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Review

Histone modifications: A review about the presence of this epigenetic phenomenon in carcinogenesis

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ABSTRACT

Among the epigenetic changes, histone acetylation has been recognized as a fundamental process that strongly affects gene expression regulation. Disrupt of this phenomenon has been linked to carcinogenesis. In this review, we analysed studies reporting the process of histone modification, the enzymes associated and affected genes concerning human malignancies and histone enzyme inhibitor drugs used in cancer treatment. Variable degrees of expression of HDACs (histone deacetylases) and HATs (histone acetyltransferases) are found in many human malignant tissues and the histones acetylation seems to influence different processes including the progression of cell cycle, the dynamics of chromosomes, DNA recombination, DNA repair and apoptosis. Thus, the control of aberrant activity and/or expression of these proteins have been favorable in treatment of diseases as cancer. HDACi have shown efficacy in clinical trials in solid and hematological malignancies. Therefore, the development and use of HDACs inhibitors are increasing, leading to continue studying these enzyme expressions and behavior, aiming to determine tumors that will respond better to this type of treatment.

Contents

1. Introduction

Epigenetic is an interesting and relatively recent field in biology, referring to the regulation of gene expression, without alterations in DNA sequence and with a heritable pattern during cell division. Progress has been made in knowledge of epigenetic modifications in normal and diseased tissues [1,2]. It is known that these modifications are reversible and play a key role in develop ment of some disorders [3]. Researches in epigenetics have provided new insights into some kinds of diseases, especially human malignancies, neurodevelopmental disorders (Alzheimer's, Parkinson's and Huntington's diseases, multiple sclerosis and epilepsy) [4] and autoimmune sickness (rheumatoid arthritis [5], type 1 diabetes [6] and lupus erythematosus [7]). Besides the already known genetic alterations, the epigenetic deregulation is of great importance in the development of malignant tumors [8] becoming an obvious focus of research in this field [9,2].

The main types of epigenetic information are: a) DNA methylation where the addition of a methyl group to 5-carbon of cytosine in CpG islands [10] promotes gene silencing and also involves histone deacetylation through interaction with co-repressor complexes [11]; b) miRNAs [12,13], small non-coding RNAs involved in the regulation of fundamental cellular processes and crucial to transcription and translation [14], which deregulation have been related to many human cancers pathogenesis [15]; and, c) histone

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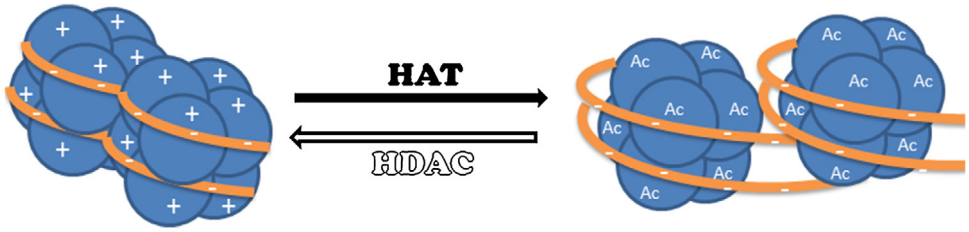

Fig. 1. HAT and HDAC action. Acetylation catalyzed by HAT affects transcription through neutralization of the positive charge of histones, weakens interactions between DNA and histone or among nucleosomes, thus reducing chromatin compaction and favoring gene transcription. In an opposite way, HDACs promote deacetylation returning it to chromatin compaction and transcriptional silencing.

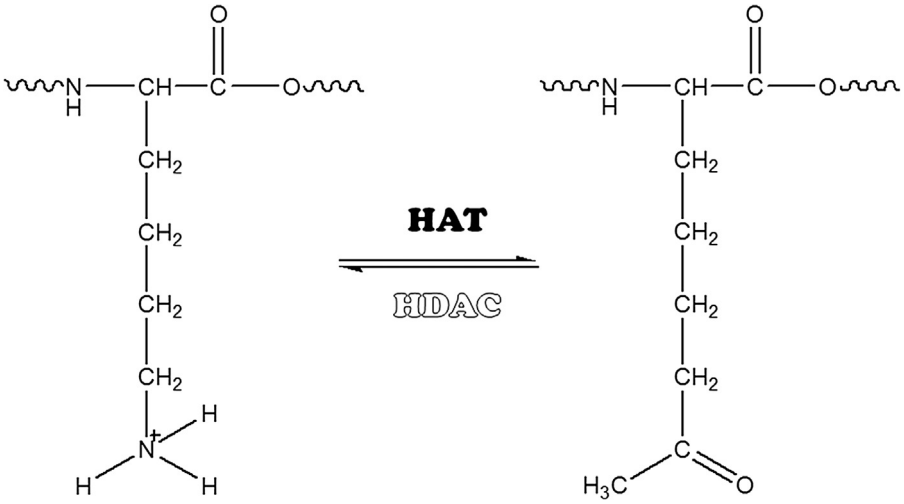

Fig. 2. Histone structure modifications mediated by HAT and HDAC. The figure shows lysine at histone N-terminal tails have lysines suffering acetylation (HAT action) and deacetylation (HDAC action). In cellular pH, of approximately 7.4, the amine group is positively charged. When catalyzed by HAT, an acetyl group is added to its structure and the positive charge is neutralized. On the other hand, when HDAC acts an opposite mechanism occurs.

modifications, characterized mainly by alterations in the acetylation status, also providing access or not of transcription factors to sequences of nucleotides [16].

This literature review aimed to analyze studies reporting the process of histone modification, the enzymes related and affected genes concerning human malignancies as well histone deacetylase inhibitors (HDACi) drugs already used for cancer treatment.

2. Histones, histone modifications and related enzymes

Histones are proteins that, together with DNA, comprises the nucleosome formed by the core histone octamer (two heterodimers of H2A and H2 B along with two heterodimers of H3 and H4), which is wrapped by two turns of 147-base-paired DNA strand [17], while the H1 protein establishes and maintains the higher-order chromatin structures [18]. Each histone comprising the octamer within the nucleosome is rich in lysine tails extending out of it and, therefore, the accessibility to the DNA in the nucleosome is, in part, controlled by modifications of these tails [19].

Histones may be submitted to several post-translational modifications as ribosylation, ubiquitynation and sumoylation of lysines, phosphorylation of serines and threonines, acetylation or methylation of lysines and arginines. Lysine residues in histone tails have a positive charge that interacts with the negatively charged phosphate backbone of DNA. Covalent modifications lead to alterations in chromatin structure and, thus, affect accessibility of transcription factors to 'read' and/or copy the nucleotide base sequences; therefore, these structures are dynamic and have capacity of folding (heterochromatin) and unfolding (euchromatin) regulation [17].

Histone deacetylases (HDACs) and histone acetyltransferases (HATs) are enzymes that influence DNA transcription through the balance between histone acetylation and deacetylation in normal cell function. Histone acetylation reduces chromatin condensation (Fig. 1): HATs catalyse the transference of an acetyl group (negatively charged) from acetyl-CoA to the amino-terminal tail of lysine, neutralizing the histone positive charge [20]. It generates slackness between DNA-histone and also between nucleosomes, allowing access of transcription factors and, therefore, DNA transcription. On the other hand, histone deacetylation returns to original condensation: HDACs remove acetyl group recovering the positive charge, permitting interactions between negatively charged DNA and histone protein, resulting in condensation of chromatin structure (Fig. 2), which is associated with gene repression [9,21].

To date, 18 human HDACs have been identified and are classified into four classes [22–24] Class I comprises HDAC1, HDAC2, HDAC3, and HDAC8, mainly located in the cell nucleus [23,25]; Class II HDACs are located both in the nucleus and cytoplasm (HDAC4, 5, 7, and 9) or only in cytoplasm (HDAC6 and 10); Class IV includes HDAC11, which appears both in the nucleus and cytoplasm; while Class III is made up by Sirtuins which, different from the others histone deacetylases, are Zn-independent [23].

As HDAC1 and HDAC2 are inactive when produced by recombinant techniques, cofactors are necessary for its activity to occur. In vivo, its activity is triggered only within a complex of proteins related to HDACs [26]. Among them, the corepressor protein Sin3 is postulated to mediate protein-protein interactions in several regulatory systems of gene expression. As Sin3 does not display DNA binding domain, promoter targeting is achieved through interactions with other sequence-specific DNA-binding proteins, and therefore require HDACs as prosecutor of this link to achieve its repression function. Mad-Max complex is strongly induced during cell differentiation and acts suppressing cell proliferation, through