# Crucial Functions of the JMJD1/KDM3 Epigenetic Regulators in Cancer

Yuan Sui[1], Ruicai Gu[2], and Ralf Janknecht[1,2,3]

## ABSTRACT

Epigenetic changes are one underlying cause for cancer development and often due to dysregulation of enzymes modifying DNA or histones. Most Jumonji C domain-containing (JMJD) proteins are histone lysine demethylases (KDM) and therefore epigenetic regulators. One JMJD subfamily consists of JMJD1A/KDM3A, JMJD1B/KDM3B, and JMJD1C/KDM3C that are roughly 50% identical at the amino acid level. All three JMJD1 proteins are capable of removing dimethyl and monomethyl marks from lysine 9 on histone H3 and might also demethylate histone H4 on arginine 3 and nonhistone proteins. Analysis of knockout mice revealed critical roles for JMJD1 proteins in fertility, obesity, metabolic syndrome, and heart disease. Importantly, a plethora of studies demonstrated that especially JMJD1A and JMJD1C are overexpressed in various tumors, stimulate cancer cell proliferation and invasion, and facilitate efficient tumor growth. However, JMJD1A may also inhibit the formation of germ cell tumors. Likewise, JMJD1B appears to be a tumor suppressor in acute myeloid leukemia, but a tumor promoter in other cancers. Notably, by reducing methylation levels on histone H3 lysine 9, JMJD1 proteins can profoundly alter the transcriptome and thereby affect tumorigenesis, including through upregulating oncogenes such as *CCND1, JUN*, and *MYC*. This epigenetic activity of JMJD1 proteins is sensitive to heavy metals, oncometabolites, oxygen, and reactive oxygen species, whose levels are frequently altered within cancer cells. In conclusion, inhibition of JMJD1 enzymatic activity through small molecules is predicted to be beneficial in many different cancers, but not in the few malignancies where JMJD1 proteins apparently exert tumor-suppressive functions.

## Introduction

The seminal role of gene mutations in cancer development has been recognized for a long time, but more recent studies have revealed a similarly important role of epigenetic changes. Histone (de)methylation is intimately involved in the underlying chromatin alterations, and the family of Jumonji C (JmjC) domain-containing (JMJD) proteins is primarily responsible for histone lysine demethylation. In humans, JMJD proteins constitute a large protein family with more than 30 members, most of which are reportedly endowed with histone lysine demethylase activity and thus often referred to as KDMs (lysine demethylases). This lysine demethylation activity is a reflection of two consecutive chemical reactions: hydroxylation of the methylated ε-amino group followed by spontaneous release of formaldehyde, only the former being a truly JMJD-dependent process (**Fig. 1A**). Consistent with their inherent hydroxylase activity, JMJD proteins have been shown to also hydroxylate amino acid residues, including aspartate, asparagine, histidine, unmethylated lysine, or arginine, as well as tRNA (1, 2). For all these activities, JMJD proteins require the cofactors oxygen and 2-oxoglutarate (also known as α-ketoglutarate) whereas carbon dioxide and succinate are by-products (**Fig. 1A**), which makes JMJD activity sensitive to the metabolic state of a cell.

The JMJD protein family is quite heterogeneous (**Table 1**). Its members can be subdivided by molecular weight into large (>100 kDa) and small (<100 kDa) proteins, by their specificity with regard to histone lysine demethylation, and by the presence of functional domains (1–3). One subfamily of JMJD proteins consists of three members, JMJD1A–C (or KDM3A–C). Two conserved domains have been identified in JMJD1A–C that are required for their catalytic activity (4–6): the JmjC catalytic center and a C6 zinc finger (**Fig. 2**), the latter one found in only one other JMJD protein, Hairless (HR). In addition, JMJD1 proteins possess a conserved LXXLL motif (**Fig. 2**), a protein–protein interaction motif originally found in coactivators mediating their binding to nuclear receptors, yet the role of this JMJD1 LXXLL motif has remained unresolved. JMJD1A/KDM3A is more closely related to JMJD1B/KDM3B (59.64% identity at the amino acid sequence level) than to JMJD1C/KDM3C (45.37% identity), and also JMJD1B shares less than half of its amino acids (47.88%) with JMJD1C, indicating that JMJD1C is evolutionarily most distant from the other two JMJD1 proteins. Although HR is very similar to JMJD1 proteins (**Table 1**), it is not regarded as an additional member of this subfamily, because HR is at most 33.47% identical to a JMJD1 protein and displays great variance even in the conserved functional domains as well as in the LXXLL motif (Supplementary Fig. S1).

All three JMJD1 proteins have been established to utilize mono- and dimethylated lysine 9 on histone H3 (H3K9) as substrates *in vitro* and *in vivo* (**Fig. 1B**), whereas trimethylated H3K9 is not a substrate (4–6). But JMJD1 proteins can indirectly cause reduction of trimethylated H3K9 levels by depleting its precursor, dimethylated H3K9. No other methylated histone lysine residue bar H3K9 is targeted by JMJD1, and this limited specificity toward mono-/dimethylated H3K9 is another characteristic that sets JMJD1 enzymes apart from all other JMJD proteins except HR (**Table 1**). Given that tri- and dimethylated H3K9 are prominent marks of heterochromatin and associated with inactive genes (7),

[1]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma. [2]Department of Cell Biology, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma. [3]Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, Oklahoma.

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**Corresponding Author:** Ralf Janknecht, University of Oklahoma Health Sciences Center, 975 NE 10th Street, BRC-1464, Oklahoma City, OK 73104. Phone: 1-405-2712377. E-mail: ralf-janknecht@ouhsc.edu

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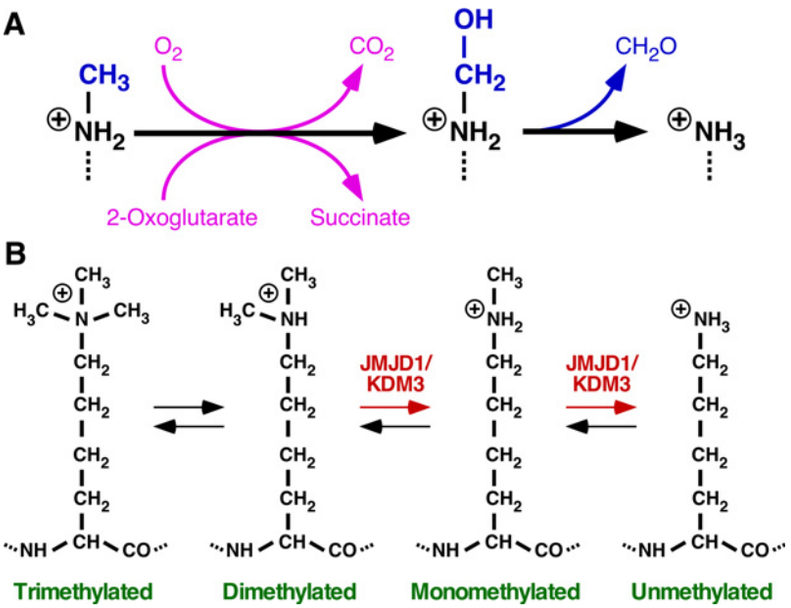


**Figure 1.**
Lysine demethylation by JMJD1/KDM3 proteins. **A,** First, hydroxylation of the methylated (in this case, monomethylated) ε-amino group occurs. The resultant hemiaminal is chemically labile, releasing formaldehyde ($CH_2O$) and thereby leading to a demethylated ε-amino group. **B,** Dynamic equilibrium between the unmethylated and methylated states of a lysine residue. JMJD1/KDM3 proteins catalyze the conversion of di- to monomethylated and of mono- to unmethylated lysine 9 on histone H3.

removal (indirectly and directly, respectively) of these histone marks by JMJD1 enzymes is expected to increase initiation of gene transcription. However, monomethylated H3K9 is frequently found at active genes (7), so its removal by JMJD1 proteins could potentially contribute to decreased transcription. As such, the net impact on gene transcription of JMJD1-mediated changes of the H3K9 methylation status cannot generally be predicted and may vary dependent on the gene promoter, cell type, or physiological state of a cell.

JMJD1-mediated demethylation may not be restricted to H3K9. For instance, JMJD1A has been shown to demethylate *in vitro* peptides encompassing amino acids 1–15 of histone H3, in which lysine 9 was replaced by a monomethylated, asymmetrically dimethylated, or symmetrically dimethylated arginine residue, suggesting that JMJD1A could also function as an arginine demethylase. However, multiple peptides with methylated arginine residues known to naturally exist in histone H3 or H4 were not targeted by JMJD1A, and no supporting *in vivo* evidence for an arginine demethylase activity has been supplied (8), raising doubts whether JMJD1A demethylates histone arginine residues under physiological conditions. But both *in vitro* and *in vivo* evidence strongly indicates that JMJD1B demethylates monomethylated and symmetrically dimethylated arginine 3 on histone H4 (9). Thus, JMJD1 enzymatic activity is likely to extend beyond the demethylation of H3K9.

## The Normal: Upkeeping a Variety of Biological Functions

All three *JMJD1* genes are widely expressed, and their mRNA expression levels are mostly comparable (**Fig. 3**), although corresponding protein expression data are needed to better understand their tissue distribution. Regardless, this suggests JMJD1 proteins to be ubiquitously expressed and thus to potentially have pleiotropic functions in humans. However, no single JMJD1 protein appears to be essential, as first demonstrated with *Jmjd1a* knockout mice. But several abnormalities were observed: male *Jmjd1a* knockout mice were infertile, had smaller testes and defects in spermatogenesis, and often even displayed male-to-female sex reversal, which is probably due to the fact that JMJD1A-mediated removal of H3K9 methylation is needed for activation of the promoter of the Y-chromosomal *Sry* gene that encodes for the male sex–determining factor (10, 11). In contrast, female *Jmjd1a* knockout mice were fertile. Male *Jmjd1b*$^{-/-}$ mice presented with greatly reduced fertility, which was caused by lower numbers of mature sperm, reduced sperm motility, and impaired sexual behavior (12). Female *Jmjd1b*$^{-/-}$ mice had normally developed reproductive organs, yet they were essentially infertile due to multiple defects, including decreased ovulation capacity, fertilization rate, embryo implantation, and survival. In addition, both male and female *Jmjd1b* knockout mice, although born at normal weight, were of smaller body size soon after birth and also frequently died before weaning (13); *Jmjd1b*$^{-/-}$ mice also presented with impaired hematopoiesis, including a reduction in red blood cell count and an increase in white blood cells and neutrophils (9). In contrast, *Jmjd1c* knockout mice displayed no change in body size and survival, and females were reproductively normal. The same was true for young male *Jmjd1c*$^{-/-}$ mice, but fertility and testis size hugely decreased after three months of age, possibly due to increased apoptosis of germ cells (14). The common male infertility phenotype of *Jmjd1* knockout mice may hint at overlapping functions, whereas the greatest severity of this phenotype observed upon *Jmjd1a* knockout may be a reflection of its expression being much higher in testes in comparison with *Jmjd1b* and *Jmjd1c*, as observed for human *JMJD1* mRNA levels (**Fig. 3**). In support of JMJD1 redundancy, mice with knockout in any three, but not two, of the four *Jmjd1a* and *Jmjd1b* alleles died during embryogenesis (15).

Other consequences of *Jmjd1a* knockout were the development of adult obesity and metabolic syndrome and a defective ability to respond to cold temperature. This involved defects in gene expression in both skeletal muscle and brown adipose tissue. In particular, loss of JMJD1A caused inhibition of expression of PPARα and UCP1, two important regulators of energy balance (16, 17). In addition, JMJD1A can form a complex with PPARγ in beige adipose cells, thereby reducing dimethylation of H3K9 and leading to the transcription of genes that mediate the response against chronic cold exposure (18). Similarly, JMJD1C may affect metabolism. For instance,

**Table 1.** Human JMJD proteins and their subfamilies.

| Name | Molecular weight | Domain(s) in addition to JmjC | Lysine targets on histones H3 or H4 |
|---|---|---|---|
| JMJD1A/KDM3A<br>JMJD1B/KDM3B<br>JMJD1C/KDM3C | >100 kDa | C6 Zn-finger | $H3K9me_{2/1}$ |
| HR | >100 kDa | C6 Zn-finger | $H3K9me_{2/1}$ |
| JMJD2A/KDM4A<br>JMJD2B/KDM4B<br>JMJD2C/KDM4C | >100 kDa | JmjN, PHD, Tudor | $H3K9me_{3/2}$, $H3K36me_{3/2}$ |
| JMJD2D/KDM4D<br>JMJD2E/KDM4E<br>JMJD2F/KDM4F | <100 kDa | JmjN | $H3K9me_{3/2}$ |
| JARID1A/KDM5A<br>JARID1B/KDM5B<br>JARID1C/KDM5C<br>JARID1D/KDM5D | >100 kDa | JmjN, ARID, PHD, C5HC2 Zn-finger | $H3K4me_{3/2}$ |
| JARID2/JMJ | >100 kDa | JmjN, ARID, C5HC2 Zn-finger | |
| KDM2A/FBXL11<br>KDM2B/FBXL10 | >100 kDa | CXXC Zn-finger, PHD, F-box, LRR | $H3K4me_3$ (only KDM2B), $H3K36me_{2/1}$ |
| JMJD3/KDM6B<br>UTX/KDM6A<br>UTY/KDM6C | >100 kDa | TPR (only UTX and UTY) | $H3K27me_{3/2}$ |
| KDM7A/KIAA1718<br>KDM7B/PHF8<br>KDM7C/PHF2 | >100 kDa | PHD | $H3K9me_2$, $H3K9me_1$ (only KDM7B), $H3K27me_2$ (not KDM7C), $H4K20me_1$ (not KDM7C) |
| HIF1AN/FIH | <100 kDa | | |
| HSPBAP1 | <100 kDa | | |
| JMJD4 | <100 kDa | | |
| JMJD5/KDM8 | <100 kDa | | $H3K36me_2$ |
| JMJD6 | <100 kDa | | |
| JMJD7 | <100 kDa | | |
| JMJD8 | <100 kDa | | |
| NO66/JMJD9 | <100 kDa | | $H3K4me_{3/2/1}$, $H3K36me_{3/2}$ |
| MINA/MINA53/JMJD10 | <100 kDa | | $H3K9me_3$ |
| TYW5 | <100 kDa | | |

Abbreviations: ARID, AT-rich interaction domain; JmjN, Jumonji N domain; LRR, leucine-rich repeat; PHD, plant homeodomain; TPR, tetratricopeptide repeat domain.

phosphorylation of JMJD1C by mTOR strengthened its interaction with USF-1, a seminal transcription factor in lipogenesis. This was shown to reduce H3K9 methylation and increase promoter activity of many genes that become upregulated upon feeding, hinting at an important role for JMJD1C in normal lipogenesis (19). Likewise, JMJD1C depletion in murine 3T3-L1 cells increased dimethylation of H3K9 at the promoters of *C/ebpα, C/ebpβ*, and *Pparγ* that should reduce the expression of these key adipogenic transcription factors. Consequently, JMJD1C depletion reduced accumulation of triglycerides and the size of lipid droplets upon adipogenesis induction in 3T3-L1 cells (20). Notably, *Jmjd1c* ablation in mouse livers also resulted into reduced lipogenesis and triglyceride levels and suppressed glucose intolerance and insulin resistance upon diet-induced obesity, suggesting that inhibition of JMJD1C may be beneficial for treating obesity-related maladies (19). This contrasts the predicted harmful inhibition of JMJD1A, as its catalytic inactivity should phenocopy the above-described deleterious effects of its knockout on the metabolic state.

Analysis of the myocardium of patients with a hypertrophic heart revealed an upregulation of JMJD1A, suggesting a possible involvement of JMJD1A in the development of this disease. To prove so, both myocyte-selective transgenic and whole-body knockout *Jmjd1a* mice were analyzed and they displayed exacerbated or reduced, respectively, left ventricular hypertrophy and fibrosis of the heart in response to pressure overload. JMJD1A overexpression especially reactivated fetal genes that have been implicated in hypertrophic growth. Furthermore, JMJD1A bound to the promoter of the *Timp1* gene, which encodes for an extracellular matrix protein and metallopeptidase inhibitor known to be involved in fibrosis, decreased dimethylation of H3K9 and thus induced *Timp1* transcription. Importantly, knockdown of *Timp1* in cardiomyocytes suppressed to a great extent the fibrotic effects of JMJD1A overexpression, indicating a seminal role of TIMP1 as a downstream effector of JMJD1A (21). This suggests that inhibition of JMJD1A may be helpful in the treatment of heart hypertrophy and fibrosis, and the same may apply for JMJD1C (22). In contrast, JMJD1A may be beneficial in the recovery from myocardial infarction. This was shown with a $Jmjd1a^{-/-}$ rat model, in which an abnormal macrophage polarization may explain the observed impaired cardiac repair process after infarction (23). Consistently, adenovirus-mediated delivery of JMJD1A to the heart mitigated the injuries associated with myocardial infarction (24).

JMJD1 proteins may also be important for normal intellectual development and behavior. For instance, truncating and missense mutations in *JMJD1B* were associated with intellectual disability and short stature (25), the latter reminiscent of the growth defects found in $Jmjd1b^{-/-}$ mice (13). In addition, *JMJD1C* mutations have been found in patients with intellectual disability and Rett syndrome that is phenotypically similar to autism (26). Also, a premature stop codon was identified in the *JMJD1A* gene and associated with developmental delay, autism, and status epilepticus, but currently only one such patient has been identified (27). This indicates the need to screen for

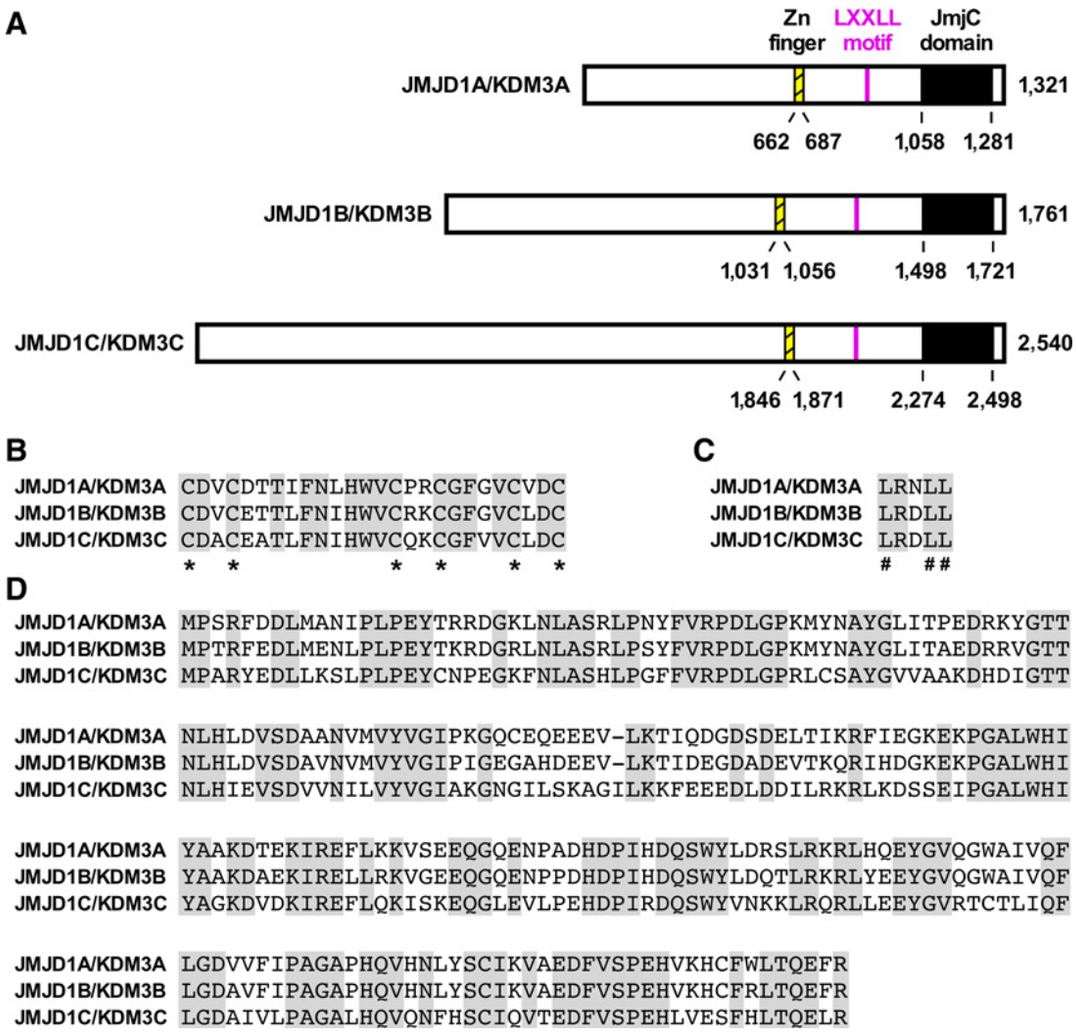


**Figure 2.**

Homology between the JMJD1/KDM3 proteins. **A,** Scheme of the JMJD1/KDM3 proteins derived from the NCBI reference sequences for human JMJD1A (NP_060903.2), JMJD1B (NP_057688.3), and JMJD1C (NP_116165.1). However, there are many splice variants that can result into different length isoforms. **B,** Alignment of the zinc fingers. Conserved cysteine residues are marked by asterisks, and amino acids conserved between all three proteins are highlighted in gray. **C,** Alignment of the conserved LXXLL motifs spanning amino acids 885–889 in JMJD1A, 1293–1297 in JMJD1B and 2066–2070 in JMJD1C. The conserved leucine residues are marked by "#." **D,** Alignment of the JmjC domains (as defined by UniProt).

*JMJD1* mutations in larger population studies. Experimental validation in cell culture and animal models is needed to substantiate that these *JMJD1* mutations are underlying causes for the observed abnormalities.

OCT4, which is a crucial stem cell transcription factor, is capable of inducing *Jmjd1a* transcription in mouse embryonic stem cells. And JMJD1A downregulation induced differentiation of these cells, the first time showing the functional relevance of a JMJD1 protein in upkeeping a stem cell phenotype (28). However, another report showed that only combined loss of JMJD1A and JMJD1B compromised maintenance of embryonic stem cells (15). JMJD1A may additionally promote reactivation of OCT4 during reprogramming to pluripotency, but the underlying mechanism is not yet known (29). OCT4 is also capable of recruiting JMJD1C to oppose dimethylation of H3K9, and JMJD1C induces expression of both OCT4 and KLF4, another stem cell factor. Accordingly, JMJD1C was required for efficient somatic cell reprogramming and embryonic stem cell self-renewal (30, 31). This ability of JMJD1 proteins to promote stemness may also be relevant in cancer stem–like cells (32–34).

## The Good: Keeping Tumors in Check

Aside from their roles in normal homeostasis and development, JMJD1 proteins appear to be sometimes involved in preventing the genesis of malignancies. Fittingly, analysis of human germ cell tumors (e.g., seminomas and embryonal carcinomas) revealed downregulation of JMJD1A at the mRNA and protein level. Notably, subcutaneous injection of *Jmjd1a*$^{-/-}$ compared with wild-type embryonic stem cells into nude mice led to larger tumors, but there was no growth difference between wild-type and *Jmjd1a*$^{-/-}$ embryonic stem cells *in vitro*. Rather, *Jmjd1a* knockout led to more microvessels in tumors. *Jmjd1a* knockout consistently induced changes in the expression of

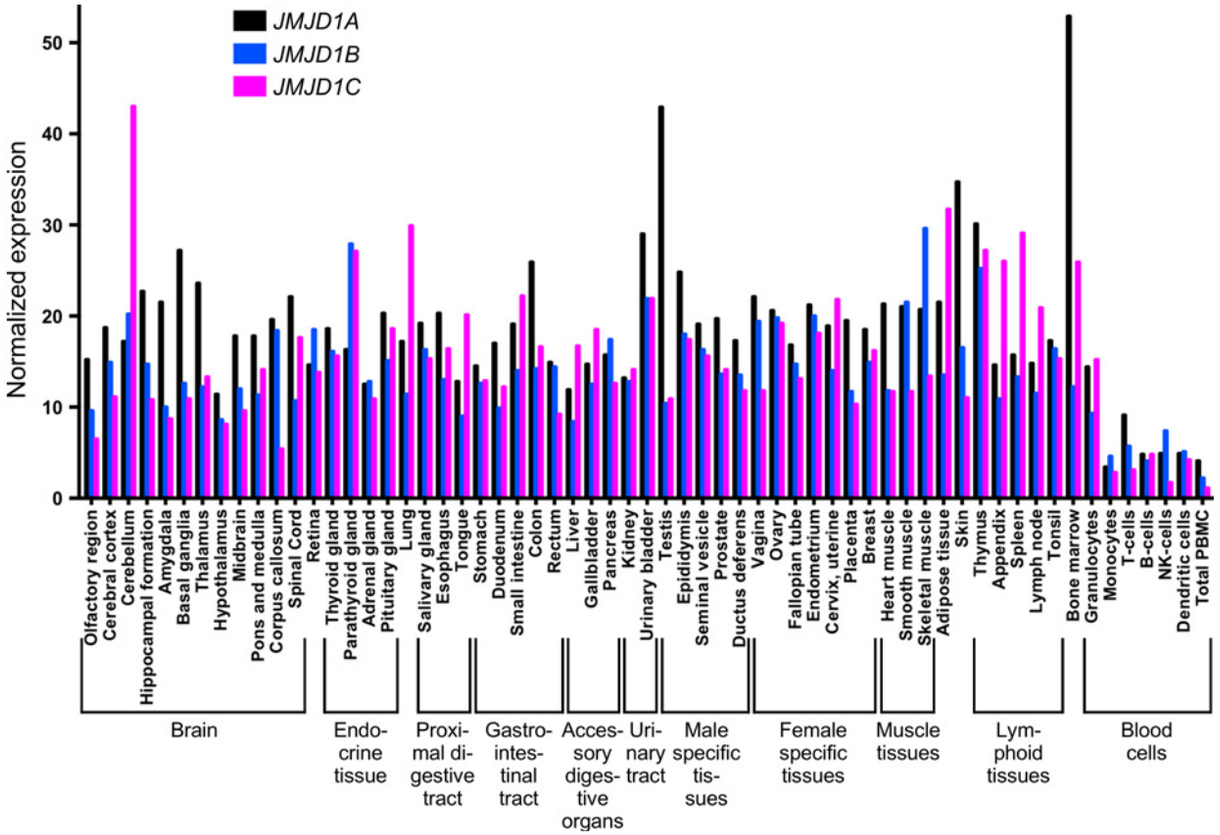


**Figure 3.**

*JMJD1* mRNA expression in human tissues. Shown are the consensus data sets derived from the Human Protein Atlas (www.proteinatlas.org).

angiogenesis-related genes, especially downregulation of antiangiogenic factors (35). This suggests that JMJD1A can repress angiogenesis and could thereby suppress germ cell tumorigenesis. Interestingly, germline missense mutations in *JMJD1C* were found to be enriched in intracranial germ cell tumors, but whether these mutations inactivate JMJD1C function and thereby drive germ cell tumorigenesis is unknown (36).

*JMJD1B* was originally cloned as a candidate tumor suppressor gene located in the 5q31 chromosomal region that is often deleted in myelodysplasia and acute myeloid leukemia (AML). Accordingly, JMJD1B overexpression reduced clonogenic efficiency of a myelodysplasia or AML cell line with 5q deletion (37, 38). Analysis of AML patients revealed that JMJD1B is underexpressed and low mRNA levels correlate with an unfavorable prognosis (38, 39). In addition, JMJD1B downregulation promoted proliferation of NB4 cells, which express the PML–RARA fusion oncoprotein characteristic of the acute promyelocytic subtype of AML. Mechanistically, JMJD1B induced alterations of H3K9 methylation that were suggested to restrict chromatin accessibility for PML–RARA, thereby blunting the oncogenic potential of this transcription factor (39). However, this may seem counterintuitive, because JMJD1B activity is in general supposed to remove heterochromatin marks and thus make chromatin more accessible for transcription factors. JMJD1B also promoted PML–RARA degradation upon all-trans retinoic acid treatment of NB4 cells, thereby facilitating their differentiation into mature granulocytes (39). But one other study reported the conflicting observation of JMJD1B inhibiting the all-trans retinoic acid induced differentiation of the AML cell line HL-60 (5). Altogether, a preponderance of data currently suggests that JMJD1B may be a tumor suppressor in AML.

## The Bad: Contribution to Tumorigenesis

In contrast to the putative tumor suppressor role of JMJD1B, JMJD1C has been identified as a promoter of AML by stimulating cell survival and stem cell self-renewal. Different mechanisms may apply, including by serving as a coactivator of the RUNX1–RUNX1T1 oncogenic fusion transcription factor to reduce dimethylated H3K9 at respective target genes or by cooperating with the HOXA9 transcription factor (40–43). Hitherto, a role for JMJD1A in AML is unknown, but a tumor-promoting function has been described for many solid tumors. This was for the first time in colorectal cancer, where JMJD1A is overexpressed at the mRNA and protein level, and high expression correlated with reduced survival and increased metastasis. Downregulation of JMJD1A in human colorectal cancer cell lines was reported to reduce cell growth *in vitro* and tumor size in xenograft models, impair *in vitro* cell invasion, and suppress metastasis *in vivo*. Moreover, *Jmjd1a*$^{-/-}$ mice were protected from chemically induced colon carcinogenesis. Mechanistically, JMJD1A was shown to bind to the β-catenin oncoprotein and coactivate β-catenin targets such as the *MYC* and *CCND1* oncogenes through reducing dimethylation of H3K9 (34, 44–47). Other potential ways how JMJD1A may facilitate

colorectal tumorigenesis include coactivating the STAT3 transcription factor, which can be activated by IL6 and IL11 and thereby contribute to an inflammatory response furthering cancer formation, and stimulating the expression of the Hippo pathway effector YAP1 (48, 49). Although fewer data are available for JMJD1B and JMJD1C, this also points to a tumor-promoting role of these homologs in the colon and rectum and they may perform overlapping functions with JMJD1A, indicating potential redundancy (34, 50). Bioinformatics revealed that the expression of all three *JMJD1* genes is significantly correlated in colorectal adenocarcinomas and many other tumors (Supplementary Table S1). Although the reason for this is unknown, it indicates that high JMJD1A expression is likely concurrent with high JMJD1B/JMJD1C levels in colorectal adenocarcinomas. This implies that simultaneous inhibition of all three JMJD1 proteins is desirable to combat this malignancy.

Both JMJD1A and JMJD1C are capable of interacting with the androgen receptor and thereby promoting androgen-dependent gene transcription (4, 51). JMJD1A mRNA and protein levels are upregulated in human prostate tumors, whereas downregulation of JMJD1A led to reduced prostate cancer cell proliferation, survival, and tumorigenesis in xenografts. This could be due to impaired recruitment of the androgen receptor to and activation of the *MYC* oncogene or due to reduced binding of JMJD1A to the promoter of *SNAIL* that encodes an important epithelial-to-mesenchymal transition factor. Further, JMJD1A-mediated activation of *MYC* and *SNAIL* transcription was associated with H3K9 demethylation (52, 53). Another mechanism by which JMJD1A could promote prostate tumorigenesis involves its interaction with the HNRNPF-splicing factor, which resulted into alternative splicing leading to the generation of the V7 variant of androgen receptor that is one underlying cause of castration resistance of prostate tumors (54). JMJD1B can also stimulate growth of castration-resistant prostate cancer cells, but it apparently does not affect androgen signaling (55). Altogether, JMJD1 proteins have convincingly been shown to be promoters of prostate cancer.

In breast cancer, JMJD1A is overexpressed and was necessary for estrogen receptor function, although it remains unresolved whether these two proteins bind each other. JMJD1A downregulation in breast cancer cells impaired their ability for invasion as well as growth *in vitro* and in xenografts. Thus, JMJD1A is predicted to have oncogenic functions in the breast, and this may entail upregulation of the *MYC, JUN*, and *CCND1* oncogenes through reducing H3K9 dimethylation as well as repression of the TP53 tumor suppressor protein. The latter may be due to JMJD1A-mediated reduction of lysine 372 methylation on TP53, a methylation mark known to increase TP53 stability and nuclear localization. However, compelling experiments are lacking to evaluate if JMJD1A brings this about through direct demethylation of TP53 (32, 56–58).

Apart from the above-mentioned carcinomas, a variety of *in vitro* data with cancer cell lines, analysis of mouse models, and/or overexpression in human tumor samples strongly implicated enzymatically active JMJD1A as a tumor promoter in many other cancers, including bladder cancer (59, 60), hepatocellular carcinoma (61, 62), non–small cell lung carcinoma (63), ovarian cancer (33), cervical cancer (64), and pancreatic ductal adenocarcinoma (65). JMJD1A may additionally function to drive Ewing sarcoma development (66) and is required for multiple myeloma cell survival (67). Also, JMJD1C is overexpressed in esophageal cancer and needed for efficient cell proliferation (68), and the same applies for JMJD1B and hepatocellular carcinoma (69). As such, there is a wealth of evidence to suggest that especially JMJD1A performs oncogenic functions in many different cancers through modulation of H3K9 methylation. It is noteworthy that this epigenetic function of JMJD1A and JMJD1C can be regulated through phosphorylation (19, 48, 70), indicating that altered signaling and kinase activities in tumor cells might profoundly affect the oncogenic potential of JMJD1 proteins.

Gain-of-function mutations are often a hallmark of an oncoprotein. Analysis of *JMJD1* gene alterations revealed a low mutation and amplification frequency in most tumor types (Supplementary Fig. S2) and no clustering of mutations was observable in the catalytic center or elsewhere throughout the JMJD1 proteins (Supplementary Fig. S3). This argues that the tumor-driving function of JMJD1 proteins will rarely be linked to mutational events, but more likely associated with upregulation of *JMJD1* transcription or stabilization/activation of JMJD1 proteins. However, this needs further investigation, including the experimental analysis whether any of the observed *JMJD1* mutations lead to a gain of function (or a loss of function in cases where JMJD1 proteins act as tumor suppressors).

## Hypoxia and JMJD1 Activity

One difference between a solid tumor and corresponding normal tissue is that the effective oxygen concentration is mostly lower in tumors. A key oxygen-sensing system that lets tumors cope with hypoxia comprises the hypoxia-inducible factor (HIF), a transcriptional regulator consisting of an $\alpha$ and a $\beta$ subunit. The $\alpha$ subunit is exquisitely sensitive to oxygen as it is stabilized under hypoxia, which leads to the expression of a hypoxia-induced gene-expression program (71). Notably, *JMJD1A* is a hypoxia-inducible gene, and both HIF1$\alpha$ and HIF2$\alpha$ were shown to bind to and activate the *JMJD1A* gene promoter (44, 72). Moreover, JMJD1A bound to HIF1$\alpha$ and functioned as a coactivator to facilitate upregulation of many hypoxia-sensitive genes (44, 60), highlighting how JMJD1A could promote tumorigenesis by furthering the adaptation of tumors to hypoxia. The interaction of JMJD1A with HIF1$\alpha$ also establishes a feed-forward loop whereby JMJD1A autoregulates its own expression under hypoxia. Accordingly, hypoxia may (partially) account for the upregulation of JMJD1A expression observed in many human tumors. No corresponding reports have been published to assess if *JMJD1B* and *JMJD1C* transcription is also regulated by HIF.

Hypoxia may also temper JMJD1A activity. This is due to the fact that oxygen is an essential cofactor for its catalytic activity (see **Fig. 1A**) and the corresponding Michaelis–Menten constant is quite high with 7.6% $O_2$ (73). Given that the oxygen concentration is approximately between 0.5% and 2% in tumors versus 4% to 10% in normal tissue, this can lead to a substantial reduction of JMJD1A catalytic activity within the hypoxic environment of a tumor (Supplementary Fig. S4). More investigations are needed to define the actual impact of tumor hypoxia on the *in vivo* catalytic activity of JMJD1A or its homologs and how this influences tumor initiation and progression.

## JMJD1 Modulation by (Onco) metabolites

Another essential cofactor of JMJD1 proteins is 2-oxoglutarate, which is an integral part of the tricarboxylic acid cycle (**Fig. 4**). Therefore, its intracellular concentration will vary depending on the supply of nutrients and along which metabolic pathways a cell proceeds, which can also be influenced by oxygen availability. Cancer cells present with a myriad of changes in metabolism, one of which is aerobic glycolysis that can potentially reduce 2-oxoglutarate levels by blocking the utilization of pyruvate to generate acetyl-CoA, which is required to replenish the tricarboxylic acid cycle by producing citrate.

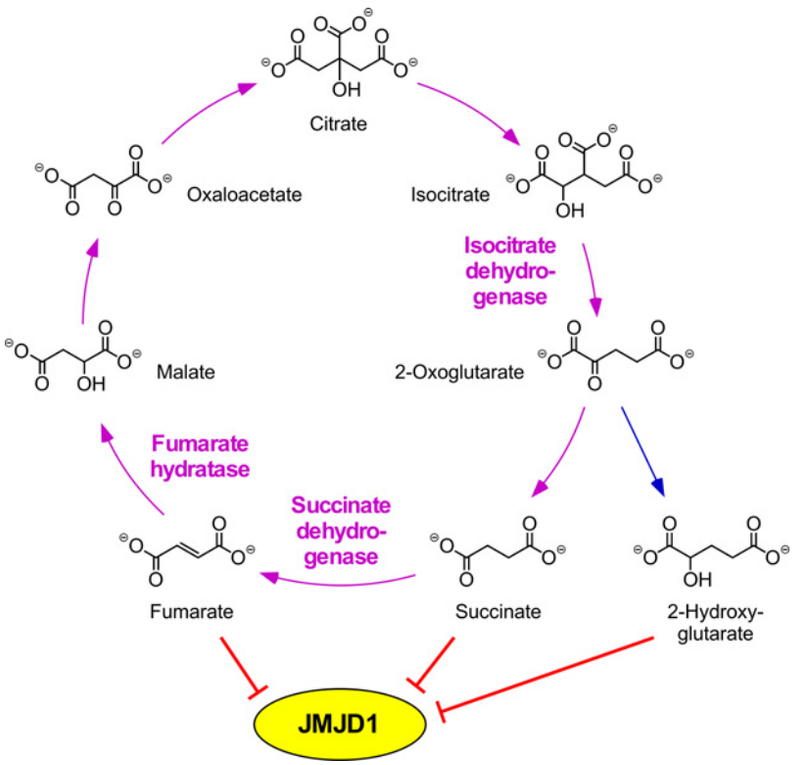


**Figure 4.**
Inhibition of JMJD1 proteins by oncometabolites. Shown are the tricarboxylic acid cycle and the production of the oncometabolites succinate, fumarate, and 2-hydroxyglutarate that may inhibit catalytic activity of JMJD1 proteins. Loss-of-function mutations in succinate dehydrogenase and fumarate hydratase lead to the accumulation of fumarate and succinate, whereas neomorphic gain-of-function mutations in isocitrate dehydrogenase cause the reduction of 2-oxoglutarate into 2-hydroxyglutarate.

But this could be counterbalanced by increased glutaminolysis, which can produce 2-oxoglutarate and is often enhanced in cancer cells. Interestingly, there is some evidence that 2-oxoglutarate could function as an anticancer agent (74). Not only JMJD1 proteins but many more enzymes, including other JMJD proteins or the epigenetic TET proteins involved in DNA demethylation, are dependent on 2-oxoglutarate. Hence, altering 2-oxoglutarate levels would not be a specific means to modulate JMJD1 enzymatic activity, and increased JMJD1 catalytic activity may counteract a potential anticancer effect of 2-oxoglutarate in many carcinomas where JMJD1 proteins exert protumorigenic functions.

Succinate is a byproduct of JMJD1 catalytic activity (see **Fig. 1A**) and it functions as a competitive end product inhibitor. Likewise, fumarate competes with 2-oxoglutarate in the catalytic center of many 2-oxoglutarate–dependent enzymes and thereby inhibits their activity. Thus, loss-of-function mutations in either succinate dehydrogenase or fumarate hydratase will result into accumulation of succinate or fumarate (**Fig. 4**), and such mutations have been observed in a wide variety of tumors, including paraganglioma, pheochromocytoma, neuroblastoma, renal cell carcinoma, thyroid cancer, and gastrointestinal stromal tumors. Succinate and fumarate have been labeled as oncometabolites, because their abnormally high levels drive tumorigenesis (75). Neomorphic mutations in isocitrate dehydrogenase have been observed in low-grade glioma, glioblastoma, cholangiocarcinoma, chondrosarcoma, and AML and lead to the production of another oncometabolite, 2-hydroxyglutarate (**Fig. 4**), which can also compete with 2-oxoglutarate in the catalytic center of JMJD proteins (75). Altogether, this indicates that changes in succinate, fumarate, and 2-hydroxyglutarate levels likely alter JMJD1 catalytic activity, but if this is relevant in any tumor type needs to be explored.

## Inactivation through Losing the Grip on Iron

JMJD proteins complex $Fe^{2+}$ within their JmjC domain, and this $Fe^{2+}$ ion is required for their catalytic activity (1). Iron levels are generally elevated within cancer cells (76), suggesting that this may indiscriminately increase JMJD enzymatic activity. However, cancer cells also often present with elevated levels of reactive oxygen species (ROS), which may lead to oxidation of $Fe^{2+}$ to $Fe^{3+}$ (77), thereby potentially decreasing JMJD activity (**Fig. 5**). Furthermore, ascorbate (vitamin C) has been shown to promote the catalytic

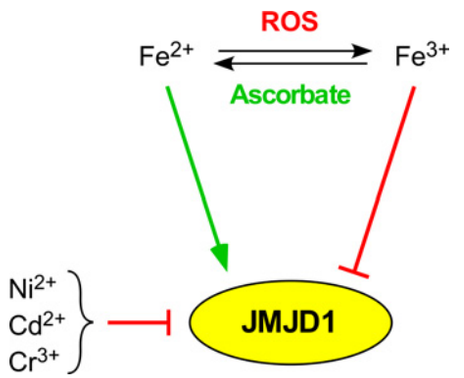


**Figure 5.**
Essential role of $Fe^{2+}$ for JMJD1 catalytic activity. ROS, ascorbate, and heavy metals potentially modulate JMJD1 proteins by influencing their association with $Fe^{2+}$.

activity of many JMJD proteins, including JMJD1A (4), probably by preventing the oxidation of $Fe^{2+}$ through scavenging ROS. Ascorbate has also been suggested to have anticancer activity, and this may in part be by counteracting harmful epigenetic changes induced by dysregulation of JMJD and TET proteins (78). In this regard, ascorbate stimulated JMJD1A/B activity in mouse embryonic fibroblasts and thereby triggered the demethylation of H3K9 (79), establishing that JMJD1 activity can potentially be regulated by ascorbate. However, more data are needed to discern how iron, ROS, and ascorbate levels modulate JMJD1 proteins and whether this impacts tumorigenesis.

$Fe^{2+}$ in JMJD1A can be displaced by $Ni^{2+}$ and this inhibited demethylase activity (80). This suggests that other heavy metals such as cadmium and chromium may also inactivate JMJD1 proteins through displacement of $Fe^{2+}$ (**Fig. 5**). As such, the inactivation of JMJD1 proteins may play a role in heavy metal–induced carcinogenesis and development of other maladies, including hypertension, renal dysfunction, osteoporosis, and mental retardation (81).

## Beyond Epigenetics

Consistent with an epigenetic function through demethylating H3K9, JMJD1 proteins are predominantly localized within the nucleus of many cell lines (4, 37, 82). But a significant cytoplasmic residence, even sometimes chiefly, has also been observed (10, 26, 46). JMJD1 intracellular localization may also be variable, as shown for mouse embryonic fibroblasts or MDA-MB-231 breast cancer cells where JMJD1A became more cytosolic upon growth arrest due to serum starvation or upon reduction of extracellular matrix stiffness, respectively. Moreover, cytoplasmic JMJD1A has been proposed to facilitate rearrangements of the cytoskeleton during spermatogenesis, and this activity may be conducted in cooperation with its interaction partner, the heat shock protein 90 (83, 84). Binding of JMJD1A to the cytoskeleton possibly impacts on actin dynamics and ciliogenesis (85). At the moment, the molecular details how JMJD1 proteins perform nonepigenetic functions within the cytosol are unclear, but this may plausibly involve the demethylation, or hydroxylation, of nonhistone proteins.

Even nuclear JMJD1 proteins may perform functions unrelated to epigenetics. This was demonstrated for JMJD1C, which supported the RAP80–BRCA1-dependent pathway of DNA double-strand break repair via homologous recombination. The mechanism proposed is that JMJD1C induces the demethylation of dimethylated lysine 45 in the DNA-repair factor MDC1, thereby promoting binding of MDC1 to the RNF8 ubiquitin ligase that leads to MDC1 polyubiquitylation and subsequent recruitment of RAP80–BRCA1 (86). This has the caveat that *in vitro* proof demonstrating that MDC1 is indeed a JMJD1C substrate has not yet been provided. In contrast, both *in vitro* and *in vivo* evidence for demethylation of monomethylated lysine 224 in the coactivator PGC-1α by JMJD1A has been furnished (73). Thus, JMJD1A is likely to demethylate and thereby regulate other nonhistone proteins, many of which may perform functions unrelated to epigenetics.

## Conclusion

A multitude of publications have implicated JMJD1A as a driver of tumorigenesis in a variety of different cancers. Less evidence hints at JMJD1B and JMJD1C as potential oncogenic proteins. And there are persuasive data to suggest that JMJD1B is a tumor suppressor, especially in AML, and JMJD1A and JMJD1C may also be tumor suppressive in germ cell tumors. Hence, there seems to be a context-dependent ability of JMJD1 proteins to be pro- or antitumorigenic.

Where JMJD1 proteins are thought to be oncogenic, it opens up obvious avenues of therapeutic intervention, particularly because the activity of JMJD1 proteins is most often dependent on their catalytic activity. In these cases, small-molecule JMJD1 inhibitors should be developed and such inhibitors were already shown to be effective in leukemia cells (87). Because JMJD1 proteins seem to be often co-overexpressed in tumors, a pan-JMJD1 inhibitor might be most effective. However, this may not be when JMJD1 proteins exert opposite activities, such as in AML, where JMJD1B acts like a tumor suppressor whereas JMJD1C exerts pro-oncogenic activities. Here, a JMJD1C-specific inhibitor that does not affect JMJD1B would be needed.

It might be more difficult to therapeutically target JMJD1 proteins in those tumors where they function as tumor suppressors. One way would be through compounds that induce allosteric activation of JMJD1 activity and another way could be through forced overexpression, which is currently more hypothetical than practical. However, there might be an alternative: inhibit the opposing histone methyltransferase(s) with small-molecule drugs to normalize the methylation status of H3K9. This strategy has been shown to be feasible: genetic or pharmacological inhibition of the G9a/EHMT2 methyltransferase reduced H3K9 methylation levels back to normal in *Jmjd1a*$^{-/-}$ germ cell tumors or male gonads. Importantly, this suppressed tumorigenesis or male-to-female sex reversal, respectively, induced by the absence of JMJD1A activity (35, 88).

Although catalytic activity of JMJD1 proteins is required for many aspects of their function, there are instances when this is not essential. For instance, JMJD1A interacts with the SWI/SNF chromatin remodeling complex, and this scaffolding function is not dependent on demethylase activity, yet facilitates induction of gene transcription (70). A similar demethylase-independent scaffolding function has been proposed for the JMJD1A-mediated stabilization of the GLI1 transcription factor (89). Also independent of catalytic activity, JMJD1A may bind to and thereby inhibit the HUWE1 ubiquitin ligase, which could lead to stabilization of one of its clients, the MYC oncoprotein (52). For these reasons, inhibition of JMJD1 catalytic activity will not always disable JMJD1 function, and therefore different strategies to constrain JMJD1 activity (e.g., antisense oligonucleotides, shRNA-loaded nanoparticles) may be needed in some tumors for efficacious therapy.

Three decades have gone by since the first discovery of a JMJD1 protein (90). However, only the realization 15 years ago that these proteins are histone demethylases and epigenetic regulators has sparked a larger interest into these fascinating enzymes. Still, we do not know many mechanisms of action, including the range of enzymatic activities JMJD1 proteins are capable of, nor comprehensively their biological functions in normal and diseased tissues. But sufficient knowledge has been amassed to spur the development of therapies targeting JMJD1 proteins in many malignancies, including major ones such as colorectal, breast, and prostate cancers. Hopefully, such JMJD1-focused therapies will find their way into the clinic in the not too distant future.

### Authors' Disclosures

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