Aberrant Epigenetic Landscape in Cancer: How Cellular Identity Goes Awry

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Appropriate patterns of DNA methylation and histone modifications are required to assure cell identity, and their deregulation can contribute to human diseases, such as cancer. Our aim here is to provide an overview of how epigenetic factors, including genomic DNA methylation, histone modifications, and microRNA regulation, contribute to normal development, paying special attention to their role in regulating tissue-specific genes. In addition, we summarize how these epigenetic patterns go awry during human cancer development. The possibility of "resetting" the abnormal cancer epigenome by applying pharmacological or genetic strategies is also discussed.

Introduction

Normal development appears to take place through a unidirectional process characterized by a step-wise decrease in developmental potential and an activation of specific gene programs that trigger differentiation into specialized cell types. Once established, temporal and spatial activation and silencing of specific genes in a cell-type-specific pattern must be stable over many cell generations and long after inductive developmental signals have disappeared. Equally important, a cell must silence expression of genes specific to other cell types to secure its fate. Repression must be maintained throughout the life of the individual in normal development, and epigenetic mechanisms, which are defined as heritable changes in gene function that do not alter the primary DNA sequence, are ideal for regulating such events. The best-studied epigenetic modification is DNA methylation, which consists of the addition of a methyl group to carbon 5 of the cytosine within the dinucleotide CpG. It has been estimated that 3%–6% of cytosines are methylated in normal tissues and that this DNA methylation is necessary for controlling gene expression of tissue-specific, housekeeping or imprinted genes and also for maintaining genomic stability through silencing transposable elements of the genome (Esteller, 2007).

DNA methylation does not work alone and occurs in the context of other epigenetic modifications, such as histone modifications. Histone tails may undergo many posttranslational chemical modifications, including acetylation, methylation, phosphorylation, ubiquitylation, and sumoylation. For instance, the different statuses of acetylation and methylation of specific lysine residues are considered crucial histone marks affecting chromatin structure and gene expression (Kouzarides, 2007). Additionally, recent advances in the rapidly evolving field of epigenetics have demonstrated the extensive role of noncoding RNAs, especially miRNA expression, in maintaining global expression patterns during normal development (Sharma et al., 2010). Although several small-scale studies of specific epigenetic marks have provided limited information about the regulation of genes from different pathways, there is a need for knowledge in a broader perspective. A range of matters remains to be resolved, such as the relationships between the epigenetic players (the "epigenetic code") and how the environment and/or aging modulate the epigenetic marks. Some of this could be achieved by analyzing patterns on a genome-wide scale, an approach that has at last become possible thanks to recent technological advances (Bernstein et al., 2007; Barski et al., 2007; Irizarry et al., 2009).

It is clear that a comprehensive knowledge of the human epigenome will allow a fuller understanding of normal development, aging, abnormal gene control in cancer, and other diseases, as well as the role of the environment in human health. This is the main goal of the International Human Epigenome Consortium (IHEC) and the Roadmap Epigenomics Program at NIH Fund (http://nihroadmap.nih.gov/epigenomics); however, we must bear in mind that there is no single epigenome but, rather, many different ones that are characteristic of normal and diverse pathological states. It is clear that the information extracted from the whole-genome assays will help us understand the role of epigenetic marks in normal development and in diseases such as cancer. The aim of the present review is to provide an overview of how epigenetic factors, including genomic DNA methylation, histone modifications, and microRNA regulation, contribute to normal development, paying special attention to their role in the establishment of cell identity. In the second part, we will focus on how tissue-specific epigenetic patterns go awry during human cancer development.

Epigenetic Changes during Normal Development

It is well described that DNA methylation patterns undergo genome-wide alterations that occur immediately after fertilization and during early preimplantation development (Mayer et al., 2000; Reik et al., 2001) and that enrichment of individual histone modifications (such as H3K9me, H3K4me and H3K27me3) also varies in a specific manner at different stages of development (Reik, 2007). Apart from the extensive chromatin remodeling that occurs during early differentiation, epigenetic factors must guarantee the activation and maintenance of