future research. Finally, MCMs in liver cancer are specifically discussed, and future perspectives are provided.

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