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Editorial

Review on epigenetics in cancer gene therapy: series I

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In this first series dedicated to Epigenetics, *Cancer Gene Therapy* has deliberately assembled diverse reviews on topical areas relevant to our understanding of the cancer cell.

In recent years, there has been a surge of interest in the study of cancer and epigenetics, most notably into mechanisms that could be used to modify chromatin architecture in a willing effort to perturb its behavior. Intriguingly, it is technically achievable to modulate the complex architecture and nucleoprotein filament of chromosomes. Studies using histone deacetylase and genomic methylation inhibitors illustrate that chromatin reorganization and decondensation can be achieved over several Mb of DNA.[1,2] Epigenetic modifiers can rapidly reactivate genes repressed in cancer and are currently being tested in clinical trials. The mechanisms by which these drugs function on the epigenome is not yet clear, although changes in chromatin structure do appear to accompany changing transcriptional activity.[3] Hyperacetylation of histones and increased chromatin accessibility are just two features associated with gene reactivation. Pharmacological reactivation of silent genes in cancer is an intense area of study and histone deacetylase inhibitors are generally effective against hypomethylated promoter sequences.[4] The tumor suppressor p16 gene is silenced by DNA methylation and strategies to reactivate include prior cell exposure to trichostatin A and 5-aza-2′-deoxycytidine (5adC) to unlock repressive chromatin structures.[5] Studies that examine the molecular machineries that localize on hypermethylated sequences have revealed significant changes in methyl-CpG binding domain family members such as MeCP2, MBD1, MBD2 and MBD3 complexes are associated with gene repression in cancer.[6–9] These and other studies show exquisite changes in DNA methylation, and histone modifications can significantly alter the determinants associated with repression and chromatin conformation.

In a future review article in *Cancer Gene Therapy*, McNamara and colleagues discuss engineered transcriptional regulators capable of perturbing chromatin to regulate gene expression. The discovery of Cys2His2 motif of zinc-finger proteins (ZFP) and the structural and functional adaptability has made it possible to design modules to dock the major groove of DNA with remarkable specificity. The regulation of gene expression is achieved using engineered ZFP fused to activation or repression domains. Equally impressive is the power of ZFP to modify the chromatin landscape of target genes. For example, the domains of histone methyltransferases such as Suv39h1 and G9a can be targeted to achieve histone H3K9 methylation and associated repression of the VEGF-A promoter.[10] The authors elegantly examine what is known about targeting ZFP to integrate, assimilate and regulate endogenous chromatin structure and function.

There is now considerable evidence that suggests aberrant CpG methylation associated with tumor suppressor genes is correlated with carcinogenesis. The protein tyrosine phosphatase (PTP) gene joins the rank of a growing number of identified putative tumor suppressor genes repressed by CpG methylation.[11] Repression of genes critical for the control of normal cell growth is a characteristic of neoplasia. The article by Jacob and Motiwala, in pages 665–672 of this issue, examines the role of epigenetic modification of PTP and have put together a comprehensive review of the current state of literature examining silencing. Originally observed in rats fed a folate/methyl-deficient diet, PTP is methylated in preneoplastic nodules and hypothesized to reflect an early tumor marker.[12] In human lung cancer, PTP transcription is inversely correlated with promoter methylation that is responsive to 5adC.[13] The authors also review genome-based therapeutic concepts using epigenetic modifiers to reactivate gene activity.

It is becoming widely appreciated that epigenetic mechanisms crosstalk between DNA methylation, histone modifications and chromatin remodeling machineries and play important roles in regulating nuclear function. RNA interference (RNAi) is an evolutionarily conserved mechanism that involves short double-stranded RNA to target and silence mRNA that share the same sequence identity. Recent developments have revealed that components of the RNAi pathway are also involved in regulating critical aspects of the epigenome.[14] In support of this view, transcriptional gene silencing can be achieved by the specialized formation of centromeric heterochromatin mediated by RNAi in plants and yeast.[15,16] In human cells, short interfering RNA have been demonstrated to silence expression by a mechanism mediated by genomic methylation of the target sequence.[17,18] Although this is the best evidence so far for mammalian RNAi-mediated genomic methylation, the mechanisms by which it occurs are not known. The results to these studies suggest that transcriptional repression can be associated with RNAi and raises important questions about silencing and changes in epigenetic regulation. The article by

Karagiannis and El-Osta, which will be published in issue 10, focuses on recent developments in the use of RNAi technologies and potential clinical applications. RNAi has revolutionized our understanding of genome function and has quickly become an essential tool in molecular biology. Already, in the short time since its original discovery, a number of commercially validated siRNAs are now available to translate functional genomics in model biological systems. Furthermore, short interfering RNAs have the potential to treat disease and there is great promise for the gene therapy-based platform as a new therapeutic modality as well as drug target identification and validation.

The purpose of the *Epigenetics Series* in *Cancer Gene Therapy* is a response to the extraordinary interest of epigenetics in cancer biology and therapy. The goal is to highlight important developments in the area and it is hoped the review series will continue to develop and mature with emerging research activity.

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