Published in final edited form as:

Mol Carcinog. 2022 April ; 61(4): 392–396. doi:10.1002/mc.23390.

Histone demethylase JMJD1A in cancer progression and therapeutic resistance

Hee-Young Jeon[1,2], **Hyunju Ryu**[1,2], **Majid Pornour**[1,2], **Jianfei Qi**[1,2,*]

[1]Department of Biochemistry and Molecular Biology, University of Maryland, Baltimore, MD, USA.

[2]Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA.

Abstract

JMJD1A (also called KDM3A) belongs to the JmjC family of histone demethylases. It specifically removes the repressive mono- or di-methyl marks from H3K9 and thus contributes to the activation of gene transcription. JMJD1A plays a key role in a variety of biological processes such as spermatogenesis, metabolism, sex determination and stem cell activity. JMJD1A is upregulated in various types of cancers, and can promote cancer development, progression and therapeutic resistance. JMJD1A can epigenetically regulate the expression or activity of transcription factors such as c-Myc, AR, ER, β-catenin, et al. Expression and activity of JMJD1A in cancer cells can be regulated at transcriptional, post-transcriptional and post-translational levels. Targeting JMJD1A may repress the oncogenic transcription factors as a potential anti-cancer therapy.

Keywords

histone demethylase; JMJD1A; KDM3A; prostate cancer; cancer progression; epigenetics; transcriptional regulation

Introduction

Methylation of histone H3 at lysine 9 (H3K9me) is a repressive histone mark associated with gene silencing or transcriptional repression. H3K9 methylation can occur as mono-methylation (me1), di-methylation (me2) or tri-methylation (me3). H3K9 methylation can be removed by several histone demethylases, among which is JMJD1A that selectively demethylates mono- and dimethylated H3K9 (H3K9me1/2)[1]. JMJD1A, also called lysine demethylase 3A (KDM3A), belongs to the Jumonji C (JmjC) family of histone demethylases, which are the Fe(II) and α-ketoglutarate (KG)-dependent dioxygenases and characterized by a catalytic JmjC domain. JMJD1A can promote expression or activity of several transcription factors via H3K9 demethylation, thereby regulating a variety of biological processes such as spermatogenesis, metabolism, sex determination and stem cell activity[2–5]. JMJD1A expression is upregulated in many malignancies such as sarcoma, neuroblastoma, and cancers in breast, cervix, lung, kidney, liver, stomach and colon[6–12]. We found that JMJD1A was highly upregulated in aggressive prostate cancer, and promoted

*Correspondence – Jianfei Qi, Greenebaum Comprehensive Cancer Center, Department of Biochemistry and Molecular Biology, University of Maryland School of Medicine, 655 W Baltimore St, Baltimore, MD, 21201 USA. JQI@som.umaryland.edu.

prostate cancer progression and therapeutic resistance[13–17]. Here, we will review the mechanisms of JMJD1A and its regulation in prostate cancer as well as other cancer types.

1. JMJD1A in prostate cancer

The androgen receptor (AR) regulates gene expression promoting PCa cell proliferation and survival. Thus, androgen deprivation therapy (ADT), which suppresses AR activity, is the first-line treatment for metastatic prostate cancer. Despite initial clinical remission after ADT, disease invariably re-occurs in 2–3 years and progresses to a lethal stage called Castration-Resistant Prostate Cancer (CRPC). The major driver of CRPC is re-activation of AR transcriptional activity via multiple mechanisms, such as AR overexpression/mutation/splicing, overexpression of AR co-factors, and intratumoral androgen biosynthesis[18]. Second-generation AR pathway inhibitors (enzalutamide and abiraterone) were developed to repress AR signaling and treat CRPC. These treatments extend survival, but CRPC eventually becomes drug-resistant, driven by reactivated AR signaling[19]. We found that JMJD1A was highly upregulated in CRPC relative to primary prostate cancer in a tissue microarray (TMA)[20]. JMJD1A was also upregulated in the enzalutamide-resistant prostate cancer cells, and knockdown of JMJD1A re-sensitized the resistant cells to enzalutamide[20]. On the contrary, ectopic overexpression of JMJD1A in the androgen-sensitive prostate cancer cells conferred resistance to enzalutamide[20]. These results support a key role for JMJD1A in CRPC progression and enzalutamide resistance. The profiling array studies on the JMJD1A-knockdown prostate cancer cells revealed AR and c-Myc as the top transcription factors in the JMJD1A-dependent gene expression, indicating that JMJD1A is a key regulator of AR and c-Myc in prostate cancer cells[14,15].

1.1 JMJD1A regulation of AR in prostate cancer cells

AR belongs to the nuclear receptor superfamily. It consists of an N-terminal transactivation domain, a DNA binding domain, a hinge region, and a C-terminal ligand-binding domain. In the absence of ligand, AR is sequestered in the cytoplasm by a chaperone complex. Upon ligand binding, AR changes conformation, dissociates from the chaperone complex, and translocates into nucleus to regulate gene expression. JMJD1A harbors a LXXLL motif, which can interact with the ligand-binding domain of AR[1]. JMJD1A-AR interaction promotes the AR chromatin binding through H3K9 demethylation of example AR target genes[1,14,15]. In our ChIP-seq studies, androgen response element (ARE) is one of the top transcription motifs enriched in the JMJD1A peaks. JMJD1A knockdown reduced the AR ChIP-seq signals with the concomitant increase of H3K9me2 signals on the AR-binding sites (ABSs)[15]. Thus, the ChIP-seq studies confirm that JMJD1A enhances the global AR chromatin binding by removing the repressive H3K9 methylation marks from the AR target genes. Furthermore, we found that JMJD1A could promote the generation of AR splicing variant-7 (AR-V7), an additional mechanism for JMJD1A in regulation of AR activity. AR-V7 is generated by alternative splicing using a cryptic exon3b located in the intron 3 of AR gene. AR-V7 lacks the ligand-binding domain and is thus constitutively active in the absence of ligand. Formation of AR-V7 is one of key mechanisms in resistance of prostate cancer to the AR-targeted therapy. We found that JMJD1A interacted with the splicing factor HNRNPF, and JMJD1A-HNRNPF interaction promoted the binding of

HNRNPF to a triple G motif in the exon3b[16]. HNRNPF, in turn, recruited the splicing machinery to the exon 3b for the splicing and generation of AR-V7. The H3K9 demethylase activity of JMJD1A was not required for the generation of AR-V7. Thus, JMJD1A regulates AR chromatin binding and AR-V7 splicing dependent on and independent of its H3K9 demethylase activity, respectively.

1.2 JMJD1A regulation of c-Myc in prostate cancer

c-Myc is a key oncogenic transcription factor for many cancer types including prostate cancer. Knockdown of JMJD1A reduced the c-Myc levels in both AR-positive and AR-negative prostate cancer cells; JMJD1A staining was positively correlated with c-Myc staining in a human prostate cancer TMA[14]. These results indicate a key role for JMJD1A in promoting the expression of c-Myc in prostate cancer. We found that JMJD1A can use three mechanisms to regulate c-Myc levels and activities in prostate cancer cells. (1) JMJD1A can induce H3K9 demethylation on a c-Myc gene enhancer to promote the transcription of c-Myc mRNA[14]. (2) JMJD1A can interact with HUWE1, one of E3 ubiquitin ligases known to target the ubiquitination-mediated degradation of c-Myc[14]. JMJD1A-HUWE1 interaction attenuates the HUWE1/c-Myc interaction, thereby inhibiting the HUWE1-mediated degradation of c-Myc and enhancing the c-Myc protein stability. (3) JMJD1A can interact with c-Myc, function as a c-Myc coactivator and promote the chromatin recruitment of c-Myc through H3K9 demethylation[17]. Consistent with the key role of c-Myc in cell proliferation, knockdown of JMJD1A reduced the level of c-Myc and inhibited the proliferation of prostate cancer cells in vitro or in xenograft models, whereas re-expression of c-Myc in the JMJD1A-knockdown cells partly rescued the proliferation defect[14]. In addition, we found that JMJD1A promoted expression of several DNA repair factors (e.g., NBS1, BARD1, DNA-PK, et al) via c-Myc. Thus, the JMJD1A regulation of c-Myc can promote the double-stand break repair after genotoxic stress, and confer the resistance of prostate cancer cells to X-ray irradiation or PARP inhibitor treatment[17,21].

2. Transcription factors regulated by JMJD1A in other cancer types

In breast cancer cells, JMJD1A can function as a co-activator for estrogen receptor (ER), and promote the chromatin recruitment of ER through H3K9 demethylation[22]. Hormone therapy with the ER modulator tamoxifen is an effective treatment for the ER-positive breast cancer, but resistance to the tamoxifen invariably occurs. Consistent with the JMJD1A regulation of ER, knockdown of JMJD1A reduced the expression of ER target genes and inhibited the proliferation of tamoxifen-resistant breast cancer cells. Moreover, JMJD1A was found to upregulate the expression of c-Myc through H3K9 demethylation, and this could promote transformation of human primary mammary cells upon the transduction with Large T antigen, TERT, and RAS (V12)[23]. Thus, similar to the JMJD1A regulation of AR and c-Myc in prostate cancer, JMJD1A can regulate ER and c-Myc in breast cancer to promote tumor progression and hormone therapy resistance. In addition to H3K9 demethylation, JMJD1A can also induce the demethylation of non-histone proteins. For example, in breast cancer cells, JMJD1A can demethylate tumor suppressor p53 at K372 to inhibit p53 activity for the expression of pro-apoptotic genes such as PUMA, NOXA or

BAX[6]. Thus, knockdown of JMJD1A in breast cancer cells can enhance the apoptosis in response to chemotherapeutic drugs[6].

In colorectal cancer cells, JMJD1A can upregulate the expression of β-catenin and function as a coactivator for β-catenin to promote the Wnt signaling and colorectal tumorigenesis[24,25]. Importantly, JMJD1A can upregulate the expression of c-Myc, a well-established β-catenin target gene, in colorectal cancer cells[24]. On the other hand, JMJD1A-mediated regulation of β-catenin can upregulate the expression of P-glycoproteins (P-gp) and programmed cell death-ligand 1 (PD-L1), thereby conferring multidrug resistance and T cell dysfunction/exhaustion in colon cancer[26]. Thus, targeting JMJD1A can significantly enhance doxorubicin (DOX)-induced immune-stimulatory immunogenic cell death. Moreover, JMJD1A can upregulate expression of YAP1, which is a coactivator for transcription factor TEAD, through H3K9 demethylation of YAP1 gene promoter; JMJD1A also promote the recruitment of TEAD1 to the hippo target genes[27]. Thus, by upregulating YAP1 expression and increasing the chromatin recruitment of TEAD1, JMJD1A can activate the hippo signaling to promote the colorectal tumorigenesis. Finally, JMJD1A can also function as a coactivator for ETS transcription factor ETV1 to promote the colorectal tumorigenesis[28].

In Hela cells derived from cervical cancer, JMJD1A can function as a coactivator for STAT3 and promote the recruitment of STAT3 to the c-Myc gene promoter through H3K9 demethylation. Thus, JMJD1A can promote the JAK2-STAT3 signaling to promote proliferation and motility of Hela cells[29]. As noted above, JMJD1A can regulate expression and/or activity of c-Myc in prostate, breast, colorectal and cervical cancer. These results support c-Myc as a key downstream effector in the JMJD1A-dependent tumorigenesis of multiple cancer types.

HIF-1α is a master transcription factor for gene expression under hypoxia, a common feature of solid tumors. HIF-1α can transcriptionally upregulate the expression of JMJD1A mRNA in various cell types under hypoxia[30–33]. In bladder cancer cells, JMJD1A was reported to interact with HIF-1α and promote the expression of select HIF targets (such as those involved in glucose metabolism) through H3K9 demethylation[34]. Thus, JMJD1A can promote glycolysis metabolism and bladder cancer progression.

3. Regulation of JMJD1A in prostate cancer

Several mechanisms have been identified to regulate the activity of JMJD1A in cancers. We found that JMJD1A interacted with two ubiquitin ligases in prostate cancer, HUWE1 and STUB1. HUWE1 induced the K27/K29-linked non-canonical ubiquitination of JMJD1A at K918[17]. This non-canonical ubiquitination has no effect on the JMJD1A protein levels, but can recruit p300 to promote expression of select c-Myc target genes. Inhibition of this non-canonical ubiquitination of JMJDA lowered the expression of DNA repair factors, inhibited DNA double-strand break repair and sensitized the response of prostate cancer cells to irradiation, etoposide or PAR inhibitors[17]. On the contrary, STUB1 can induce the canonical ubiquitination and degradation of JMJD1A[20]. JMJD1A protein is upregulated in CRPC relative to primary prostate cancer, whereas JMJD1A mRNA shows no changes between

CPRC and primary prostate cancer in the TCGA prostate cancer dataset. Interestingly, STUB1 proteins levels were lower in CRPC than primary prostate cancer, supporting that downregulation of STUB1 level may contribute to upregulation of JMJD1A protein in CRPC. We also found that acetyltransferase p300 induced the acetylation of JMJD1A at K421, a modification that recruited the bromodomain family member BRD4 to block JMJD1A-STUB1 interaction and thus inhibit JMJD1A degradation. Acetylation-mediated JMJD1A-BRD4 interaction also promoted the recruitment of acetylated JMJD1A to AR targets. Furthermore, enzalutamide-resistant prostate cancer cell showed the increased level of both total and K421-acetylated JMJD1A, supporting the relevance of acetylation-mediated upregulation of JMJD1A in enzalutamide resistance. Although selective JMJD1A inhibitors are not yet available, we found that p300 inhibitor that inhibits JMJD1A acetylation or BET inhibitor that blocks JMJD1A-BRD4 interaction can be used to destabilize JMJD1A and inhibit the proliferation of enzalutamide-resistant prostate cancer cells[20]. These results suggest that JMJD1A acetylation at K421 may serve as target for potential CRPC therapy.

4. Regulation of JMJD1A in other cancer types

JMJD1A expression or activity is also regulated in other cancer types. (1) Transcriptional regulation of JMJD1A. HIF-1α can bind to the JMJD1A promoter and transcriptionally upregulate the transcription of JMJD1A mRNA in various cancer cells under hypoxia[30–33]. JMJD1A facilitates the expression of a subset of hypoxia-induced genes, to promote tumor progression[33,35–37]. (2) Phosphorylation of JMJD1A. For example, ACK1 can phosphorylate tyrosine 1114 located in the JmjC domain of JMJD1A to promote ER activity in breast cancer cells[38]. JAK2 can induce tyrosine phosphorylation of JMJD1A at residue 1101 to increase the demethylase activity of JMJD1A and co-activation of STAT3 in Hela cells[29]. Protein kinase A (PKA) can induce phosphorylation of JMJD1A at serine 265 following DNA damage, and that phosphorylation regulates alternative splicing of cell-cycle genes in breast cancer cells[39]. (3) Alternative splicing of JMJD1A mRNA. Acetylation of PHF5A, a component of U2 snRNPs, was reported to reduce the retention of JMJD1A intron 3 during the JMJD1A mRNA splicing, thereby leading to enhanced stability of JMJD1A mRNA in colorectal cancer[40]. (4) Regulation of JMJD1A by microRNAs (miRNAs). JMJD1A mRNA can be targeted and repressed by several tumor-suppressive miRNAs such as miR-627 in colorectal cancer cells[41], miR-22 in Ewing Sarcoma cells[42] and let-7c in non-small lung cancer cells (NSCLC)[8].

Conclusion

JMJD1A plays a key role in driving progression and therapeutic resistance of several cancer types. JMJD1A regulates the expression or activity of several oncogenic transcription factors through its H3K9 demethylase activity. Thus, JMJD1A may serve as a promising target for potential anti-cancer therapy. Selective inhibitors targeting the demethylase activity of JMJD1A are not yet available[43]. More future efforts are needed to identify and develop the selective JMJD1A inhibitors targeting its demethylase activity. Further, JMJD1A can function independent of its demethylase activity (e.g., JMJD1A-HNRNPF interaction for alterative splicing of AR-V7 or JMJD1A-HUWE1 interaction in attenuating the HUWE1/c-

Myc interaction). Proteolysis targeting chimera (PROTAC) may be a potential tool to induce JMJD1A degradation and thus inhibit both its catalytic-dependent and -independent function in cancer progression and therapeutic resistance.

Acknowledgments

This work is supported by NCI grant R01CA207118 and R01CA244667 (to J.Q.).

Reference

1. Yamane K, Toumazou C, Tsukada Y, et al. JHDM2A, a JmjC-containing H3K9 demethylase, facilitates transcription activation by androgen receptor. Cell. 2006;125(3):483–495. [PubMed: 16603237]
2. Okada Y, Scott G, Ray MK, Mishina Y, Zhang Y. Histone demethylase JHDM2A is critical for Tnp1 and Prm1 transcription and spermatogenesis. Nature. 2007;450(7166):119–123. [PubMed: 17943087]
3. Tateishi K, Okada Y, Kallin EM, Zhang Y. Role of Jhdm2a in regulating metabolic gene expression and obesity resistance. Nature. 2009;458(7239):757–761. [PubMed: 19194461]
4. Loh YH, Zhang W, Chen X, George J, Ng HH. Jmjd1a and Jmjd2c histone H3 Lys 9 demethylases regulate self-renewal in embryonic stem cells. Genes Dev. 2007;21(20):2545–2557. [PubMed: 17938240]
5. Kuroki S, Matoba S, Akiyoshi M, et al. Epigenetic regulation of mouse sex determination by the histone demethylase Jmjd1a. Science. 2013;341(6150):1106–1109. [PubMed: 24009392]
6. Ramadoss S, Guo G, Wang CY. Lysine demethylase KDM3A regulates breast cancer cell invasion and apoptosis by targeting histone and the non-histone protein p53. Oncogene. 2017;36(1):47–59. [PubMed: 27270439]
7. Liu J, Zhu M, Xia X, Huang Y, Zhang Q, Wang X. Jumonji domain-containing protein 1A promotes cell growth and progression via transactivation of c-Myc expression and predicts a poor prognosis in cervical cancer. Oncotarget. 2016;7(51):85151–85162. [PubMed: 27835890]
8. Zhan M, Wen F, Liu L, Chen Z, Wei H, Zhou H. JMJD1A promotes tumorigenesis and forms a feedback loop with EZH2/let-7c in NSCLC cells. Tumour Biol. 2016;37(8):11237–11247. [PubMed: 26945572]
9. Guo X, Shi M, Sun L, et al. The expression of histone demethylase JMJD1A in renal cell carcinoma. Neoplasma. 2011;58(2):153–157. [PubMed: 21275466]
10. Yamada D, Kobayashi S, Yamamoto H, et al. Role of the hypoxia-related gene, JMJD1A, in hepatocellular carcinoma: clinical impact on recurrence after hepatic resection. Ann Surg Oncol. 2012;19 Suppl 3:S355–364. [PubMed: 21607773]
11. Yang H, Liu Z, Yuan C, et al. Elevated JMJD1A is a novel predictor for prognosis and a potential therapeutic target for gastric cancer. Int J Clin Exp Pathol. 2015;8(9):11092–11099. [PubMed: 26617828]
12. Uemura M, Yamamoto H, Takemasa I, et al. Jumonji domain containing 1A is a novel prognostic marker for colorectal cancer: in vivo identification from hypoxic tumor cells. Clin Cancer Res. 2010;16(18):4636–4646. [PubMed: 20823141]
13. Qi J, Nakayama K, Cardiff RD, et al. Siah2-dependent concerted activity of HIF and FoxA2 regulates formation of neuroendocrine phenotype and neuroendocrine prostate tumors. Cancer Cell. 2010;18(1):23–38. [PubMed: 20609350]
14. Fan L, Peng G, Sahgal N, et al. Regulation of c-Myc expression by the histone demethylase JMJD1A is essential for prostate cancer cell growth and survival. Oncogene. 2016;35(19):2441–2452. [PubMed: 26279298]
15. Wilson S, Fan L, Sahgal N, Qi J, Filipp FV. The histone demethylase KDM3A regulates the transcriptional program of the androgen receptor in prostate cancer cells. Oncotarget. 2017;8(18):30328–30343. [PubMed: 28416760]

16. Fan L, Zhang F, Xu S, et al. Histone demethylase JMJD1A promotes alternative splicing of AR variant 7 (AR-V7) in prostate cancer cells. Proc Natl Acad Sci U S A. 2018;115(20):E4584–E4593. [PubMed: 29712835]
17. Fan L, Xu S, Zhang F, et al. Histone demethylase JMJD1A promotes expression of DNA repair factors and radio-resistance of prostate cancer cells. Cell Death Dis. 2020;11(4):214. [PubMed: 32238799]
18. Watson PA, Arora VK, Sawyers CL. Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat Rev Cancer. 2015;15(12):701–711. [PubMed: 26563462]
19. Schmidt KT, Huitema ADR, Chau CH, Figg WD. Resistance to second-generation androgen receptor antagonists in prostate cancer. Nat Rev Urol. 2021;18(4):209–226. [PubMed: 33742189]
20. Xu S, Fan L, Jeon HY, et al. p300-Mediated Acetylation of Histone Demethylase JMJD1A Prevents Its Degradation by Ubiquitin Ligase STUB1 and Enhances Its Activity in Prostate Cancer. Cancer Res. 2020;80(15):3074–3087. [PubMed: 32522824]
21. Jeon HY, Hussain A, Qi J. Role of H3K9 demethylases in DNA double-strand break repair. J Cancer Biol. 2020;1(1):10–15. [PubMed: 32696030]
22. Wade MA, Jones D, Wilson L, et al. The histone demethylase enzyme KDM3A is a key estrogen receptor regulator in breast cancer. Nucleic Acids Res. 2015;43(1):196–207. [PubMed: 25488809]
23. Zhao QY, Lei PJ, Zhang X, et al. Global histone modification profiling reveals the epigenomic dynamics during malignant transformation in a four-stage breast cancer model. Clin Epigenetics. 2016;8:34. [PubMed: 27034728]
24. Peng K, Su G, Ji J, et al. Histone demethylase JMJD1A promotes colorectal cancer growth and metastasis by enhancing Wnt/beta-catenin signaling. J Biol Chem. 2018;293(27):10606–10619. [PubMed: 29802196]
25. Li J, Yu B, Deng P, et al. KDM3 epigenetically controls tumorigenic potentials of human colorectal cancer stem cells through Wnt/beta-catenin signalling. Nat Commun. 2017;8:15146. [PubMed: 28440295]
26. Liu J, Zhao Z, Qiu N, et al. Co-delivery of IOX1 and doxorubicin for antibody-independent cancer chemo-immunotherapy. Nat Commun. 2021;12(1):2425. [PubMed: 33893275]
27. Wang HY, Long QY, Tang SB, et al. Histone demethylase KDM3A is required for enhancer activation of hippo target genes in colorectal cancer. Nucleic Acids Res. 2019.
28. Oh S, Song H, Freeman WM, Shin S, Janknecht R. Cooperation between ETS transcription factor ETV1 and histone demethylase JMJD1A in colorectal cancer. Int J Oncol. 2020;57(6):1319–1332. [PubMed: 33174020]
29. Kim H, Kim D, Choi SA, et al. KDM3A histone demethylase functions as an essential factor for activation of JAK2-STAT3 signaling pathway. Proc Natl Acad Sci U S A. 2018;115(46):11766–11771. [PubMed: 30377265]
30. Beyer S, Kristensen MM, Jensen KS, Johansen JV, Staller P. The histone demethylases JMJD1A and JMJD2B are transcriptional targets of hypoxia-inducible factor HIF. J Biol Chem. 2008;283(52):36542–36552. [PubMed: 18984585]
31. Pollard PJ, Loenarz C, Mole DR, et al. Regulation of Jumonji-domain-containing histone demethylases by hypoxia-inducible factor (HIF)-1alpha. Biochem J. 2008;416(3):387–394. [PubMed: 18713068]
32. Wellmann S, Bettkober M, Zelmer A, et al. Hypoxia upregulates the histone demethylase JMJD1A via HIF-1. Biochem Biophys Res Commun. 2008;372(4):892–897. [PubMed: 18538129]
33. Krieg AJ, Rankin EB, Chan D, Razorenova O, Fernandez S, Giaccia AJ. Regulation of the histone demethylase JMJD1A by hypoxia-inducible factor 1 alpha enhances hypoxic gene expression and tumor growth. Mol Cell Biol. 2010;30(1):344–353. [PubMed: 19858293]
34. Wan W, Peng K, Li M, et al. Histone demethylase JMJD1A promotes urinary bladder cancer progression by enhancing glycolysis through coactivation of hypoxia inducible factor 1alpha. Oncogene. 2017;36(27):3868–3877. [PubMed: 28263974]
35. Mimura I, Nangaku M, Kanki Y, et al. Dynamic change of chromatin conformation in response to hypoxia enhances the expression of GLUT3 (SLC2A3) by cooperative interaction of hypoxia-inducible factor 1 and KDM3A. Mol Cell Biol. 2012;32(15):3018–3032. [PubMed: 22645302]

36. Chakraborty D, Cui W, Rosario GX, et al. HIF-KDM3A-MMP12 regulatory circuit ensures trophoblast plasticity and placental adaptations to hypoxia. Proc Natl Acad Sci U S A. 2016;113(46):E7212–E7221. [PubMed: 27807143]

37. Osawa T, Tsuchida R, Muramatsu M, et al. Inhibition of histone demethylase JMJD1A improves anti-angiogenic therapy and reduces tumor-associated macrophages. Cancer Res. 2013;73(10):3019–3028. [PubMed: 23492365]

38. Mahajan K, Lawrence HR, Lawrence NJ, Mahajan NP. ACK1 tyrosine kinase interacts with histone demethylase KDM3A to regulate the mammary tumor oncogene HOXA1. J Biol Chem. 2014;289(41):28179–28191. [PubMed: 25148682]

39. Baker M, Petasny M, Taqatqa N, et al. KDM3A regulates alternative splicing of cell-cycle genes following DNA damage. RNA. 2021;27(11):1353–1362. [PubMed: 34321328]

40. Wang Z, Yang X, Liu C, et al. Acetylation of PHF5A Modulates Stress Responses and Colorectal Carcinogenesis through Alternative Splicing-Mediated Upregulation of KDM3A. Mol Cell. 2019;74(6):1250–1263 e1256. [PubMed: 31054974]

41. Padi SK, Zhang Q, Rustum YM, Morrison C, Guo B. MicroRNA-627 mediates the epigenetic mechanisms of vitamin D to suppress proliferation of human colorectal cancer cells and growth of xenograft tumors in mice. Gastroenterology. 2013;145(2):437–446. [PubMed: 23619147]

42. Toomey EC, Schiffman JD, Lessnick SL. Recent advances in the molecular pathogenesis of Ewing's sarcoma. Oncogene. 2010;29(32):4504–4516. [PubMed: 20543858]

43. Maes T, Carceller E, Salas J, Ortega A, Buesa C. Advances in the development of histone lysine demethylase inhibitors. Curr Opin Pharmacol. 2015;23:52–60. [PubMed: 26057211]