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Invited review

Jumonji histone demethylases as emerging therapeutic targets

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ABSTRACT

The methylation status of lysine residues in histones determines the transcription of surrounding genes by modulating the chromatin architecture. Jumonji domain-containing histone-lysine demethylases (Jmj-KDMs) remove the methyl moiety from lysine residues in histones by utilizing Fe^{2+} and α-ketoglutarate. Since genetic alterations in Jmj-KDMs occur in various human cancers, the roles of Jmj-KDMs in cancer development and progression have been investigated, but still controversial. The KDM7 subfamily, which belongs to the Jmj-KDM family, is an emerging class of transcriptional coactivators because its members erase the repressive marks H3K9me2/1, H3K27me2/1, and H4K20 me1. Recently, KDM7C (alternatively named PHF2) was discovered as a new KDM7 member and identified to play a tumor-suppressive role through the reinforcement of p53-driven growth arrest and apoptosis. In this article, we generally reviewed the roles of Jmj-KDMs in human cancers and more discussed the molecular functions and the clinical significances of KDM7C.

Contents

1. Introduction

The architecture of eukaryotic chromatin plays a crucial role in the epigenetic regulation of gene expression. It is dynamically modulated through the post-translational modification, including acetylation, methylation, phosphorylation, and ubiquitination, of histone proteins at their N-terminal tails [1]. Of these modifications, the methylation status of lysine residues in histones marks surrounding genes to be turned "on" or "off" for transcription. For example, trimethylation of H3K4, H3K36, and H3K79 is a representative marker for euchromatin, which is loosely packed for active transcription. In contrast, mono-methylation of H4K20, di-/tri-methylation of H3K9, and tri-methylation of H3K27 mark heterochromatin, where the chromatin structure is too tight to be accessed by transcription factors [2,3]. Through this process, histone-lysine methylation controls the precise regulation of gene expression. Histone methylation is catalyzed by the histone-lysine methyltransferases (HMTs), and is reversed by the histone-lysine demethylases (KDMs) [4]. In the past decade, many efforts have been made to understand the roles of histone methylation and demethylation in diverse biological progresses, including embryonic development, stem cell renewal, and differentiation.

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Interestingly, a lot of reports have shown that the deregulation of histone methylation or demethylation alters the expression of tumor-promoting or tumor-suppressive genes, leading to cancer initiation, development, and progression [5]. We here review KDMs and their roles in cancer development, and discuss the recently identified KDM7 subfamily.

2. Jumonji domain-containing histone-lysine demethylases

The histone-lysine demethylase (KDM) superfamily is divided into two families based on the properties of the enzymatic reactions they catalyze, the flavin adenine dinucleotide (FAD)-dependent amine oxidases and the Fe^{2+}/α-ketoglutarate-dependent dioxygenases [6]. The latter possess the conserved catalytic domain "Jumonji (Jmj)". To date, more than 30 Jmj-containing KDMs (Jmj-KDMs) have been identified, and the majority seems to function as demethylases or hydroxylases. Aside from the Jmj domain, two tertiary KDM features play pivotal roles in recognizing their specific targets. First, Jmj-KDMs are associated with a large multimeric complex, which may guide Jmj-KDMs to histones surrounding specific target genes. Second, other conserved domains in Jmj-KDMs participate in the target-specific reaction, and they include plant homeodomain (PHD), Tudor, zinc finger (zf-C2HC4), F-box, AT-rich interactive domain (ARID), and leucine-rich region (LRR) [7–9]. The targets (substrates) and essential domains of Jmj-KDMs are summarized in Table 1.

3. Expression of Jmj-KDMs in human cancers

Since genetic alterations in Jmj-KDMs have been reported in various human cancers, Jmj-KDMs are believed to be involved in cancer development. However, the precise roles of Jmj-KDMs in cancers are still unclear. In some human cancers, Jmj-KDMs are genetically mutated, deleted, or translocated, and are subsequently down-regulated. However, Jmj-KDMs are genetically amplified and up-regulated in other cases [8–10]. The conflicting findings on expressions of Jmj-KDMs in cancers are summarized in Table 2. For instance, KDM2A is upregulated in lung, breast, and gastric cancers, but down-regulated in prostate cancer, and glioblastoma [11–15]. KDM2B was found to be essential for cell proliferation in AML, and to be overexpressed in pancreatic ductal adenocarcinoma, and bladder cancer [16–18]. However, KDM2B expression is suppressed in prostate cancer and glioblastoma [14,15]. KDM3A is highly expressed in various cancers, including breast, prostate, colon, kidney, and liver cancers [19–23]. KDM4A is silenced or down-regulated in bladder cancer, while it is overexpressed in breast cancer [24,25]. KDM4B is overexpressed in malignant peripheral nerve sheath tumor [26]. KDM4C is genetically amplified and required for cell proliferation in breast cancer, squamous cell carcinoma, esophageal cancer, prostate cancer, diffuse large B cell lymphoma, and medulloblastoma [27–34]. KDM5A is highly expressed in lung and hematopoietic cancers, but down-regulated in melanoma [35–38]. KDM5B is overexpressed in breast, prostate, and bladder cancers [39–41]. KDM5C is overexpressed and acts as a putative oncogene in prostate cancer [42], but KDM5D is suppressed in this cancer [43]. On the contrary, KDM5C is genetically mutated in renal cancinoma [44]. Notably, KDM6A, which is well characterized to demethylate H3K27me3/2, is down-regulated in many types of human cancers including lung, liver, esophageal, renal, multiple myeloma, transitional cell carcinoma of bladder, and leukemia, while it is overexpressed only in breast cancer [44–52]. KDM6B is upregulated in leukemia, lung, liver, and prostate cancers [51,53–55]. MINA and NO66, which possess only jumonji-C domain, are highly expressed in non-small-cell lung cancer [56,57].

4. Roles of the KDM7 subfamily in human diseases

The KDM7 subfamily demethylates H3K9me2/1, H3K27me2/1, and H4K20 me1 to create a more permissive chromatin environment for transcription of its target genes, which is why this family is considered an emerging class of transcriptional coactivators. KDM7 consists of three members, KDM7A (alternatively named KIAA1718), KDM7B (PHF8), and KDM7C (PHF2) [3]. Given that mutations of PHF8 are associated with X-linked mental retardation and cleft lip/cleft palate [58–62], PHF8 is believed to be essential for neuronal differentiation and craniofacial development. In addition, genetic alterations of PHF8 have been reported in various human cancers. PHF8 is overexpressed in laryngopharyngeal squamous cell carcinoma, and its levels positively correlate with the clinical cancer stages [63]. Intriguingly, the oncogenic features of PHF8 were also demonstrated in non-small cell lung cancer and esophageal squamous cell carcinoma. The depletion of PHF8 in esophageal squamous cell carcinoma cells induced apoptotic cell death, and inhibited cancer colony-formation, migration, and invasion [64]. PHF8 is overexpressed in human lung cancer tissues at both the mRNA and protein levels. A knock-down of PHF8 in lung cancer cell lines also demonstrated that PHF8 is required for cancer cell survival, cancer colonization, and *in vivo* growth of grafted tumors. Interestingly, the tumor promoting action of PHF8 is thought to be due to the overexpression of the oncogenic miR-21, which down-regulates the tumor suppressor PTEN and subsequently stimulates tumor growth and invasion in non-small cell lung cancer. Since miR-21 is decreased by PHF8 knock-down, PHF8 seems to be responsible for miR-21 overexpression in the cancer cells [65]. Likewise, PHF8 positively regulates the promotion of prostate cancer by expressing microRNAs. Ma et al. checked PHF8 expression in a prostate tissue array containing normal and cancer regions, and found that PHF8 is overexpressed in cancer tissues. They also demonstrated that PHF8 promotes prostate cancer growth and that this action is closely related with miR-125b overexpression [66]. Considering such critical roles of PHF8 in tumor growth, PHF8 could be a biomarker for cancer prognosis or a potential target for cancer therapy. Another KDM7 member, KIAA1718 is known to induce pro-neural differentiation through transcriptional activation of the *FGF4* gene [67]. However, the involvement of KIAA1718 in cancer development still remains an open question. PHF2, which is recently discovered as a new KDM7 member, is thought to participate in diverse biological processes. For example, PHF2 is phosphorylated and activated by PKA during gluconeogenesis, and in turn interacts with and demethylates the AT-rich interactive domain-containing 5B (ARID5B). Then, the PHF2-ARID5B complex is recruited to its target promoters and activates transcription by erasing the repressive H3K9me2 mark [68]. In addition, the PHF2-ARID5B complex is known to be involved in chondrogenesis during skeletal development. The complex promotes the Sox9-driven transcription of chondrogenic genes by removing the repressive mark H3K9me2 [69]. Besides chondrogenesis, osteogenesis is also promoted by PHF2. PHF2 participates in osteoblast differentiation and maturation by regulating Runx2, which is a transcription factor that controls the expression of multiple osteogenic genes [70]. From a biochemical aspect, PHF2 regulates Sox9 and Runx2 in quite different ways. As was previously mentioned, PHF2 facilitates Sox2-driven transcription in chondrocytes by remodeling the chromatin architecture surrounding Sox2 target genes. However, in osteoblasts, PHF2 promotes DNA binding of Runx2 by directly demethylating mouse Runx2 at Lys245 (at Lys238 in human Runx2), rather than by demethylating histones on Runx2 target genes. By examining *in vivo* models, the authors also suggested that PHF2 could be a promising target for treating bone fractures and impaired bone development [70]. This report provided new insight into PHF2 as a post-translational