Dna Methylation And Cancer Therapy Reprint

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Dna Methylation And Cancer Therapy Reprint

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CURTIS GAVIN

Histone Modifications in Therapy Academic Press
Epigenetics is one of the most exciting and rapidly developing areas of modern genetics with applications in many disciplines from medicine to agriculture. The most common form of epigenetic modification is DNA methylation, which plays a key role in fundamental developmental processes such as embryogenesis and also in the response of organisms to a wide range of environmental stimuli. Indeed, epigenetics is increasing regarded as one of the major mechanisms used by animals and plants to modulate their genome and its expression to adapt to a wide range of environmental factors. This book brings together

a group of experts at the cutting edge of research into DNA methylation and highlights recent advances in methodology and knowledge of underlying mechanisms of this most important of genetic processes. The reader will gain an understanding of the impact, significance and recent advances within the field of epigenetics with a focus on DNA methylation.

Targeting the DNA Methylation Machinery in Cancers Academic Press

This book provides a broad and rich outline of the epigenetic mechanisms involved in cancer progression and the generation of metastasis. It describes the tumor suppressor genes undergoing transcriptional silencing by CpG island promoter hypermethylation in the different tumor types of the human anatomy and their association with tumoral behaviour. It also provides a comprehensive insightful look at the molecular players involved in DNA methylation, histone modification and chromatin remodelling complexes causing epigenetic lesions linked to the metastasic phenotypes. Finally, it explains how epigenetic lesions associated with cancer spreading can be targeted using new and potent chemotherapy drugs. The book is a state-of-the-art reference to all scientific researchers and clinicians interested in the understanding of the biological processes leading to tumor dissemination and to

those that are keen to translate this knowledge to a better management of cancer patients. Each contributor is a specialist in their epigenetic area and their joint effort has created a unique view of the DNA methylation, histone and chromatin changes that define cancer metastasis.

DNA Methylation and Cancer Therapy

Springer

Epigenetic Mechanisms in Cancer provides a comprehensive analysis of epigenetic signatures that govern disease development, progression and metastasis. Epigenetic signatures dictating tumor etiologies present an opportunity for biomarker identification which has broad potential for improving diagnosis, prognosis, prediction, and risk assessment. This volumes offers a unique evaluation of signature differences in childhood, sex-specific and race-specific cancers, and in doing so broadly illuminates the scope of epigenetic biomarkers in clinical environments. Chapters detail the major epigenetic process in humans consisting of DNA methylation, histone modifications and microRNAs (miRNAs) involved in the initiation, progression and metastasis of tumors. Also delineated are recent technologies such as next generation sequencing that are used to identify epigenetic profiles (primarily methylation analysis) in samples (normal, benign and cancerous) and which are highly important to the analysis of epigenetic outcomes. Offers broad

coverage that is applicable to audiences in various area of cancer research - population studies, diagnostics, prognosis, prediction, therapy, risk, etc. Provides critical review analysis of the topics that will clarify and delineate the potential roles of epigenetic signatures in cancer management Covers basic, as well as, clinical areas of epigenetic mechanisms in tumorigenesis Features contributions by leading experts in the field Provides comprehensive coverage of current epigenetic signatures involved in the etiology of various cancers and miRNAs

Bioengineering and Cancer Stem Cell Concept

Frontiers Media SA

This book explores the role of cancer stem cells in the diagnosis, treatment, and cure of cancers. This book also tackles novel methodology for cancer stem cell marker identification, cancer stem cell respiration and metabolism, genetic and epigenetic mechanisms including DNA methylation, and mi-RNA assemble. It also emphasizes the role of Bioinformatics techniques, which provide a novel methodology for modeling cancer outcomes. The authors investigate the difference between cancer stem cells and normal stem cells, along with the concept of targeted cancer stem cell therapy. Although the theoretical explanations of cancer stem cell involvement in leukemia and solid cancers are controversial, there is now

little doubt that cancer stem cells exist within otherwise heterogeneous cancer cell population. The brief examines the two leading theories, hierarchical and the stochastic/cancer stem cell model. Researchers, professors and advanced-level students focused on bioengineering and computer science will find this book to be a valuable resource. It is a very good source of critical references for understanding of this problem, and a useful tool for professionals in related fields.

Epigenetics and Cancer

Springer

DNA Methylation and Complex Human Disease reviews the possibilities of methyl-group-based epigenetic biomarkers of major diseases, tailored epigenetic therapies, and the future uses of high-throughput methylome technologies. This volume includes many pertinent advances in disease-bearing research, including obesity, type II diabetes, schizophrenia, and autoimmunity. DNA methylation is also discussed as a plasma and serum test for non-invasive screening, diagnostic and prognostic tests, as compared to biopsy-driven gene expression analysis, factors which have led to the use of DNA methylation as a potential tool for determining cancer risk, and diagnosis between benign and malignant disease. Therapies are at the heart of this volume and the possibilities of DNA demethylation. In cancer, unlike genetic mutations, DNA methylation and

histone modifications are reversible and thus have shown great potential in the race for effective treatments. In addition, the authors present the importance of high-throughput methylome analysis, not only in cancer, but also in non-neoplastic diseases such as rheumatoid arthritis. Discusses breaking biomarker research in major disease families of current health concern and research interest, including obesity, type II diabetes, schizophrenia, and autoimmunity

Summarizes advances not only relevant to cancer, but also in non-neoplastic disease, currently an emerging field Describes wholly new concepts, including the linking of metabolic pathways with epigenetics Provides translational researchers with the knowledge of both basic research and clinic applications of DNA methylation in human diseases

DNA Methylation: Development, Genetic Disease and Cancer

Springer Science & Business Media

Cell Press Reviews: Cancer Therapeutics informs, inspires, and connects cancer researchers at all stages in their careers with timely, comprehensive reviews written by leaders in the field and curated by Cell Press editors. The publicatio offers a broad view of some of the most compelling topics in cancer therapeutics including: Genetic approaches for personal oncology Targeting epigenetic dysregulation and protein interaction networks Vaccines and

antibodies in cancer immunotherapy Tumor heterogeneity and chemotherapy resistance Tumor associated macrophages in anticancer treatment Contributions come from leading voices in the field, including: - Daniel A. Haber, Director of Massachusetts General Hospital Cancer Center and Professor at Harvard Medical School - Tony Kouzarides, Professor at the University of Cambridge, Deputy Director of the Wellcome Trust/Cancer Research UK Gurdon Institute, and a founder of the cancer drug discovery company Chroma Therapeutics - Charles L. Sawyers, Chair of the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center, President of the American Association for Cancer Research, member of the presidentially appointed National Cancer Advisory Board, and recipient of the 2013 Breakthrough Prize in Life Sciences Cell Press Reviews: Cancer Therapeutics is part of the Cell Press Reviews series, which features reviews published in Cell Press primary research and Trends reviews journals. Provides timely, comprehensive articles on a wide range of topics in cancer therapeutics Offers insight from experts on genetic, molecular, and cellular aspects of cancer therapy Features reviews on basic science advances translated into drug discovery and therapeutic approaches Includes articles originally published in Cell, Cancer Cell, Trends in Genetics,

Trends in Molecular Medicine, and Trends in Pharmacological Sciences

Epigenetic Markers
Springer Science & Business Media
Expert laboratory and clinical researchers from around the world review how to design and evaluate studies of tumor markers and examine their use in breast cancer patients. The authors cover both the major advances in sophisticated molecular methods and the state-of-the-art in conventional prognostic and predictive indicators. Among the topics discussed are the relevance of rigorous study design and guidelines for the validation studies of new biomarkers, gene expression profiling by tissue microarrays, adjuvant systemic therapy, and the use of estrogen, progesterone, and epidermal growth factor receptors as both prognostic and predictive indicators. Highlights include the evaluation of HER2 and EGFR family members, of p53, and of UPA/PAI-1; the detection of rare cells in blood and marrow; and the detection and analysis of soluble, circulating markers.

DNA Methylation: Development, Genetic Disease and Cancer
Springer Science & Business Media
Genes interact with the environment, experience, and biology of the brain to shape an animal’s behavior. This latest volume in Advances in Genetics, organized according to the most widely used model organisms, describes the

latest genetic discoveries in relation to neural circuit development and activity. Explores the latest topics in neural circuits and behavior research in zebrafish, drosophila, C.elegans, and mouse models Includes methods for testing with ethical, legal, and social implications Critically analyzes future prospects

The Histone Code and Beyond Springer Science & Business Media

This thesis investigates epigenetics in cancer with particular emphasis on breast cancer. There are two major themes, see Figure above. The first theme relates to the potential for assessing and developing more efficient epigenetic drugs while the second theme investigates mechanism of downregulation of ANKRD11, a putative tumour suppressor gene, in human breast cancer. This thesis is in the publication format with Chapters 1 and 3 as published articles, Chapter 2 submitted for publication and Chapter 4 as a manuscript in preparation. Theme 1: To improve the epigenetic-based therapeutic approach (Chapter 1 and 2). One of the roles that epigenetics plays in cancer development is the inhibition of transcription of tumour suppressor genes. Chapter 1, published as a review in Biodrugs, examines the knowledge of currently available therapeutic approaches related to epigenetic mechanisms such as DNA methylation for cancer treatment. Drug-related issues that could influence the application of

therapeutics for clinical use are reviewed and possible developments to improve the clinical use of the drugs explored. Epigenetic-based drugs are emerging as anti-cancer therapies in the clinic. Existing demethylating agents have poor pharmacological properties that limit their clinical use, and the application of nano-based encapsulation to resolve these issues is discussed. Chapter 2, submitted as an original research article to Biodrugs, presents the development and assessment of an assay to allow comparison of epigenetic-related drugs in a high throughput format. Decitabine is encapsulated in a liposomal formulation and the potency of this newly formulated decitabine and existing drugs are effectively compared using the developed assay system. Further development and validation of the assay system and the liposomal formulated decitabine, not included in the submitted manuscript are included as supplementary data. Theme 2: Investigation of gene silencing mechanism of tumour suppressor ANKRD11 (Chapter 3 and 4). ANKRD11 is novel gene that was previously characterised in our laboratory, and found to be a putative tumour suppressor gene and a p53-coactivator (Neilsen et al. 2008). Chapter 3, published in European Journal of Cancer, investigates the mechanism of downregulation of ANKRD11 in human breast

cancer. This chapter identifies the promoter sequence of ANKRD11, demonstrates the critical region of the ANKRD11 promoter subjected to DNA methylation, and associates the DNA methylation levels of ANKRD11 with its gene expression and clinical data. Further analysis of the DNA methylation pattern of this gene revealed a putative GLI1 transcription-factor binding site within the localised region of the promoter that is methylated. Chapter 4, presented as a manuscript in preparation, further explores the relationship between ANKRD11 and GLI1 in breast cancer. GLI1 is a Hedgehog signalling transcription factor, which has been shown to be involved in breast cancer development. This study analyses the transcriptional activity of ANKRD11 in the cells overexpressed with GLI1 and quantifies differential expression of these two genes in different stages of breast cancer. Future experiments to confirm and extend these exciting preliminary findings are discussed. The final chapter of this thesis summarises the findings of these studies and possible future research directions. The impact of these findings for the development of anti-cancer drugs, and the possible role of expression of ANKRD11 and GLI1 in breast cancer are highlighted.

Epigenetic Therapy of Cancer IntechOpen

Methylation of DNA at cytosine residues as well as post-translational

modifications of histones, including phosphorylation, acetylation, methylation and ubiquitylation, contribute to the epigenetic information carried by chromatin. These changes play an important role in the regulation of gene expression by modulating the access of regulatory factors to the DNA. The use of a combination of biochemical, genetic and structural approaches has allowed demonstration of the role of chromatin structure in transcriptional control. The structure of nucleosomes has been elucidated and enzymes involved in DNA or histone modifications have been extensively characterized. Since deregulation of epigenetic marks has been reported in many cancers, a better understanding of the underlying molecular mechanisms bears the promise that new drug targets may soon be found. The newest developments in this quickly developing field are presented in this book.

Introduction to Epigenetics Springer

"One of the elements commonly seen in cancer is the change in methylation status of the genome. These aberrations in methylation appear to be critical for the neoplastic phenotype and manifest as changes to gene expression of oncogenes and tumour suppressors. In addition to epigenetic alterations, the proteins involved in maintaining the plastic methylation status of the genome, DNA methyltransferases and demethylases, also show

methylation-independent protein-protein interactions that have effects on cell cycle progression and proliferation. As changes in gene expression and mitotic regulation are seminal elements of cancer, and because several methylated DNA binding proteins show differential expression in a wide variety of cancers, these proteins serve as prime targets for anticancer therapies. This thesis relates to exploring both current and forthcoming possibilities and mechanisms of utilizing the DNA methylation machinery for pharmacological intervention of cancer. Chapter two deals with an antisense drug, currently in clinical trials, targeted to reduction of DNA methyltransferase 1, the maintenance methylation enzyme in mammalian cells. Our data indicate that the existence of a common truncation mutation of the adenomatous polyposis coli gene seen in some forms of sporadic and familial colorectal cancer may lead to downstream upregulation of DNA methyltransferase 1, as reconstitution of the wildtype protein reduces DNA methyltransferase 1 mRNA and protein. Reduction of the transcripts of this methylation enzyme with an antisense oligonucleotide decreases the tumourigenicity of these colorectal cancer cells, and provides a rationale for use of this drug in colorectal cancer patients and prophylactic treatment of adenomatous polyposis

coli mutation-bearing individuals. Chapter three describes the rationale, design, and in vitro and in vivo testing of antisense molecules against the methylated DNA binding protein MBD2. These drugs red" --

Regulation of the Epigenome and Its Implications in Cancer Therapy CRC Press

Studies have shown that alterations of epigenetics and microRNAs (miRNAs) play critical roles in the initiation and progression of human cancer. Epigenetic silencing of tumor suppressor genes in cancer cells is generally mediated by DNA hypermethylation of CpG island promoter and histone modification such as methylation of histone H3 lysine 9 (H3K9) and tri-methylation of H3K27. MiRNAs are small non-coding RNAs that regulate expression of various target genes. Specific miRNAs are aberrantly expressed and play roles as tumor suppressors or oncogenes during carcinogenesis. Important tumor suppressor miRNAs are silenced by epigenetic alterations, resulting in activation of target oncogenes in human malignancies. Stem cells have the ability to perpetuate themselves through self-renewal and to generate mature cells of various tissues through differentiation. Accumulating evidence suggests that a subpopulation of cancer cells with distinct stem-like properties is responsible for tumor initiation, invasive growth, and metastasis formation, which is defined as cancer stem cells. Cancer stem

cells are considered to be resistant to conventional chemotherapy and radiation therapy, suggesting that these cells are important targets of cancer therapy. DNA methylation, histone modification and miRNAs may be deeply involved in stem-like properties in cancer cells. Restoring the expression of tumor suppressor genes and miRNAs by chromatin modifying drugs may be a promising therapeutic approach for cancer stem cells. In this Research Topic, we discuss about alterations of epigenetics and miRNAs in cancer and cancer stem cell and understand the molecular mechanism underlying the formation of cancer stem cell, which may provide a novel insight for treatment of refractory cancer.

DNA Methylation Machinery as Molecular Targets for Cancer Therapeutics Springer Science & Business Media

"Cancer cells have aberrant DNA methylation patterns which are characterized by hypomethylation of a large set of promoters and hypermethylation of tumor suppressor genes. The dynamic nature of the epigenome makes it a valuable target for therapeutic interventions. This thesis focuses on understanding the use of various inhibitors towards DNA methylation-related proteins and their respective anti-cancer activities at both global and gene-specific levels. The widely used demethylating agent 5-azacytidine and 5-aza-2'-deoxycytidine (5-azaCdR) are FDA-approved drugs

for the treatment of myelodysplastic syndrome. However, these nucleoside analogs which trap the DNA methyltransferases (DNMTs) are non-specific. Studies have shown that 5-azaCdR induced pro-metastatic genes and caused long distance metastasis. This raises serious safety concerns for their clinical use. On the contrary, targeting the DNMTs individually or in combination did not result in dramatic induction of pro-metastatic genes as with 5-azaCdR treatment. In particular, single DNMT1-specific inhibition resulted in maximum growth suppression when compared to inhibition of all three major DNMTs, while not increasing cell invasiveness. DNMT1 has been shown to be important for cancer growth. Our study supports the idea that DNMT1 has a major role in cancer over the other DNMTs and that DNMT1 inhibitors could be effective anti-cancer drugs. 5-azaCdR has nevertheless been proven to be a potent suppressor of cancer growth. We tested the idea of a combinatorial treatment that may minimize its side-effects on cell invasion while maintaining its growth suppressor effects. The methyl-CpG binding protein 2 (MBD2) protein has been shown to demethylate pro-metastatic genes. Its inhibition in concurrent with 5-azaCdR treatment synergistically suppressed cancer growth, while reversed the 5-azaCdR-induced invasion. In order

to have a deeper understanding of the impact of the treatments, microarrays studies on the methylome and transcriptome of the treated cells were carried out. Bioinformatics analysis indicated that the combined treatment suppressed gene networks that were involved in cell mobility, while synergistically enhanced gene networks that were involved in cell death. This data indicate that combining 5-azaCdR treatment with MBD2 inhibition results in more potent anti-cancer effects than either treatment alone. In order to explore the currently available drugs that inhibit MBD2, we tested the combination of S-adenosylmethionine (SAM) with 5-azaCdR on the same cancer cell lines. SAM remethylated gene promoters of pro-metastatic genes and repressed 5-azaCdR-induced invasion similarly to MBD2 inhibition. We then investigated the relationship between SAM and MBD2 downregulation and observed hypermethylation on both CpG and non-CpG sites in the MBD2 promoter upon SAM treatment. Interestingly, inhibition of MBD2 using short interference RNA also resulted in hypermethylation of its own promoter. This observation suggested that SAM treatment could directly downregulate MBD2 expression, which is further downregulated through a feedback loop. These results also suggested that SAM treatment could have a direct effect on MBD2

promoter, which in turn affects multiple MBD2 targets that are involved in invasion. Together, the data from this thesis support the idea that targeting the epigenome could be a highly efficacious anti-cancer therapy and that combining drugs that target DNA methylation could increase the potency over individual treatments." --

Epigenetics in Cancer

Academic Press

Epigenetics of Cancer Prevention, Volume Ten is the first to look at epigenetics and chemoprevention together. Although there is numerous scientific data available on how epigenetics can lead to cancer and how chemoprevention can be beneficial in the treatment of, or improvement of quality of life, together they will set an advanced understanding for the reader in this upcoming field of chemoprevention influencing epigenetics. This book discusses molecular epigenetic targets of natural products, such as green tea polyphenols, curcumin and resveratrol, and organ specific epigenetic targets related to diverse types of cancer, for example prostate, colorectal, breast, lung and skin cancers. Additionally, it encompasses a discussion on research methods and limitations to study epigenetics and epigenomics of chemopreventive drugs and personalized cancer treatment with phytochemicals. The book is ideal for cancer

researchers, health care professionals and all individuals who are interested in cancer prevention research and its clinical applications, especially in natural remedies. Lists natural agents, including nutraceuticals, and their effects on normal or tumor genome Addresses various epigenetic systems and mechanisms in the regulation and support of the mammalian genome Discusses how various parts of dietary phytochemicals can influence or modify epigenetic mechanisms in several types of cancer

Epigenetics and Cancer

Bentham Science Publishers

This open access textbook leads the reader from basic concepts of chromatin structure and function and RNA mechanisms to the understanding of epigenetics, imprinting, regeneration and reprogramming. The textbook treats epigenetic phenomena in animals, as well as plants. Written by four internationally known experts and senior lecturers in this field, it provides a valuable tool for Master- and PhD-students who need to comprehend the principles of epigenetics, or wish to gain a deeper knowledge in this field. After reading this book, the student will: Have an understanding of the basic toolbox of epigenetic regulation Know how genetic and epigenetic information layers are interconnected Be able to explain complex epigenetic phenomena by understanding the

structures and principles of the underlying molecular mechanisms Understand how misregulated epigenetic mechanisms can lead to disease
DNA Methylation, Epigenetics and Metastasis BoD – Books on Demand
"The regulation of the genome by the epigenetic modifications of DNA methylation and histone modification is increasingly recognized as a vital factor in the development, physiology and pathology of vertebrates. There is mounting evidence suggesting that both aberrant DNA methylation and histone modifications are common events in cancer. This has lead to the establishment of both DNMTs and HDACs as important targets in cancer therapy. There are currently several clinical trials that are testing inhibitors of both DNMTs and HDACs as anticancer agents. This thesis attempts to understand the roles that DNMT1 and HDAC1 play in the regulation of gene expression and epigenomic inheritance. In the first chapter, we examined the effects of DNMT1 inhibitors on gene expression and found that DNMT1 can regulate gene expression independent of its DNA methyltransferase activity. This novel role of DNMT1 has challenged a widely accepted theory that the mechanism of DNMT1 inhibitors involves inhibition of the catalytic activity of DNMT1, thus leading to demethylation and reexpression of tumor suppressors previously silenced by methylation.

In chapter 2, we further examined different roles of DNMT1. We showed that different DNMT1 inhibitors inhibit different DNMT1 functions and produce different effects on gene expression. Our data suggests that inhibition of DNMT1 enzymatic activity can produce serious long-term effects as a result of massive non-selective demethylation of the genome. In contrast, reduction of DNMT1 levels was shown to result in a rapid arrest of cell growth, limited demethylation and induction of stress-response genes. We hypothesize that these effects are a result of the activation of an epigenetic check point that has evolved to protect the cell from undergoing replication in the absence of DNMT1. In chapter 3, we further explore the roles of DNMT1 in methylation independent regulation of gene expression, which has been suggested to in" -- **Epigenetics of Cancer Prevention** CRC Press This volume explores the epigenetic alterations and their association with various human cancers. Considering one of human cancer as an example, individual chapters are focused on defining the role of epigenetic regulators and underlying mechanisms in cancer growth and progression. Epigenetic alteration including DNA methylation, histone modification, nucleosome positioning and non-coding RNAs expression are involved in a complex network of regulating expression of oncogenes and tumor suppressor

genes and constitute an important event of the multistep process of carcinogenesis. Recent advances in the understanding of the epigenetic regulation and detailed information of these epigenetic changes in various cancers provide new avenues of advancements in diagnostics, prognostics, and therapies of this highly fatal disease.

DNA Methylation

Academic Press

DNA Methylation and Cancer TherapySpringer Science & Business Media

Cutting Edge Therapies for Cancer in the 21st Century Springer

Methylation of DNA at cytosine residues as well as post-translational modifications of histones, including phosphorylation, acetylation, methylation and ubiquitylation, contribute to the epigenetic information carried by chromatin. These changes play an important role in the regulation of gene expression by modulating the access of regulatory factors to the DNA. The use of a combination of biochemical, genetic and structural approaches has allowed demonstration of the role of chromatin structure in transcriptional control. The structure of nucleosomes has been elucidated and enzymes involved in DNA or histone modifications have been extensively characterized. Since deregulation of epigenetic marks has been reported in many cancers, a better understanding of the underlying molecular mechanisms bears the promise that new drug targets may soon be

found. The newest developments in this quickly developing field are presented in this book.

Biomarkers in Breast Cancer Inst za onkologiju i radiol

Roughly two-thirds of all breast cancers are Estrogen Receptor a (ER)-positive and can be treated with an anti-estrogen such as Tamoxifen, however resistance occurs in 33% of women who take the drug for more than 5 years. In addition to this acquired antiestrogen resistance, de novo- or intrinsic-resistance occurs primarily in ER-negative tumors but also occasionally in ER-positive tumors. Aberrant DNA promoter methylation, a major epigenetic mechanism by which gene expression is altered in cancer, is thought to play a role in this resistance. To date, few studies have examined promoter methylation and Tamoxifen resistance in breast cancer. Of the studies conducted, one detected drug-specific promoter methylation and gene expression profiles in an ER-positive, Tamoxifen-selected MCF-7 derivative cell line. However, studies using both ER-positive and -negative, Tamoxifen-selected cell lines have not been described until now. To develop an understanding of Tamoxifen-resistance and identify novel pathways and targets of aberrant methylation, I first analyzed two Tamoxifen-resistant clones of MCF-7, one that retained expression of ER (TMX2-11) and one that

lost expression of the gene (TMX2-28) after 6-months of Tamoxifen treatment, by Illumina HumanMethylation450 BeadChip (HM450BC). I found that prolonged treatment with Tamoxifen induced hypermethylation and hypomethylation throughout the genome. Compared to MCF-7, the ER-positive line, TMX2-11 had 4,000 hypermethylated sites, while the ER-negative line, TMX2-28 had over 33,000. Analysis of CpG sites in both TMX2-11 and TMX2-28 revealed that the two Tamoxifen-selected lines share 3,000 hypermethylated CpG sites with 21% of those sites being located in the promoter region. Promoter methylation and expression of two genes, MAGED1 and ZNF350, in both Tamoxifen-resistant cell lines demonstrated cell line-specific responses to treatment with 5-aza-2'deoxycitidine (5-Aza). Sixteen additional genes involved in signal transduction, cell adhesion, transcriptional repression, inflammatory response, cell proliferation and hormone response were chosen for further analysis based on their shared hypermethylation or their reduced expression in TMX2-28 as detected in a previously completed expression array. Five genes, RORA, THBS1, CAV2, TGF[beta]2, and BMP2 had decreased expression in TMX2-28, but not TMX2-11 as compared to MCF-7, and 5-Aza increased expression of the genes. This indicates that Tamoxifen is affecting a set of genes similarly in both the ER-positive and -

negative breast cancer cell lines, however overall methylation changes are more pronounced in the ER-negative line. Our data as well as others suggest that DNA methylation may be contributing to Tamoxifen-resistance. I hypothesized that both ER-positive and ER-negative second human breast tumors occurring after anti-estrogen treatment would be hypermethylated. I characterized the methylation profiles of 70 human breast tumor samples using the HM450BC. These data confirm previous findings that ER-positive breast tumors have more hypermethylated CpG sites than ER-negative tumors. Stratification of the tumors by ER-positive first and second tumor sets shows that methylation is greater in first tumors.. Additionally, I saw that first tumors from ipsilateral pairs had higher methylation than the second tumors; in contrast, second tumors from contralateral pairs had higher methylation than in the first tumor. These data, together with the fact that tumor progression is associated with an increase in methylation, are consistent with the prediction that ipsilateral, not contralateral, tumors are more likely to be a true recurrence. Pathway analysis was conducted to provide insight into biomarkers associated with tumors that recur. Two pathways, 'homophilic cell adhesion via plasma membrane adhesion molecules' and 'cell fate commitment', were selected for further

analysis. ER-positive first tumors that recurred as either ER-positive or ER-negative compared with non-recurrent tumors shared hypermethylated genes in the homophilic cell adhesion pathway. ER-positive first tumors that recurred as ER-negative compared with ER-positive first tumors that recurred as ER-positive were associated with a unique set of hypermethylated genes in the cell fate commitment pathway. To examine the association of methylation changes in my tumor data set with breast cancer patient survival data, Kaplan-Meier plots were created using TGCA breast cancer data available online. Expression of the genes only hypermethylated in each individual comparison group in the homophilic cell adhesion pathway was linked to overall survival. These data suggest that the genes hypermethylated only in ER-positive tumors recurring as ER-negative are a potential signature for poor survival. The underlying mechanisms of anti-estrogen resistance are poorly understood. Variable responses to breast cancer therapy highlights the need for biomarkers that can effectively guide treatment. The findings presented here underscore the potential use of breast tumor stratification based on methylation biomarkers in guiding treatment.

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