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**Tumor Progression and Therapeutic Resistance** - Wafik S. El-Deiry 2005
This volume presents the entire breadth of translational cancer research and brings together members of academia and industry in the expectation of accelerating interactions and progress in the field. A variety of key topics are presented, beginning with discovery of molecular targets and pathways (oncogene, cell survival, tumor suppression, cell death), host-neoplasm interactions (cell adhesion, matrix proteases), early detection, monitoring progression, understanding tumor progression and metastasis, immune surveillance, in vivo molecular imaging, animal models, drug discovery including chemistry, high-throughput assays, mechanism determination, target validation, therapeutic window and some progress in clinical trials for more advanced agents and targets.

**Diverse Effects of Hypoxia on Tumor Progression** - M. Celeste Simon 2010-09-28
Hypoxia, defined as reduced oxygen tension, is a common physiological phenomenon in both normal embryonic development and malignancy progression. Although severe hypoxia is generally toxic for both normal tissue and tumors, neoplastic cells gradually adapt to prolonged hypoxia though additional genetic and genomic changes with a net result that hypoxia promotes tumor progression and therapeutic resistance. Hypoxia promotes cancer progression by regulating various aspects of cancer biology, including radiotherapy resistance, metabolism, angiogenesis and invasion/migration.

**Tumor Microenvironment Promotes Cancer Progression, Metastasis, and Therapeutic Resistance** - Shian-Ying Sung 2007

**Impact of Cancer Plasticity on Drug Resistance and Treatment in Solid Tumors** - Dong-Hua Yang 2020-12-24

**New Targets in Tumor Angiogenesis to Block Tumor Re-growth and Therapeutic Resistance** - Nicklas Bassani 2017
Antiangiogenic drugs are used clinically for treatment of different types of cancers and in the case of...
renal cell carcinoma (RCC) are now standard first-line treatments (Rini, 2009). Nevertheless, these agents mainly serve to stabilize the disease but are not able to eliminate all tumor cells and resistance eventually develops concomitant with progression (Kerber and Folkman, 2002). Using different orthoxenograft mouse models of RCC we confirmed that inhibitors of the VEGF pathway have a therapeutic window of effectiveness but unfortunately adaptation and tumor relapse always occur. Several different mechanisms of resistance to antiangiogenics have been already described, many concerning the activation of compensatory signals that produce re-vascularization and tumor re-growth. (Bergers and Hanahan, 2008). In our study we determined that even if resistance is characterized by the up-regulation of the pro-angiogenic enzyme ECGF1 (previous data from the lab); re-vascularization does not occur, the vascular trimming is maintained by the treatment pointing to an alternative mode of adaptation. Using two different approaches, we demonstrated that PD-ECGF1 is responsible of the acquisition of resistance to anti-angiogenics. In fact, its enzymatic inhibition as second-line treatment post resistance resulted in the arrest and stabilization of tumor growth. PD-ECGF1 inhibition did not increase the anti-vascular effect of DC101, confirming that resistance was vessel independent, but dramatically affected tumor cell proliferation and apoptosis. Considering the numerous proprieties ascribed to its final metabolite 2-deoxy-D-ribose (Ikeda et al., 2006; Bjinsdorp et al., 2008), we evaluated its role, finding that recombinant 2-deoxy-D-ribose nullified the effect of AEAC on 786O- and Ren28 tumor growth rescuing tumor cell proliferation and apoptosis, without promoting re-vascularization. Overall these findings, confirmed also in an in vitro setting, demonstrate that tumor stroma plays a minor role in this model of anti-angiogenics resistance, and that PD-ECGF1 acts mainly intracellularly supporting tumor cell proliferation and protecting from apoptosis by its enzymatic activity and final metabolite 2-deoxy-D-ribose. Using a genetic approach in which PD-ECGF1 protein expression was silenced as a second line of treatment post DC101-resistance, mimicking what done pharmacologically, we confirmed and improved the anti-tumoral response described, without perceiving any doxycycline toxic effect. In fact, PD-ECGF1 genetic knock down resulted in a complete arrest of tumor progression enhancing the merely partial stabilization produce by AEAC treatment in 786O- tumor bearing mice. Unfortunately VEGFR-blockers can't be used in vitro on cancer cells, and to verify this hypothesis we decided to mimic the final effects of anti-angiogenic treatments, finding that under nutrient deprivation conditions cancer cells significantly up-regulate PD-ECGF1 expression, and metabolizing thymidine acquired considerable growth advantages. Finally, the analysis of plasma and tissue samples of ccRCC patients from the Bellvitge Hospital confirm in a clinical set that PD-ECGF1 is exclusively found in pathologic conditions, where if highly expressed correlates with poor prognosis, suggesting that might represent a good therapeutic predictor factor. Moreover, the analysis of tissues biopsies before and after anti-angiogenic treatment revealed that whilst PD-ECGF1 treatment-induce up-regulation was a common feature, the patients that unfortunately didn't respond showed the sharp difference, confirming PD-ECGF1 as a possible therapeutic target. -- TDX.

Application of the Single Cell Genomics in Deciphering Tumor Heterogeneity and Its Role in Tumor Progression and Drug Resistance-Nemanja Marjanovic 2021 Tumor progression, from the single mutated cell to the advanced stages of cancer, represents an evolutionary process. During tumor progression, cancer cells acquire new genetic mutations, becoming more heterogeneous, leading to tumor progression and resistance to therapy. However, clear genetic drivers of progression, metastasis, and therapeutic resistance are identified in only a subset of tumors, pointing to non-genetic contributors to cancer progression. Also, somatic evolution in cancer is occurring at the level of the single cell. Therefore, the application of the single cell genomic method is crucial for deciphering phenotypic heterogeneity. Here, we profiled single cell transcriptomes from genetically engineered mouse lung tumors at seven stages spanning tumor progression from atypical adenomatous hyperplasia to lung adenocarcinoma. The diversity of transcriptional states spanned by tumor cells increased over time and was reproducible across tumors and mice, but was not explained by genomic copy number variation. Cancer cells progressively adopted alternate lineage identities, computationally predicted to be mediated through a common transitional, high-plasticity cell state (HPCS). HPCS cells prospectively isolated from mouse tumors had robust potential for phenotypic switching and tumor formation and were more chemoresistant in mice. Our study reveals transitions that connect cell states across tumor evolution and motivates therapeutic targeting of the
Molecular Mechanisms of Tumor Cell Resistance to Chemotherapy
Benjamin Bonavida 2013-07-04 This volume gives the latest developments in on the mechanisms of cancer cell resistance to apoptotic stimuli, which eventually result in cancer progression and metastasis. One of the main challenges in cancer research is to develop new therapies to combat resistant tumors. The development of new effective therapies will be dependent on delineating the biochemical, molecular, and genetic mechanisms that regulate tumor cell resistance to cytotoxic drug-induced apoptosis. These mechanisms should reveal gene products that directly regulate resistance in order to develop new drugs that target these resistance factors and such new drugs may either be selective or common to various cancers. If successful, new drugs may not be toxic and may be used effectively in combination with subtoxic conventional drugs to achieve synergy and to reverse tumor cell resistance. The research developments presented in this book can be translated to produce better clinical responses to resistant tumors.

Programmed Cell Death in Cancer Progression and Therapy
Roya Khosravi-Far 2007-12-29 Programmed cell death (PCD) plays pivotal roles in tumor progression, cancer therapeutics and resistance of tumor cells to therapy. This book examines the mechanisms involved in mediating and regulating PCD in cancer. It also provides a detailed indication of the utility of PCD in cancer therapy. The book features chapters on the current and future of RNA interference in therapeutics and Pathways involved in Stem Cell Survival and Death.

New Aspects of Cancer Stem Cell Biology
Ugo Cavallaro 2020-11-23 The cancer stem cell (CSC) paradigm represents one of the most prominent breakthroughs of the last decades in tumor biology. CSCs are that subpopulation within a tumor that can survive conventional therapies and as a consequence are able to fuel tumor recurrence. Nevertheless, the biological characteristics of CSCs and even their existence, remain the main topic among tumor biologists debates. The difficulty in achieving a better definition of CSC biology may actually be explained by the plasticity of such a cell subpopulation. Indeed, the emerging view is that CSCs represent a dynamic “state” of tumor cells that can acquire stemness-related properties under specific circumstances, rather than referring to a well-defined group of cells. Regardless of their origin, it is clear that designing novel antitumor treatments based on the eradication of CSCs will only be possible upon unraveling the biological mechanisms that underlie their pathogenic role in tumor progression and therapy resistance. The Special Issue on “New aspects of cancer stem cell biology: implications for innovative therapies” aims at highlighting recent insights into CSC features that can make them an attractive target for novel therapeutic strategies.

Cancer Stem Cells: New Horizons in Cancer Therapies
Surajit Pathak 2020-10-17 This book discusses the recent developments in the therapeutic implications of cancer stem cells for the effective diagnosis, prognosis, and treatment of cancer. It summarizes the various stem cells of common cancers including colon, pancreas, lungs, prostate, melanoma, and glioblastoma, and reviews the potential role of cancer stem cells in tissue aggressiveness, examining the functional contribution of cancer stem cells in the establishment and recurrence of cancerous tumors. Further, it explores the potential of cancer stem cells as novel therapeutic targets for the treatment and prevention of tumor progression. The book also discusses the various approaches for detecting, isolating, and characterizing different cancer stem cells and signaling pathways that control their replication, survival, and differentiation. Lastly, it explores the key features and mechanisms of drug resistance, chemo-resistance, and radio-resistance in cancer stem cells to improve therapeutic rationale.

Abrogating the Protumorigenic Impact of Tumor-infiltrating Myeloid Cells During Prostate Cancer Therapy
Jemima Escamilla 2013 Despite recent advances in treatment modalities for advanced prostate cancer (PCa) and castration-resistant prostate cancer (CRPC), PCa continues to be a major cause of morbidity and mortality in American men. An improved understanding of the tumor microenvironment and immune surveillance has
The primary cause of treatment failure is the development of cellular resistance to the cytotoxic effects of cancer therapeutics. Both cell intrinsic and extrinsic mechanisms can underlie this acquired therapeutic resistance. More recently, the tumor microenvironment, and more importantly tumor-related inflammation, have emerged as crucial players in promoting cancer initiation and progression, invasion and metastasis, and resistance to both conventional and targeted therapies. In particular, there have been fundamental leaps in our understanding of the complex roles of tumor-infiltrating myeloid cells (TIMs). TIMs are a heterogeneous population of monocytic and granulocytic myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs) that have a profound impact on tumor development. TIMs have been reported to promote tumor growth. In PCa, first-line radiotherapy (RT) and blockade of androgen signaling have potent anti-cancer effects, but PCa patients inevitably develop resistance mechanisms to evade therapy. Recently, elevated inflammation has been demonstrated after RT and androgen inhibition, yet the impact of this aberrant inflammation and the potential therapeutic options for preventing resistance in PCa have been largely unexplored. Therefore, we sought to further understand the impact of inflammation in acquired resistance to these two important therapeutic strategies, and whether combinatorial therapies may prevent resistance and improve therapeutic effectiveness.

Our laboratory and others have shown a critical role for macrophage colony-stimulating factor-1 (M-CSF-1, CSF-1) signaling through its receptor, CSF1R, in the recruitment of TIMs to tumors, which promote cancer progression. Using murine models of prostate cancer, we found that RT resulted in pronounced increases in CSF-1 expression in PCa cells, which was transcriptionally regulated by the non-receptor tyrosine kinase, ABL1 (c-Abl), highly correlating with increased TIM recruitment. Importantly, utilizing a CSF1R inhibitor, PLX3397, in combination with RT resulted in significant depletion of TIMs and delayed RT tumor recurrence. In parallel, the potential impact of TIMs in therapeutic resistance to androgen blockade therapy (ABT) was also interrogated. Similarly to RT, we found that inhibiting androgen signaling using the novel androgen receptor inhibitor MDV3100 (Enzalutamide) resulted in enhanced expression anti-inflammatory cytokine IL-10 and Th2 cytokine IL-13 in PCa cells, as well as CSF-1 expression in PCa cells and in mice sera. Moreover, cellular interactions between macrophages and PCa cells treated with MDV3100 skewed macrophages to a protumorigenic "alternative" activation state. In addition, tumors grown in surgically castrated mice showed increased CSF-1 expression in serum and in whole tumors compared to sham surgery mice, resulting in a considerable increase in TAM infiltration. More importantly, TAM blockade using PLX3397 in combination with castration resulted in a significant delay in the onset of CRPC. Lastly, we sought to further investigate potential mechanisms underlying TIM-mediated resistance to androgen depletion. Cytotoxic effects of androgen depletion are primarily due to induction of apoptosis after inhibition of androgen receptor (AR) signaling. Insulin-like growth factor 1 receptor (IGF1R) signaling is a well-established mode of CRPC development due to its anti-apoptotic and mitogenic functions. Furthermore, the Th2 cytokine IL-13, is known to induce IGF-1 expression in macrophages. Interestingly, we found that the increased IL-13 expression from MDV3100 treated Myc-CaP cells, correlated with increased macrophage IGF-1 expression. Subsequently, macrophage-derived IGF-1 levels correlated with increased p-IGF1R staining in tumors from castrated mice versus sham surgery controls. Additionally, tumors grown in castrated mice showed a significant increase in IGF-1 expression, and a subsequent reduction of IGF-1 levels upon macrophage depletion with PLX3397. Macrophage depletion also correlated with decreases in Ki67 proliferation index, as well as delayed onset of CRPC. Collectively, these data suggest that a strong interplay between TIMs and tumor cells generate a pro-tumor microenvironment that favors therapeutic resistance in PCa. Overall, these studies increase our understanding of the complex role of TIMs in the prostatic microenvironment, and argue in favor of their contribution to PCa progression and therapeutic resistance to RT and therapies targeting androgen signaling. The rational targeted therapies pursued here and other combinatorial approaches hold promise to improve the long-term efficacy of new therapeutics and ultimately improve patient lives.

**Regulators of the Breast Tumor Immune Microenvironment**

Yeni Romero 2020 Tumors consist of a diverse population of cancer cells as well as various tumor-infiltrating immune cells, soluble factors, and extracellular matrix proteins, which are collectively known as the tumor immune microenvironment (TIME). The interactions between cancer cells and their microenvironment heavily influence tumor progression and therapeutic
responses, often leading to tumor immune evasion and therapeutic resistance. Understanding these complex interactions will help develop novel strategies to target tumor cells or improve the efficacy of existing therapies. The goal of my research was to explore the role of two regulators of the tumor immune microenvironment, PD-L1 and regulatory T cells, in triple negative breast cancer (TNBC). Programmed death-ligand 1 (PD-L1) is a negative regulator of the immune system that acts as a "brake" to keep the body's immune responses under control. However, in cancer, PD-L1 expression leads to immune evasion and poor disease outcomes. In breast cancer, PD-L1 expression is most upregulated in the TNBC subtype. Under certain circumstances, transmembrane PD-L1 can be cleaved, generating a soluble form containing an intact receptor-binding domain. In my research, I investigated the cleavage of PD-L1 expressed on the surface of tumor cells. I found that a ~37-kDa N-terminal cleavage product of PD-L1 is released to the culture media. Analysis of the ~18-kDa C-terminal PD-L1 fragment demonstrated that this fragment is unstable and readily eliminated by lysosomal degradation. Furthermore, I identified ADAM10 and ADAM17, two members of the cell surface family of ADAM metalloproteases, as mediators of the cleavage of transmembrane PD-L1. Regulatory T cells (Tregs) are a subset of T cells that play a role in regulating or suppressing other immune cells. Tregs regulate the immune response to self and foreign antigens and help prevent autoimmune diseases by maintaining immune homeostasis. In cancer, Tregs are involved in tumor development and progression by inhibiting effector cells and reducing anti-tumor immunity. In TNBC, infiltration of Tregs into the TIME is often associated with resistance to anti-PD-L1 therapy and poor patient survival. Therefore, a better understanding of the mechanisms regulating the numbers of Tregs in the TIME of TNBC is necessary to tackle the problem of immunotherapy resistance. Claudin-low breast tumors are known to have increased numbers of tumor-infiltrating lymphocytes, specifically Tregs, as well as upregulated expression levels of ADAM12, an active ADAM metalloprotease. My goal was to investigate the role of ADAM12 in T cell accumulation to the tumor microenvironment in vivo using a mouse transplantation model of claudin-low breast cancer. Specifically, I investigated the accumulation of Tregs and other T cell subsets to tumors with or without expression of ADAM12. I found that the frequency of Tregs in tumor immune infiltrates was increased in tumors that lacked ADAM12 expression. Collectively, these findings give insight into the complex regulatory roles that PD-L1 and Tregs play in the breast cancer TIME.

**Tumor Hypoxia** Zhong Yun 2016-12-22 Tumors often start out as a benign growth, but gradually progress toward the malignant stage over a relatively long period of time. Tumor progression results from accumulated genetic mutations and inheritable epigenetic modifications that enable clonal evolution and selection of new clonal populations of tumor cells with aggressive characteristics including metastasis and therapy resistance. Increasing amounts of experimental evidence suggests that tumor microenvironment play a significant role in directing clonal evolution and determining clonal cell fate, which eventually leads to emergence of malignant tumor cell clones. Hypoxia is the most commonly observed feature of tumor microenvironment. Tumor hypoxia is significantly associated with malignant progression and predicts poor patient outcomes. This book provides detailed and up-to-date treaties on the role of hypoxia as a major driving force in tumor microenvironment to elicit cellular adaptation and clonal selection via genetic mutations and epigenetic modifications, to facilitate cancer stem cell maintenance, to enhance metastasis, to augment therapy resistance, and to evade immune surveillance.

**Genes and Cancer** Guy-Joseph Lemamy 2019-09-11 Cancer is a malignant tumor caused by DNA damage, which leads to uncontrolled cell growth. Tumor progression is locally favored by the mitogenic effects of hormones or growth factors, which stimulate the tumor's growth, or the activation of vascular endothelial growth factor receptor, which induces angiogenesis and leads to metastasis. About 300 out of 25,000 genes that set up the human genome are involved in cancer pathology. These genes are divided into three groups: oncogenes, tumor suppressor genes, and DNA repair genes. Activated oncogenes promote the development of cancer, whereas the tumor suppressor and DNA repair genes have a protective role by respectively inhibiting cell cycle progression and inducing apoptosis, or by repairing DNA damage occurring during the cell cycle. This book discusses the issue of tumor suppressor genes through chapters written by experts using advanced biochemistry, cell, and molecular biology tools. The tumor suppressor genes can be used as markers of risk to identify populations with...
high risk or targets for cancer treatment and therapeutic resistance. We hope that the work provided in this book will be useful for researchers and students and will increase knowledge of the understanding of cancer and improve its treatment.

Genomic Instability and Cancer Metastasis-Chris Maxwell 2014-12-04
Metastasis is the primary cause of mortality associated with cancer, and tumor genomic heterogeneity is a likely source for the cells that support cancer progression, resistance to therapy, and disease relapse. This book connects cancer metastasis with genomic instability in a comprehensive manner. Section 1 outlines the fundamental mechanisms responsible for these cellular and tissue phenotypes. Section 2 discusses in silico, in vitro, and in vivo models used for the experimental study of these processes. Section 3 reviews emerging themes (ex., microenvironment, mechanotransduction, and immunomodulation), and Section 4 highlights new therapeutic approaches to overcome the unique challenges presented by the heterogeneous and metastatic tumor. This book is intended for undergraduates and postgraduates with an interest in the areas of medicine, oncology, and cancer biology as well as for the content expert searching for thorough reviews of current knowledge in these areas.

Finding Common Ground to Treat Primary and Metastatic Cancer- Albert Lo 2016
Primary carcinomas and metastases are complex organ-like structures composed of malignant parenchymal epithelial tissues and a desmoplastic stroma formed by accumulation of hematopoietic cells, mesenchymal stromal cells and extracellular matrix. The crosstalk between malignant epithelial cells and tumor stroma is becoming increasingly appreciated as a key determinant in tumor development, progression and metastasis, as well as inducing resistance to various cancer treatments including chemotherapy, radiotherapy and immunotherapy. Mechanistic understanding of how the tumor-stromal interaction contributes to tumor progression and therapeutic resistance will advance cancer therapies and improve clinical management, especially for patients with metastatic disease. Fibroblast activation protein (FAP) is a membrane surface protease found overexpressed in cancer-associated stromal cells. Overexpression of FAP is associated with tumor progression, metastasis and recurrence, and predicts a poorer prognosis in many types of human tumors. The central goal of my thesis project is to investigate whether FAP protease and/or FAP protease-expressing stromal cells play essential roles in tumor progression and metastasis. In collaboration with Drs. Steven Albelda and Carl June's groups, we generated chimeric antigen receptor (CAR) T cells redirected against FAP+ stromal cells to study their impact on tumor progression. Conditional depletion of FAP+ stromal cells by FAP-CAR T cells restrains tumor progression without causing severe toxicity. Mechanistic investigations revealed that FAP+ stromal cells promote tumor growth via immune suppression and immune-independent remodeling of the stromal microenvironment. Additionally, using FAP-deficient mice, I found that FAP protease promotes early malignant cell seeding and pulmonary metastatic outgrowth, possibly through regulating coagulation pathways and the inflammatory response, respectively. Finally, I observed that FAP protease promotes pancreatic cancer development, as its deletion delays the progression of preneoplastic lesions and tumor formation in a genetically engineered mouse model of pancreatic ductal carcinoma. FAP protease is also essential for inducing pancreatic cancer resistance to necrotic cell death and promoting metastasis and outgrowth in multiple target organs. Together, these findings demonstrate that molecular and cellular targeting of FAP represents a promising therapeutic approach for a variety of solid tumors.

Epigenetics and Cancer-Fazlul H. Sarkar 2013-05-29
Overall, this book illustrates the complexities of the regulation and deregulation of genes mediated through epigenetics in the development and progression of human malignancies. All the articles have been carefully chosen to represent several cancer systems with state of our knowledge on the role of epigenetic deregulation of microRNAs (miRNAs) and their target mRNAs along with epigenetic deregulation of mRNAs. This book also illustrates the role of several dietary agents, collectively called nutraceuticals or natural agents in modulating the epigenetic reprogramming of miRNAs and mRNAs for the prevention and/or treatment of human malignancies. It is well known that genetic aberrations, especially inherited through parents (somatic genetic alterations) contribute to the development of less than 10% of all cancer yet epigenetic alterations in genes especially through selective methylation and acetylation appears to be responsible for the development and progression
of the vast majority of all cancers. Therefore, understanding the role of epigenetics in the regulation of genes especially through deregulated expression of miRNAs as presented in this book will allow scientists to devise targeted therapeutic strategies for re-expression of the lost genes or down-regulate the genes that are over-expressed in order to eradicate cancer. It is hoped that targeting epigenetics will not only target cancer cells but it will also target the tumor microenvironment (more like the entire tumor environment such as the entire host) for achieving better treatment outcomes for patients diagnosed with cancer which will lead to achieve the long-term objective for complete eradication of cancer. This book contains fifteen chapters which begins with the concept of systems and network biology for investigating the epigenetics of cancer followed by a series of articles on the role of miRNAs and their target genes in the biology of pancreatic cancer and other cancers such as breast, kidney, prostate and colon. Since it is becoming increasingly clear that cancer stem cells (CSCs) are important in the development and progression of cancer, and CSCs are important in therapeutic resistance, treatment failure and tumor recurrence, thus the importance of CSCs and epigenetics has been highlighted by a very timely article on epigenetic variations of stem cell markers in cancer including miRNAs. Moreover, just targeting heterogeneous cancer cell populations may not be optimal to eradicate tumors and for which one must take a holistic approach for developing drugs that could also target the tumor microenvironment and tumor dormancy that are regulated through epigenetics. Keeping abreast with this thought process the concluding chapter provides a concept towards curative cancer therapy with maspin, which could be a unique window of opportunity to target tumor dormancy. Therefore, it suggest that targeting the tumor dormancy and the tumor microenvironment using novel therapeutics specifically by targeting epigenetics would become the future of medicine.

Cancer Drug Resistance-Beverly A. Teicher 2007-11-09 Leading experts summarize and synthesize the latest discoveries concerning the changes that occur in tumor cells as they develop resistance to anticancer drugs, and suggest new approaches to preventing and overcoming it. The authors review physiological resistance based upon tumor architecture, cellular resistance based on drug transport, epigenetic changes that neutralize or bypass drug cytotoxicity, and genetic changes that alter drug target molecules by decreasing or eliminating drug binding and efficacy. Highlights include new insights into resistance to antiangiogenic therapies, oncogenes and tumor suppressor genes in therapeutic resistance, cancer stem cells, and the development of more effective therapies. There are also new findings on tumor immune escape mechanisms, gene amplification in drug resistance, the molecular determinants of multidrug resistance, and resistance to taxanes and Herceptin.

Multi-Drug Resistance in Cancer-Jun Zhou 2012-08-09 Chemotherapy is one of the major treatment options for cancer patients; however, the efficacy of chemotherapeutic management of cancer is severely limited by multidrug resistance, in that cancer cells become simultaneously resistant to many structurally and mechanistically unrelated drugs. In the past three decades, a number of mechanisms by which cancer cells acquire multidrug resistance have been discovered. In addition, the development of agents or strategies to overcome resistance has been the subject of intense study. This book contains comprehensive and up-to-date reviews of multidrug resistance mechanisms, from over-expression of ATP-binding cassette drug transporters such as P-glycoprotein, multidrug resistance-associated proteins, and breast cancer resistance peptide to the drug ratio-dependent antagonism and the paradigm of cancer stem cells. The book also includes strategies to overcome multidrug resistance, from the development of compounds that inhibit drug transporter function to the modulation of transporter expression. In addition, this book contains techniques for the detection and imaging of drug transporters, methods for the investigation of drug resistance in animal models, and strategies to evaluate the efficacy of resistance reversal agents. The book intends to provide a state-of-the-art collection of reviews and methods for both basic and clinician investigators who are interested in cancer multidrug resistance mechanisms and reversal strategies. Tianjin, China Jun Zhou v Contents Preface. .. ix 1 Multidrug Resistance in Cancer .. 1 Bruce C. Baguley 2 Multidrug Resistance in Oncology and Beyond: From Imaging of Drug Efflux Pumps to Cellular Drug Targets .. 

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A recent surge in stem cell research has ignited a field of discovery into tumor progression and therapeutic resistance. The criteria that define cancer stem cells are continuing to evolve. Stem Cells to Tumor Development—Cancer stem cells remain a controversial topic and the etiology and progression of EOC.

Ten articles detail established and novel in vivo and in vitro model systems. These include primary and immortalized cell culture in 2D and 3D as well as genetically engineered, transgenic, spontaneous, syngeneic, classical xenograft and patient derived xenograft mouse models. The generation of genetically engineered mouse models of HG-SOC has been a major dilemma as models with the oncogenic aberrations common in the human malignancy do not accurately recapitulate HG-SOC. Conversely, commonly used HG-SOC cell lines have been found to not harbor the expected genetic changes. These issues as well as the rapid acceptance of patient derived xenograft models are reviewed. Five articles discuss different aspects of the tumor microenvironment including its role in therapy resistance, disease progression and metastasis. Mutation of BRCA1/2 continues to be the best defined risk factor for HG-SOC. Three articles discuss BRCA-loss in the context of disease development, targeted therapies and changes in preventative measures proposed for mutation carriers in light of the recent advances in knowledge regarding the origins of this malignancy. An image of HG-SOC with reduced BRCA1 expression is featured on the cover (image by VM Howell). A major clinical issue for patients with HG-SOC is the development of therapy resistance. Five articles focus on therapy resistance and different ways to overcome resistance. Overall, this eBook is an outstanding resource to aid researchers design their programs of research and determine the most appropriate and up-to-date EOC model systems to address their research questions.

**Stem Cells and Cancer**—Rebecca G. Bagley 2009-04-20 Significance of Stem Cells to Tumor Development Cancer stem cells remain a controversial topic and the criteria that define cancer stem cells are continuing to evolve. A recent surge in stem cell research has ignited a field of discovery into many human diseases including diabetes, neuropathologies, and cancer. By replacing specific differentiated cells that have either been lost or died, stem cell therapy proves to be a very promising approach to the treatment of many debilitating diseases. Though stem cells may provide therapeutic benefit under certain conditions, they are also often implicated in the initiation, progression, and therapeutic resistance of malignant disease. This first edition of Stem Cells and Cancer is intended to give a current perspective on the role of stem cells in cancer and strategies for novel therapies directed toward tumor stem cells. The current cancer stem cell hypothesis is presented in several chapters with distinctions made between the hierarchical and stochastic models of tumor cell development. “Stemness,” self-renewal, pluripotency, clonality, and tumorigenicity are important concepts applied towards defining cancer stem cells. Signaling pathways such as Wnt, Sonic Hedgehog, Notch, and Bmi-1 that are involved in differentiation, proliferation, and survival are implicated in the malignant process. Additional chapters address the identification of cancer stem cell populations through the evaluation of molecular markers such as CD133, CD44, and CD24, for example, or by Hoechst dye exclusion to recognize ‘side populations.’ Mesenchymal and hematopoietic stem cells are described as well as mouse models that are employed to elucidate the properties and functionality of stem cells in cancer and the stem cell niche. This book encompasses a wide variety of human cancers that include but are not limited to leukemia, gliomas, breast, and prostate cancers. Resistance to conventional therapies, genetic versus epigenetic changes that affect therapeutic response and strategies to prevent disease recurrence are challenges have been incorporated into this volume. Stem Cells and Cancer represents a compendium of cutting edge research by experts in the field and will be instrumental in the study of this intriguing line of investigation for many years to come. Rebecca Bagley is a senior scientist at Genzyme Corporation and has worked in the biotechnology industry for 20 years with degrees in biology from Wellesley College and Harvard University. Her expertise in drug development spans a wide range of approaches including immunotherapies, gene and protein therapies, and small molecule delivery with publications in journals such as Molecular Cancer Therapeutics, Cancer Research, and Microvascular Research. Her current research focuses on stem cells, tumor vasculature, and target validation. Dr. Beverly A. Teicher is Vice President of Oncology Research at Genzyme Corporation. Dr. Teicher completed a PhD in Bioorganic Chemistry at the Johns Hopkins University.
University and postdoctoral training at Yale University School of Medicine. Dr. Teicher joined Dana-Farber Cancer Institute as an Assistant Professor of Pathology and rose to Associate Professor of Medicine and Radiation Therapy, Harvard Medical School at Dana-Farber Cancer Institute and Joint Center for Radiation Therapy. Dr. Teicher is an active member of the international scientific community having authored or co-authored more than 400 scientific publications. She has edited eight books, is senior editor for the journal Clinical Cancer Research and is series editor for the Cancer Drug Discovery and Development book series.

Tumor Microenvironment - Alexander Birbrair 2020-02-10 Revealing essential roles of the tumor microenvironment in cancer progression, this volume focuses on non-hematopoietic cells within the tumor microenvironment. Further, it teaches readers about the roles of distinct constituents of the tumor microenvironment and how they affect cancer development. Topics include fibroblasts, adipocytes, mesenchymal stem cells, stellate cells, and more. Taken alongside its companion volumes, Tumor Microenvironment: Non-Hematopoietic Cells updates us on what we know about the different aspects of the tumor microenvironment as well as future directions. Useful for introducing the newer generation of researchers to the history of how scientists focused in the tumor microenvironment and how this knowledge is currently applied for cancer treatments, it will be essential reading for advanced cell biology and cancer biology students as well as researchers seeking an update on research in the tumor microenvironment. All of the chapter authors are renowned international experts in the cancer biology field in specific subfields that will be the focus of their chapters.

Resistance to Molecular Therapies for Hepatocellular Carcinoma - Augusto Villanueva 2017-09-07 This volume evaluates the clinical patterns of resistance to sorafenib, the impact of trial design in the second-line setting and the current gold standard to define radiological resistance; describes the molecular mechanisms responsible for treatment resistance in HCC patients, including components of the immune system and tumor microenvironment; determines the role of the cancer stem cell phenotype in resistance; reviews the experimental models to study resistance; and addresses new approaches to overcome resistance to sorafenib, using successful examples from other malignancies.

PEAK1 Function in Breast Cancer Stroma - Sarkis Gabriel Hamalian 2018 The cellular and molecular heterogeneity of solid tumors presents a significant hurdle in the effort to develop effective anti-cancer therapies. Since PEAK1 (Pseudopodium-Enriched Atypical Kinase One) is a cytoskeleton-associated kinase that regulates growth factor receptor-integrin crosstalk to promote cell state plasticity and mesenchymal cell phenotypes, we hypothesized that PEAK1 expression in the mesenchymal compartment of the breast cancer (BC) microenvironment may contribute to tumor progression and/or therapy resistance. We report that elevated stromal expression of PEAK1 predicts breast cancer recurrence and that the correlation between PEAK1 and mesenchymal marker levels increases in the stroma of patients with relapsed disease. In agreement with these data, PEAK1 is expressed in patient-derived breast cancer-associated fibroblasts (CAFs) and other mesenchymal stroma cell (MSC) types. Co-xenografting CAFs or MSCs with HER2-positive and ER-positive breast cancer cells increased primary tumor mass and promoted targeted therapy resistance. Notably, PEAK1 knockdown in MSCs abrogated these in vivo pro-tumorigenic microenvironment phenotypes. To determine whether these PEAK1-dependent pro-tumorigenic effects of CAFs and MSCs are mediated by paracrine or juxtacrine mechanisms, breast cancer cells were grown in CAF/MSC conditioned media (CM) or co-culture conditions. Both CAF/MSC CM and co-culture conditions increased breast cancer cell proliferation/survival and resistance to HER2-targeted therapies, and MSC expression of PEAK1 was necessary for both CM- and co-culture-mediated breast cancer cell survival and therapy resistant phenotypes. Analysis of the MSC proteome revealed that PEAK1 sustains expression and BC secretome induced secretion of Cripto (TDGF1). Finally, elevated PEAK1/Cryptic levels predict poor breast cancer patient outcome. Taken together, this work identifies new PEAK1-dependent tumor microenvironment signaling vulnerabilities that may be harnessed to improve patient responses to current therapeutic interventions.

Metastatic Progression and Tumour Heterogeneity - Fred Hollande
Improved understanding of the cellular and molecular makeup of tumors in the last 30 years has unraveled a previously unexpected level of heterogeneity among tumor cells as well as within the tumor microenvironment. The concept of tumor heterogeneity underlines the realization that different tumors can display significant differences in their genomic content as well as in their overall behavior. Our capacity to better understand the heterogeneous make up of tumors has very important consequences on our ability to design efficient therapeutic strategies to improve patient survival. This book highlights several aspects of tumor heterogeneity in the context of metastatic development and summarize some of the challenges posed by heterogeneity for tumor diagnostics and therapeutic management of tumors.

Current Applications for Overcoming Resistance to Targeted Therapies - Myron R. Szewczuk 2019-07-15

Targeted therapies were initially developed to exploit the upregulation and dependence on key oncogenic pathways critical to cancer progression. Additionally, they also presented as a method to overcome chemoresistance by supplementing conventional therapeutic regimens with targeted therapies. However, the development of resistance to these combinatorial approaches has led to the reassessment of currently available therapeutic options to overcome resistance to targeted therapy. This book aims to provide an update on the advancements in the therapeutic arms race between cancer, clinicians and scientists alike to overcome resistance to targeted therapies. Subject experts provide a comprehensive overview of the challenges and solutions to resistance to several conventional targeted therapies in addition to providing a discussion on broad topics including targeting components of the tumor microenvironment, emerging therapeutic options, and novel areas to be explored concerning nanotechnology and the epigenome.

Defining the Role of Neuropilin-2 in Macrophages: Implications in Tumor Associated Macrophages in Pancreatic Cancer - Sohini Roy 2017

Macrophages are extremely heterogeneous and highly plastic hematopoietic cells that reside in all tissues and act as a bridge between the innate and adaptive arms of the immune responses. Besides, they undertake a wide array of housekeeping functions like, clearance of cellular debris that arise due to regular turnover in tissues, iron homeostasis, immune surveillance as well as tissue repair processes post inflammation. They are also causally associated with several clinical conditions, including cancer where the infiltration of macrophages contribute to disease progression, metastasis and therapy resistance, and thereby poor clinical outcome. Neuropilins (NRPs) are non-tyrosine kinase cell surface glycoproteins expressed in all vertebrates and widely conserved across species. The two isoforms, NRP1 and NRP2 are mainly known for their role as co-receptors for class III Semaphorins and for members of the vascular endothelial growth factor (VEGF) family of molecules. Both NRP1 and NRP2 are overexpressed in many cancers, exert pleiotropic effects in various aspects of cancer pathobiology and correlate with the stage and grade of the disease and poor survival. Intriguingly, additional immunoregulatory roles for NRPs have been reported in myeloid and lymphoid cells, in normal physiological as well as different pathological conditions, including cancer, various immunological disorders, and bone diseases. In comparison to NRP1, the overall comprehensive function of NRP2 in macrophages and factors that govern those functions is not well known. Therefore, the enveloping goal of this dissertation is to comprehensively understand the role and function of NRP2 in macrophages and their implication in tumor associated macrophages in solid tumor. In the first part of the dissertation, we primarily investigated the expression pattern of NRP2 during the differentiation of macrophages under inflammatory (M1) and immunosuppressive (M2) polarizing conditions. We observed although NRP2 is not expressed at a detectable level in monocytes, its expression is upregulated during the differentiation of monocytes precursors to either M1 or M2 type mature macrophages. We identified a novel function of NRP2 in regulating phagocytosis in macrophages by modulating the levels of Rab5+ early phagosomes and Rab7+ late phagosomes. In NRP2 depleted macrophages clearance of bacteria or yeast components was delayed and these cells exhibited elevated number of early phagosomes and decreased number of late phagosomes. Since pancreatic cancer (PC) typifies the complex architecture of a tumor stroma and tumor associated macrophages are abundantly present here, the second part of the dissertation is aimed at elucidating the implication of NRP2 regulated phagocytosis in TAMs in this lethal disease. The expression NRP2 in TAMs in human and mouse PC tissues was assessed. Due to nutrient limiting conditions and rapid
proliferation of tumor cells in the TME, many of the cancer cells undergo apoptosis. TAMs efferocytose these dying tumor cells, an event that polarizes them further to pro-tumoral type and contribute to relapse and therapy resistance. We observed that in the absence of NRP2, clearance of apoptotic cells was delayed. The implication of this observation in PC progression was tested using a subcutaneous tumor model. Upon depletion of NRP2 in TAMs, tumors were smaller. Of note, NRP2 depletion did not affect TAM recruitment to, or angiogenesis but recruited and activated anti-tumor CD8 cells into the TME. Further, RNA-Seq analysis of CD11b+ TAMs isolated from tumors indicated that many genes associated with either endosomal/phagosomal maturation, recycling and exocytosis, immune modulation and leukocyte recruitment and activation are deregulated following NRP2 depletion. Further, NRP2 depletion downregulated many of the immunosuppressive genes and cytokines in macrophages that may be important for either suppression of T cell response or induce Treg formation. The data further suggested that NRP2 is important for efferocytosis and maintaining TAM-like phenotype in intratumoral macrophages, thus helping to create a tumorigenic immunosuppressive environment in the TME. Taken together, studies in this dissertation document a requirement for NRP2 in macrophage phagocytosis. Further, regulation of efferocytosis in TAMs by NRP2 have implications in TAM functions and tumor progression. Hence, targeting NRP2 axis in TAMs may help re-engineer the immunosuppressive stroma in the TME and emerge as potential therapy in combination with chemotherapy or other adjuvant therapies.

Computational Analysis of Cell-cell Communication in the Tumor Microenvironment - Manu Prajapati Kumar 2019 Cell-cell communication between malignant, immune, and stromal cells influences many aspects of in vivo tumor biology, including tumorigenesis, tumor progression, and therapeutic resistance. As a result, targeting receptor-ligand interactions, for instance with immune check-point inhibitors, can provide significant benefit for patients. However, our knowledge of this complex network of cell-cell interactions in a tumor microenvironment is still incomplete, and there is a need for systematic approaches to study cell-cell communication. This thesis presents computational approaches for characterizing cell-cell communication networks in three different experimental studies. In the first study, we modeled metastatic triple negative breast cancer in the liver using a microphysiological system and identified inflammatory cytokines secreted by the microenvironment that result in the proliferation of dormant metastases. In the second study, we used single-cell RNA sequencing (scRNA-seq) to quantify receptor-ligand interactions in six syngeneic mouse tumor models. To identify specific receptor-ligand interactions that predict tumor growth rate and immune infiltration, we used receptor-ligand interactions as features in regression models. For the third study, we extended our scRNA-seq approach to include inferences of single-cell signaling pathway and transcription factor activity. We then identified protein-protein interaction networks that connect extra-cellular receptor-ligand interactions to intra-cellular signal transduction pathways. Using this approach, we compared inflammatory versus genetic models of colorectal cancer and identified cancer-associated-fibroblasts as drivers of a partial epithelial-to-mesenchymal transition in tumor cells via MAPK1 and MAPK14 signaling. Overall, the methods developed in this thesis provide a foundational computational framework for constructing "multi-scale" models of communication networks in multi-cellular tissues.

Tumor Progression and Metastasis - 2020-04-08 This book offers significant coverage on different aspects of cancer from risk factors to the mechanisms leading to tumor progression and metastasis. Although tremendous progress has been made in cancer research and treatment, cancer metastasis remains a major unmet clinical need. The life and death of many cancer patients hangs on the degree of metastasis. This book provides new perspectives for diagnosis and cancer therapy. It includes new technologies and a new basis for current cancer therapies. To guarantee the high quality of this book, important topics are included and rigorously discussed in a simple and authentic way. The book addresses important challenges governing tumor progression and metastasis and brings new responses to both diagnosis and therapy. This book is a great source of knowledge and will be useful for researchers, medical doctors, oncologists, graduate and medical students, continued medical educators, health care providers, and all individuals interested in understanding cancer and its challenges.
Microfluidic Models of Tumor-stroma Interactions to Study the Interplay of Cancer Cells with Their Surrounding Microenvironment - Danh Truong 2018

According to the World Health Organization, cancer is one of the leading causes of death around the world. Although early diagnostics using biomarkers and improved treatments with targeted therapy have reduced the rate of cancer related mortalities, there remain many unknowns regarding the contributions of the tumor microenvironment to cancer progression and therapeutic resistance. The tumor microenvironment plays a significant role by manipulating the progression of cancer cells through biochemical and biophysical signals from the surrounding stromal cells along with the extracellular matrix. As such, there is a critical need to understand how the tumor microenvironment influences the molecular mechanisms underlying cancer metastasis to facilitate the discovery of better therapies. This thesis described the development of microfluidic technologies to study the interplay of cancer cells with their surrounding microenvironment. The microfluidic model was used to assess how exposure to chemoattractant, epidermal growth factor (EGF), impacted 3D breast cancer cell invasion and enhanced cell motility speed was noted in the presence of EGF validating physiological cell behavior. Additionally, breast cancer and patient-derived cancer-associated fibroblast (CAF) cells were co-cultured to study cell-cell crosstalk and how it affected cancer invasion. GPNMB was identified as a novel gene of interest and it was shown that CAFs enhanced breast cancer invasion by up-regulating the expression of GPNMB on breast cancer cells resulting in increased migration speed. Lastly, this thesis described the design, biological validation, and use of this microfluidic platform as a new in vitro 3D organotypic model to study mechanisms of glioma stem cell (GSC) invasion in the context of a vascular niche. It was confirmed that CXCL12-CXCR4 signaling is involved in promoting GSC invasion in a 3D vascular microenvironment, while also demonstrating the effectiveness of the microfluidic as a drug screening assay. Taken together, the broader impacts of the microfluidic model developed in this dissertation include, a possible alternative platform to animal testing that is focused on mimicking human physiology, a potential ex vivo platform using patient-derived cells for studying the interplay of cancer cells with its surrounding microenvironment, and development of future therapeutic strategies tailored toward disrupting key molecular pathways involved in regulatory mechanisms of cancer invasion.

Hegel and Feminist Social Criticism - Jeffrey A. Gauthier 1997-01-01

Hypoxia, defined as reduced oxygen tension, is a common physiological phenomenon in both normal embryonic development and malignancy progression. Although severe hypoxia is generally toxic for both normal tissue and tumors, neoplastic cells gradually adapt to prolonged hypoxia though additional genetic and genomic changes with a net result that hypoxia promotes tumor progression and therapeutic resistance. Hypoxia promotes cancer progression by regulating various aspects of cancer biology, including radiotherapy resistance, metabolism, angiogenesis and invasion/migration.

The Role of Serum Ferritin in Breast Tumorigenesis - Ahmed A. Alkhateeb 2013

Prognostic and Therapeutic Applications of RKIP in Cancer - Benjamin Bonavida 2020-02-03

Prognostic and Therapeutic Applications of RKIP in Cancer provides updated reviews on the chemistry, signaling, pre-clinical and clinical activities, and role of RKIP expression levels for diagnostics, prognosis and potential interventions. The development of novel compounds and conjugates that selectively induce RKIP expression in cancer open a novel era of new therapeutics and their potential in the treatment of highly resistant cancers and metastases. Edited and written by internationally renowned experts in the field of novel therapeutics for cancer, this book is a valuable source for cancer researchers, medical scientists, clinicians, clinical pharmacologists, and graduate students. Provides an update from experts in the field on diagnostics, prognostics and therapeutics Brings a clear overview of recent findings and references, as well as summaries, significant molecular pathways, and conclusions in each chapter Provides a general introductory chapter on contributions in the field and a chapter summary, with synthesized findings and a projection of future goals.

Expression Levels of the Nuclear Coactivator AIB1 in Drug
Resistance and Tumor Progression of Triple Negative Breast Cancer
Francisco Rodolfo Saenz 2019 Breast cancer is the most diagnosed cancer and the most frequent cause of cancer mortality in women worldwide. Immunoreactive assays as well as gene expression profiling of breast cancer have shown a high degree of heterogeneity resulting in subtypes with prognostic value for treatment response. The triple negative breast cancer (TNBC) subtype lacks the expression of hormone receptors (ER/PR) and the amplification of HER2 but it expresses basal keratin markers. TNBC represents 15-20% of all invasive breast cancer cases in the United States (US). Clinical, molecular, and genetic characteristics of TNBC include early-onset, aggressive phenotype, higher histological grade, and poor outcome. Attributable risk factors associated with TNBC include reproductive stage and age, race, and genetic factors. Disproportional mortality rates in TNBC affect premenopausal women of African ancestry compared to women of European ancestry. The nuclear receptor coactivator Amplified in Breast Cancer 1 (AIB1) plays a major role in the progression of hormone- and HER2-dependent breast cancers. Here, we examined AIB1’s role in TNBC. We determined that acute depletion of AIB1 by shRNA significantly reduces cell survival in basal-like (BL) and mesenchymal (M) TNBC cell lines. Surviving cells with reduced AIB1 (AIB1LOW) can be maintained with stably low mRNA and protein levels of AIB1 in vitro and as xenografts in vivo. (BL2) HCC1806 AIB1LOW cells proliferate independent of serum supplementation and show delayed adhesion kinetics to cell culture dishes. Also, AIB1LOW cells from (BL2) and (M) subtypes of TNBC show a significant reduced tube-formation phenotype when cultured on a basement membrane. Similarly, chemotherapy treatments using (BL2) HCC1806 cell line also resulted in a surviving AIB1LOW population with decreased tube-formation capacity. Gene expression analysis of (BL2) HCC1806 AIB1LOW cell lines revealed a significant enrichment in pro-inflammatory pathways in vitro. Orthotopic injections using limiting dilutions of (BL2) HCC1806 AIB1LOW resulted in smaller size tumors and reduced incidence of pulmonary metastases in immunocompromised mice. Transcriptomic analysis of xenograft tissues revealed that (BL2) HCC1806 AIB1LOW tumor cells had significantly reduced expression in tissue remodeling related genes. Overall, our data suggest that therapeutic interventions such as chemotherapy induces reduction of AIB1 protein in surviving TNBC cell lines in vitro. Chemotherapy-induced AIB1LOW TNBC cells may represent a model of therapy resistance often associated to dormant cells contributing to recurrence or metastasis in TNBC.

Mesenchymal Stromal Cells as Tumor Stromal Modulators-Marcela Bolontrade 2016-10-24 Mesenchymal stromal/ stem cells (MSCs) represent a heterogeneous cell population with immunomodulating, tissue repairing, differentiating, migratory and angiogenic abilities, making them important tools for clinical and translational research. An understanding of the role of MSCs in modulating tumor growth provides a glimpse into their role in non-pathological tissue remodeling and potential regenerative tissue therapies. Mesenchymal Stromal Cells as Tumor Stromal Modulators is a comprehensive source for the understanding of the role of MSCs as ubiquitous connective tissue cell components, which may have both direct and indirect effects on the tumor microenvironment and potential for regenerative therapeutics for various diseases. Using cancer as a model disease, this book explores the transformative role MSCs play in the recruitment of disease cells, cell repair and immunological defenses. Explores the biology of mesenchymal stromal cells (MSCs) and tissue related function Discusses the bidirectional communication between tumor stroma and MSCs derived from bone marrow, from adipose tissue and from other tissue types Provides in-depth analysis of the effects of MSCs on key processes that regulate disease progression, such as angiogenesis, metastatic potential, invasion, proliferation, tumor immune privileges

Breast Cancer Chemosensitivity-Dihua Yu 2009-12-30 In Breast Cancer Chemosensitivity, a group of world leading experts review critical aspects of resistance to systemic therapy in breast cancer patients. Beginning with a clinical overview of the problem, the book then focuses on the latest findings of molecular mechanisms of drug resistance. Coverage provides an example of using novel approaches for chemosensitization of breast cancer cells that gives readers an idea about the future direction in breast cancer treatment. It allows those who are interested in breast cancer therapy to get a jump-start on critical issues in breast cancer therapeutic resistance.

Metabolism in Cancer-Thorsten Cramer 2016-08-24 This textbook
Regulation of Cancer Progression by Pseudopodium-Enriched Atypical Kinase 1 (PEAK1)-Theresa Ann Reno 2013

In a migrating cell, actin polymerization and assembly drive membrane protrusion leading to the formation of pseudopodia. Repeated cycles of membrane extension at the front and tail retraction at the back facilitate cell translocation. Proliferating cancer cells can aberrantly turn on migration signals that activate the actin cytoskeleton machinery to drive cell locomotion. These motile cells are highly dangerous because they can leave the primary tumor site, invade the surrounding tissues, and gain access to the circulation, where they travel to distant organs and form secondary tumors. Unfortunately, there are no therapeutic treatments available that target migrating cancer cells and the majority of cancer patients succumb to metastatic disease. Recently, there has been a drive to uncover proteins associated with cell migration that can be targeted for therapy. In order to understand the spatiotemporal regulation of proteins involved in the migration machinery, our lab has analyzed the proteome of the cell pseudopodia. Of the proteins identified, we chose to further characterize Pseudopodium-Enriched Atypical Kinase 1 (PEAK1). The goal of this thesis was to elucidate the role of PEAK1 in cancer cell migration and metastasis. Here, I report that PEAK1 is upregulated in human malignancies, including human PDACs. Oncogenic KRas induced a PEAK1-dependent kinase amplification loop between Src, PEAK1, and ErbB2 to drive PDAC tumor growth and metastasis in vivo. Surprisingly, blockade of ErbB2 expression increased Src-dependent PEAK1 expression, PEAK1-dependent Src activation, and tumor growth in vivo, suggesting a mechanism for the therapeutic resistance of patients with PDAC. Importantly, PEAK1 inactivation sensitized PDAC cells to trastuzumab and gemcitabine therapy suggesting that therapeutics that target PEAK1 in combination with gemcitabine may improve patient outcome. To further elucidate the mechanism by which PEAK1 regulates cancer cell migration, I used a mutagenesis approach to study the function of different functional sites in PEAK1. I discovered that the C-terminal proline-rich region of PEAK1 and the phosphorylation status of tyrosine 665 are essential for PEAK1-mediated focal adhesion dynamics and cancer cell migration. Mutation of the C-terminal proline-rich region decreased cancer cell viability and sensitized cells to DNA damage-induced apoptosis. Altogether, these data suggest that PEAK1 is a promising biomarker and therapeutic target in human malignancies.

Glioblastoma Resistance to Chemotherapy: Molecular Mechanisms and Innovative Reversal Strategies-Ramasamy Paulmurugan 2021-06-25

Glioblastoma Resistance to Chemotherapy: Molecular Mechanisms and Innovative Reversal Strategies brings current knowledge from an international team of experts on the science and clinical management of glioblastoma chemoresistance. The book discusses topics such as molecular mechanisms of chemoresistance, experimental models to study chemoresistance, chemoresistance to drugs other than Temozolomide, and specific strategies to reverse chemoresistance. Additionally, it encompasses information on how to mitigate chemoresistance by targeted enhancement of p53 function. This book is a valuable resource for cancer researchers, oncologists, neuro-oncologists and other members of the biomedical field. Glioblastoma (GBM) is the most invasive and malignant primary brain tumor in humans with poor survival after diagnosis, therefore it is imperative that molecular and cellular mechanisms behind therapy resistant GBM cells, as well as the therapeutic strategies available to counter the resistance are comprehensively understood. Provides comprehensive, core knowledge related to the entire discipline of glioblastoma chemoresistance, from its...
many etiological mechanisms, to specific strategies to reverse resistance
Presents current information from an international team of experts on the
basic science, pre-clinical research, and clinical management of
glioblastoma chemoresistance Discusses molecular and cellular mechanisms
behind therapy resistant glioblastoma cells, as well as the therapeutic
strategies available to counter this resistance

Cancer Stem Cells-Huiping Liu 2016-08-16 Cancer Stem Cells: Targeting
the Roots of Cancer, Seeds of Metastasis, and Sources of Therapy
Resistance introduces the basic concepts and advanced understanding of
cancer stem cells, covering general overviews, organ-specific
identifications, and their characteristic mechanisms. The book also explores
innovative therapeutic strategies in preclinical and clinical trials to target
cancer stem cells, remove the roots of cancer, eliminate the seeds of
metastasis, overcome the resistance of therapies, and contribute to the
eradication of cancer. The book includes contributions from leading,
worldwide experts in the field, helping readers embrace new hope in their
quest to eradicate cancer with emerging clinical trials on treating cancer
stem cells in combination with other therapies. Provides an authoritative
and complete overview of cancer stem cells Includes comprehensive
coverage of current therapeutic strategies targeting cancer stem cells
Deepens a reader’s technical expertise in cancer stem cell biology