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Epigenetic control of gene expression: Potential implications for cancer treatment

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ABSTRACT

Epigenetic changes are defined as inherited modifications that are not present in DNA sequence. Gene expression is regulated at various levels and not only in response to DNA modifications. Examples of epigenetic control are DNA methylation, histone deacetylation and mi-RNA expression. Methylation of several tumor suppressor gene promoters is responsible for their silencing and thus potentially sustain cancerogenesis. Similarly, histone deacetylation can lead to oncogene activation. mi-RNA are small (18–20 nucleotides) non-coding RNA fragments capable of inhibiting other m-RNA, ultimately altering the balance in oncogene and tumor suppressor gene expression. It has been shown that growth of several tumor types can be stimulated by epigenetic changes in various phases of cancerogenesis, and drugs able to interfere with these mechanisms can have a positive impact on tumor progression. As matter of fact, epigenetic changes are dynamic and can be reversed by epigenetic inhibitors. Recently, methyltransferase and histone deacetylase inhibitors have attracted the attention of researchers and clinicians as they potentially provide alternative therapeutic options in some cancers. Drugs that inhibit DNA methylation or histone deacetylation have been studied for the reactivation of tumor suppressor genes and repression of cancer cell growth. Epigenetic inhibitors work alone or in combination with other therapeutic agents.

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To date, a number of epigenetic inhibitors have been approved for cancer treatment. The main challenge in the field of epigenetic inhibitors is their lack of specificity. In this review article we describe their mechanisms of action and potential in cancer treatment.

1. Background

Epigenetics means "beyond genetic" or "other than genetic" and is defined as a group of inheritable changes in gene expression occurring without alterations in DNA sequence. In the eukaryotic nucleus, DNA is compacted in a structure defined as chromatin, whose basic unit is the nucleosome. Each nucleosome is formed by a multiproteic complex named "histone", surrounded by about 145–147 pairs of DNA bases. Histone is an octamer constituted by four pairs of proteins, called H3, H4, H2A and H2B. The very long molecules of DNA are firstly "supercoiled" and then packaged onto histones, allowing to their compression into a single cell (Luger et al., 1997). Regions of chromatin may assume two different conformations, according to the degree of DNA coiling: euchromatin, which is characterized by a more relaxed DNA and allows gene transcription, and hetero-chromatin, which is associated to the presence of super-coiled DNA that cannot bind to gene transcription machinery. The variable balance between euchromatin and eterochromatin allows cells to modulate gene expression, resulting in significant changes in their phenotypes and biological functions (Venkatesh and Workman, 2015). This feature accomplishes that, starting to the same DNA sequence, cells may differentiate in very different ways. The bidirectional conversion between euchromatin and heterochromatin is determined by epigenetic regulation. Overall, three main mechanisms of epigenetic regulation have been identified. Two of them, including DNA methylation and histone covalent modification, influence the type of chromatin, whereas the third is based on the expression of micro-RNAs (Suzuki and Bird, 2008; Chen et al., 2014).

1.1. DNA methylation

DNA methylation results from the transfer of a methyl group to the 5′ position of a cytosine. A family of enzymes named DNA-methyl transferase (DNMT) allows this reaction. Specific DNA sequences particularly rich in cytosine and guanine nucleotide pairs, named CpG regions, are the preferred target of DNMTs. In human DNA, CpG regions are not randomly distributed, as they are concentrated in short CpG-enriched DNA fragments, called CpG islands. About 60% of all gene promoters are rich of CpG islands, and thus these genes can be epigenetically regulated. There are two known types of DNMT, namely DNMT1, which preserves pre-existing pattern of methylation after cell replication, and DNMT3 A and B, so-called "de novo" DNMT, which methylate previously unmethylated DNA (Bernstein et al., 2007; Meissner et al., 2008).

1.2. Histone covalent changes

Besides the chemical changes in DNA molecule caused by methylation, covalent modifications of the histone core can also play an important role in epigenetic regulation. Different enzymes are able to interact with histones and methylate, acetylate, phosphorylate, or ubiquitylate them. The results of these modifications are chromatin relaxation and gene transcription, or as the opposite, chromatin compaction and gene repression. While DNA methylation silences gene expression, histone modifications can either activate or silence genes, depending on the residues added, on the targeted histones and finally on the extent of the modification (Li et al., 2007). As an example, lysine acetylation at the histone N-terminal is able to eliminate the positive charge of histones, allowing negatively charged DNA to separate from them and acquire a transcription-ready configuration. On the other hand, histone lysine methylation causes transcriptional activation or repression depending on the position of the methylated lysine. Histones acetylation is mediated by histone acetyl transferase (HAT), whereas deacetylation is catalyzed by histone deacetylases (HDAC). Several protein lysine methyl-transferases are involved in histone methylation, but the most acknowledged are the Polycomb repression complex, and the "SET and MYND" domain-containing proteins. The preferred target of acetylation and methylation are the H3 and H4 core histones as the vast majority of covalent modifications involve them. Generally, histone H3K9 (lysine in position 9 of the H3 histone), H3K27 and H4K20 methylation are associated with gene repression. On the contrary, methylation of H3K4 and H3K36, as well as acetylation of H3 and H4 generally, identifies areas of active gene expression (Li et al., 2011; Strahl and Allis, 2000).

1.3. miRNA regulation

Micro RNAs (miRNAs) are short (18–20 nucleotides) non-coding RNAs, which bind target messenger RNA (mRNAs) via partial or complete match of their 3′ untranslated regions and lead to their degradation and post-transcriptional gene silencing. Many human miRNAs loci are located within intronic regions. MiRNAs are able to exert epigenetic control upon cell cycle, apoptosis and other crucial biologic processes (Rouhi et al., 2008; Della Vittoria Scarpati et al., 2014).

In this review article, we highlight the important impact of epigenetics on cancer development and progression. We also describe current therapeutic approaches employing drugs able to target the "epigenetic code".

2. Epigenetics and cancer

Cancer is the result of DNA aberrations causing deregulation of cell cycle, apoptosis and cell survival. DNA mutations involving oncogenes (OG) the genes able to promote cell survival and tumor suppressor genes (TSG) are well known to be responsible for cancer initiation, promotion and progression. Nevertheless, recent data have suggested a crucial role for epigenetic mechanisms in cancer development. Indeed, carcinogenesis, cannot be explained only by genetic alterations, but also involve epigenetic processes, such as DNA methylation, histone modifications and miRNA deregulation (Esteller, 2008). Interestingly, a number of epidemiological studies have highlighted the tight correlation between epigenetic DNA changes and exposure to environmental pollutants, such as arsenic (Argos et al., 2015) (http://spes.campaniatrasparente.it/wp-content/uploads/2016/09/Protocollo_Spes.pdf). Several lines of evidence support the hypothesis that, in several solid tumors, extensive DNA methylation involves TSG promoters, leading to cell cycle deregulation and ultimately cancer progression (Jones and Baylin, 2007; Iwama et al., 2004). Similarly, H3 and H4 histones lysine deacetylation determines downregulation of several TSGs and genes involved in DNA repair. Histone methylation can induce OG activation and TSG silencing, depending on the site of histone modification (Yang et al., 2009; Seligson et al., 2009).