Histone Lysine Methylation

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The level and state of histone lysine methylation depends not only on the activity of histone methyltransferases (KMTs) but also on the counteracting activity of histone lysine demethylases (KDMs). The variety of methylation sites and differentially methylated states describes the level of complexity of signaling mediated by histone lysine methylation, which is involved in transcription regulation, gene silencing, genome stability and RNA processing.

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1. Histone Lysine Methylation

Epigenetic landscapes functionally define the chromatin architecture and they are shaped by the coordinated activity of “writers”, “readers” and “erasers”. “Writers” introduce covalent chemical modifications into DNA and histone tails, the “erasers” modulate the amount of these modifications and the “readers” recognize and bind the chemical modifications which induce functional effects in the chromatin architecture and DNA binding of transcription factors (TFs). Among the writers, histone methyltransferases catalyze the introduction of methyl groups in specific lysine and arginine residues at the amino terminal ends of the histone core [1], mainly at histones H3 and H4. Lysine methylation involves the ε-amine group of lysine at different positions of H3. Methylation events at K4, K9, K27, K36 and K79 are the most studied and characterized. Lysine can be mono-, di- or trimethylated. The level and state of histone lysine methylation depends not only on the activity of histone methyltransferases (KMTs) but also on the counteracting activity of histone lysine demethylases (KDMs). The variety of methylation sites and differentially methylated states describes the level of complexity of signaling mediated by histone lysine methylation, which is involved in transcription regulation, gene silencing, genome stability and RNA processing.

2. Histone Lysine 4 Methyltransferases

The enzymes responsible for histone lysine methylation (KMTs) contain a common active domain known as Su(var)3–9, Enhancer of zeste and Trithorax (SET), originally identified in yeast (SET1). Three SET1 homologs were subsequently identified in *Drosophila melanogaster*, including dSet1, Trithorax (Trx) and Trithorax-related [2], and 23 canonical SET-containing histone KMTs and one seven-beta-strand (7βS)-containing domain KMT (hDOT1L) with proven methyltransferase activity in mammals [3][4][5]. Some KMTs are highly selective. Each KMT methylates a specific lysine but not others located at different positions in the H3 polypeptide chain. For instance, the KMT that methylates H3K36 does not methylate H3K4, and the only KMT able to methylate H3K79 is hDOT1L [6][7][8][9][10]. In addition, a lysine can be specifically targeted by multiple enzymes. This redundancy allows specific activities to occur in a context-dependent manner. For instance, the same lysine may be modified by a different enzyme as a function of the histone’s genomic localization (enhancer versus promoter regions) but also to generate different methylation states (dimethylation versus trimethylation). KMT activity depends also on the specific lysine methylation state to add new methyl groups [11][12][13][14][15]. H3K4 methylation is one of the most studied and characterized histone lysine methylations. H3K4 can be mono-(H3K4me1), di-(H3K4me2) or tri-(H3K4me3). In mammals, H3K4 methylation is catalyzed by six SET domain-containing KMTs, namely SET1A/KMT2F, SET1B/KMT2G, MLL1/KMT2A, MLL2/KMT2B, MLL3/KMT2C and MLL4/KMT2D. Each of these enzymes is a component of multimeric complexes that may or may not contain other proteins such as WDR5, RbBP5, ASH2L and DPY30 [3]. These complexes are not redundant, as their activity marks H3K4 not only at functionally distinct loci but also at specific target genes determining different methylation states related to the recruitment of distinct “readers” [16][17]. For instance, multimeric complexes containing MLL1 and MLL2 trimethylate H3K4 at the promoter region of Hox gene clusters, which require the correct transcriptional regulation for hematopoietic development [18][19]. MLL2 is responsible for the tri-methylation of H3K4 of bivalent domains which is necessary for a mechanism aiming to maintain a paused transcriptional state in a targeted gene [20][21]. MLL3 and MLL4 monomethylate H3K4 located at the enhancer

regions involved in cell type-specific gene expression [22][23][24][25]. Recent studies have revealed that the activity of KMT complexes is stimulated by the monoubiquitylation of histone H2B, and that distinct subunits components may have a role in determining the levels and state of H3K4 methylation [26][27][28].

3. Histone Lysine 4 Demethylases

To date, more than 30 KDM family members have been reported, and most of them contain a Jumonji domain, with the exception of KDM1A and KDM1B [29]. As for KMTs, KDMs target methylated lysines in H3, mainly at K4, K27, K9, K36 and K56, and in H4 at K20. KDMs demethylate specific lysines and not others located in different positions of the histone polypeptide chain. For instance, H3K27me3 is demethylated by KDM6B, which is not able to demethylate H3K4me3. KDMs may have distinct genomic localization and biological effects [30]. In mammals, H3K4 demethylation is catalyzed by the Jumonji, AT-rich interactive domain 1 (KDM5) and lysine-specific histone demethylase (KDM1) protein families. The KDM5 family is composed of four members designated KDM5A–D, and these enzymes are 2-oxoglutarate-dependent dioxygenases which require Fe^{2+} and O_2 for their function in order to undergo the hydroxylation necessary to remove methyl groups [31]. All members contain conserved domains of five types: the ARID (DNA-binding domain), C5HC2 zinc finger, Jumonji C (JmjC), Jumonji N (JmjN) and plant homeodomain finger (PHD) (histone-binding domain) domains [32]. The KDM1 family is composed of the KDM1A member and its homolog, KDM1B, which are both Flavin Adenine Dinucleotide (FAD) -dependent histone lysine demethylases [33][34]. The KDM1A consists of three domains: the amine oxidase domain, the FAD binding domain and the SWIRM domain. In particular, the FAD binding domain consists of a Tower domain, which interacts with RE1-Silencing Transcription factor (REST), a transcription factor essential for demethylation activity [35]. KDM1B, however, does not bind REST [36][37]. KDM5A-D and KDM1A-B proteins have histone demethylases activity towards particular histone H3K4 methylation states; for instance, KDM5A demethylates H3K4me3/2 and processively H3K4me1, and KDM1 demethylates H3K4me1/2, with KDM1A also demethylating H3K9 [38][39][40][41][42][43][44]. KDM5A, KDM5C and KDM1A proteins form complexes with transcriptional repressors such as REST and KMTs establishing repressive chromatin marks [45][46]. Members of the KDM5 andKDM1 families may differ in their functions and biological effects. The KDM5A-D proteins are associated with transcriptional repression, as H3K4me3 is considered to be a transcriptional activating signal, since it is globally distributed, mainly at the promoters of the transcribed genes, and seems fundamental for recruiting the preinitiation factor Transcription Factor IID (TFIID) to certain gene promoters, even if loss of H3K4me3 does not always affect gene transcription [47]. However, KDM5A and B proteins may interact with different partners or complexes with transcriptional repressive functions such as Polycomb Repressive Complex 2 [46][48]. KDM5A interacts with the SIN3B-containing deacetylase and the nucleosome remodeling and deacetylase (NuRD) complexes [49]. KDM5B interacts with NuRD and KDM1A [50][51], whereas KDM5C interacts with the repressive H3K9 and H3K27 methyltransferase G9a in complex with histone deacetylases (HDACs) and REST [52]. Moreover, KDM5B protein may interact directly with HDACs mediating their recruitment to specific sites [53]. However, the activity of KDM5A–D also seems related, in some cases, to transcriptional activation, although it is not clear if this effect depends on demethylase activity or not [54][55]. As for the KDM5 protein family, KDM1 demethylase activity is also related to transcriptional repression. However, KDM1A, as it can demethylate H3K9, may be associated with transcriptional activation [56][57][58]. For instance, when KDM1A interacts with androgen and estrogen nuclear hormone receptors (AR and ER), it can demethylate H3K9me1/2, thus facilitating gene transcription [59][60]. Moreover, a neuron-specific isoform of KDM1An (also known as LSD1n) can target H3K20me2 controlling transcriptional elongation of a neuronal gene network [61]. Garcia-Bassets et al. [62] reported that 80% of the promoters occupied by KDM1A were bound to RNA polymerase II, suggesting that KDM1A was associated more often with active genes rather than the inactive genes. The formation of a protein complex including KDM1A, Rest corepressor (CoREST) and Growth factor independence (GFI) 1 proteins is also noteworthy [63]. This complex target represses a gene regulatory network that is necessary for normal hematopoiesis. KDM1A–GFI interaction may be disrupted by pharmacological molecules rescuing blast cell differentiation in acute myeloid leukemia with MLL translocations[64]and restoring the normal H3K4me3 state at targeted gene promoters. KDM1A is also found to be associated with long non-coding RNAs (LncRNAs) such as HOX Transcript Antisense RNA(HOTAIR), TElomeric Repeat-containing RNA (TERRA) and Steroid receptor RNA activator (SRA) [65]. Several non-histone proteins have been recognized as targets of KDM1A activity such as p53[66], MYPT1 [67], E2F1 [68], and HIF-1α [69], which determine different effects on protein stability. JARID1 and LSD demethylases are involved in various cellular processes, including cell proliferation, embryonic mesenchymal transition, stemness, differentiation, cell motility, autophagy and senescence [70][71], and their dysregulation is also closely associated with embryonic development [72], human cancer development and other diseases[73].

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