

## 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 cancer biology related studies.

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**Key words:** cancer; biology; life; research; literature

### 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 related studies.

Abaan, O. D., E. C. Polley, et al. "The exomes of the NCI-60 panel: a genomic resource for cancer biology and systems pharmacology." *Cancer Res.* 2013 Jul 15;73(14):4372-82. doi: [10.1158/0008-5472.CAN-12-3342](https://doi.org/10.1158/0008-5472.CAN-12-3342). Epub 2013 Jul 15.

The NCI-60 cell lines are the most frequently studied human tumor cell lines in cancer research. This panel has generated the most extensive cancer pharmacology database worldwide. In addition, these cell lines have been intensely investigated, providing a unique platform for hypothesis-driven research focused on enhancing our understanding of tumor biology. Here, we report a comprehensive analysis of coding variants in the NCI-60 panel of cell lines identified by whole exome sequencing, providing a list of possible cancer specific variants for the community. Furthermore, we identify pharmacogenomic correlations between specific variants in genes such as TP53, BRAF, ERBBs, and ATAD5 and anticancer agents such as nutlin, vemurafenib, erlotinib, and bleomycin showing one of many ways the data could be used to validate and generate novel hypotheses for

further investigation. As new cancer genes are identified through large-scale sequencing studies, the data presented here for the NCI-60 will be an invaluable resource for identifying cell lines with mutations in such genes for hypothesis-driven research. To enhance the utility of the data for the greater research community, the genomic variants are freely available in different formats and from multiple sources including the CellMiner and Ingenuity websites.

Adam, J., M. Yang, et al. "Rare insights into cancer biology." *Oncogene.* 2014 May 15;33(20):2547-56. doi: [10.1038/onc.2013.222](https://doi.org/10.1038/onc.2013.222). Epub 2013 Jul 1.

Cancer-associated mutations have been identified in the metabolic genes succinate dehydrogenase (SDH), fumarate hydratase (FH) and isocitrate dehydrogenase (IDH), advancing and challenging our understanding of cellular function and disease mechanisms and providing direct links between dysregulated metabolism and cancer. Some striking parallels exist in the cellular consequences of the genetic mutations within this triad of cancer syndromes, including accumulation of oncometabolites and competitive inhibition of 2-oxoglutarate-dependent dioxygenases, particularly, hypoxia-inducible factor (HIF) prolyl hydroxylases, JmjC domain-containing histone demethylases (part of the JMJD family) and the ten-eleven translocation (TET) family of 5methyl cytosine (5mC) DNA hydroxylases. These lead to activation of HIF-dependent oncogenic pathways and inhibition of histone and DNA demethylation. Mutations in FH, resulting in loss of enzyme activity, predispose affected individuals to a rare cancer, hereditary leiomyomatosis and renal cell cancer (HLRCC), characterised by benign smooth muscle cutaneous and uterine tumours (leiomyomata) and an aggressive form

of collecting duct and type 2 papillary renal cancer. Interestingly, loss of FH activity results in the accumulation of high levels of fumarate that can lead to the non-enzymatic modification of cysteine residues in multiple proteins (succination) and in some cases to their disrupted function. Here we consider that the study of rare diseases such as HLRCC, combining analyses of human tumours and cell lines with in vitro and in vivo murine models has provided novel insights into cancer biology associated with dysregulated metabolism and represents a useful paradigm for cancer research.

Amend, S. R. and K. J. Pienta Ecology meets cancer biology: the cancer swamp promotes the lethal cancer phenotype, *Oncotarget*. 2015 Apr 30;6(12):9669-9678.

As they grow, tumors fundamentally alter their microenvironment, disrupting the homeostasis of the host organ and eventually the patient as a whole. Lethality is the ultimate result of deregulated cell signaling and regulatory mechanisms as well as inappropriate host cell recruitment and activity that lead to the death of the patient. These processes have striking parallels to the framework of ecological biology: multiple interacting ecosystems (organ systems) within a larger biosphere (body), alterations in species stoichiometry (host cell types), resource cycling (cellular metabolism and cell-cell signaling), and ecosystem collapse (organ failure and death). In particular, as cancer cells generate their own niche within the tumor ecosystem, ecological engineering and autotrophication displace normal cell function and result in the creation of a hypoxic, acidic, and nutrient-poor environment. This "cancer swamp" has genetic and epigenetic effects at the local ecosystem level to promote metastasis and at the systemic host level to induce cytokine-mediated lethal syndromes, a major cause of death of cancer patients.

Aprile, G., F. Leone, et al. "Tracking the 2015 Gastrointestinal Cancers Symposium: bridging cancer biology to clinical gastrointestinal oncology." *Onco Targets Ther.* 2015 May 22;8:1149-56. doi: 10.2147/OTT.S82624. eCollection 2015.

The 2015 Gastrointestinal Cancers Symposium (San Francisco, CA, USA; January 15-17) is the world-class conference co-sponsored by the American Society of Clinical Oncology, the American Society for Radiation Oncology, the American Gastroenterological Association Institute, and the Society of Surgical Oncology, in which the most innovative research results in digestive tract oncology are presented and discussed. In its twelfth edition, the meeting has provided new insights focusing on the underpinning biology and clinical management of gastrointestinal malignancies. More than 3,400 health

care professionals gathered from all over the world to share their experiences on how to bridge the recent novelties in cancer biology with everyday medical practice. In this article, the authors report on the most significant advances, didactically moving on three different anatomic tracks: gastroesophageal malignancies, pancreatic and biliary cancers, and colorectal adenocarcinomas.

Atsumi, T., R. Singh, et al. "Inflammation amplifier, a new paradigm in cancer biology." *Cancer Res.* 2014 Jan 1;74(1):8-14. doi: 10.1158/0008-5472.CAN-13-2322. Epub 2013 Dec 20.

Tumor-associated inflammation can induce various molecules expressed from the tumors themselves or surrounding cells to create a microenvironment that potentially promotes cancer development. Inflammation, particularly chronic inflammation, is often linked to cancer development, even though its evolutionary role should impair nonself objects including tumors. The inflammation amplifier, a hyperinducer of chemokines in nonimmune cells, is the principal machinery for inflammation and is activated by the simultaneous stimulation of NF-kappaB and STAT3. We have redefined inflammation as local activation of the inflammation amplifier, which causes an accumulation of various immune cells followed by dysregulation of local homeostasis. Genes related to the inflammation amplifier have been genetically associated with various human inflammatory diseases. Here, we describe how cancer-associated genes, including interleukin (IL)-6, Ptgs2, ErbB1, Gas1, Serpine1, cMyc, and Vegf-alpha, are strongly enriched in genes related to the amplifier. The inflammation amplifier is activated by the stimulation of cytokines, such as TNF-alpha, IL-17, and IL-6, resulting in the subsequent expression of various target genes for chemokines and tumor-related genes like BCL2L11, CPNE7, FAS, HIF1-alpha, IL-1RAP, and SOD2. Thus, we conclude that inflammation does indeed associate with the development of cancer. The identified genes associated with the inflammation amplifier may thus make potential therapeutic targets of cancers.

Benard, J. and C. J. Larsen "[Explicative models of cancer biology: an enlarged vision]." *Bull Cancer.* 2013 Jul-Aug;100(7-8):697-713. doi: 10.1684/bdc.2013.1752.

The second half of the 20th century has been dominated by genetic models of tumors that provided conceptual tools explaining tumor genesis and its evolution. Other domains--epigenetics, cell metabolism--appeared that generated a more complex landscape of tumor physiopathology. Moreover, the

discovery of tumor stem cells and intratumoral heterogeneity are likely to explain recurrence. A major difficulty is that every tumor behaves as an organ that evolves in function of its microenvironment. By integrating all the new data in more and more sophisticated models, the major goals may emerge from the characterisation of new markers for diagnosis and prognosis and from the selection of pertinent and efficient new therapeutic targets.

Bonilla-Velez, J., E. A. Mroz, et al. "Impact of human papillomavirus on oropharyngeal cancer biology and response to therapy: implications for treatment." *Otolaryngol Clin North Am.* 2013 Aug;46(4):521-43. doi: 10.1016/j.otc.2013.04.009. Epub 2013 Jun 27.

Oropharyngeal squamous cell carcinoma (OPSCC) originating from human papillomavirus infection has emerged as a new entity in head and neck cancer, defining a subset of patients with distinct carcinogenesis, risk factor profiles, and clinical presentation that show markedly improved survival than patients with classic OPSCC. De-escalation of therapy and identification of relevant biomarkers to aid in patient selection are actively being investigated. This review addresses the implications of these findings in clinical care.

Borcherding, N., D. Kusner, et al. "ROR1, an embryonic protein with an emerging role in cancer biology." *Protein Cell.* 2014 Jul;5(7):496-502. doi: 10.1007/s13238-014-0059-7. Epub 2014 Apr 22.

Receptor tyrosine kinase-like orphan receptor 1 (ROR1) is a member of the ROR family consisting of ROR1 and ROR2. RORs contain two distinct extracellular cysteine-rich domains and one transmembrane domain. Within the intracellular portion, ROR1 possesses a tyrosine kinase domain, two serine/threonine-rich domains and a proline-rich domain. RORs have been studied in the context of embryonic patterning and neurogenesis through a variety of homologs. These physiologic functions are dichotomous based on the requirement of the kinase domain. A growing literature has established ROR1 as a marker for cancer, such as in CLL and other blood malignancies. In addition, ROR1 is critically involved in progression of a number of blood and solid malignancies. ROR1 has been shown to inhibit apoptosis, potentiate EGFR signaling, and induce epithelial-mesenchymal transition (EMT). Importantly, ROR1 is only detectable in embryonic tissue and generally absent in adult tissue, making the protein an ideal drug target for cancer therapy.

Brachner, A. and R. Foisner "Lamina-associated polypeptide (LAP)2alpha and other LEM proteins in

cancer biology." *Adv Exp Med Biol.* 2014;773:143-63. doi: 10.1007/978-1-4899-8032-8\_7.

The LEM proteins comprise a heterogeneous family of chromatin-associated proteins that share the LEM domain, a structural motif mediating interaction with the DNA associated protein, Barrier-to-Autointegration Factor (BAF). Most of the LEM proteins are integral proteins of the inner nuclear membrane and associate with the nuclear lamina, a structural scaffold of lamin intermediate filament proteins at the nuclear periphery, which is involved in nuclear mechanical functions and (hetero-)chromatin organization. A few LEM proteins, such as Lamina-associated polypeptide (LAP)2alpha and Ankyrin and LEM domain-containing protein (Ankle)1 lack transmembrane domains and localize throughout the nucleoplasm and cytoplasm, respectively. LAP2alpha has been reported to regulate cell proliferation by affecting the activity of retinoblastoma protein in tissue progenitor cells and numerous studies showed upregulation of LAP2alpha in cancer. Ankle1 is a nuclease likely involved in DNA damage repair pathways and single nucleotide polymorphisms in the Ankle1 gene have been linked to increased breast and ovarian cancer risk. In this review we describe potential mechanisms of the involvement of LEM proteins, particularly of LAP2alpha and Ankle1 in tumorigenesis and we provide evidence that LAP2alpha expression may be a valuable diagnostic and prognostic marker for tumor analyses.

Bridge, G., S. Rashid, et al. "DNA mismatch repair and oxidative DNA damage: implications for cancer biology and treatment." *Cancers (Basel).* 2014 Aug 5;6(3):1597-614. doi: 10.3390/cancers6031597.

Many components of the cell, including lipids, proteins and both nuclear and mitochondrial DNA, are vulnerable to deleterious modifications caused by reactive oxygen species. If not repaired, oxidative DNA damage can lead to disease-causing mutations, such as in cancer. Base excision repair and nucleotide excision repair are the two DNA repair pathways believed to orchestrate the removal of oxidative lesions. However, recent findings suggest that the mismatch repair pathway may also be important for the response to oxidative DNA damage. This is particularly relevant in cancer where mismatch repair genes are frequently mutated or epigenetically silenced. In this review we explore how the regulation of oxidative DNA damage by mismatch repair proteins may impact on carcinogenesis. We discuss recent studies that identify potential new treatments for mismatch repair deficient tumours, which exploit this non-canonical role of mismatch repair using synthetic lethal targeting.

Bustamante-Marin, X., J. A. Garness, et al. "Testicular teratomas: an intersection of pluripotency, differentiation and cancer biology." Int J Dev Biol. 2013;57(2-4):201-10. doi: 10.1387/ijdb.130136bc.

Teratomas represent a critical interface between stem cells, differentiation and tumorigenesis. These tumors are composed of cell types representing all three germ layers reflecting the pluripotent nature of their cell of origin. The study of these curious tumors became possible when Leroy Stevens identified the 129 mouse strain as a model of spontaneous testicular teratoma and later isolated a substrain carrying the Ter mutation, a potent modifier of tumor incidence. Early studies with 129 mice lead to the discovery of embryonal carcinoma (EC) cells which played a foundational role in the embryonic stem (ES) cell field and the study of pluripotency. The cells of origin of testicular teratomas are germ cells. During early development, primordial germ cells diverge from somatic differentiation and establish their pluripotent nature, maintaining or re-expressing core pluripotency genes; Oct4, Sox2 and Nanog. It is believed that a misregulation of male germ cell pluripotency plays a critical role in teratoma development. Several mouse models of teratoma development have now been identified, including a chromosome substitution strain, 129-Chr19(MOLF), conditional Dmrt1 and Pten alleles and the Ter mutation in the Dnd1 gene. However, it is still unknown what role somatic cells and/or physiology play in the sensitivity to teratoma development. These unusual tumors may hold the key to understanding how pluripotency is regulated in vivo.

Compagno, D., L. D. Gentilini, et al. "Glycans and galectins in prostate cancer biology, angiogenesis and metastasis." Glycobiology. 2014 Oct;24(10):899-906. doi: 10.1093/glycob/cwu055. Epub 2014 Jun 16.

Prostate cancer is the second most common cause of cancer and the sixth leading cause of cancer death among men worldwide. While localized prostate cancer can be cured, advanced and metastatic prostate cancer remains a significant therapeutic challenge. Malignant transformation is associated with important modifications of the cellular glycosylation profile, and it is postulated that these changes have a considerable relevance for tumor biology. Metastasis is a multiphasic process that encompasses angiogenesis, the spread of tumor cells and their growth at distant sites from the primary tumor location. Recognition of glycoconjugates by galectins, among other lectins, plays a fundamental role in the metastatic spread, tumor immune escape and the neovascularization process. Particularly in prostate cancer, both carbohydrates and galectins have been implicated in many cellular processes such as proliferation,

apoptosis, migration and invasion. However, a limited number of studies assessed their potential implications in the induction of metastasis in prostate cancer patients or in animal models. Moreover, the role of galectin-glycan interactions in vivo still remains poorly understood; concerted effort should thus be made in order to shed some light on this question. This review summarizes current evidence on both the expression and role of glycans and galectins in prostate cancer, particularly turning our attention to the angiogenic and metastatic processes.

Damrauer, J. S., K. A. Hoadley, et al. "Intrinsic subtypes of high-grade bladder cancer reflect the hallmarks of breast cancer biology." Proc Natl Acad Sci U S A. 2014 Feb 25;111(8):3110-5. doi: 10.1073/pnas.1318376111. Epub 2014 Feb 11.

We sought to define whether there are intrinsic molecular subtypes of high-grade bladder cancer. Consensus clustering performed on gene expression data from a meta-dataset of high-grade, muscle-invasive bladder tumors identified two intrinsic, molecular subsets of high-grade bladder cancer, termed "luminal" and "basal-like," which have characteristics of different stages of urothelial differentiation, reflect the luminal and basal-like molecular subtypes of breast cancer, and have clinically meaningful differences in outcome. A gene set predictor, bladder cancer analysis of subtypes by gene expression (BASE47) was defined by prediction analysis of microarrays (PAM) and accurately classifies the subtypes. Our data demonstrate that there are at least two molecularly and clinically distinct subtypes of high-grade bladder cancer and validate the BASE47 as a subtype predictor. Future studies exploring the predictive value of the BASE47 subtypes for standard of care bladder cancer therapies, as well as novel subtype-specific therapies, will be of interest.

Diaz, L., M. Diaz-Munoz, et al. "Mechanistic Effects of Calcitriol in Cancer Biology." Nutrients. 2015 Jun 19;7(6):5020-50. doi: 10.3390/nu7065020.

Besides its classical biological effects on calcium and phosphorus homeostasis, calcitriol, the active vitamin D metabolite, has a broad variety of actions including anticancer effects that are mediated either transcriptionally and/or via non-genomic pathways. In the context of cancer, calcitriol regulates the cell cycle, induces apoptosis, promotes cell differentiation and acts as anti-inflammatory factor within the tumor microenvironment. In this review, we address the different mechanisms of action involved in the antineoplastic effects of calcitriol.

Downs, D. M. and D. C. Ernst "From microbiology to cancer biology: the Rid protein family prevents

cellular damage caused by endogenously generated reactive nitrogen species." Mol Microbiol. 2015 Apr;96(2):211-9. doi: 10.1111/mmi.12945. Epub 2015 Feb 26.

The Rid family of proteins is highly conserved and broadly distributed throughout the domains of life. Genetic and biochemical studies, primarily in *Salmonella enterica*, have defined a role for RidA in responding to endogenously generated reactive metabolites. The data show that 2-aminoacrylate (2AA), a reactive enamine intermediate generated by some pyridoxal 5'-phosphate-dependent enzymes, accumulates in the absence of RidA. The accumulation of 2AA leads to covalent modification and inactivation of several enzymes involved in essential metabolic processes. This review describes the 2AA hydrolyzing activity of RidA and the effect of this biochemical activity on the metabolic network, which impacts organism fitness. The reported activity of RidA and the consequences encountered in vivo when RidA is absent have challenged fundamental assumptions in enzymology, biochemistry and cell metabolism regarding the fate of transiently generated reactive enamine intermediates. The current understanding of RidA in *Salmonella* and the broad distribution of Rid family proteins provide exciting opportunities for future studies to define metabolic roles of Rid family members from microbes to man.

Dowsett, T., E. Verghese, et al. "The value of archival tissue blocks in understanding breast cancer biology." J Clin Pathol. 2014 Mar;67(3):272-5. doi: 10.1136/jclinpath-2013-201854. Epub 2013 Oct 29.

Pathological reporting of breast cancer has evolved alongside scientific advances. Such advances have led to recognition of different molecular classes of breast cancer resulting in improved disease management. The aim of this study was to establish whether these advances could be applied to archival breast cancer cases dating from the 1940s to assess historical trends. Important observations included the marked differences in pathological reporting, size of tumour and in ER $\alpha$  expression throughout the decades.

Dufey, E., H. Urra, et al. ER proteostasis addiction in cancer biology: Novel concepts, *Semin Cancer Biol.* 2015 Apr 27. pii: S1044-579X(15)00028-0. doi: 10.1016/j.semcancer.2015.04.003.

Endoplasmic reticulum (ER) stress is generated by various physiological and pathological conditions that induce an accumulation of misfolded proteins in its lumen. ER stress activates the unfolded protein response (UPR), an adaptive reaction to cope with protein misfolding to and restore proteostasis. However, chronic ER stress results in apoptosis. In

solid tumors, the UPR mediates adaptation to various environmental stressors, including hypoxia, low in pH and low nutrients availability, driving positive selection. Recent findings support the concept that UPR signaling also contributes to other relevant cancer-related event that may not be related to ER stress, including angiogenesis, genomic instability, metastasis and immunomodulation. In this article, we overview novel discoveries highlighting the impact of the UPR to different aspects of cancer biology beyond its known role as a survival factor to the hypoxic environment observed in solid tumors.

Ellis, M. J., M. Gillette, et al. "Connecting genomic alterations to cancer biology with proteomics: the NCI Clinical Proteomic Tumor Analysis Consortium." Cancer Discov. 2013 Oct;3(10):1108-12. doi: 10.1158/2159-8290.CD-13-0219.

The National Cancer Institute (NCI) Clinical Proteomic Tumor Analysis Consortium is applying the latest generation of proteomic technologies to genomically annotated tumors from The Cancer Genome Atlas (TCGA) program, a joint initiative of the NCI and the National Human Genome Research Institute. By providing a fully integrated accounting of DNA, RNA, and protein abnormalities in individual tumors, these datasets will illuminate the complex relationship between genomic abnormalities and cancer phenotypes, thus producing biologic insights as well as a wave of novel candidate biomarkers and therapeutic targets amenable to verification using targeted mass spectrometry methods.

Emmert-Streib, F., S. D. Zhang, et al. "Computational cancer biology: education is a natural key to many locks." BMC Cancer. 2015 Jan 15;15:7. doi: 10.1186/s12885-014-1002-2.

**BACKGROUND:** Oncology is a field that profits tremendously from the genomic data generated by high-throughput technologies, including next-generation sequencing. However, in order to exploit, integrate, visualize and interpret such high-dimensional data efficiently, non-trivial computational and statistical analysis methods are required that need to be developed in a problem-directed manner. **DISCUSSION:** For this reason, computational cancer biology aims to fill this gap. Unfortunately, computational cancer biology is not yet fully recognized as a coequal field in oncology, leading to a delay in its maturation and, as an immediate consequence, an under-exploration of high-throughput data for translational research. Here we argue that this imbalance, favoring 'wet lab-based activities', will be naturally rectified over time, if the next generation of scientists receives an academic education that provides a fair and competent introduction to computational

biology and its manifold capabilities. Furthermore, we discuss a number of local educational provisions that can be implemented on university level to help in facilitating the process of harmonization.

Errington, T. M., E. Iorns, et al. "An open investigation of the reproducibility of cancer biology research." *Elife*. 2014 Dec 10;3. doi: [10.7554/eLife.04333](https://doi.org/10.7554/eLife.04333).

It is widely believed that research that builds upon previously published findings has reproduced the original work. However, it is rare for researchers to perform or publish direct replications of existing results. The Reproducibility Project: Cancer Biology is an open investigation of reproducibility in preclinical cancer biology research. We have identified 50 high impact cancer biology articles published in the period 2010-2012, and plan to replicate a subset of experimental results from each article. A Registered Report detailing the proposed experimental designs and protocols for each subset of experiments will be peer reviewed and published prior to data collection. The results of these experiments will then be published in a Replication Study. The resulting open methodology and dataset will provide evidence about the reproducibility of high-impact results, and an opportunity to identify predictors of reproducibility.

Fabbi, M., G. Carbotti, et al. "Context-dependent role of IL-18 in cancer biology and counter-regulation by IL-18BP." *J Leukoc Biol*. 2015 Apr;97(4):665-75. doi: [10.1189/jlb.5RU0714-360RR](https://doi.org/10.1189/jlb.5RU0714-360RR). Epub 2014 Dec 29.

IL-18 is a proinflammatory and immune regulatory cytokine, member of the IL-1 family. IL-18 was initially identified as an IFN-gamma-inducing factor in T and NK cells, involved in Th1 responses. IL-18 is produced as an inactive precursor (pro-IL-18) that is enzymatically processed into a mature form by Casp1. Different cells, such as macrophages, DCs, microglial cells, synovial fibroblasts, and epithelial cells, express pro-IL-18, and the production of bioactive IL-18 is mainly regulated at the processing level. PAMP or DAMP molecules activate inflammasomes, which trigger Casp1 activation and IL-18 conversion. The natural inhibitor IL-18BP, whose production is enhanced by IFN-gamma and IL-27, further regulates IL-18 activity in the extracellular environment. Inflammasomes and IL-18 represent double-edged swords in cancer, as their activation may promote tumor development and progression or oppositely, enhance anti-tumor immunity and limit tumor growth. IL-18 has shown anti-tumor activity in different preclinical models of cancer immunotherapy through the activation of NK and/or T cell responses and has been tested in clinical studies in cancer patients. However, the dual role of IL-18 in different

experimental tumor models and human cancers raises critical issues on its therapeutic use in cancer. This review will summarize the biology of the IL-18/IL-18R/IL-18BP system and will address the role of IL-18 and its inhibitor, IL-18BP, in cancer biology and immunotherapy.

Findlay, V. J., C. Wang, et al. "Epithelial-to-mesenchymal transition and the cancer stem cell phenotype: insights from cancer biology with therapeutic implications for colorectal cancer." *Cancer Gene Ther*. 2014 May;21(5):181-7. doi: [10.1038/cgt.2014.15](https://doi.org/10.1038/cgt.2014.15). Epub 2014 May 2.

Although mortality from colorectal cancer (CRC) is decreasing, CRC is still the second highest cause of cancer-related deaths in America. Chemotherapy and radiation therapy now have central roles in our strategies to fight cancer, although we continue to lack novel strategies overcoming therapeutic resistance. Molecular mechanisms of therapeutic resistance in CRC continue to be under intense investigation. In this review, we highlight the recent evidence linking epithelial-to-mesenchymal transition (EMT) with aggressive tumor biology as well as with the cancer stem cells (CSCs) across multiple organ systems including colon cancer. Furthermore, in the era of neo-adjuvant treatment, the clinical implications are concerning that our treatments may have the potential to induce more aggressive cancer cells through EMT, perhaps even generating CSCs more capable of metastasis and further resistant to treatment. This concern and potential reality highlights the critical need for further understanding the impact of clinical therapy on the pathobiology of cancer and further supports the need to therapeutically target the CSC. Besides serving as potential biomarkers for aggressive tumor biology and therapeutic resistance, EMT and CSC molecular pathways may highlight novel therapeutic targets as strategies for improving the response to conventional anti-neoplastic agents translating into improved oncologic outcomes.

Fonseca, N. A., A. C. Gregorio, et al. "Bridging cancer biology and the patients' needs with nanotechnology-based approaches." *Cancer Treat Rev*. 2014 Jun;40(5):626-35. doi: [10.1016/j.ctrv.2014.02.002](https://doi.org/10.1016/j.ctrv.2014.02.002). Epub 2014 Feb 22.

Cancer remains as stressful condition and a leading cause of death in the western world. Actual cornerstone treatments of cancer disease rest as an elusive alternative, offering limited efficacy with extensive secondary effects as a result of severe cytotoxic effects in healthy tissues. The advent of nanotechnology brought the promise to revolutionize many fields including oncology, proposing advanced

systems for cancer treatment. Drug delivery systems rest among the most successful examples of nanotechnology. Throughout time they have been able to evolve as a function of an increased understanding from cancer biology and the tumor microenvironment. Marketing of Doxil(R) unleashed a remarkable impulse in the development of drug delivery systems. Since then, several nanocarriers have been introduced, with aspirations to overrule previous technologies, demonstrating increased therapeutic efficacy besides decreased toxicity. Spatial and temporal targeting to cancer cells has been explored, as well as the use of drug combinations co-encapsulated in the same particle as a mean to take advantage of synergistic interactions in vivo. Importantly, targeted delivery of siRNA for gene silencing therapy has made its way to the clinic for a "first in man" trial using lipid-polymeric-based particles. Focusing in state-of-the-art technology, this review will provide an insightful vision on nanotechnology-based strategies for cancer treatment, approaching them from a tumor biology-driven perspective, since their early EPR-based dawn to the ones that have truly the potential to address unmet medical needs in the field of oncology, upon targeting key cell subpopulations from the tumor microenvironment.

Fuziwara, C. S. and E. T. Kimura "MicroRNA Deregulation in Anaplastic Thyroid Cancer Biology." *Int J Endocrinol.* 2014;2014:743450. doi: [10.1155/2014/743450](https://doi.org/10.1155/2014/743450). Epub 2014 Aug 19.

Anaplastic thyroid cancer (ATC) is among the most lethal types of cancers, characterized as a fast-growing and highly invasive thyroid tumor that is unresponsive to surgery and radioiodine, blunting therapeutic efficacy. Classically, genetic alterations in tumor suppressor TP53 are frequent, and cumulative alterations in different signaling pathways, such as MAPK and PI3K, are detected in ATC. Recently, deregulation in microRNAs (miRNAs), a class of small endogenous RNAs that regulate protein expression, has been implicated in tumorigenesis and cancer progression. Deregulation of miRNA expression is detected in thyroid cancer. Upregulation of miRNAs, such as miR-146b, miR-221, and miR-222, is observed in ATC and also in differentiated thyroid cancer (papillary and follicular), indicating that these miRNAs' overexpression is essential in maintaining tumorigenesis. However, specific miRNAs are downregulated in ATC, such as those of the miR-200 and miR-30 families, which are important negative regulators of cell migration, invasion, and epithelial-to-mesenchymal transition (EMT), processes that are overactivated in ATC. Therefore, molecular interference to restore the expression of tumor suppressor miRNAs, or to blunt overexpressed

oncogenic miRNAs, is a promising therapeutic approach to ameliorate the treatment of ATC. In this review, we will explore the importance of miRNA deregulation for ATC cell biology.

Gill, B. J. and J. L. West "Modeling the tumor extracellular matrix: Tissue engineering tools repurposed towards new frontiers in cancer biology." *J Biomech.* 2014 Jun 27;47(9):1969-78. doi: [10.1016/j.jbiomech.2013.09.029](https://doi.org/10.1016/j.jbiomech.2013.09.029). Epub 2013 Oct 9.

Cancer progression is mediated by complex epigenetic, protein and structural influences. Critical among them are the biochemical, mechanical and architectural properties of the extracellular matrix (ECM). In recognition of the ECM's important role, cancer biologists have repurposed matrix mimetic culture systems first widely used by tissue engineers as new tools for in vitro study of tumor models. In this review we discuss the pathological changes in tumor ECM, the limitations of 2D culture on both traditional and polyacrylamide hydrogel surfaces in modeling these characteristics and advances in both naturally derived and synthetic scaffolds to facilitate more complex and controllable 3D cancer cell culture. Studies using naturally derived matrix materials like Matrigel and collagen have produced significant findings related to tumor morphogenesis and matrix invasion in a 3D environment and the mechanotransductive signaling that mediates key tumor-matrix interaction. However, lack of precise experimental control over important matrix factors in these matrices have increasingly led investigators to synthetic and semi-synthetic scaffolds that offer the engineering of specific ECM cues and the potential for more advanced experimental manipulations. Synthetic scaffolds composed of poly(ethylene glycol) (PEG), for example, facilitate highly biocompatible 3D culture, modular bioactive features like cell-mediated matrix degradation and complete independent control over matrix bioactivity and mechanics. Future work in PEG or similar reductionist synthetic matrix systems should enable the study of increasingly complex and dynamic tumor-ECM relationships in the hopes that accurate modeling of these relationships may reveal new cancer therapeutics targeting tumor progression and metastasis.

Irish, J. M. and D. B. Doxie "High-dimensional single-cell cancer biology." *Curr Top Microbiol Immunol.* 2014;377:1-21. doi: [10.1007/82\\_2014\\_367](https://doi.org/10.1007/82_2014_367).

Cancer cells are distinguished from each other and from healthy cells by features that drive clonal evolution and therapy resistance. New advances in high-dimensional flow cytometry make it possible to systematically measure mechanisms of tumor initiation, progression, and therapy resistance on

millions of cells from human tumors. Here we describe flow cytometry techniques that enable a "single-cell" view of cancer. High-dimensional techniques like mass cytometry enable multiplexed single-cell analysis of cell identity, clinical biomarkers, signaling network phospho-proteins, transcription factors, and functional readouts of proliferation, cell cycle status, and apoptosis. This capability pairs well with a signaling profiles approach that dissects mechanism by systematically perturbing and measuring many nodes in a signaling network. Single-cell approaches enable study of cellular heterogeneity of primary tissues and turn cell subsets into experimental controls or opportunities for new discovery. Rare populations of stem cells or therapy-resistant cancer cells can be identified and compared to other types of cells within the same sample. In the long term, these techniques will enable tracking of minimal residual disease (MRD) and disease progression. By better understanding biological systems that control development and cell-cell interactions in healthy and diseased contexts, we can learn to program cells to become therapeutic agents or target malignant signaling events to specifically kill cancer cells. Single-cell approaches that provide deep insight into cell signaling and fate decisions will be critical to optimizing the next generation of cancer treatments combining targeted approaches and immunotherapy.

Jimenez, C. R. and H. M. Verheul "Mass spectrometry-based proteomics: from cancer biology to protein biomarkers, drug targets, and clinical applications." Am Soc Clin Oncol Educ Book. 2014:e504-10. doi: [10.14694/EdBook\\_AM.2014.34.e504](https://doi.org/10.14694/EdBook_AM.2014.34.e504).

Proteomics is optimally suited to bridge the gap between genomic information on the one hand and biologic functions and disease phenotypes at the other, since it studies the expression and/or post-translational modification (especially phosphorylation) of proteins--the major cellular players bringing about cellular functions--at a global level in biologic specimens. Mass spectrometry technology and (bio)informatic tools have matured to the extent that they can provide high-throughput, comprehensive, and quantitative protein inventories of cells, tissues, and biofluids in clinical samples at low level. In this article, we focus on next-generation proteomics employing nanoliquid chromatography coupled to high-resolution tandem mass spectrometry for in-depth (phospho)protein profiling of tumor tissues and (proximal) biofluids, with a focus on studies employing clinical material. In addition, we highlight emerging proteogenomic approaches for the identification of tumor-specific protein variants, and targeted multiplex mass spectrometry strategies for large-scale biomarker

validation. Below we provide a discussion of recent progress, some research highlights, and challenges that remain for clinical translation of proteomic discoveries.

Kitajima, Y. and K. Miyazaki "The Critical Impact of HIF-1a on Gastric Cancer Biology." Cancers (Basel). 2013 Jan 10;5(1):15-26. doi: [10.3390/cancers5010015](https://doi.org/10.3390/cancers5010015).

Hypoxia inducible factor-1 (HIF-1) monitors the cellular response to the oxygen levels in solid tumors. Under hypoxia conditions, HIF-1a protein is stabilized and forms a heterodimer with the HIF-1beta subunit. The HIF-1 complex activates the transcription of numerous target genes in order to adapt the hypoxic environment in human cancer cells. In gastric cancer patients, HIF-1a activation following extended hypoxia strongly correlates with an aggressive tumor phenotype and a poor prognosis. HIF-1a activation has been also reported to occur via hypoxia-independent mechanisms such as PI3K/AKT/mTOR signaling and ROS production. This article argues for the critical roles of HIF-1a in glucose metabolism, carcinogenesis, angiogenesis, invasion, metastasis, cell survival and chemoresistance, focusing on gastric cancer.

Koutsogiannouli, E., A. G. Papavassiliou, et al. "Complexity in cancer biology: is systems biology the answer?" Cancer Med. 2013 Apr;2(2):164-77. doi: [10.1002/cam4.62](https://doi.org/10.1002/cam4.62). Epub 2013 Feb 17.

Complex phenotypes emerge from the interactions of thousands of macromolecules that are organized in multimolecular complexes and interacting functional modules. In turn, modules form functional networks in health and disease. Omics approaches collect data on changes for all genes and proteins and statistical analysis attempts to uncover the functional modules that perform the functions that characterize higher levels of biological organization. Systems biology attempts to transcend the study of individual genes/proteins and to integrate them into higher order information. Cancer cells exhibit defective genetic and epigenetic networks formed by altered complexes and network modules arising in different parts of tumor tissues that sustain autonomous cell behavior which ultimately lead tumor growth. We suggest that an understanding of tumor behavior must address not only molecular but also, and more importantly, tumor cell heterogeneity, by considering cancer tissue genetic and epigenetic networks, by characterizing changes in the types, composition, and interactions of complexes and networks in the different parts of tumor tissues, and by identifying critical hubs that connect them in time and space.

Latha, T. S., K. Panati, et al. "Ovarian cancer biology and immunotherapy." Int Rev Immunol. 2014

Oct;33(5):428-40. doi:  
[10.3109/08830185.2014.921161](https://doi.org/10.3109/08830185.2014.921161). Epub 2014 Jun 9.

Ovarian cancer is the most lethal malignancy of the female reproductive system and the fifth leading cause of cancer death in women. In the year 2012 alone, United States had 22,280 new ovarian cancer cases and 15,500 deaths were reported. About 7%-10% of ovarian cancers result from an inherited tendency to develop the disease. Ovarian cancer has the ability to escape the immune system because of its pathological interactions between cancer cells and host immune cells in the tumor microenvironment create an immunosuppressive network that promotes tumor growth, protects the tumor from immune system. The levels of immune suppressive elements like regulatory T cells, plasmacytoid dendritic cells and cytokines such as IL-10, IL-6, TNF-alpha, and TGF-beta are elevated in the tumor microenvironment. Vascular endothelial growth factor is known to have an immune suppressing role besides its angiogenic role in the tumor microenvironment. Ovarian cancer is associated with high mortality partly due to difficulties in early diagnosis and development of metastases. These problems may overcome by developing accurate mouse models that should mimic the complexity of human ovarian cancer. Such animal models are better suited to understand pathophysiology, metastases, and also for preclinical testing of targeted molecular therapeutics. Immunotherapy is an area of active investigation and off late many clinical trials is ongoing to prevent disease progression. The main aim of dendritic cells vaccination is to stimulate tumor specific effector T cells that can reduce tumor size and induce immunological memory to prevent tumor relapse.

Lazzari, C., G. Spitaleri, et al. "Targeting ALK in patients with advanced non small cell lung cancer: biology, diagnostic and therapeutic options." *Crit Rev Oncol Hematol*. 2014 Mar;89(3):358-65. doi:  
[10.1016/j.critrevonc.2013.09.003](https://doi.org/10.1016/j.critrevonc.2013.09.003). Epub 2013 Sep 26.

The discovery of EML4-ALK fusion gene in a subgroup of patients with lung adenocarcinoma led to the development of a new class of agents, the ALK inhibitors, and dramatically improved the clinical outcome of these patients. The striking results from clinical trials with crizotinib, the first ALK inhibitor evaluated, allowed the accelerated approval of crizotinib from the USA Food and Drug Administration (FDA). Despite the high initial results, patients acquire resistance to crizotinib, and different next generation ALK kinase inhibitors have been developed. In the current review, we will analyze the biology of EML4-ALK gene, the acquired resistance mechanisms to crizotinib, the therapeutic strategies, currently under evaluation, designed to overcome

crizotinib resistance, and the open issues that need to be addressed in order to improve outcome in ALK+ Non Small Cell Lung Cancer (NSCLC) patients.

Looijenga, L. H., H. Stoop, et al. "Testicular cancer: biology and biomarkers." *Virchows Arch*. 2014 Mar;464(3):301-13. doi: [10.1007/s00428-013-1522-1](https://doi.org/10.1007/s00428-013-1522-1). Epub 2014 Feb 1.

The term "human germ cell tumors" (GCTs) refers to a heterogeneous group of neoplasms, all with a defined histological appearance. They have specific epidemiological characteristics, clinical behavior, and pathogenesis. Histologically, GCTs contain various tissue elements, which are homologs of normal embryogenesis. We have proposed a subclassification of GCTs in five subtypes, three of which preferentially occur in the testis. These include teratomas and yolk sac tumors of neonates and infants (type I), seminomas and nonseminomas of (predominantly) adolescents and adults (type II), and spermatocytic seminomas of the elderly (type III). Both spontaneous and induced animal models have been reported, of which the relevance for human GCTs is still to be clarified. Multidisciplinary studies have recently shed new light on the (earliest steps in the) pathogenesis of GCTs, mainly in regard of malignant type II GCTs (germ cell cancer (GCC)). This review discusses novel understanding of the pathogenesis of (mainly) GCC, focusing on identification of informative diagnostic markers suitable for application in a clinical setting. These include OCT3/4, SOX9/FOXL2, SOX17/SOX2, as well as embryonic microRNAs. These markers have been identified through studies on normal embryogenesis, specifically related to the gonads, including the germ cell lineage. Their strengths and limitations are discussed as well as the expected future approach to identify the group of individuals at highest risk for development of a GCC. The latter would allow screening of defined populations, early diagnosis, optimal follow-up, and potentially early treatment, preventing long-term side effects of systemic treatment.

Mader, R. M., T. Brodowicz, et al. "Translating the molecular analysis of cancer biology into therapeutic concepts." *Cancer Biomark*. 2014;14(2-3):87-91. doi:  
[10.3233/CBM-130382](https://doi.org/10.3233/CBM-130382).

The rapidly evolving understanding of tumour biology offers novel opportunities for therapeutic interventions. This information already has been used to select appropriate systemic treatment. To take full advantage of this knowledge, however, the different levels of interaction in an organism need to be integrated to link cellular mechanisms, stromal effects and the implications for organs and the whole organism. Although very challenging and ambitious,

this understanding would closely link tumour biology, biomarker validation and rational therapeutic decisions.

Marino, F. E., G. Risbridger, et al. "Re-evaluating the role of activin-beta in cancer biology." *Cytokine Growth Factor Rev.* 2015 May 28. pii: S1359-6101(15)00046-5. doi: 10.1016/j.cytogfr.2015.05.003.

Transforming growth factor-beta (TGF-beta) superfamily signaling pathway and its ligands are essential regulators of cellular processes such as proliferation, differentiation, migration, and survival. Alteration of this pathway results in uncontrolled proliferation and cancer progression. This review focuses on a specific member of the TGF-beta superfamily: activin-betaC. After its initial discovery, activin-betaC has been considered non-biologically relevant. Therefore, for years several experimental designs have ignored the potential contribution of this molecule to the final biological outcome. Here we focus on recent advances in the activin field, with a particular emphasis on activin-betaC, its antagonistic mechanism, and the physiological relevance of activin-betaC actions in reproductive and cancer biology. Covering a novel and previously unexplored function of activin-betaC on cancer associated weight loss and muscle metabolism, this review suggests an imminent need to re-evaluate the function of activin-betaC in biological systems and advances the understanding of how activin-betaC antagonizes the activin signaling pathway. Thus, challenging activin biologists to consider the impact of activin-betaC when interpreting their work.

Martinez, C. H., A. K. Williams, et al. "Perineural invasion and TRUS findings are complementary in predicting prostate cancer biology." *Can J Urol.* 2013 Apr;20(2):6696-701.

**INTRODUCTION:** Clinical variables with more accuracy to predict biologically insignificant prostate cancer are needed. We evaluated the combination of transrectal ultrasound-guided biopsy of the prostate (TRUSBx) pathologic and radiologic findings in their ability to predict the biologic potential of each prostate cancer. **MATERIALS AND METHODS:** A total of 1043 consecutive patients who underwent TRUSBx were reviewed. Using pathologic criteria, patients with prostate cancer (n = 529) and those treated with radical prostatectomy (RP) (n = 147) were grouped as: "insignificant" (Gleason score  $\leq$  6, prostate-specific antigen (PSA) density  $\leq$  0.15 ng/ml, tumor in  $\leq$  50% of any single core, and  $<$  33% positive cores) and "significant" prostate cancer. TRUSBx imaging and pathology results were compared with the RP specimen to identify factors predictive of "insignificant" prostate cancer.

**RESULTS:** TRUSBx pathology results demonstrated perineural invasion in 36.4% of "significant" versus 5.4% of "insignificant" prostate cancers ( $p < 0.01$ ) and pathologic invasion of periprostatic tissue in 7% of significant versus 0% of insignificant prostate cancers ( $p < 0.01$ ). TRUS findings concerning for neoplasia were associated with significant tumors ( $p < 0.01$ ). Multivariable analysis demonstrated perineural invasion in the biopsy specimen ( $p = 0.03$ ), PSA density ( $p = 0.02$ ) and maximum tumor volume of any core ( $p = 0.02$ ) were independently predictive of a significant prostate cancer. **CONCLUSIONS:** TRUS findings concerning for measurable tumor and perineural invasion in TRUSBx specimens appear to be complementary to Epstein's pathologic criteria and should be considered to aid in the determination whether a prostate cancer is organ-confined and more likely to be biologically insignificant.

Masoudi-Nejad, A. and Y. Asgari "Metabolic cancer biology: structural-based analysis of cancer as a metabolic disease, new sights and opportunities for disease treatment." *Semin Cancer Biol.* 2015 Feb;30:21-9. doi: 10.1016/j.semcancer.2014.01.007. Epub 2014 Feb 2.

The cancer cell metabolism or the Warburg effect discovery goes back to 1924 when, for the first time Otto Warburg observed, in contrast to the normal cells, cancer cells have different metabolism. With the initiation of high throughput technologies and computational systems biology, cancer cell metabolism renaissances and many attempts were performed to revise the Warburg effect. The development of experimental and analytical tools which generate high-throughput biological data including lots of information could lead to application of computational models in biological discovery and clinical medicine especially for cancer. Due to the recent availability of tissue-specific reconstructed models, new opportunities in studying metabolic alteration in various kinds of cancers open up. Structural approaches at genome-scale levels seem to be suitable for developing diagnostic and prognostic molecular signatures, as well as in identifying new drug targets. In this review, we have considered these recent advances in structural-based analysis of cancer as a metabolic disease view. Two different structural approaches have been described here: topological and constraint-based methods. The ultimate goal of this type of systems analysis is not only the discovery of novel drug targets but also the development of new systems-based therapy strategies.

Nik-Zainal, S. "Insights into cancer biology through next-generation sequencing." *Clin Med.* 2014 Dec;14 Suppl 6:s71-7. doi: 10.7861/clinmedicine.14-6-s71.

Cancer is the ultimate disorder of the genome, characterised not by just one or two mutations, but by hundreds to thousands of acquired mutations that have been accrued through the development of a tumour. Thanks to the recent increase in the speed of sequencing offered by modern sequencing technologies, we are no longer restricted to exploring tiny fragments of protein-coding portions of the human genome. We can now read all the genetic material in human cells. Here, the framework of a next-generation sequencing experiment is explained, giving insight into the advances and difficulties posed by processing the enormous datasets generated through these methods. Some of the recent insights into tumour biology, that exploit the extraordinary surge in scale and the digital nature of next-generation sequencing, are highlighted, including cancer gene discovery, the detection of mutation signatures and cancer evolution. Technological and intellectual developments are starting to shape the personalized cancer genomic profiles of tomorrow. Let's train the next-generation of clinicians to be able to read them from today.

Obeid, E. I. and S. D. Conzen "The role of adrenergic signaling in breast cancer biology." Cancer Biomark. 2013;13(3):161-9. doi: 10.3233/CBM-130347.

Adrenergic signaling results from the effects of the catecholamines epinephrine and norepinephrine, on alpha- and beta-adrenergic receptors. In breast cancer, preclinical models suggest that this pathway may influence breast cancer progression through 1) increasing tumor cell survival after exposure to chemotherapeutic agents; 2) increasing breast cancer cell proliferation; and 3) altering the tumor microenvironment in angiogenesis and the inflammatory response. Epidemiologic data have suggested a correlation between drugs that indirectly affect the adrenergic pathway and breast cancer incidence. In addition, there is retrospective evidence suggesting that the use of beta-adrenergic blockers in early stage breast cancer patients correlates with an increased time to recurrence. Here we review evidence from both pre-clinical models and epidemiological studies that have examined the question of whether adrenergic signaling may modify breast cancer biology.

O'Flanagan, C. H. and C. O'Neill "PINK1 signalling in cancer biology." Biochim Biophys Acta. 2014 Dec;1846(2):590-8. doi: 10.1016/j.bbcan.2014.10.006. Epub 2014 Oct 23.

PTEN-induced kinase 1 (PINK1) was identified initially in cancer cells as a gene up-regulated by overexpression of the major tumor suppressor, PTEN. Loss-of-function mutations in

PINK1 were discovered subsequently to cause autosomal recessive Parkinson's disease. Substantial work during the past decade has revealed that PINK1 regulates several primary cellular processes of significance in cancer cell biology, including cell survival, stress resistance, mitochondrial homeostasis and the cell cycle. Mechanistically, PINK1 has been shown to interact on a number of levels with the pivotal oncogenic PI3-kinase/Akt/mTOR signalling axis and to control critical mitochondrial and metabolic functions that regulate cancer survival, growth, stress resistance and the cell cycle. A cytoprotective and chemoresistant function for PINK1 has been highlighted by some studies, supporting PINK1 as a target in cancer therapeutics. This article reviews the function of PINK1 in cancer cell biology, with an emphasis on the mechanisms by which PINK1 interacts with PI3-kinase/Akt signalling, mitochondrial homeostasis, and the potential context-dependent pro- and anti-tumorigenic functions of PINK1.

Pezzella, F. and K. Gatter "Non-angiogenic tumours unveil a new chapter in cancer biology." J Pathol. 2015 Feb;235(3):381-3. doi: 10.1002/path.4474.

The term 'angiogenesis' was coined in 1787 and the role of vessels in cancer has been studied ever since. In 1971 Folkman introduced the hypothesis, until now widely accepted, that tumour growth is strictly dependent on angiogenesis. However, the discovery that tumours can also grow without angiogenesis by exploiting pre-existing vessels, both in humans and more recently in mice, has demonstrated that this is not always the case. These observations highlight a new aspect of the interaction between vessels and tumours and demonstrate the existence of a previously unrecognized group of tumours that grow without angiogenesis and whose biology is, so far, largely unknown.

Pilatova, K., K. Greplova, et al. "Role of platelet chemokines, PF-4 and CTAP-III, in cancer biology." J Hematol Oncol. 2013 Jun 24;6:42. doi: 10.1186/1756-8722-6-42.

With the recent addition of anti-angiogenic agents to cancer treatment, the angiogenesis regulators in platelets are gaining importance. Platelet factor 4 (PF-4/CXCL4) and Connective tissue activating peptide III (CTAP-III) are two platelet-associated chemokines that modulate tumor angiogenesis, inflammation within the tumor microenvironment, and in turn tumor growth. Here, we review the role of PF-4 and CTAP-III in the regulation of tumor angiogenesis; the results of clinical trial using recombinant PF-4 (rPF-4); and the use of PF-4 and CTAP-III as cancer biomarkers.

Romano, S., A. D'Angelillo, et al. Pleiotropic roles in cancer biology for multifaceted proteins FKBPs. *Biochim Biophys Acta*. 2015 Jan 13. pii: S0304-4165(15)00023-9. doi: 10.1016/j.bbagen.2015.01.004.

**BACKGROUND:** FK506 binding proteins (FKBP) are multifunctional proteins highly conserved across the species and abundantly expressed in the cell. In addition to a well-established role in immunosuppression, FKBP's modulate several signal transduction pathways in the cell, due to their isomerase activity and the capability to interact with other proteins, inducing changes in conformation and function of protein partners. Increasing literature data support the concept that FKBP's control cancer related pathways. **SCOPE OF THE REVIEW:** The aim of the present article is to review current knowledge on FKBP's roles in regulation of key signaling pathways associated with cancer. **MAJOR CONCLUSIONS:** Some family members appear to promote disease while others are protective against tumorigenesis. **GENERAL SIGNIFICANCE:** FKBP's family proteins are expected to provide new biomarkers and small molecular targets, in the near future, increasing diagnostic and therapeutic opportunities in the cancer field. This article is part of a Special Issue entitled *Proline-Directed Foldases: Cell Signaling Catalysts and Drug Targets*.

Sanchez-Mejias, A. and Y. Tay "Competing endogenous RNA networks: tying the essential knots for cancer biology and therapeutics." *J Hematol Oncol*. 2015 Mar 28;8:30. doi: 10.1186/s13045-015-0129-1.

A recently discovered dimension of post-transcriptional gene regulation involves co-regulatory crosstalk between RNA transcripts, which compete for common pools of microRNA (miRNA) molecules. These competing endogenous RNAs (ceRNAs), or natural miRNA sponges, have an active role in regulating miRNA availability within the cell and form intertwined regulatory networks. Recent reports have implicated diverse RNA species including protein-coding messenger RNAs and non-coding RNAs as ceRNAs in human development and diseases including human cancer. In this review, we discuss the most recent discoveries that implicate natural miRNA decoys in human cancer biology, as well as exciting advances in the study of ceRNA networks and dynamics. The structure and topology of intricate genome-scale ceRNA networks can be predicted computationally, and their dynamic response to fluctuations in ceRNA and miRNA levels can be studied via mathematical modeling. Additionally, the development of new methods to quantitatively determine absolute expression levels of miRNA and ceRNA molecules have expanded the capacity to accurately study the efficiency of ceRNA crosstalk in

diverse biological models. These major milestones are of critical importance to identify key components of ceRNA regulatory networks that could aid the development of new approaches to cancer diagnostics and oligonucleotide-based therapeutics.

Sanchez-Rivera, F. J. and T. Jacks "Applications of the CRISPR-Cas9 system in cancer biology." *Nat Rev Cancer*. 2015 Jul;15(7):387-95. doi: 10.1038/nrc3950. Epub 2015 Jun 4.

The prokaryotic type II CRISPR-Cas9 (clustered regularly interspaced short palindromic repeats-CRISPR-associated 9) system is rapidly revolutionizing the field of genetic engineering, allowing researchers to alter the genomes of a large range of organisms with relative ease. Experimental approaches based on this versatile technology have the potential to transform the field of cancer genetics. Here, we review current approaches for functional studies of cancer genes that are based on CRISPR-Cas, with emphasis on their applicability for the development of next-generation models of human cancer.

Silva, J. L., L. P. Rangel, et al. "Expanding the prion concept to cancer biology: dominant-negative effect of aggregates of mutant p53 tumour suppressor." *Biosci Rep*. 2013 Jul 25;33(4). pii: e00054. doi: 10.1042/BSR20130065.

p53 is a key protein that participates in cell-cycle control, and its malfunction can lead to cancer. This tumour suppressor protein has three main domains; the N-terminal transactivation domain, the CTD (C-terminal domain) and the core domain (p53C) that constitutes the sequence-specific DBD (DNA-binding region). Most p53 mutations related to cancer development are found in the DBD. Aggregation of p53 into amyloid oligomers and fibrils has been shown. Moreover, amyloid aggregates of both the mutant and WT (wild-type) forms of p53 were detected in tumour tissues. We propose that if p53 aggregation occurred, it would be a crucial aspect of cancer development, as p53 would lose its WT functions in an aggregated state. Mutant p53 can also exert a dominant-negative regulatory effect on WT p53. Herein, we discuss the dominant-negative effect in light of p53 aggregation and the fact that amyloid-like mutant p53 can convert WT p53 into more aggregated species, leading into gain of function in addition to the loss of tumour suppressor function. In summary, the results obtained in the last decade indicate that cancer may have characteristics in common with amyloidogenic and prion diseases.

Simmons, G. E., Jr., W. M. Pruitt, et al. "Diverse roles of SIRT1 in cancer biology and lipid metabolism." *Int*

J Mol Sci. 2015 Jan 5;16(1):950-65. doi: 10.3390/ijms16010950.

SIRT1, an NAD(+)-dependent deacetylase, has been described in the literature as a major player in the regulation of cellular stress responses. Its expression has been shown to be altered in cancer cells, and it targets both histone and non-histone proteins for deacetylation and thereby alters metabolic programs in response to diverse physiological stress. Interestingly, many of the metabolic pathways that are influenced by SIRT1 are also altered in tumor development. Not only does SIRT1 have the potential to regulate oncogenic factors, it also orchestrates many aspects of metabolism and lipid regulation and recent reports are beginning to connect these areas. SIRT1 influences pathways that provide an alternative means of deriving energy (such as fatty acid oxidation and gluconeogenesis) when a cell encounters nutritive stress, and can therefore lead to altered lipid metabolism in various pathophysiological contexts. This review helps to show the various connections between SIRT1 and major pathways in cellular metabolism and the consequence of SIRT1 deregulation on carcinogenesis and lipid metabolism.

Singh, D., G. Upadhyay, et al. Recent advances in pancreatic cancer: biology, treatment, and prevention. Biochim Biophys Acta. 2015 May 11;1856(1):13-27. doi: 10.1016/j.bbcan.2015.04.003.

Pancreatic cancer (PC) is the fourth leading cause of cancer-related death in United States. Efforts have been made towards the development of the viable solution for its treatment with constrained accomplishment because of its complex biology. It is well established that pancreatic cancer stem cells (CSCs), albeit present in a little count, contribute incredibly to PC initiation, progression, and metastasis. Customary chemo and radiotherapeutic alternatives, however, expands general survival, the related side effects are the significant concern. Amid the most recent decade, our insight about molecular and cellular pathways involved in PC and role of CSCs in its progression has increased enormously. Presently the focus is to target CSCs. The herbal products have gained much consideration recently as they, usually, sensitize CSCs to chemotherapy and target molecular signaling involved in various tumors including PC. Some planned studies have indicated promising results proposing that examinations in this course have a lot to offer for the treatment of PC. Although preclinical studies uncovered the importance of herbal products in attenuating pancreatic carcinoma, limited studies have been conducted to evaluate their role in clinics. The present review provides a new insight to recent advances in pancreatic cancer biology, treatment and current status of herbal products in its anticipation.

Theocharis, A. D., S. S. Skandalis, et al. Insights into the key roles of proteoglycans in breast cancer biology and translational medicine. Biochim Biophys Acta. 2015 Apr;1855(2):276-300. doi: 10.1016/j.bbcan.2015.03.006. Epub 2015 Mar 28.

Proteoglycans control numerous normal and pathological processes, among which are morphogenesis, tissue repair, inflammation, vascularization and cancer metastasis. During tumor development and growth, proteoglycan expression is markedly modified in the tumor microenvironment. Altered expression of proteoglycans on tumor and stromal cell membranes affects cancer cell signaling, growth and survival, cell adhesion, migration and angiogenesis. Despite the high complexity and heterogeneity of breast cancer, the rapid evolution in our knowledge that proteoglycans are among the key players in the breast tumor microenvironment suggests their potential as pharmacological targets in this type of cancer. It has been recently suggested that pharmacological treatment may target proteoglycan metabolism, their utilization as targets for immunotherapy or their direct use as therapeutic agents. The diversity inherent in the proteoglycans that will be presented herein provides the potential for multiple layers of regulation of breast tumor behavior. This review summarizes recent developments concerning the biology of selected proteoglycans in breast cancer, and presents potential targeted therapeutic approaches based on their novel key roles in breast cancer.

Thorek, D. L., M. J. Evans, et al. "Prostate-specific kallikrein-related peptidases and their relation to prostate cancer biology and detection. Established relevance and emerging roles." Thromb Haemost. 2013 Sep;110(3):484-92. doi: 10.1160/TH13-04-0275. Epub 2013 Aug 1.

Kallikreins are a family of serine proteases with a range of tissue-specific and essential proteolytic functions. Among the best studied are the prostate tissue-specific KLK2 and KLK3 genes and their secreted protease products, human kallikrein 2, hK2, and prostate-specific antigen (PSA). Members of the so-called classic kallikreins, these highly active trypsin-like serine proteases play established roles in human reproduction. Both hK2 and PSA expression is regulated by the androgen receptor which has a fundamental role in prostate tissue development and progression of disease. This feature, combined with the ability to sensitively detect different forms of these proteins in blood and biopsies, result in a crucially important biomarker for the presence and recurrence of cancer. Emerging evidence has begun to suggest a role for these kallikreins in critical vascular events.

This review discusses the established and developing biological roles of hK2 and PSA, as well as the historical and advanced use of their detection to accurately and non-invasively detect and guide treatment of prostatic disease.

Upheber, S., A. Karle, et al. "Alternative splicing of KAI1 abrogates its tumor-suppressive effects on integrin alphavbeta3-mediated ovarian cancer biology." *Cell Signal*. 2015 Mar;27(3):652-62. doi: [10.1016/j.cellsig.2014.11.028](https://doi.org/10.1016/j.cellsig.2014.11.028). Epub 2014 Nov 27.

Loss or downregulation of the tumor-suppressor KAI1 correlates with poor cancer patient prognosis. KAI1 functions by interacting with other proteins, including integrin cell adhesion and signaling receptors. We previously showed that KAI1 physically and functionally crosstalks with the tumor-biologically relevant integrin alphavbeta3, thereby suppressing ovarian cancer cell migration and proliferation. Interestingly, in metastases, a KAI1 splice variant had been identified, indicating poor patient prognosis. Thus, we here characterized differential effects of the two KAI1 proteins upon their cellular restoration. Opposite to KAI1, KAI1-splice reduced alphavbeta3-mediated cell adhesion, thereby inducing cell migration. This was accompanied by elevated alphavbeta3 levels and drastically elevated focal adhesion kinase activation, however, without any obvious colocalization with alphavbeta3, as observed for KAI1. Moreover, codistribution of KAI1 with the cell/cell-adhesion molecule E-cadherin was abrogated in KAI1-splice. Whereas KAI1 diminished cell proliferative activity, KAI1-splice prominently enhanced cell proliferation concomitant with elevated transcription and cell-surface expression of the epidermal growth factor receptor. Thus KAI1-splice does not only counteract the tumor-suppressive actions of KAI1, but - beyond that - promotes alphavbeta3-mediated biological functions in favor of tumor progression and metastasis.

Vardabasso, C., D. Hasson, et al. "Histone variants: emerging players in cancer biology." *Cell Mol Life Sci*. 2014 Feb;71(3):379-404. doi: [10.1007/s00018-013-1343-z](https://doi.org/10.1007/s00018-013-1343-z). Epub 2013 May 8.

Histone variants are key players in shaping chromatin structure, and, thus, in regulating fundamental cellular processes such as chromosome segregation and gene expression. Emerging evidence points towards a role for histone variants in contributing to tumor progression, and, recently, the first cancer-associated mutation in a histone variant-encoding gene was reported. In addition, genetic alterations of the histone chaperones that specifically regulate chromatin incorporation of histone variants are rapidly being uncovered in numerous cancers.

Collectively, these findings implicate histone variants as potential drivers of cancer initiation and/or progression, and, therefore, targeting histone deposition or the chromatin remodeling machinery may be of therapeutic value. Here, we review the mammalian histone variants of the H2A and H3 families in their respective cellular functions, and their involvement in tumor biology.

Wansleben, S., J. Peres, et al. "T-box transcription factors in cancer biology." *Biochim Biophys Acta*. 2014 Dec;1846(2):380-91. doi: [10.1016/j.bbcan.2014.08.004](https://doi.org/10.1016/j.bbcan.2014.08.004). Epub 2014 Aug 19.

The evolutionarily conserved T-box family of transcription factors have critical and well-established roles in embryonic development. More recently, T-box factors have also gained increasing prominence in the field of cancer biology where a wide range of cancers exhibit deregulated expression of T-box factors that possess tumour suppressor and/or tumour promoter functions. Of these the best characterised is TBX2, whose expression is upregulated in cancers including breast, pancreatic, ovarian, liver, endometrial adenocarcinoma, glioblastomas, gastric, uterine cervical and melanoma. Understanding the role and regulation of TBX2, as well as other T-box factors, in contributing directly to tumour progression, and especially in suppression of senescence and control of invasiveness suggests that targeting TBX2 expression or function alone or in combination with currently available chemotherapeutic agents may represent a therapeutic strategy for cancer.

Weiswald, L. B., S. Richon, et al. "A short-term colorectal cancer sphere culture as a relevant tool for human cancer biology investigation." *Br J Cancer*. 2013 Apr 30;108(8):1720-31. doi: [10.1038/bjc.2013.132](https://doi.org/10.1038/bjc.2013.132). Epub 2013 Mar 28.

BACKGROUND: Ex vivo colospheres have been previously characterised as a colorectal cancer (CRC) well-rounded multicellular model, exclusively formed by carcinoma cells, and derived from fresh CRC tissue after mechanical dissociation. The ability to form colospheres was correlated with tumour aggressiveness. Their three-dimensional conformation prompted us to further investigate their potential interest as a preclinical cancer tool. METHODS: Patient-derived CRC xenografts were used to produce numerous colospheres. Mechanism of formation was elucidated by confocal microscopy. Expression analysis of a panel of 64 selected cancer-related genes by real-time qRT-PCR and hierarchical clustering allowed comparison of colospheres with parent xenografts. In vitro and in vivo assays were performed for migration and chemosensitivity studies. RESULTS: Colospheres, formed by tissue remodelling

and compaction, remained viable several weeks in floating conditions, escaping anoikis through their strong cell-cell interactions. Colospheres matched the gene expression profile of the parent xenograft tissue. Colosphere-forming cells migrated in collagen I matrix and metastasised when subrenally implanted in nude mice. Besides, the colosphere responses to 5-fluorouracil and irinotecan, two standard drugs in CRC, reproduced those of the in vivo original xenografts. CONCLUSION: Colospheres closely mimic biological characteristics of in vivo CRC tumours. Consequently, they would be relevant ex vivo CRC models.

The above contents are the collected information from Internet and public resources to offer to the people for the convenient reading and information disseminating and sharing.

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