REVIEW ARTICLE

The Emerging Role of Histone Demethylases in Renal Cell Carcinoma

Xiaoqiang Guo1,2,3, Qiaoxia Zhang1

1State Engineering Laboratory of Medical Key Technologies Application of Synthetic Biology, Key Laboratory of Medical Reprogramming Technology, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen, Guangdong, China; 2Department of Urology, Shenzhen Second People's Hospital, The First Affiliated Hospital of Shenzhen University, Shenzhen, Guangdong, China; 3Laboratory of Molecular Iron Metabolism, College of Life Science, Hebei Normal University, Shijiazhuang, Hebei, China

Abstract

Renal cell carcinoma (RCC), the most common kidney cancer, is responsible for more than 100,000 deaths per year worldwide. The molecular mechanism of RCC is poorly understood. Many studies have indicated that epigenetic changes such as DNA methylation, noncoding RNAs, and histone modifications are central to the pathogenesis of cancer. Histone demethylases (KDMs) play a central role in histone modifications. There is emerging evidence that KDMs such as KDM3A, KDM5C, KDM6A, and KDM6B play important roles in RCC. The available literature suggests that KDMs could promote RCC development and progression via hypoxia-mediated angiogenesis pathways. Small-molecule inhibitors of KDMs are being developed and used in preclinical studies; however, their clinical relevance is yet to be established. In this mini review, we summarize our current knowledge on the putative role of histone demethylases in RCC.

Keywords: histone demethylases; KDM3A; KDM5C; KDM6A; KDM6B; renal cell carcinoma

Introduction

Renal cell carcinoma (RCC) accounts for 2%–3% of all adult malignancies and causes more than 100,000 deaths per year worldwide (1). Radical or partial nephrectomy of the tumor at an early stage remains the mainstay of curative therapy (2). Metastases are present at the time of initial diagnosis in approximately one-third of patients, which are generally resistant to chemotherapy and radiation therapy (3). A better understanding of molecular mechanisms of RCC is necessary for improvement of treatment outcomes. Epigenetics refers to functionally relevant changes in the genome that affect the expression of specific genes without the involvement of changes in the DNA sequence (4). The common epigenetic events include DNA methylation, changes in noncoding RNAs and posttranslational modifications (PTMs) of histone. PTMs of histone involve the covalent modification of histone through acetylation, methylation, and phosphorylation (5). PTMs of histone regulate DNA replication, transcription, and
repair of many biological processes (6). Histone methylation, a process by which methyl groups are transferred to lysine or arginine residues of histone, is a type of PTM of histone. Histone methylation influences many biological processes in the context of development and cellular responses (7). Abnormality of histone methylation can lead to various disorders including cancer (8). In this mini review, we summarize the emerging role of histone demethylases, key players in histone methylation, in RCC.

**Histone Demethylases and RCC**

In 2004, the first histone demethylase KDM1 was discovered, and in the earlier days histone methylation was thought to be irreversible (9, 10). In 2006, several jumonji C (JmjC)-domain-containing demethylases were identified (11, 12), and subsequent studies showed that histone methylation is reversible. Histone demethylases play a key role in eukaryotic transcription (activation or repression) and other chromatin-dependent processes such as chromosome condensation and DNA damage (13). These demethylases have been implicated in the control of gene expression and cell fate decisions (14, 15). Many histone demethylases have been linked to human diseases (15–17), including RCC (Table 1).

**KDM3A**

KDM3A (also named as JMJD1A, JHDM2A) is an H3K9me1/2 demethylase of JmjC family and plays an essential role in spermatogenesis and adipogenesis (13, 14). KDM3A is also involved in other cellular processes such as cell cycle, embryonic and adult stem cell renewal, and differentiation of vascular smooth muscle (15). KDM3A has been implicated in the development and progression of several malignancies, including hepatocellular carcinoma and gastric cancer (16, 17). We and other researchers have reported that overexpression of KDM3A is associated with RCC development (18, 19). RCC samples from patients showed a higher expression of KDM3A when compared with normal noncancerous regions of the kidneys. Furthermore, KDM3A was highly expressed around blood vessels of RCC samples (18). KDM3A was also associated with an increase in hypoxia-inducible factor 1-alpha (HIF-1α) (18). In vitro experiments with the RCC cell line 786-0 showed that KDM3A was higher in hypoxic conditions than in normoxic conditions. Taken together, these findings (18) suggest the potential role of KDM3A in RCC development and progression via hypoxia-mediated angiogenesis pathway.

**KDM5C**

KDM5C (also known as JARID1C) is an H3K4me1/2 demethylase that plays an important role in brain development and function. Mutations of KDM5C can lead to X-linked mental retardation (23). KDM5C abnormality was also associated with cancer development. For example, KDM5C was significantly upregulated in breast cancer tissues compared with paired normal breast tissues, and was positively correlated with metastasis (24). Inactivating mutations of KDM5C were identified in 101 clear cell RCC (ccRCC) cases using massive parallel sequencing technologies (20). Further studies in 132 ccRCC patients showed that KDM5C was mutated in 4% of the cases (21).

**KDM6A and KDM6B**

KDM6A (also named as UTX) is an H3K27me2/3 demethylase, that is, essential for normal embryonic development and tissue-specific differentiation (25). Inactivating somatic mutations of KDM6A have been identified in RCC (26). Our results showed that expression of KDM6A is upregulated in RCC (22). KDM6B, also known as JMJD3, is another H3K27me2/3 demethylase that plays important roles in inflammatory response and senescence (27). We found that KDM6B is also overexpressed in RCC, and maybe involved in oncogene-induced senescence (22). Thus, both KDM6A and KDM6B appear to have a proto-oncogenic role in RCC.

**Possible Mechanisms of Histone Demethylases in RCC Development**

RCC is a hypoxia-related cancer because inactivating mutations of the tumor suppressor von Hippel-Lindau (VHL) gene are frequent in RCC than in other cancers. VHL is a ubiquitin ligase and its inactivation leads to increased protein stability of HIF1-α (28). HIF can change global patterns of histone modifications through transactivation of several histone demethylases (29, 30). Histone demethylases such as

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**Table 1.** Histone demethylases implicated in RCC.

| Nomenclature | Official symbol | Substrate | Function | References |
|--------------|----------------|-----------|----------|------------|
| KDM3A        | JMJD1A         | H3K9me1/2 | Metabolism, reproduction | (18, 19)   |
| KDM5C        | JARID1C        | H3K4me1/2 | Neural development | (20, 21)   |
| KDM6A        | UTX            | H3K27me2/3| Development | (22)       |
| KDM6B        | JMJD3          | H3K27me2/3| Inflammatory response, senescence | (22)       |

RCC, renal cell carcinoma.
KDM3A, KDM3B, KDM4B, KDM5A, and KDM6B have been identified as HIF regulated demethylases (31). KDM3A has been established as a hypoxia-induced demethylase by several researchers (32–35). Upregulation of KDM3A mRNA and protein could be observed in RCC cell lines (786-0) exposed to hypoxia (1% O2) or iron scavengers (deferoxamine treatment). There is a hypoxia response element in the promoter region of the KDM3A gene, which can be bound by HIF-1α (33, 35). KDM6B was recently identified as a new hypoxia-inducible histone demethylase (36, 37). The expressions of KDM6A and KDM6B are also regulated by nicotine and nickel (38, 39), which are thought to induce RCC (40).

Histone demethylases can act as coactivators of certain nuclear factors including androgen receptor (AR), estrogen receptor, and HIF-1α. KDM3A is not only the coactivator of AR (13) but also the coactivator of HIF-1α (41). KDM3A can further increase specific genes expression, such as GLUT3, adrenomedullin, c-Myc, FGFR2, HGF, and ANG2 (41–43). VHL inactivation in RCC can decrease H3K4me3 levels through KDM5C, which alters gene expression including IGFBP3 and GDF15 (44). In contrast, KDM5C inactivation can lead to genomic instability in RCC (45). These findings indicate that several histone demethylases can be induced under hypoxia which in turn regulate the expression of cancer-related genes, and trigger RCC development.

Is There a Therapeutic Potential for KDM Inhibitors in RCC?

Current targeted therapies for metastatic RCC mainly include mTOR inhibitors, VEGFA receptor tyrosine kinase inhibitors, and anti-VEGFA antibodies (46). However, their efficacies are limited, and there is a need to identify new targets. Histone demethylases are one of the promising targets (47). There is increasing interest in targeting KDMs with small molecules for therapeutic purposes (48). Several high-throughput screening strategies have been developed to screen for small-molecule inhibitors of KDMs (49). Many histone demethylase inhibitors are being developed and tested (50, 51), including GSK-J1/GSK-J4 (KDM6B inhibitor) and NSC 636819 (KDM4A/KDM4B inhibitor). Research has indicated that GSK-J4 has potent antitumor role both in cell lines and animal models of glioma by inhibiting the KDM6B activity and increasing H3K27 methylation (51). Although histone demethylase inhibitors have substantial medicinal potential for the treatment of cancer (52), the major challenge is that these inhibitors are either characterized by low specificity or that their target enzymes have low substrate specificity (53). Furthermore, to date, no conclusive data are available on the efficacy of histone demethylase inhibitors on RCC. However, given that several compounds such as vitamins C and D have regulatory effects on expression or activity of histone demethylases including KDM3A and KDM6B (54, 55), targeting histone demethylases appears to be a potential therapeutic option for RCC (56).

Conclusion

The past decade has witnessed tremendous improvements in the management of metastatic RCC through the introduction of many targeted therapies in clinical practice. Despite this, metastatic RCC still remains a difficult disease to treat. Better understanding of the molecular mechanisms that govern RCC development and progression will enable the development of novel compounds. There is emerging evidence that histone demethylases play a role in the development and progression of RCC, at least in part, via hypoxia-mediated angiogenesis pathway. This is particularly important given that hypoxia-induced angiogenesis pathway plays a crucial role in RCC progression, largely mediated by aberrations of the VHL gene. Furthermore, most of the targeted therapies inhibit the angiogenesis pathway. Thus, inhibition of histone demethylases, because of their perceived role in hypoxia-mediated angiogenesis, is a promising field for future exploration. In addition, the role of currently available targeted therapies on histone demethylases is another area for future research.

Conflict of interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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