

Clinical Pharmacology: Epigenetic Drugs at a Glance

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Editorial

Epigenetics consists in heritable genetic modifications that alter gene function and expression without changes in DNA sequence. There are several epigenetics mechanisms, including: histone protein modification, covalent DNA modification, and regulation of noncoding RNA (e.g. miRNA) [1]. Histones modifications comprise in add or remove functional groups of histone tails resulting in changes in the configuration of chromatin and, consequently, affecting gene transcription. Covalent DNA modification is responsible for introducing methyl groups in CpG islands in DNA, which also results in alteration of gene expression. Noncoding RNA can inhibit mRNA translation into protein and induce mRNA degradation [2-4].

The discovery of enzymes and small molecules responsible to regulate epigenetic mechanisms has become a promising approach in the last years, mainly in the field of oncology. Despite the advances, the role of pharmaceutical drugs able to interfere in epigenetic status is not completely comprehended. Azacitidine and decitabine were the first FDA-approved drugs acting as DNA Methyltransferase (DNMT), Modulator for Myelodysplastic Syndrome (MDS) treatment. These drugs inhibit the DNA Methylation in MDS and avoid gene silencing. Both drugs are examples of drug interfering in epigenetic mechanisms. Other examples include Histone Deacetylase (HDAC) inhibitors, such as vorinostat and romidepsin, approved by FDA for cutaneous T-cell lymphoma. HDAC are epigenetic enzymes that remove acetyl groups from histone tails and downregulate gene expression. The inhibition of HDACs is a strategy for inducing gene expression, especially those abnormally silenced in cancer [5,6].

Recently, a number of drugs were discovered to be involved in epigenetic mechanisms even after the FDA had approved them a long time ago. For instance, the mood stabilizer and antiepileptic valproic acid was described as a potent HDAC inhibitor. It acts by blocking the histone acetylation on histone protein H3 and H4 leading to an overexpression of genes involved in the biosynthesis of dopamine, norepinephrine, and epinephrine such as tyrosine hydroxylase [7,8]. The statins are another example of drugs that were discovered latter to affect epigenetic status. Initially designed to inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase, this class may also act as HDAC inhibitors. It was demonstrated that the inhibition of histone H3 and H4 by statins resulted in a reduction of endothelial expression of the proinflammatory atherosclerosis-associated cytokines interleukin-8 and monocyte chemoattractant protein-1 [9]. Moreover, recent studies suggested that statins modulate miRNA activity [10]. Likewise, several others FDA-approved drugs has been raising the hypothesis of modulate the epigenetic status, including

methotrexate, procainamide, thalidomide, isotretinoin, neuroleptics, general anesthetics, synthetic estrogens, beta-blockers, chloroquine and fluoroquinolone antibiotics, and Cox-2 inhibitors [11]. The aforementioned show only a few examples of drugs that modulate the epigenetic network and may lead to patients either beneficial or side effects. It is likely that many other FDA-approved drugs may also act in epigenetic mechanisms [1]. Therefore, a research focusing on alteration of epigenetic process and investigation of its consequences in human health is an interesting approach to be investigated, mainly for drugs used by patients during long-term therapy. In addition, the lack of information in the literature become this researches a fruitful area in the clinical pharmacology field.

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