Histone Demethylases: Insights into Human

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Histone methylation is a three-step process that includes the integral roles of “writers”, or histone methyltransferases (HMTs), “readers,” or histone methylation-recognizing proteins, and “erasers,” or histone demethylases (HDMs). Histone methylation and demethylation regulate genes, either by relaxing histone tails to permit transcription factors and other proteins to contact the DNA, or by wrapping histone tails around the DNA, thereby blocking access. These changes impact nucleosomal characteristics and, henceforth, their interactions with other proteins.

Keywords: epigenetics ; transcription ; histone demethylases

1. Introduction

Cancer is one of the most complex non-communicable diseases, characterized by uncontrolled and aberrant cell proliferation that leads to the formation of cellular aggregates and localized tumors. Globally, approximately 20 million individuals are affected by various malignancies, with around 10 million people dying from them each year [1][2]. Dysregulation of epigenetic changes has also been linked to the development of cellular resistance to therapies and the onset of carcinogenesis [3][4][5][6]. The term "epigenetics" refers to events that can influence gene expression without modifying the DNA sequence. DNA methylation, histone modifications, and the control of post-transcriptional gene expression by noncoding RNA are the main mechanisms underlying epigenetic regulation [7][8][9][10]. It has been revealed that uncontrolled, dynamic epigenetic modifications can initiate poorly prognosed cancer development. Recent studies suggest fluctuations in the expression of oncogenes and tumor suppressor genes due to uncontrolled epigenetic changes in the malignant cells. This scenario necessitates the exploration of a potential therapy to mitigate cancer incidence [10][11][12] The majority of aberrant, epigenetically modified genes participate in the cell cycle, cellular invasion, DNA repair, and genetic instability pathways, thereby perturbing genomic normalcy [13][14][15][16][17][18][19].

Histone modifications are responsible for chromatin compaction, nucleosome dynamics, and transcription regulation [20][21][22]. Dysregulation of these mechanisms, whether by gain or loss of functions, overexpression or suppression, chromosomal translocations, inhibition by promoter hypermethylation, or mutations of the histone-modifying enzymes/complexes, even at the histone modification site, is often observed in the development of cancer [12][23][24]. Depending on the cell type/tissue, variegated histone modifications, resulting in tissue-specific gene expression profiles that characterize certain biological activities at cellular levels, shall establish either normal or disease conditions [9][22][25][26][27][28].

Cellular signals, both internal and external, are subjected to histone modifications. Several chemical modifications occur on histones at various amino acid residues, the most common of which are acetylation, phosphorylation, methylation, and ubiquitylation [6][29][30]. Distinct forms of histone modifications have been found at 130 different residues on the core and linker histones [31]. These histone modifications can be found in the globular core regions of histone proteins, as well as in the amino- or carboxy-terminal tails that extend from the surface of the nucleosome [21]. Among all, histone methylation is imperative in many biological processes, including cell cycle progression, immunological response, and signal transduction [32]. Furthermore, histone methylation/demethylation is associated with diseases such as globin abnormalities and neurological disorders. Histone methylation/demethylation is prominently linked to cellular oncogenesis and proliferation, and it has been found to be altered in many cancer cells [33][34][35].

Because histone methylation is a reversible process, it may be possible to employ this epigenetic regulation to bring about a positive change in the function of oncogenes and tumor suppressor genes in cancers. Considering the tissue-specific functional epigenetic landscape, it is quite tedious to acknowledge the multiple or singular modifications that are consistent in normal cells and therefore also in any abnormal or cancer cells. Hence, it will be equally demanding to extract or invent individual epigenetic modifications, signal transductions, and gene expression profiles that are scaled to a systemic level.

2. Insights into Histone Demethylases

Histone methylation is a three-step process that includes the integral roles of “writers”, or histone methyltransferases (HMTs), “readers,” or histone methylation-recognizing proteins, and “erasers,” or histone demethylases (HDMs). Histone methylation and demethylation regulate genes, either by relaxing histone tails to permit transcription factors and other proteins to contact the DNA, or by wrapping histone tails around the DNA, thereby blocking access [36]. These changes impact nucleosomal characteristics and, henceforth, their interactions with other proteins. Histone methylation entails the addition (through writer enzymes) or elimination (via eraser enzymes) of methyl groups, mostly on the lysine (K) or arginine (R) amino acids of histone; however, it has also been witnessed on glutamine, aspartate, and histidine residues [37]. Histone methylation does not affect the molecule’s overall charge, in contrast to acetylation and phosphorylation, wherein the methyl donor in histone methylation processes is S-Adenosylmethionine (SAMe). Lysines can be monomethylated (me1), dimethylated (me2), or trimethylated (me3) on their -amino group, whereas arginines can be monomethylated, symmetrically dimethylated (me2s), or asymmetrically dimethylated (me2a) on their guanidinyl group [37]. Until the discovery of lysine-specific demethylase 1 (LSD1), which demethylates mono- and dimethyl groups in H3K4 [38], it was thought that methylation of histone residues was permanent, hereditary, and irreversible. The dynamics of histone methylation and demethylation on gene regulation are now better understood due to the ground-breaking discovery of histone demethylases in 2004 [38]. Histone demethylases can mainly be divided into two groups, based on their functions when demethylating histones. The first class of histone demethylases (LSD1, as aforementioned) belongs to the family of enzymes known as flavin-dependent amine oxidases. The second class of histone demethylases belongs to the family of JmjC domain, which catalyzes the oxidation of ferrous ions and uses ketoglutarate as a cofactor to demethylate histone lysine [11]. Additionally, the cohort of histone lysine demethylase (KDM) is classified into sub-families KDM1 to KMD9, and other types of proteins that are also involved in histone demethylation [39] (**Table 1**).

Table 1. List and site of human lysine- and arginine-specific histone demethylase.

Family	Coding Gene	Other Names	Site of Histone Modification
KDM1	KDM1A	LSD1	H3K4me1/2, H3K9me1/2
	KDM1B	LSD2	H3K4me1/2, H3K9me1/2
KDM2	KDM2A	JHDM1A	H3K36me1/2
	KDM2B	JHDM1B	H3K4me3, H3K36me1/2, H3K79me2/3,
KDM3	KDM3A	JMJD1A	H3K9me1/2
	KDM3B	JMJD1B	H3K9me1/2; H4R3me2/me1
	KDM3C	JMJD1C	H3K9me1/2
	KDM3D	HR, ALUNC	H3K9me1/2
KDM4	KDM4A	JMJD2A	H3K9me3, H3K36me3, H4K20me3
	KDM4B	JMJD2B	H3K9me2/3, H3K36me2/3
	KDM4C	JMJD2C	H3K9me2/3, H3K36me2/3
	KDM4D	JMJD2D	H3K9me2/3, H3K36me2/3,
	KDM4E	JMJD2E	H3K9me2/3, H3K36me2/3
KDM5	KDM5A	JARID1A	H3K4me2/3
	KDM5B	JARID1B	H3K4me2/3
	KDM5C	JARID1C	H3K4me2/3
	KDM5D	JARID1D	H3K4me2/3
KDM6	KDM6A	UTX	H3K27me2/3
	KDM6B	JMJD3	H3K27me2/3
	KDM6C	UTY	H3K27me3

Family	Coding Gene	Other Names	Site of Histone Modification
KDM7	KDM7A	JHDM1D	H3K9me1/2, H3K27me1/2, H4K20me1/2
	KDM7B	PHF8	H3K4me3, H3K9me1/2, H3K27me1/2, H3K36me2, H4K20me1/2
	KDM7C	PHF2	H3K9me1/2, H3K27me1/2, H4K20me3
KDM8	KDM8	JMJD5	H3K36me2/3, H3R2me1/2, H4R3me1/2
KDM9	KDM9	RSBN1	H4K20me2
Other types	JMJD6	PSR	H3R2me1/2, H4R3me1/2
	JMJD7	PLAEG4B	H3Rme1/2, H4Rme1/2
	JMJD9	RIOX1	H3K4me1/2/3, H3K36me2/3
	JMJD10	RIOX2	H3K9me3
	JARID2	JMJ	H3K9me1, H3K27me3

LSD1 has a flavin-dependent amine oxidase (AO) domain and a SWIRM domain. With the help of the AO domain, it oxidizes the amine in a FAD-dependent way to remove H3K4me1/2, while the SWIRM domain identifies and binds to DNA [40]. The zinc-finger domain, in addition to the SWIRM and AO domains, is present in LSD2, a paralog of LSD1; while LSD2 demethylates gene body regions, LSD1 demethylates the promoter and enhancer regions of genes [41]. The catalytic JmjC domain is a characteristic feature of the second family of KDM, which can be categorized into seven subfamilies in humans based on the homology of the JmjC domain. Two cofactors, Fe (II) and 2-oxoglutarate, are bound in the JmjC domain of the enzyme, and function as cofactors in the catalytic process to create a highly active oxoferryl (Fe (IV) = O) intermediate that hydroxylates the -methyl groups of the substrate methylated lysine. The resultant lysyl hemiaminal is unstable and disintegrates, releasing the nitrogen's methyl group as formaldehyde. JmjC demethylase members have been revealed to demethylate the trimethylated lysines, demonstrating that this mechanism is capable of demethylating lysine in all three methylation states. (mono-, di-, and tri-methylated lysine) [11][23][39][42][43].

The human genome codes for five protein arginine deiminases (PADs), which function to remove methyl groups from arginine. These enzymes transform peptidyl arginine into citrulline in a calcium-dependent manner. It has been determined that PAD4 is a demethylase that transforms monomethylated arginine into citrulline by demethylating histones [43][44]; however, whether PAD4 performs as a strict histone demethylase is subject to discussion. JMJD6, a member of the Jumonji-domain histone demethylase (JHDM) family of histone lysine demethylases, is shown to have histone arginine demethylase activity rather than lysine demethylase activity [45]. Additionally, the Jumanji C domain-containing subset of lysine demethylases KDM3A, KDM4E, KDM5C, and KDM6B also exhibits a site-specific arginine demethylase function [46].

Overall, histone methylation and demethylation's dynamic nature and effects on gene expression and cellular functions highlight the significance of how it is related to human health. Further study in this area has the potential to reveal fresh perspectives on the causes of disease and open up new directions for the creation of innovative treatment strategies.

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