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KEY=CANCER - FINLEY TATE

Endocrine Therapy and Growth Regulation of Breast Cancer

Springer Science & Business Media Key questions involved in the treatment of disseminated breast cancer are discussed in this well-presented overview. It is the result of an initiative taken by the Swiss Group for Clinical Cancer Research to reveal the most recent developments in experimental and clinical research. The topics discussed include: the comparison of in vitro cultures of epithelial cells with breast cancer cells, the effect of steroids and their antagonists, the involvement of suppressor genes in tumour progression, the modulation of transforming growth factors by estrogen, and prognostic factors such as cERB-2 and EGF-R in breast cancer.

Adhesion-Dependent Regulation of Cell Growth and Apoptosis in Human Breast Cancer

We have studied the role of the actin cytoskeleton and myosin II in adhesion-dependent signaling and regulation of apoptosis in normal and transformed epithelial cells. Normal epithelial cells require attachment to the extracellular matrix (ECM) for survival, and disruption of cell-ECM interactions results in induction of apoptosis, a phenomenon termed "anoikis". By contrast, transformed cells do not require interaction with the ECM and do not undergo apoptosis when grown in suspension. This property plays a critical role in the ability of cancerous cells to metastasize. We have found that activation of myosin II is a critical step in the generation of signals that prevent programmed cell death. In addition, these studies show that transformed epithelial "escape" apoptosis due to constitutive activation of signaling pathways dependent on myosin II. We have identified key-signaling pathways that are altered in transformed cells and thereby contribute to the ability of tumor cells to escape anoikis. Collectively these studies provide important new information regarding specific pathways that regulate myosin II and identify potential therapeutic targets for the treatment of breast cancer, as well as other cancers.

Estrogen Receptor and Breast Cancer

Celebrating the 60th Anniversary of the Discovery of ER

Springer The discovery of ER by Dr. Elwood Jensen exactly 60 years ago has not only led to the birth of a whole new vital nuclear receptor research field but also made a rapid, direct and lasting impact on the treatment and prevention of breast cancer. Since that landmark discovery, tremendous progress has been made in our understanding of the molecular functions of ER and development of targeted therapies against ER pathways for breast cancer treatment. However, there is currently no book available addressing these discoveries and recent advancement in a historical and systematic fashion. This book is intended to provide comprehensive, most up-to-date information on the history and recent advancement of ER and breast cancer by world renowned leaders in the field. These chapters include the history of the discovery of ER; physiological and pathological roles of ER; recent discovery of ER cistrome, transcriptome and its regulation of noncoding RNAs such as microRNAs and enhancer RNAs in breast cancer; development and clinical practices of the first targeted therapy Tamoxifen and other antiestrogens for breast cancer treatment; structural basis of ER and antiestrogen actions; molecular insights into endocrine resistance; the role of ER mutants, ER-beta and environmental estrogens in breast cancer; and emerging state-of-the-art therapeutic approaches currently in development to overcome treatment resistance and future perspectives. The book will provide undergraduate and graduate students, basic scientists and clinical cancer researchers, residents, fellows, as well as clinicians, oncology educators and the general public a thorough and authoritative review of these exciting topics.

Hormonal Regulation of Mammary Tumors

Volume II: Peptide and Other Hormones

Springer Science & Business Media The concept that hormones influence tumor growth originated in 1889 with the proposal of Albert Schinzinger who suggested that breast cancer is related to the ovaries. Several years later, Sir George Beatson observed that remission of disseminated breast cancer could be achieved in premenopausal patients by performing bilateral oophorectomy. As a result of the contri butions of Hedley Atkins, Charles Huggins and others, additive and ablative hormonal therapies have been widely used for the treatment of advanced breast cancers for several decades. Model systems to study the effects of hormones on growth and regression of breast tumors have been available for many years; however, the complexities of the hormonal environment have rendered in vivo studies difficult in man and experimental animals. Recently, the availability of long-term cultures of breast cancer cells has stimulated many investigators to use these cell lines to unravel the mechanisms of hormone action. Because of the extreme diversity and complexity of advances regarding the endocrinology of the breast and breast cancers, a multi-authored review was deemed necessary. It has been gratifying to receive contributions from many noted scholars. In Volume I of this monograph, the influence of steroid hormones and their antagonists upon normal and neoplastic tissues of the mammary gland are presented. In Volume II, the effects of peptide and other hormones are reviewed.

Regulation of the Opioid Growth Factor-Opioid Growth Factor Receptor Axis in the Progression of Triple Negative Breast Cancer and Its Potential as a Therapeutic Agent

Triple negative breast cancer (TNBC) is an extremely aggressive form of breast cancer characterized by tissues lacking estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor (HER2). TNBC accounts for approximately 15% of all breast cancers diagnosed worldwide, and frequently affects younger women, women of color, and those from lower socioeconomic countries. TNBC has an increased likelihood of recurrence and a twofold greater mortality risk compared to other types of breast cancer, as well as a tendency to metastasize outside the breast. The financial burden for patients with TNBC is considerable, as costs are increased by 50% compared to other breast cancers.The median survival rate for patients with metastatic TNBC is only 13 months. Lack of hormone receptors and frequent de novo or acquired chemotherapy resistance renders almost all therapies ineffective. Thus, there is a critical need to develop TNBC treatments that target the underlying biology of tumor growth. A novel biological pathway has been studied in a wide variety of human cancers that may provide knowledge on progression of TNBC and serve as an effective treatment. The opioid growth factor -- opioid growth factor receptor axis is a determinant of cell proliferation in both normal cells and neoplasia. OGF inhibits cell proliferation by upregulating the cyclin dependent inhibitory kinases p16 and p21, arresting cells in the transition from G0/G1 phase to S phase of the cell cycle and halting DNA synthesis. The proposed experiments investigated the presence of the OGF-OGFr axis in MDA-MB-231 TNBC cells in vitro and in vivo and assessed whether expression of peptide or receptor changes with cancer progression, and whether OGF serves as an effective treatment for TNBC. For cell culture studies, log phase cells were compared with confluent and post-confluent cultures to mimic early and advanced stages of cancer growth. Semi-quantitative immunohistochemistry and western blot analysis comparing log phase and confluent cells, as well as small and large tumors, revealed that both OGF and its receptor are significantly reduced in advanced stages of squamous cell carcinoma of the head and neck, as well as ovarian, cancers. These observations were extended and confirmed in human breast cancer using MDA-MB-231 and MCF-7 cancer cell lines grown in vitro and in vivo. A mechanism of action involving OGF inhibition of growth was demonstrated utilizing BrdU incorporation that indicated a decrease in DNA synthesis in TNBC cells treated with OGF. Confluent cells were less responsive to OGF treatment than log phase cells. The data suggest that OGFr expression is reduced in TNBC with tumor progression, and that tumor progression may lead to deficits in the OGF-OGFr axis. Nonetheless, OGF was shown to significantly decrease cell growth relative to controls, indicating its potential as an effective biological treatment for TNBC.

Genes, Oncogenes, and Hormones

Advances in Cellular and Molecular Biology of Breast Cancer

Springer Science & Business Media This volume is the third edited by Drs. Dickson and Lippman in the `Advances in Cellular and Molecular Biology of Breast Cancer' series. It continues to explore the scientific thermes begun in the first two volumes: oncogenes and antioncogenes, growth factors, steriods, and stromalepithelial interactions. Rapid and important progress has continued to take place in all of these areas, especially the possibility that the new molecular understanding of regulation of growth, differentiation and metastases will lead to better tumor prognosis and treatment. For this reason this volume begins with two excellent chapters in this area. Genes, Oncogenes, and Hormones is divided into five sections: (1) the progression of node negative to positive breast cancer, (2) suppressor genes and regulation growth factors, (3) oncogenes and stimulatory growth factors, (4) steroidal hormone receptors, (5) differentiation and function of breast cancer epithelium and stroma. This volume will be useful to clinical researchers, basic researchers, and students in the breast cancer field. It complements and adds to the previous two volumes edited by Drs. Lippman and Dickson in this series.

Estrogen and Antiestrogen Regulation of Breast Cancer Cell Growth

Indole-3-carbinol Regulation of Breast Cancer Cell Growth

Regulatory Mechanisms in Breast Cancer

Advances in Cellular and Molecular Biology of Breast Cancer

Springer Science & Business Media In Breast Cancer: Cellular and Molecular Biology [Kluwer Academic Pub lishers, 1988], we tried to present an introduction to the emerging basic studies on steroid receptors, oncogenes, and growth factors in the regulation of normal and malignant mammary epithelium. The response to this volume was superb, indicating a tremendous interest in basic growth regulatory mechanisms governing breast cancer and controlling its malignant progres sion. In the two years since its publication, much new and exciting in formation has been published and the full interplay of regulatory mechanisms is now beginning to emerge. We have divided this book into four sections that we hope will unify important concepts and help to crystallize areas of consensus and/or disagreement among a diverse group of basic and clinical scientists working on the disease. The first section is devoted to studies on oncogenes, antioncogenes, proliferation, and tumor prognosis. The first chapter, by Sunderland and McGuire, introduces the characteristics of breast cancer as studied by patho logists to establish prognostic outcome. Of particular interest is a new proto oncogene called HER-2 (or neu), which is rapidly becoming accepted as a valuable new tumor marker of poor prognosis. The second chapter, by Lee Bookstein and Lee, introduces the best known antioncogene, the retinoblas toma antioncogene, whose expression is sometimes lost in breast cancer. Malignant progression appears to be influenced by the balance of proto oncogene and antioncogene expression.

Caveolins in Cancer Pathogenesis, Prevention and Therapy

Springer Science & Business Media Caveolins are important structural proteins of Caveolae, small invaginations of the membrane. They have been shown to play an important role in the pathogenesis of multiple cancers. In this volume, we will mainly focus on the importance of Caveolin-1 in breast, prostate, lung, skin, colon, pancreatic and brain cancers with also a mention of the novel role of Caveolin-3 in breast cancer.

Extracellular Targeting of Cell Signaling in Cancer

Strategies Directed at MET and RON Receptor Tyrosine Kinase Pathways

John Wiley & Sons International experts present innovative therapeutic strategies to treat cancer patients and prevent disease progression Extracellular Targeting of Cell Signaling in Cancer highlights innovative therapeutic strategies to treat cancer metastasis and prevent tumor progression. Currently, there are no drugs available to treat or prevent metastatic cancer other than non-selective, toxic chemotherapy. With contributions from an international panel of experts in the field, the book integrates diverse aspects of biochemistry, molecular biology, protein engineering, proteomics, cell biology, pharmacology, biophysics, structural biology, medicinal chemistry and drug development. A large class of proteins called kinases are enzymes required by cancer cells to grow, proliferate, and survive apoptosis (death) by the immune system. Two important kinases are MET and RON which are receptor tyrosine kinases (RTKs) that initiate cell signaling pathways outside the cell surface in response to extracellular ligands (growth factors.) Both kinases are oncogenes which are required by cancer cells to migrate away from the primary tumor, invade surrounding tissue and metastasize. MET and RON reside on both cancer cells and the support cells surrounding the tumor, called the microenvironment. MET and RON are activated by their particular ligands, the growth factors HGF and MSP, respectively. Blocking MET and RON kinase activation and downstream signaling is a promising therapeutic strategy for preventing tumor progression and metastasis. Written for cancer physicians and biologists as well as drug discovery and development teams in both industry and academia, this is the first book of its kind which explores novel approaches to inhibit MET and RON kinases other than traditional small molecule kinase inhibitors. These new strategies target key tumorigenic processes on the outside of the cell, such as growth factor activation by proteases. These unique strategies have promising potential as an improved alternative to kinase inhibitors, chemotherapy, or radiation treatment.

Bidirectional Regulation of YAP and ALDH1A1

Breast cancer is the second leading cause of cancer death for women in the United States. Approximately, 1 in 5 women will recur with cancer within 10 years of completing treatment and recent publications have suggested that breast cancer stem cells confer resistance to therapy. These reports highlight aldehyde dehydrogenase 1A1 (ALDH1A1) and Yes-associated protein (YAP) as a biomarker and key mediator of the stem cell phenotype respectively. To further understand how YAP and ALDH1A1 facilitate chemoresistance, this study investigated how ALDH1A1 specific inhibition affected YAP activity and growth of basal-like breast cancer cells, which are enriched in cancer stem cells. Intriguingly, attenuation of growth by ALDH1A1 inhibition was observed when cells were plated on a reconstituted basement membrane. Further, the inhibition of cell growth correlated with cytosolic retention of YAP and a reduction in YAP signaling. In a complementary analysis, the overexpression of YAP correlated with an increased level of ALDH1A1 transcript. Results from this study indicate a novel mechanism by which basal-like breast cancer cells utilize YAP to maintain the stem cell phenotype and also suggest ALDH1A1 as a potential therapeutic target for breast cancer therapy.

Breast Cancer

From Biology to Medicine

BoD – Books on Demand Breast Cancer - From Biology to Medicine thoroughly examines breast cancer from basic definitions, to cellular and molecular biology, to diagnosis and treatment. This book also has some additional focus on preclinical and clinical results in diagnosis and treatment of breast cancer. The book begins with introduction on epidemiology and pathophysiology of breast cancer in Section 1. In Section 2, the subsequent chapters introduce molecular and cellular biology of breast cancer with some particular signaling pathways, the gene expression, as well as the gene methylation and genomic imprinting, especially the existence of breast cancer stem cells. In Section 3, some new diagnostic methods and updated therapies from surgery, chemotherapy, hormone therapy, immunotherapy, radiotherapy, and some complementary therapies are discussed. This book provides a succinct yet comprehensive overview of breast cancer for advanced students, graduate students, and researchers as well as those working with breast cancer in a clinical setting.

Regulation of the Protein Kinase C Delta Isoform by Estrogen in the MCF-7 Human

Breast Cancer Cell Line and a Role for Protein Kinase C Delta in Growth Regulation

Previous evidence in our laboratory demonstrated the ability of estrogen to regulate specifically the protein kinase C (PKC) δ isoform in the rat and rabbit corpus luteum. The purpose of this study was to evaluate estrogen's ability to regulate PKC, specifically the PKC δ isoform, in the estrogen responsive, MCF-7 human breast cancer cell line. With the increasingly characterized role of PKC δ in growth regulation, we were interested to also determine the ability of PKC δ to regulate growth in the MCF-7 cell line. Treatment of MCF-7 cells with 10$\sp{-10}$ through 10$\sp{-8}$ M estrogen for 7 days down-regulated specifically PKC δ mRNA and protein; expression of other PKC isoforms was unchanged. These concentrations of estrogen were maximally proliferative for the MCF-7 cells and an inverse correlation between PKC δ expression and proliferation in MCF-7 cells was observed. PKC δ protein levels were found to be 10 fold higher in MCF-7 compared to the estrogen receptor-negative, MDA-MB 231 cells which grow aggressively in the absence of estrogen. In view of the inverse correlation between PKC δ expression and proliferation in MCF-7 cells we wished to determine whether activation of PKC δ could signal growth inhibition. Phorbol ester treatments that lead to G1 growth arrest and induction of the cyclin-dependent kinase inhibitor p21$\rm\sp{Waf1/Cip1}$ in MCF-7 cells promoted activation of PKC δ, as evidenced in immunecomplex phosphorylation assays. To show that phorbol ester stimulated G1 growth arrest could be mediated by the induction of p21$\rm\sp{Waf1/Cip1}$ by activated PKC $\delta,$ we demonstrated that constitutively active PKC δ in the absence but not in the presence of dominant negative PKC δ activated the WAF1/CIP1 promoter-luciferase construct in transient transfection assays. Activated PKC δ can therefore signal the transcriptional induction of p21$\rm\sp{WAF1/CIP1}.$ Our results are consistent with the hypothesis that modulation of PKC δ expression and activation state provides a pathway for growth regulation in breast cancer cells.

Development of a Breast Cancer Stem Cell Model and the Inhibitory Regulation of Small Molecule Phytochemicals on Various Stages of Human Breast Cancer Cells

The development of clinical breast cancer is a multistep process that manifests itself as a disease with various distinct phenotypes. At present, it is believed that a neoplastically-transformed cell undergoes many heterogeneous changes and mutations before evolving into a tumorous or invasive breast cancer. Due to the heterogeneity of breast cancer, a single therapeutic strategy is rarely completely effective for all patients. Current therapeutic options such as hormone antagonists, radiation and chemotherapy have many deleterious side effects which demonstrates a need for a more efficacious therapy alternative that can not only target varying phenotypes but also ameliorates harsh side effects. In addition, it is essential to identify compounds that can slow the promotion of the disease from preneoplastic lesions to invasive breast cancer. This thesis details the generation of a novel breast cancer stem cell model and the molecular mechanism of two small molecule phytochemicals, indole-3-carbinol (I3C), and artemisinin, target breast cancer stem cells and luminal A, estrogen sensitive breast cancer, respectively. We show that ectopic expression of HER2, a member of the epidermal growth factor receptor family, in MCF-10AT preneoplastic mammary epithelial cells induces a phenotype with the molecular markers of breast cancer stem cells expression: CD44+/CD24-/ALDH-1+ with highly expressing levels of stem cell marker, nucleostemin. These cells are capable of forming tumorspheres in 3-D cultures, indicative of a population highly enriched with stem cells. Furthermore, as few as 30,000 cells are able to form viable mammary tumors in athymic mouse xenograft models. In breast cancer stem cells, I3C induces apoptosis by selectively targeting nucleostemin and activating the p53 apoptotic pathway. I3C induces the proteolytic degradation of Akt1 and thereby functionally inactivates MDM2. Loss of MDM2 phosphorylation and its subsequent inactivation frees p53 to induce apoptosis. Coupled with the activation of nucleostemin by I3C, nucleostemin sequesters MDM2 away from p53 further enhancing the apoptotic effect. Knockdown of nucleostemin prevents the I3C apoptotic effects, suggesting the selective role of I3C on breast cancer stem cells. Also, expressing constitutively active Akt1 or a dominant negative form of p53 overrides the I3C induced apoptotic effect, highlighting the specific Akt1/MDM2/p53 pathway modulated by I3C. The preclinical results implicate I3C as a novel anti-cancer agent that can selectively target cancer stem cells especially given that I3C also increases MDM2-nucleostemin interactions and can reduce tumors volumes in vivo. We also show that artemisinin, derived from the sweet wormwood, Artemisia annua, ablates key G1 cell cycle regulators to induce growth arrest in luminal A, estrogen sensitive breast cancer as well as inhibit in vivo xenograft growth in athymic mice. Artemisinin is selective towards malignant cells, such as the MCF-7 breast cancer cell line since it is ineffective in arresting growth in nontumorigenic breast cell lines. Artemisinin exposed MCF-7 cells displayed ablated levels of cyclin-dependent kinases 2 and 4 (CDK), cyclin E, cyclin D1 as well as E2F1 at the protein and mRNA level. Promoter deletion mapping and subsequent chromatin immunoprecipitation analyses revealed that downregulation of E2F1 resulted in inhibition of CDK2 of promoter activity. Additionally, constitutive expression of E2F1 reversed the growth arrest, CDK2 and cyclin E downregulation induced by artemisinin.

Growth Factor Receptor-Directed Therapy in Human Breast Cancer

Growth factors and their receptors are crucial in the regulation of breast cancer cell growth. Since the HER-2 growth factor receptor pathway is implicated in the progression of breast cancer in the clinic, we have targeted HER-2 receptors for therapeutic intervention. Our research goals are: 1) To induce human breast tumor remission with antibody to HER-2 receptor in combination with chemotherapeutic drugs. A therapeutic advantage of antibody to HER-2 receptor combined with drugs that damage breast cell DNA has been shown. In addition, the interaction between antireceptor antibodies and DNA-reactive chemotherapy drugs is schedule-dependent for optimal antitumor activity. 2) To assess the clinical significance of HER-2 gene expression in resistance to DNA-damaging drugs. By several different measures, modulation of DNA repair pathways occurs on activation of HER-2 receptor by anti-HER-2 antibody. Moreover, the adverse prognosis in patients with HER-2- overexpressing breast cancers may be related more to acquired rather than to intrinsic drug resistance. 3) To define the role of HER-2 and heregulin gene expression in antiestrogen resistance. Although HER-2-overexpressing breast cancers are resistant to estrogens and to tamoxifen, the latter cancers are sensitive to pure antiestrogens and to tamoxifen administered in combination with antibodies that down-regulate HER-2 receptors at the cell surface.

Metastasis of Breast Cancer

Springer Science & Business Media Written by experts in the subject area, the book covers a broad range of topics in the metastasis of breast cancer, from genetics, biology to clinical management. Main topics include genetic control, biology, growth factors, cell adhesion, cell motility and invasion, natures of bone metastasis, sentinel node therapies, hormonal links, new biomarkers and detection of micrometastasis and diagnosis. This timely book also covers the current treatment options.

Membrane Estrogen and HER-2 Receptors in Human Breast Cancer

Patients with breast cancers that express estrogen receptor (ER) commonly receive anti-estrogen therapy. The efficacy of this treatment depends on tight regulation of breast growth by estrogen. However, as breast cancers progress, they often become resistant to estrogens, and most patients no longer respond to anti-estrogen therapy. New anti-estrogen treatment options are needed, and alternative therapies may result from findings showing that some ER molecules occur in plasma membranes of breast cancer cells and interact with transmembrane HER-2 growth factor receptors. Expression of HER-2 receptors occurs in many breast cancers, and the protein kinase activity of HER-2 may modulate the ligand-independent activation of ER. Active cross-communication between ER and HER-2 receptors occurs in breast tumors, leading to the promotion of cancer growth. Thus, this axis may offer a new target for therapeutic intervention. The authors have partially purified a membrane-associated form of ER in breast cancer cells and has evidence that it promotes tumor growth. Using this novel signaling pathway as a target, the authors are assessing new treatments to prevent cancer progression in models of human breast cancer. Since HER-2 overexpression in breast cancer is associated with the failure of anti-estrogen therapy, understanding the basis of interactions between ER and HER-2 receptors may help to improve patient management and survival. (1 figure, 91 refs.)

Breast Cancer

Springer Science & Business Media I am honored to write the Foreword for this first volume of the M. D. Anderson Cancer Care series, because I believe the book represents a milestone not only for M. D. Anderson but also for cancer specialists everywhere. All of us, whether we work in academic medical institu tions, medical school hospitals, community hospitals, oncology clinics, or solo practice, have seen remarkable changes in our practice over the recent decades. We know that breast cancer patients live longer, feel better, and look better than ever before, and they face this dreaded disease with more optimism than ever before. Each of us deserves to be proud of this progress. Though I am now primarily a laboratory scientist and admin istrator, I am proud of my own work on factors that control the growth of tumor cells, most prominently through regulation of EGF receptors and HER-2/neu, and the promise that work holds for women who have breast cancer. The authors represented in this volume have made important contri butions to breast cancer care. Likewise, every reader of this book has and will continue to make critical contributions to the health of women with breast cancer. I would like to express the hope here that each of us takes the opportunity to step outside our subspecialties-surgeon, internist, radiation oncologist, pathologist, radiologist, laboratory scientist-and learn how we can better integrate our work with that of other specialists.

Regulation of Anti-Proliferation in Melanoma and Breast Cancer Cells by Small Molecule Phytochemicals and Their Derivatives

Abstract Regulation of Anti-Proliferation in Melanoma and Breast Cancer Cells by Small Molecule Phytochemicals and Their Derivatives By Kevin Michael Poindexter Doctor of Philosophy in Endocrinology University of California, Berkeley Professor Gary L. Firestone, Chair Melanoma and breast cancer represent a significant portion of overall cancer burden, and many strategies have been developed to control their growth. Many of these current options have serious adverse effects and sometimes lead to therapy resistance which can complicate future treatment. Because of this, it is critical to investigate new classes and combinations of therapeutics that can overcome these drawbacks and retain effectiveness in multiple phenotypes. This thesis details the mechanism in which the combination of Indol-3-Carbinol (I3C) and Acetylsalicylic Acid (aspirin) act synergistically to slow the growth of human melanoma cells. In addition, this thesis demonstrates that the phytochemical Artemisinin and its derivative, Artesunate are able to inhibit the growth of luminal A estrogen receptor positive breast cancer cells. Finally, we utilize I3C derivatives to analyze the growth effects of different chemical functional groups in both melanoma and breast cancer cells. The combination of I3C and aspirin was able to synergistically control melanoma cell proliferation through an induction of G1 cell cycle arrest. Cell cycle arrest was due likely to a similar downregulation of Cyclin Dependent Kinase 2 (CDK2) levels which in turn is under the transcriptional control of the Microphthalmia-Associated Transcription Factor M (MITF-M). The combination of I3C and aspirin was able to significantly downregulate MITF-M protein and transcript expression. Luciferase analysis of the proximal region of the MITF-M promoter revealed that both compounds regulated promoter activation synergistically. The reduction in activation was mediated by two distinct pathways that met on the MITF-M promoter, I3C inhibited the activation of BRAF which caused a decrease in binding to the promoter of the transcriptional activator BRN-2 while aspirin downregulated [beta]-catenin/LEF1 binding to the promoter, again decreasing activity. Site directed mutagenesis of these sites proved that they were sufficient for the compounds' regulation of MITF-M transcriptional activity. These results uncover one mechanism in which aspirin controls melanoma growth, something that has not been explored, and the combination of aspirin and I3C could be utilized as a potential anti-cancer treatment in human melanoma. We also demonstrate that Artemisinin, a phytochemical derived from Artemisia annua and its derivative Artesunate are able to regulate the growth of human breast cancer cells through regulation of Cyclin A2, and cyclin dependent kinases 1 and 2 (CDK) critical regulators of the G1/M phase transition as well as G2 phase progression. Artesunate was able to achieve significant downregulation and induce growth effects at much smaller doses than its parent molecule indicating increased potency. Chromatin-immunoprecipitation indicated that Artemisinin was able to alter Sp1 binding to the Cyclin A promoter, potentially explaining its ability to regulate transcript levels. In the last chapter, we explore the effects on melanoma and breast cancer cell growth caused by 1-Benzyl-I3C derivatives. We find that small changes in structure alter growth inhibition by the compounds likely through changes in their ability to interact and alter function of target enzymes Human Neutrophil Elastase, and NEDD4-1. No compound was stronger than the parent molecule, 1-Benzyl-I3C, but all were able to induce significant changes in growth at concentrations lower than I3C. While this study is preliminary it provides information as to what potential derivatives might slow transformed cell growth in the future.

Bidirectional Signaling Between Breast Cancer and the Tumor Microenvironment Implications for Endocrine Therapy Resistant Cancer

Estrogen Receptor-alpha (ER-alpha) expression in breast cancer is a standard biomarker predicting positive response to endocrine therapies targeting the ER-alpha signaling pathway. Despite ER-alpha's predictive potential, resistance to therapies remains a significant problem. Particularly in advanced disease, response rate to endocrine therapy agent tamoxifen is as low as 30%. The microenvironment in which metastatic breast cancers reside represent an unnatural context of signaling that might contribute to therapy efficacy at these sites. Indeed, ER-alpha expression is lost in one-fifth of recurrences and metastases, and the mechanism by which this occurs is unknown. This thesis work investigates the interactions of breast cancer cells with the tumor microenvironment and associated endocrine therapy resistance. Using a microfluidic co-culture model of the tumor microenvironment, I demonstrated that ER-alpha expression is reduced in response to soluble, non-estrogenic signaling from the tumor microenvironment. Multiple factors both within and between microenvironments were found to contribute to breast cancer cell growth. The complexity of the tumor microenvironment requires the identification of targets that more broadly target extracellular signaling factors. This led me to identify alterations in stromal nuclear receptors, which as targetable regulators of gene expression represent good targets for therapy. Breast cancer cells induce down-regulation of PPAR-gamma expression in stromal fibroblasts. Activation of PPAR-gamma by agonist rosiglitazone blocks stroma-induced breast cancer cell growth, implicating the inhibition of this pathway as an essential step for breast cancer cells in setting up a permissive growth environment. This bidirectional signaling model also has two major implications. For the stroma, interaction with the breast cancer cells alters the expression of a key regulator of adipogenesis, suggesting shifts in the differentiation state of the stromal fibroblasts.

For the tumor cells, stroma-induced breast cancer cell growth induces endocrine therapy resistance. The loss of ER-alpha serves as a functional biomarker of this resistance, in which the ER-alpha-positive breast cancer cell line MCF-7 serves as a "biosensor" for the activity of the microenvironment. These results add to our understanding of the role of the tumor microenvironment in endocrine therapy resistance, and further implicate a number of novel targets for therapy in endocrine therapy-resistant breast cancer.

Transforming Growth Factor-Beta in Cancer Therapy, Volume II

Cancer Treatment and Therapy

Springer Science & Business Media Transforming Growth Factor- ß in Cancer Therapy, Vols. 1 and 2, provides a compendium of findings about the role of transforming growth factor- ß (TGF- ß) in cancer treatment and therapy. The second volume, Cancer Treatment in Therapy, is divided into three parts. The companion volume details the role of TGF- ß on basic and clinical biology.

Gene Regulation and Therapeutics for Cancer

CRC Press Differential gene regulation and targeted therapy are the critical aspects of several cancers. This book covers specific gene regulation and targeted therapies in different malignancies. It offers a comprehensive assessment of the transcriptional dysregulation in cancer, and considers some examples of transcriptional regulators as definitive oncogenic drivers in solid tumors, followed by a brief discussion of transcriptional effectors of the programs they drive, and discusses its specific targets. Most targeted therapeutics developed to date have been directed against a limited set of oncogenic drivers, exemplified by those encoding cell surface or cytoplasmic kinases that function in intracellular signaling cascades.

Cancer Metabolism: Molecular Targeting and Implications for Therapy

Frontiers Media SA Development of an effective anticancer therapeutic necessitates the selection of cancer-related or cancer-specific pathways or molecules that are sensitive to intervention. Several such critical yet sensitive molecular targets have been recognized, and their specific antagonists or inhibitors validated as potential therapeutics in preclinical models. Yet, majority of anticancer principles or therapeutics show limited success in the clinical translation. Thus, the need for the development of an effective therapeutic strategy persists.

“Altered energy metabolism” in cancer is one of the earliest known biochemical phenotypes which dates back to the early 20th century. The German scientist, Otto Warburg and his team (Warburg, Wind, Negelein 1926; Warburg, Wind, Negelein 1927) provided the first evidence that the glucose metabolism of cancer cells diverge from normal cells. This phenomenal discovery on deregulated glucose metabolism or cellular bioenergetics is frequently witnessed in majority of solid malignancies. Currently, the altered glucose metabolism is used in the clinical diagnosis of cancer through positron emission tomography (PET) imaging. Thus, the “deregulated bioenergetics” is a clinically relevant metabolic signature of cancer cells, hence recognized as one of the hallmarks of cancer (Hanahan and Weinberg 2011). Accumulating data unequivocally demonstrate that, besides cellular bioenergetics, cancer metabolism facilitates several cancer-related processes including metastasis, therapeutic resistance and so on. Recent reports also demonstrate the oncogenic regulation of glucose metabolism (e.g. glycolysis) indicating a functional link between neoplastic growth and cancer metabolism. Thus, cancer metabolism, which is already exploited in cancer diagnosis, remains an attractive target for therapeutic intervention as well. The Frontiers in Oncology Research Topic “Cancer Metabolism: Molecular Targeting and Implications for Therapy” emphases on recent advances in our understanding of metabolic reprogramming in cancer, and the recognition of key molecules for therapeutic targeting. Besides, the topic also deliberates the implications of metabolic targeting beyond the energy metabolism of cancer. The research topic integrates a series of reviews, mini-reviews and original research articles to share current perspectives on cancer metabolism, and to stimulate an open forum to discuss potential challenges and future directions of research necessary to develop effective anticancer strategies. Acknowledgment I sincerely thank the Frontiers for providing the opportunity and constant support throughout the process of this research topic and eBook production. I gratefully acknowledge all the authors for their valuable contributions. Finally, I would like to thank my brother, Saravana Kumar, G.K., whose personal sacrifices and unflinching encouragement made my career in science possible. References: Hanahan D, Weinberg RA. 2011. Hallmarks of cancer: The next generation. Cell. 144(5):646-74. Warburg O, Wind F, Negelein E. 1926. Über den stoffwechsel der tumoren in körper. Klinische Wochenschrift. 5:829-32. Warburg O, Wind F, Negelein E. 1927. The metabolism of tumors in the body. J Gen Physiol. 8(6):519-30.

Checkpoint Controls and Targets in Cancer Therapy

Springer Science & Business Media Much work over the last two decades has firmly established that loss of cell cycle checkpoint regulation, and resultant unabated cellular proliferation, is an inherent characteristic of cancer. This loss may occur through aberration in any single component involved in signal transduction pathways that orchestrate checkpoint regulation, which may manifest through either a failure to activate the checkpoint or a failure to respond to the activated checkpoint. In normal cells, checkpoint pathways are activated when genetic or cellular homeostasis is compromised, and signals are then transduced to re-stabilize homeostasis, and, failing this, to activate the apoptotic machinery to induce a cellular suicidal response. This implies that both survival and cell death pathways are induced following checkpoint activation, and that the final decision is dependant on the net result of integrating the two sets of signals. It is intriguing that checkpoint pathways are also critical in cancer therapy to provide an apoptotic stimulus when cellular damage induced by the therapeutic agent is detected by the sensor system. Therefore, it is not surprising that failure in pro-survival checkpoint response will render tumor cells hypersensitive to cytotoxics and, conversely, failure in pro-apoptotic checkpoint response will induce genetic instability and/or therapeutic resistance. Understanding the intricacies of checkpoint response is, therefore, central to the design of therapeutic regimen that will enhance antitumor effects. Although early versions of this design entail combination of cytotoxic agents with cell cycle or checkpoint inhibitors, a greater understanding of the concepts could make such combinations clinically more effective. The contributions in this book will consolidate the current state of knowledge on checkpoint responses that may lay the foundation for hypothesis-driven rational approaches in advancing the management of cancer. The immediate attraction of the book to the scientific community is that it represents a timely opportunity to build upon existing concepts of checkpoints to expand our understanding of the inner workings of the critical checkpoint machinery. The present understanding has provided ample appreciation that response to checkpoint activation is manifested through coordinated inhibition of cyclin-dependent kinase (CDK) complexes in G1, S and/or the G2 phase in order to arrest the cell cycle. Kinase inhibition can occur through several mechanisms, including inhibitory phosphorylation of CDK, destruction of the cognate cyclins, and recruitment of CDK inhibitors from the INK and WAF1/CIP1 families. However, the wealth of information from recent discoveries needs to be examined critically to consolidate our conceptual knowledge of checkpoints. At the same time, there is acute awareness in the diversity of checkpoint response between cytotoxic agents, and this serves as a reminder of the magnitude of complexity that is inherent in checkpoint regulation. This volume is intended to bring the cancer research community closer toward an improved understanding of this regulation, how checkpoint abnormalities can impact negatively on cancer therapy, and emerging strategies to target checkpoint response as a therapeutic end-point.

Autophagy

Chapter 19. Autophagy as a Sensitization Target in Cancer Therapy

Elsevier Inc. Chapters Autophagy is involved in the resistance against anticancer treatment. Both autophagy inhibitors and inducers have been demonstrated to be effective in enhancing the effect of chemotherapy and irradiation in various anticancer regimes. Currently, autophagy inhibitors are being examined in clinical trials as an adjuvant for traditional therapies. However, caution must be exercised, considering the complexity of autophagy regulation in tumorigenesis and in development of therapeutic resistance. There is also evidence suggesting that targeting autophagy may not have the desired effects. We have found that cancer cells with long-term autophagy deficiency can evade the dependence on autophagy to survive. Furthermore, some tumors are intrinsically insensitive to autophagy manipulation. Although regulation of autophagy is a promising new addition to cancer therapy, careful evaluations must be exercised when applying this strategy in clinical practice on individual bases.

Biology of Female Cancers

CRC Press Biology of Female Cancers explores what can be learned about female cancers by summarizing what is known about the mechanisms of growth regulation and genetic features associated with common forms of female cancers, including malignancies of the breast, ovary, uterus, cervix, vulva, and gestational trophoblastic disease. The book describes the etiology, incidence, pathology, staging, and treatment of each type of cancer. The risk of developing particular tumor types and how their growth may be influenced by hormones, growth factors, and cytokines is also discussed. For oncologists, gynecologists and obstetricians, cell biologists, and everyone interested in learning more about female cancers, the Biology of Female Cancers offers a comprehensive, unique approach.

Epigenetics and Cancer

Springer Science & Business Media 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 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.

Endocrinology of Breast Cancer

Springer Science & Business Media A cutting-edge review of how derangements in the hormonal and growth factor mechanisms controlling normal mammary development lead to breast cancer. Drawing on the multidisciplinary expertise of leading authorities, the book highlights the roles of oncogenes and tumor suppressor genes, spelling out the importance of autocrine/paracrine loops (e.g., stromal epithelial interactions) in supporting breast cancer cell proliferation and the progression to hormone independence. The book's many prominent contributors also illuminate significant recent advances in the biochemistry and physiology of hormone receptors and review the state-of -the-art in the endocrine therapy of breast cancer. Endocrinology of Breast Cancer provides a unique integrated overview of the most significant basic and clinical developments concerning the hormonal aspects of breast cancer.

Translation and Its Regulation in Cancer Biology and Medicine

Springer This book, for the first time, comprehensively assembles and analyzes a large body of information on the role of the fundamental mechanism of the protein biosynthesis pathway, translation, in cancer biology. It systematically explores the function of the translation machinery and its regulation, including cell signaling, in the development, maintenance and progression of human cancer. The work presented here unveils the tremendous potential and applications of this vast and exciting branch of genetic, biochemical and molecular science in cancer medicine and drug development. Chapters contributed by experts in the field take the reader on a journey that starts with a dissection of the translation machinery and its regulation in norm and cancer. Later chapters characterize etiological and pathogenetic roles that translation plays in specific cancer types. Various aspects of diagnostic, prognostic and therapeutic significance of the translation machinery and its control in cancer are discussed. Readers will discover the importance of the process of translation and its regulatory mechanisms in physiology and cancer biology. The chapters and the numerous illustrations included here were contributed by expert scientists and clinicians from renowned academic and clinical establishments in Canada, the United States of America, the United Kingdom, Italy, France, Belgium, Spain, Germany and Australia. The book conveys information and knowledge that may interest a broad range of students and scholars ranging from basic scientists to clinicians and drug developers seeking to better understand the protein synthesis and its aberrations in cancer biology and cancer medicine.

Targeting New Pathways and Cell Death in Breast Cancer

BoD – Books on Demand This book presents novel in interesting find by multiple accomplished investigators in breast cancer. These chapters elucidate new mechanisms of breast cancer cell death as well as discuss new pathways for therapeutic targeting.

Targeted Therapies in Breast Cancer

This new volume updates the reader on selected areas of targeted therapy in breast cancer, with special emphasis on chemoprevention strategies, drug resistance, biomarkers, combination chemotherapy, angiogenesis inhibition and pharmacogenomics in the context of clinical efficacy. This selected review of targeted therapies will guide the reader on effective treatment as part of an integrated programme of patient management.

Alterations in Cell Signaling Pathways in Breast Cancer Cells After Environmental Exposure

Recent human epidemiological studies suggest that up to 75% of human cancers can be attributed to environmental exposures. Understanding the biologic impact of being exposed to a lifetime of complex environmental mixtures that may not be fully characterized is currently a major challenge. Functional endpoints may be used to assess the gross health consequences of complex mixture exposures from groundwater contamination, superfund sites, biologic releases, or nutritional sources. Such endpoints include the stimulation of cell growth or the induction of a response in an animal model. An environmental exposure that upsets normal cell growth regulation may have important ramifications for cancer development. Stimulating cell growth may alter an individual's cancer risk by changing the expression of genes and proteins that have a role in growth regulatory pathways within cells. Modulating the regulation of these genes and their products may contribute to the initiation, promotion or progression of disease in response to environmental exposure. We are investigating diet-related compounds that induce cell proliferation in breast cancer cell lines. These compounds, PhIP, Flor-Essence{reg_sign} and Essiac{reg_sign}, may be part of an everyday diet. PhIP is a naturally occurring mutagen that is formed in well-cooked muscle meats. PhIP consistently causes dose-dependent breast tumor formation in rats and consumption of well-done meat has been linked to increased risk of breast cancer in women. Flor-Essence{reg_sign} and Essiac{reg_sign} herbal tonics are complementary and alternative medicines used by women who have been diagnosed with breast cancer as an alternative therapy for disease treatment and prevention. The long-term goal of this work is to identify those cellular pathways that are altered by a chemical or biologic environmental exposure and understand how those changes correlate with and or predict changes in human health risk. This project addressed this goal by measuring alterations in cell growth pathways in the human MCF-7 breast cancer cell line using functional cell proliferation and reporter assays in combination with new macroarray technology after exposure to PhIP and the herbal tonics.

Breast Cancer

Molecular Genetics, Pathogenesis, and Therapeutics

Springer Science & Business Media A comprehensive state-of-the-art summary of breast cancer research and treatment by leading authorities. The book's many distinguished contributors illuminate the biology and genetics of breast cancer, including what is known about the hereditary breast cancer genes, BRCA1 and 2, the cutting-edge cytogenic approaches, and the biology of breast cancer metastasis. In addition, the authors describe current and future methods of breast cancer treatment in depth, and discuss environment and diet as risk factors for the disease. Breast Cancer: Molecular Genetics, Pathogenesis, and Therapeutics constitutes an excellent reference and resource for all those clinical and experimental oncologists, as well as genetic counselors nurses, who need to understand the latest developments in breast cancer biology, risk, and treatment.

Targeting of the Hepatocyte Growth Factor Pathway for the Treatment of Breast Cancer

Hepatocyte growth factor (HGF) induces cell growth and cell movement and promotes tumor invasiveness. HGF is produced by fibroblasts within lung tumors, while its' receptor, the c-Met protein, is expressed on the breast tumor cells themselves. High levels of HGF expression correlate with an aggressive tumor phenotype. Expression of the c-Met protein by breast cancer cells in culture also correlates with an estrogen negative phenotype and with loss of estrogen-dependent cell growth. Thus the HGF-c-Met ligand-receptor system may be important in controlling cell growth in breast tumors that have escaped estrogen regulation, a common occurrence in breast cancer patients who fail anti-estrogen therapy. The hypothesis to be tested in this Idea Grant is that interruption of the HGF-c-Met signaling pathway will inhibit growth of estrogen-independent human breast cancer cells and could be a useful therapeutic strategy for breast cancer patients who fail endocrine therapy. We will use two approaches for these studies. (1) an anti-sense strategy that uses vectors constructed in the u6 RNA expression plasmid and delivered by cationic liposomes and (2) a recombinant HGF antagonist molecule (truncated HGF/tHGF) produced in baculovirus and delivered through injection to the peritumoral area.

Therapeutic Resistance to Anti-hormonal Drugs in Breast Cancer

New Molecular Aspects and their Potential as Targets

Springer Science & Business Media One of the main causes of failure in the treatment of breast cancer is the intrinsic presence of, or development of, drug resistance by the cancer cells. Recent studies on the mechanisms of cancer drug resistance have yielded important information highlighting both how tumour cells may escape these therapeutic constraints and that drug resistance may further impinge on tumour cell functions that may ultimately promote an adverse cell phenotype. New targets have been identified with potential therapeutic applications in resistant breast cancer leading to the subsequent evaluation of inhibitors of these targets in preclinical studies. Importantly, there is increasing evidence from such studies demonstrating the benefit of novel combination strategies as potential avenues for future drug regimens. Written by experts in the subject area, this book covers the molecular details and functional consequences of endocrine resistance in breast cancer with particular emphasis on the future applications of novel drug combinations that may be utilized to circumvent resistance and improve anti-tumour effects. This book represents a timely publication in the field of breast cancer research, providing current knowledge in the area of drug resistance and will be important reading material for clinicians and researchers alike.

Regulation of Growth and Metastases in an Estrogen Independent Breast Cancer Cell by Vitamin D Compounds

Metastatic spread of cancer continues to he the greatest barrier to cancer cure. It is ultimately the metastatic process that causes mortality of breast cancer since uncontrolled growth of malignant cells in other tissues continues at the expense of the normal function of that tissue. Understanding the molecular mechanisms of metastasis is crucial for the design and effective use of novel therapeutic strategies to combat cancer. In estrogen dependent mammary epithelial cells, estrogen ablation or anti-estrogen treatments such as Tamoxifen activate apoptosis secondary to disruption of estrogen survival signals. Anti-estrogen therapies can induce remission in patients whose tumors contain estrogen dependent cells, however prolonged treatment with anti-hormonal therapies often leads to the emergence of hormone independent cells, which is frequently associated with increased metastatic capacity and reduced survival time (Beckman, Niederacher et al 1997). Therefore, apoptosis in breast tumors consisting of estrogen independent cells would require use of agents that exploit signaling pathways which are independent from those triggered by disruption of estrogen receptor (ER) function.

Self-Eating on Demand: Autophagy in Cancer and Cancer Therapy

Frontiers Media SA Macroautophagy, the major lysosomal pathway for recycling intracellular components including whole organelles, has emerged as a key process modulating tumorigenesis, tumor–stroma interactions, and cancer therapy. An impressive number of studies over the past decade have unraveled the plastic role of autophagy during tumor development and dissemination. The

discoveries that autophagy may either support or repress neoplastic growth and contextually favor or weaken resistance and impact antitumor immunity have spurred efforts from many laboratories trying to conceptualize the complex role of autophagy in cancer using cellular and preclinical models. This complexity is further accentuated by recent findings highlighting that various autophagy-related genes have roles beyond this catabolic mechanism and interface with oncogenic pathways, other trafficking and degradation mechanisms and the cell death machinery. From a therapeutic perspective, knowledge of how autophagy modulates the tumor microenvironment is crucial to devise autophagy-targeting strategies using smart combination of drugs or anticancer modalities. This eBook contains a collection of reviews by autophagy researchers and provides a background to the state-of-the-art in the field of autophagy in cancer, focusing on various aspects of autophagy regulation ranging from its molecular components to its cell autonomous role, e.g. in cell division and oncogenesis, miRNAs regulation, cross-talk with cell death pathways as well as cell non-autonomous role, e.g. in secretion, interface with tumor stroma and clinical prospects of autophagy-based biomarkers and autophagy modulators in anticancer therapy. This eBook is part of the TransAutophagy initiative to better understand the clinical implications of autophagy in cancer.

Advances in Rapid Sex-Steroid Action

New Challenges and New Chances in Breast and Prostate Cancers

Springer Science & Business Media Breast and prostate cancers are both hormone-dependent, at least in some stages of their progression. Hormonal manipulation represents an important therapeutic approach. Although most of breast and prostate cancers initially respond to hormone therapy, most tumors reinitiate to growth. Finally, hormone-resistant and metastatic breast and prostate cancers may develop. Thus, the challenge is the dissection of mechanisms by which steroid receptor signaling pathways continue to influence cell growth and invasiveness. Compelling evidence indicates that steroid hormones elicit non-genomic responses in extra-nuclear compartment of target cells. In this cellular location, steroid-coupled receptors rapidly recruit signaling effectors or scaffold proteins and activate multiple pathways leading to proliferation, survival, migration and invasiveness. The immediate challenge is the dissection of key events regulating the steroid response of target tissues to prevent progression and improve treatment of breast and prostate cancers.

Development of a Novel Tissue Specific Aromatase Activity Regulation Therapeutic Method

Estrogen is essential for normal growth and development of the female reproductive system and breast. Lifetime exposure to estrogen may affect a woman's risk for breast cancer. Approximately 70% of breast cancers are estrogen receptor (ER) positive and adjuvant antiestrogen therapy is considered as a primary therapy for those cancer patients. In the past 2 decades, selective estrogen receptor modulators (SERMs), especially tamoxifen, have been clinically used. Although tamoxifen is a powerful blocking drug for estrogen receptor in breast cancer tissue, it is also known as a weak estrogen signal stimulator in other organs such as liver, bone and uterine. As such it is now believed that tamoxifen can slightly increase the risk of uterine cancer. While tamoxifen has been clinically used as the first line therapeutic drug, many researchers, including our research group, were developing drugs that would inhibit the production of estrogen. Estrogen is produced by the ovaries and other tissues of the body using an enzyme called aromatase. Once women have reached menopause, the ovaries no longer produce estrogen. Therefore, particularly in postmenopausal women with breast cancer, estrogen production in the breast tissue can regulate the cancer growth. Currently, the third generation of aromatase inhibitors (AIs), such as exemestane (Aromasin(trademark)), anastrazole (Arimidex(trademark)) and letrozole (Femera(trademark)), are approved by US. Food and Drug Administration and clinically used for those estrogen sensitive breast cancer patients with postmenopausal women.