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Physicochemical modifications of histones and their impact on epigenomics

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The study of histone post-translational modifications (PTMs) has made extraordinary progress over the past few years and many epigenetic modifications have been identified and found to be associated with fundamental biological processes and pathological conditions. Most histone-modifying enzymes produce specific covalent modifications on histone tails that, taken together, elicit complex and concerted processes. An even higher level of complexity is generated by the action of small molecules that are able to modulate pharmacologically epigenetic enzymes and interfere with these biochemical mechanisms. In this article, we provide an overview of histone PTMs by reviewing and discussing them in terms of their physicochemical properties, emphasizing these concepts in view of recent research efforts to elucidate epigenetic mechanisms and devise future epigenetic drugs.

Introduction

The so-called 'histone code', suggested by Strahl and Allis in 2000, refers to the idea that all PTMs occurring on histone, the protein portion of chromatin, determine the activity state of the underlying gene. Even though this concept has been adopted and widely used in epigenetic works, the term 'code' implies the existence of context-independent single modifications, or combinations thereof, responsible for a determined action on chromatin, which is still a matter of debate [1]. However, it is well documented that histone PTMs, together with DNA methylation and the action of noncoding RNA (ncRNA), represent an ensemble of epigenetic changes responsible for different states of chromatin arrangement. These heritable changes do not entail modification of the DNA sequence but are essential for transcriptional regulation; that is, the modulation of gene silencing and activation. From a molecular point of view, DNA methylation and histone PTMs reflect all the covalent alterations that nucleosomes, the subunits of chromatin, undergo in the cell. Given the large number of different modifications, the effect of PTMs in human pathophysiology is difficult to unravel because, since their discovery, many have been linked to different cellular roles. For example, several modifications have been found to be associated with metabolism [2–4] and regulation of the immune system [5–7]; by contrast, their abnormal regulation is linked to an increasing variety of pathologies, among which cancer stands out for its complexity [8,9]. The elucidation of these epigenetic phenomena can represent the basis for better understanding of biological processes along with the development of new therapies based on epigenetic-modulating compounds [10–16]. As a consequence of the increasing interest in this topic, many recent articles and reviews have reported and described new types of modification, specific histone residues that undergo PTMs and enzymes that operate these modifications [17–20]. In addition, many other studies have elucidated the impact that PTMs have on chromatin and on the recruitment of chromatin regulators, as well as their clinicopathological relevance in human disease [8,10,18,21–29]. A further level of knowledge stems from the observation that the selectivity of histone PTMs varies depending on the kind of modification: for example, acetylation is the most promiscuous histone modification, and is always associated with transcriptional activity; by contrast, methylation has a high degree of selectivity and is associated with repression or transcription, depending on the methylated residue and the number of attached methyl groups [30,31]. An intriguing aspect that has also emerged over the past few years concerns the network of cross-talking PTMs, in which two or more histone residues undergo modifications in a concerted or a subsequent manner [18,32–35].

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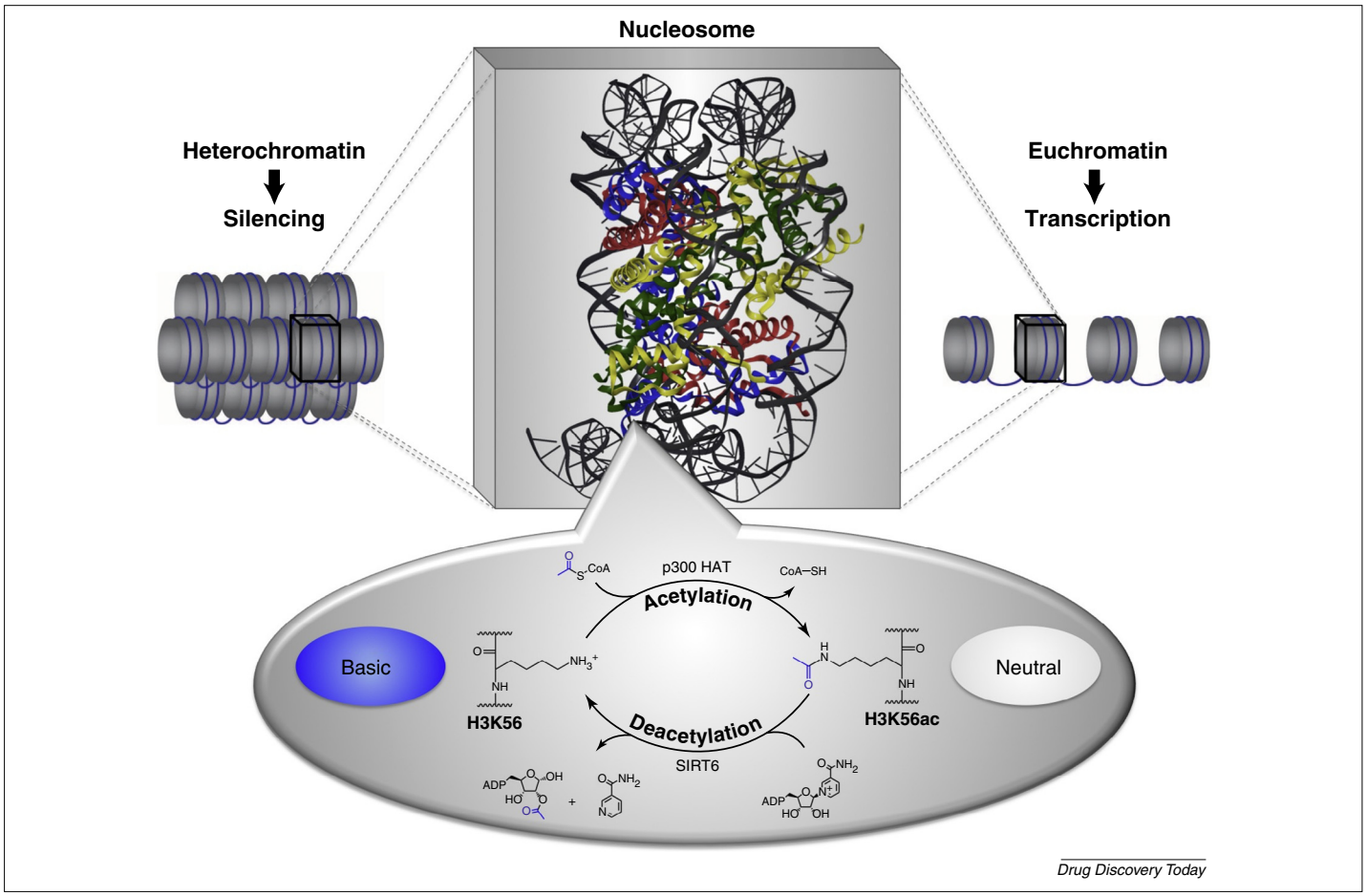

FIGURE 1

Schematic representation of histone code functioning. The build up of chromatin collectively depends on the ensemble of punctual modifications of histone, where variations in physicochemical properties of the modified residues influence the balance between heterochromatin and euchromatin. The figure exemplifies one of these local chemical modifications (acetylation and/or deacetylation) occurring at lysine 56 of histone 3 (H3K56). These chemical modifications can result in variation of physicochemical properties such as pKa, the behavior of which is mediated by the solution microenvironment of the protein.

Overall, these characteristics indicate a high complexity of epigenetic phenomena, some of which are suggestive of the histone code hypothesis as an ensemble of rules that govern the storage of epigenetic information and condition the activity of an underlying gene [36–38]. By contrast, other evidence shows that the effects of the dynamic equilibrium of these modifications act by modulating gene expression in response to external signals and, thus, do not suggest the maintenance of stable gene expression [39,40]. Although the histone code collectively depends on the ensemble of these modifications, build-up at the chromatin level is effectively operated by punctual variations of physicochemical properties of the modified residues and, consequently, their microenvironment. This sequence of events is detailed in Fig. 1 for the local acetylation and/or deacetylation of lysine 56 of the histone 3 (H3K56) [41,42]. Histone acetyltransferase (HAT) p300 can acetylate H3K56 by chemically modifying the lysine side chain, thereby changing its physicochemical properties, which contribute to modifying the nucleosome structure and chromatin remodeling. Conversely, the state of chromatin at H3K56Ac can be reversed by the NAD^+-dependent histone deacetylase sirtuin-6 (SIRT6), which removes the acetyl by re-establishing the original physicochemical microenvironment, along with nucleosome and chromatin conformations [43].

It is the dynamic equilibria of the physicochemical properties of histones that determine the major effects of chromatin remodeling, including silencing, transcription and recruitment. The facts that various PTMs occur on different histone residues and that certain modification sites are promiscuous, suggest a wide range of physicochemical properties modifications and a subtle equilibrium between the involved species [15]. In addition, modifications can trigger local effects that can be distinguishable from those occurring on higher-order chromatin structures. For example, it is well known that, globally, hyperacetylation leads to euchromatin but that, locally, and depending on the promoter, it can also repress transcription [44,45]. Although quantitative evaluation of the properties of modified and unmodified residues is difficult to dissect [46], a qualitative overview can help to shed more light on these complex processes.

Chemical modifications

Histone PTMs

From a chemical functionality point of view, histone PTMs can be divided in two main groups. The first (group I) comprises PTMs leading to the addition or removal of monofunctional, generally small, organic substituents. Modifications of this group are methylation, acetylation, phosphorylation, deimination and

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