

CANCER EPIGENETICS

Studies of epigenetic alterations started a new era of cancer research. In a few years key discoveries have changed the vision of the determinants of cancer. Genetic and epigenetic alterations accumulated within cells and the interactions of such altered cells with the surrounding stroma components in a unique host microenvironment could lead to cancer cell transformation. These alterations include irreversible aberrations in the DNA sequence of particular genes or chromosomes. They also could include potentially reversible changes, known as epigenetic modifications. The term "epigenetic" refers to all heritable changes in gene expression and chromatin organization that do not involve sequence changes in DNA. It includes three distinct and self-reinforcing mechanisms: aberrations in DNA methylation, posttranslational modifications of histones and chromatin remodeling; non-protein-coding RNAs expression: microRNA (miRNA) and small interfering RNA (siRNA) patterns. Epigenetic misregulation could essentially contribute to cancer development and progression, especially on the early stages of tumor development.

Of all epigenetic modifications, hypermethylation, which represses transcription of the promoter regions of tumor suppressor genes leading to gene silencing, has been most extensively studied. These reversible and irreversible changes can affect hundreds to thousands of genes and/or regulatory transcripts. The balance between all the enzymes and factors involved in DNA methylation and its interpretation by different groups of nuclear factors is crucial for normal cell behavior. Collectively, they result in the activation or inhibition of various biological events, thereby causing different aspects of cancer, including angiogenesis, immune escaping, metastasis, and altered cell growth and metabolism. DNA methylation plays important roles in chromatin structure modulation, transcriptional regulation and genomic stability. In higher organisms methylation protects DNA from endonuclease degradation and plays a critical role in regulating gene expression, making it essential for normal development and function. DNA methylation in humans occurs almost exclusively at CpG dinucleotides, and most CpG sequences in the genome are methylated. The modification is generally repressive to transcription and helps to maintain silencing of transposable elements, therefore enhancing genome stability. However, there are "CpG islands" associated with gene promoters that escape DNA methylation. DNA methylation normally promotes a highly condensed chromatin structure through recruitment of DNA-organizing proteins. DNA hypomethylation could lead to oncogene activation. In cancer cells it could cause chromatin decondensation and chromosomal rearrangement, which may result in chromosomal instability. Alterations in DNA methylation pattern may become an indicator for carcinogenic risk, could help in early tumor diagnostics, and could suggest a poor prognosis for cancer patients.

Histone posttranslational modifications circumscribe the greatest range of variation in epigenetic regulation, encompassing more than 50 known sites of modification. Histones are subject to several forms of modification, including acetylation, methylation, phosphorylation, citrullination, and ADP-ribosylation. Acting in concert, the combination of different histone modifications is thought to constitute a "histone code" that is interpreted in the form of specific nuclear events. Although the interplay among various histone modifications is still largely obscure, a paradigm is rapidly emerging, whereby methylation, acetylation or phosphorylation at independent sites may work in tandem with other modifications to convey unique biological consequences.

The histone deacetylase (HDAC) inhibitors are important in the developing of novel and less toxic anticancer therapy. HDAC inhibitors block histone deacetylases, which are responsible for histone deacetylation, and therefore they could modulate gene expression. HDAC inhibitors arrest growth and differentiation. Pilot studies emphasize the important place of histones' posttranslational modifications as a target of cancer therapy.

MicroRNAs (miRNA), an abundant class of small non-protein-coding RNAs, play a role in posttranscriptional regulation and function as negative gene expression regulators. miRNAs mutations or mis-expression can function as tumor suppressors and oncogenes. miRNAs have been shown to repress the expression on important cancer-related genes, and might prove useful in the diagnosis and treatment of cancer. Similar to coding genes, miRNA also possesses tissue specificity, differentiation development timing and specific expression. It has been observed that non-coding RNA, targeting CpG islands in promoter regions, is able to act in concert with both DNA and histone methylation to affect gene transcription. The understanding of the influence of non-coding RNA on transcriptional activity is still incomplete, this is an exciting new front in the field of epigenetic modifications that promises to possess answers to broader questions on transcriptional regulation and carcinogenesis.

Progress of epigenetics in today's post-genomic era should help elucidation of the molecular mechanisms of cancer and lead to better diagnosis, treatment and prevention of cancer. Cancer-specific DNA methylation patterns could be examined in detached tumor cells in bodily fluids, such as blood and urine. Detection of methylated DNA by the very sensitive (nested) methylation specific PCR (MSP) is noninvasive and relatively cheap.

Epigenetic alterations appear to play a prominent role in the initiation of cancer. Due to the reversible nature of epigenetic changes, enzymes involved in their maintenance stand as promising targets for cancer therapy.

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