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EDITORIAL

# New findings showing how DNA methylation influences diseases

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## Abstract

In 1975, Holliday and Pugh as well as Riggs independently hypothesized that DNA methylation in eukaryotes could act as a hereditary regulation mechanism that influences gene expression and cell differentiation. Interest in the study of epigenetic processes has been inspired by their reversibility as well as their potentially preventable or treatable consequences. Recently, we have begun to understand that the features of DNA methylation are not the same for all cells. Major differences have been found between differentiated cells and stem cells. Methylation influences various pathologies, and it is very important to improve the understanding of the pathogenic mechanisms. Epigenetic modifications may take place throughout life and have been related to cancer, brain aging, memory disturbances, changes in synaptic plasticity, and neurodegenerative diseases, such as Parkinson's disease and Huntington's disease. DNA methylation also has a very important role in tumor biology. Many oncogenes are activated by mutations in carcinogenesis. However, many genes with tumor-suppressor functions are "silenced" by the methylation of CpG sites in some of their regions. Moreover, the role of epigenetic alterations has been demonstrated in neurological diseases. In neuronal precursors, many genes associated with development and differentiation are silenced by CpG methylation. In addition, recent studies show that DNA methylation can also influence diseases that do not appear to be related to the environment, such as IgA nephropathy, thus affecting the expression of some genes involved in the T-cell receptor signaling. In conclusion, DNA methylation provides a whole series of fundamental information for the cell to regulate gene expression, including how and when the genes are read, and it does not depend on the DNA sequence.

**Key words:** DNA methylation; Stem cells; Enhancer; IgA nephropathy; Gene regulation

**Core tip:** DNA methylation in eukaryotes acts as a hereditary regulation mechanism that influences gene expression and cell differentiation. Recently, we have begun to understand that the features of DNA methylation are not the same for all the cells. Major differences have been found between differentiated cells and stem cells. However, epigenetic modifications may take place throughout life and influence various diseases, and they are very important for improving the understanding of pathogenic mechanisms. New studies show that DNA methylation can also influence diseases that do not appear to be related to the environment.

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## INTRODUCTION

In 1975, Holliday and Pugh as well as Riggs independently hypothesized for the first time that DNA methylation in eukaryotes could act as a hereditary regulation mechanism to influence gene expression and cell differentiation. Epigenetics was born as the study of inheritable changes in the genome that occur without modification of the DNA sequence and affect its functionality. DNA methylation is an extremely important mechanism. Together with covalent modifications of histones (proteins that compact the DNA), methylation modifies the chromatin structure and the accessibility of DNA to the regulation factors of gene expression.

DNA methylation density strongly varies with each chromosome. The sub-telomeric regions near the extremities often show a high methylation rate, which is important for controlling telomere length and recombination. In general, a lower methylation density is observed at the level of "CpG islands" and transcription initiation sites[1]. In 2008, a definition of epigenetic characteristics was formulated during the Cold Spring Harbor Meeting as a "stably inheritable phenotype deriving from a chromosomal alteration not connected to DNA variations"[2].

DNA methylation is maintained throughout the life of the affected cells and can be transmitted to subsequent cellular generations without modification of the DNA sequence. The processes responsible for epigenetic changes can take place both before and after transcription. In the first case, they are mainly represented by DNA methylation, which is bound by a covalent bond (and therefore reversible) to a methyl group coming from the universal methyl donor S-adenosylmethionine in position 5 of the cytosine residue of the CpG dinucleotide (Cytosine-phosphate-Guanidine). The phenomenon is due to the intervention of the specific enzyme DNA methyltransferase (DNMT).

The hypermethylation of DNA determines the "silencing" of the gene of interest, while hypomethylation causes activation[3]. Anomalous chromatin states that lead to abnormal gene expression patterns have been defined as epimutations, which have been detected in numerous diseases, including cancer. Epimutations can affect one or both alleles of a gene. Epimutations in cancer usually occur in somatic cells and cause cancer progression[4-8].

## FEATURES OF DNA METHYLATION ARE NOT THE SAME FOR ALL CELLS

Recently, we have begun to understand that the features of DNA methylation are not the same for all cells. Major differences have been found between differentiated cells and stem cells. For example, 99.98% of the methylated DNA regions in normal cells, such as fibroblasts, are rich in C and G, whereas the methylation in stem cells is concentrated in sequences that are rich in A and T. Moreover, embryonic cells that are induced to differentiate lose the methylation at the level of non-CG sequences, while they maintain the methylation in the sequences rich in C and G. This indicates that widespread methylation at the non-CG level is lost during differentiation.

Previous studies have hypothesized the existence of methylation almost exclusively in C and G-rich sequences in mammals, but observations led to the supposition that

non-CG methylation is a general feature, at least for human embryonic stem cells. The absence of non-CG methylation in fibroblasts coincides with a reduced presence of *de novo* DNMTs (DNMT3A, DNMT3B, and DNMT3L)-that is, enzymes that catalyze the addition of methyl groups in previously unmethylated residues. In contrast, "maintenance" methyltransferases reproduce the methylation pattern in a DNA strand based on what is present in the other filament[1].

A positive correlation between gene expression and methylation density is also observed at the level of non-CG sequences. The most expressed genes contain three times higher methylation density than unexpressed genes. However, no correlation has been detected between CpG methylation density and gene expression in stem cells. A particularly high methylation density has been observed for genes involved in RNA processes, such as splicing and RNA metabolic processes. Unexpectedly, an enrichment of non-CG methylation was found at the level of the antisense strand of the coding regions of genes, but the potential roles of this methylation are currently unknown.

Numerous studies have documented a correlation between DNA methylation and the ability of some proteins to interact with their target sequences. A decrease in DNA methylation density has been noted in correspondence with the protein interaction sites.

Another very important modality of gene expression regulation involves the "enhancer" regions, which are short DNA sequences that can to bind activating proteins, which in turn facilitate the recruitment of RNA polymerase and thus the transcription of the regulated gene. A decrease in methylation has been observed at the level of enhancers specific for fibroblasts. Conversely, at the level of specific stem enhancers, the methylation density does not change in either the embryonic stem cells themselves or in fibroblasts. This indicates the maintenance of these elements in an unmethylated state, thus preventing interference in the protein-DNA interaction process. The specific type of de-methylation (non-CG in stem cells and CG in fibroblasts) could indicate the use of different types of methylation specific to each cell type. Another paradigm of DNA methylation is that it controls aspects of cell differentiation. Obviously, this implies that methylation patterns vary in different cell types, as documented in several studies[9,10].

## METHYLATION INFLUENCES VARIOUS PATHOLOGIES

Interest in the study of epigenetic processes has been inspired by their reversibility and their potentially preventable or treatable consequences[11,12]. It is easy to understand how methylation influences various pathologies and the importance that it covers to understand better pathogenic mechanisms. In recent years, several studies have shown that DNA methylation influences many diseases. Cancer has been the most studied among the numerous diseases in which epigenetic modifications are the object of greater attention. DNA methylation also has a very important role in tumor biology.

Cancer is considered an essentially genetic disease, in which mutations alter the functioning of genes, causing the cell to proliferate in an uncontrolled manner. In recent decades, however, numerous indications have led to the suspicion that epigenetic factors-particularly DNA methylation-may be involved in the genesis of a tumor. In carcinogenesis, many oncogenes are activated by mutations[13-16]. However, many genes with tumor suppressor function are "silenced" by the methylation of CpG sites present in some regions[17].

We have known that epigenetic changes are associated with cancer, but until a few years ago, we did not know if they were the cause or a consequence of the disease. Recently, the development the new "epigenetic engineering" approach in some studies has allowed us to verify that even changes in DNA methylation alone can induce cancer. In fact, in new research, Yu *et al*[18] created a line of genetically modified mice where a small fragment of DNA adjacent to the p16 gene behaved like a magnet that attracted DNA methyltransferases and methyl groups, which hypermethylated the gene promoter and blocked the possibility of transcription. p16 has the function of blocking the cell cycle and preventing mitosis when necessary. For this reason, the p16 gene is considered a tumor-suppressor gene.

The results of the study showed that in the population of transgenic adult mice, the gene encoding p16 is more substantially activated during aging. The incidence of spontaneous tumors was higher than that in the control population of normal mice, in which the tumor suppressor gene continued to act regularly. Obviously, this kind of regulation can be extended to several other oncogenes in several other diseases. This result has profound implications for future studies because epigenetic changes are

potentially reversible. Therefore, new epigenetic therapies may be very effective for both tumors and other diseases, such as neurodevelopmental diseases, obesity, and diabetes.

The role of epigenetic alterations has also been demonstrated in neurological diseases. In neuronal precursors, many genes associated with development and differentiations are silenced by CpG methylation. The regulation of the proteins that bind to the methylated CpG is subject to mutations, duplications, and insertions. One example of a condition that depends on these processes is Rett's syndrome, which involves severe mental retardation linked to the X chromosome. Studies carried out with animal models of this disease report very interesting results in that the modifications of the CpG are at least partially reversible[19]. Epigenetic modifications may take place throughout life and have been related to brain aging, memory disturbances, and changes in synaptic plasticity[20]. The resulting alterations are increased over the years[21] and become significant in various neurodegenerative diseases, such as Parkinson's disease and Huntington's disease[14,22].

Various observations have led to the suspicion of the existence of epigenetic mechanisms in the pathogenesis of asthma, which is present in both twin homozygotes in as much as half of the cases[23]. There are complex interactions between genetics and the environment, which could lead to epigenetic modifications of the genome. One example is the demonstrated interaction between maternal smoking during pregnancy and the activity of the interleukin-1 receptor antagonist in newborns, which is associated with a significant increase in the risk of asthma[24]. In contrast, exposure to some endotoxins *in utero* appears to have a protective effect[25]. Moreover, many studies on the genetics of asthma have shown the existence of gene de-regulations that can be explained with only epigenetic alterations and DNA hypomethylation of 14 CpG sites that are gained after birth and linked with childhood asthma[26,27].

Recent studies show that DNA methylation can also influence diseases that do not appear to be related to the environment, such as IgA nephropathy (IgAN). This condition is the most common form of primary glomerulonephritis worldwide and has a strong genetic component. DNA methylation in the CD4+ T cells of IgAN patients influences the expression of some genes involved in the T-cell receptor signaling, which is the pathway that transfers the signal for the presence of antigens and activates the T-cells[28]. In particular, TRIM27 and DUSP3 genes were found to be hypomethylated in correspondence to the site that modulates their transcription, and these genes are upregulated in the CD4 T cells of IgAN patients.

The DNA region encoding vault RNA 2-1 (VTRNA2-1) non-coding RNA was also found to be hypermethylated, leading to its down-regulation. In turn, following CD3/CD28 T-cell receptor (TCR) stimulation, the lower levels of VTRNA2-1 cause a decrease in the proliferation of CD4+ T-cells, which plausibly occurs through the activation of the interferon-inducible kinase protein kinase R. Lower VTRNA2-1 levels also increase transforming growth factor beta expression. Together with DUSP3 and TRIM27, the increased transforming growth factor beta expression impairs the proliferation and activation of CD4+ T-cells, thus reducing the effect of the CD3/CD28 activation[28]. This deregulation causes reduced TCR strength and a T-cell anergy-like status. The lower activation of CD4+ T-cells and the lower TCR strength can determine Th1 polarization with higher interleukin 2 production in some biological settings. The aberrantly methylated DNA regions of CD4+ T-cells in IgAN patients thus offers a way to improve the understanding of the molecular mechanisms implicated in this disease. They could also lead to a new point of view for new therapeutic targets for the treatment of the IgAN.

In addition to these DNA methylation processes, we should also consider that various other inheritable mechanisms of post-transcriptional gene regulation can be used by cells, particularly the synthesis of non-coding microRNA, which binds to the corresponding messenger RNA and causes degradation or inhibition[29]. Recent studies also reveal an interesting interaction between these two kinds of epigenetic regulating systems. Gene expression can be affected by DNA methylation operating at a distance through the methylation or demethylation of the regulatory regions of miRNAs. The diversity of miRNA targets may produce the concurrent regulation of numerous biological pathways, such as apoptosis, cell proliferation, and migration.

Many *in vitro* and *in vivo* studies have shown that even epigenetic modifications of microRNAs can intervene in the pathogenesis of atherosclerotic lesions. For example, miR-33 inhibits the genes involved in the ability to expel cell cholesterol, the metabolism of high-density lipoproteins, lipid oxidation, and glucose metabolism. In mice, miR-33 deficiency is associated with a reduction of induced atherosclerotic lesions[30]. In neuroblastoma, a cluster of aberrantly methylated miRNA genes could lead to impaired regulation of the cell cycle, apoptosis, and the control of V-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog expression[31].

These data show that a complex arrangement of connections between epigenetically managed miRNAs and target genes may affect the control of cell homeostasis at different levels.

## CONCLUSION

The knowledge is changing in regard to the regulation of pathways and biological processes in living organisms, including humans. DNA methylation provides a whole series of fundamental information for cells to regulate their gene expression, including how and when the genes are read, and it does not depend on the DNA sequence. As discussed, these reversible DNA modifications are influenced by the surrounding context and can heavily influence diseases.

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