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The small members of the JMJD protein family: enzymatic jewels or jinxes?

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Abstract

Jumonji C domain-containing (JMJD) proteins are mostly epigenetic regulators that demethylate histones. However, a hitherto neglected subfamily of JMJD proteins, evolutionarily distant and characterized by their relatively small molecular weight, exerts different functions by hydroxylating proteins and RNA. Recently, unsuspected proteolytic and tyrosine kinase activities were also ascribed to some of these small JMJD proteins, further increasing their enzymatic versatility. Here, we discuss the ten human small JMJD proteins (HIF1AN, HSPBAP1, JMJD4, JMJD5, JMJD6, JMJD7, JMJD8, RIOX1, RIOX2, TYW5) and their diverse physiological functions. In particular, we focus on the roles of these small JMJD proteins in cancer and other maladies and how they are modulated in diseased cells by an altered metabolic milieu, including hypoxia, reactive oxygen species and oncometabolites. Because small JMJD proteins are enzymes, they are amenable to inhibition by small molecules and may represent novel targets in the therapy of cancer and other diseases.

Keywords

cancer; demethylation; hydroxylation; Jumonji; oncometabolite

1. Introduction

The Jumonji C domain-containing (JMJD) protein family consists of 33 members in humans (Fig. 1 and Table 1). Its defining element is the ~170 amino acids long Jumonji C (JmjC)

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Competing interests statement

The authors declare that there is no conflict of interest.

domain, which contains a signature HX(D/E)X_nH sequence motif capable of complexing Fe^{2+} [1,2]. In addition, the JmjC domain encompasses a 2-oxoglutarate (2OG)/α-ketoglutarate binding site, which is similar to the catalytic domains of other 2OG-dependent oxygenases [3]. The first time catalytic activity was proven for a JmjC domain was in HIF1AN (hypoxia inducible factor 1 subunit alpha inhibitor), showing that it can hydroxylate an asparagine residue [4,5]. Based on this and the known reaction mechanism of AlkB, a 2OG-dependent oxygenase capable of demethylating damaged DNA, it was postulated that JMJD proteins are endowed with the ability to hydroxylate methylated lysine residues and thereby bring about their demethylation [6] (Fig. 2A). And indeed, soon thereafter, histone lysine demethylase activity was demonstrated for a number of JMJD proteins [7,8], triggering the renaming of many JMJD enzymes into KDM (lysine demethylase) proteins.

Mechanistically, demethylation of mono-, di- or trimethylated lysine residues by JMJD proteins entails first the hydroxylation of a methyl group that generates a carbinolamine (Fig. 2A). Oxygen and 2OG are needed as cofactors, and carbon dioxide and succinate are by-products. Carbinolamines are labile and spontaneously release formaldehyde, which results into a demethylated lysine residue (Fig. 2A); since this last reaction step is thought to occur independently of JMJD proteins, these enzymes are, in sensu stricto, not demethylases [9]. Aside from attacking methylated lysine residues, JMJD proteins have been found to hydroxylate asparagine, aspartate, histidine, lysine and arginine residues as well as RNA (Fig. 2B–I). These additional activities all require oxygen and 2OG and proceed via the same mechanism as outlined for the first step of the demethylation reaction in Figure 2A. Further, the catalytic repertoire of JMJD proteins may also extend to arginine demethylation, proteolytic clipping of histones, and tyrosine phosphorylation (Table 2).

Out of the 33 human JMJD proteins, especially those with proven histone lysine demethylase activity have received much attention [1,8,10]. Notably, with the exception of JMJD2D-F, all these histone lysine demethylases (Fig. 1 and Table 1) have a molecular weight in excess of 100 kDa, one reason being the presence of (multiple) domains other than the JmjC one that are involved in chromatin regulation [1]. Likewise, JARID2, although without reported catalytic activity to date, has been extensively analyzed and weighs more than 100 kDa [11]. Here, we will instead focus on an understudied group of JMJD proteins that are evolutionarily separated (Fig. 1), are not – at least most of them – histone lysine demethylases, and are characterized by a molecular weight significantly less than 100 kDa (hence labeled as small JMJD proteins).

2. Small JMJD proteins: a diverse cast of characters

Ten proteins make up the evolutionarily distant group of small JMJD proteins in humans (Fig. 1 and Table 1), whose calculated molecular weights range from 27 to 71 kDa. In the following, we will present current knowledge about these small JMJD proteins, highlighting their diverse functions and emphasizing their potential roles in cancer and other maladies (see Table 2 for a synopsis).

2.1. HIF1AN

The major player in the response to hypoxia is the hypoxia inducible factor (HIF), which is a heterodimer consisting of an alpha and a beta subunit [12,13]. Under normoxia, the alpha subunits are rapidly turned over because of proline hydroxylation mediated by the 2OG-dependent PHD oxygenases. Under hypoxic conditions, the lack of oxygen curtails PHD activity thereby leading to the stabilization of HIF. However, a second hydroxylation event occurs under normoxia on an asparagine residue, which prevents the homologous coactivators and histone acetyltransferases, CBP and p300 [14], from binding to and activating HIF-1α [15]. The corresponding hydroxylase is HIF1AN, which binds to the inhibitory domain of HIF-1α and is capable of hydroxylating N803 in the adjacent C-terminal domain [4,5,16]. Again, hypoxia curtails the catalytic activity of HIF1AN and thereby allows full transcriptional activation of HIF. Given the important roles of oxygen sensing by HIF in development, homeostasis and diseases such as cancer, anemia or ischemic vascular disease [17,18], HIF1AN has been predicted to modulate all these physiological processes. However, HIF1AN knockout mice showed almost no defects in angiogenesis, erythropoiesis and development that are HIF-controlled processes [19], calling into question in how far HIF1AN is at all relevant for the pleiotropic functions assigned to HIF. But this may be species-specific, because downregulation of HIF1AN in zebrafish led to dramatically enhanced ectopic angiogenic sprouting due to overexpression of vascular endothelial growth factor A, suggesting that HIF1AN normally constrains the HIF-dependent transcriptional upregulation of this pro-angiogenic factor and thereby influences angiogenesis [20]. In addition, intracardial injection of shRNA directed against HIF1AN cooperated with downregulation of PHD2 during recovery after myocardial infarction in mice, resulting in improved stem cell mobilization and angiogenesis [21]; this may represent another instance when HIF1AN constrains HIF function and perhaps hints at a role for the HIF1AN-HIF interaction in repair after injury rather than normal development.

HIF-1α and HIF-2α are not the only targets of HIF1AN. It hydroxylates multiple proteins on asparagine residues in their ankyrin repeat domains that mediate protein-protein interactions. These target proteins include IκBα, a negative regulator of the NFκB signaling pathway, members of the Notch signaling pathway (NOTCH1–3), and the poly-ADP-ribosyltransferases, tankyrase-1 and −2 [22]. Furthermore, aspartate and histidine residues within ankyrin repeat domains may also become hydroxylated by HIF1AN [23,24]. While the relevance of those hydroxylation events is currently unresolved, HIF1AN-mediated hydroxylation of N242 within the cytoplasmic ankyrin repeat domain of the ion channel TRPV3 was shown to inhibit its in vitro function [25]. Also, hydroxylation of asparagine residues within the ankyrin repeat domains of the histone methyltransferases G9a/EHMT2 and GLP/EHMT1 reduced their catalytic activity. Accordingly, under hypoxia when HIF1AN activity is suppressed, G9a and GLP became more active and this led to more metastasis of ovarian cancer cells. Hence, HIF1AN inhibition is predicted to aggravate ovarian cancer progression and consistently, low levels of HIF1AN were associated with increased stage and reduced survival of ovarian cancer patients [26]. In contrast, HIF1AN may enhance breast cancer metastasis through asparagine hydroxylation and thereby inhibition of the E3 ubiquitin ligase HACE1 [27], indicating that HIF1AN inhibition may also be beneficial in cancer therapy. This is further supported by xenograft studies

demonstrating that HIF1AN downregulation suppressed and its overexpression enhanced tumor formation by colon adenocarcinoma and melanoma cells. Possibly, this entails a HIF1AN-dependent decrease of the levels of the p53 tumor suppressor [28], but how HIF1AN does so is an open question. Another ankyrin repeat domain containing protein is RIPK4, which can cause β-catenin stabilization and thereby stimulation of the Wnt signaling pathway [29]. Asparagine hydroxylation of RIPK4 by HIF1AN resulted in enhanced β-catenin-dependent transcription, presumably because RIPK4 kinase activity was stimulated [30], and HIF1AN may thereby widely promote neoplasia that β-catenin is known to stimulate [31].

In mice, knockout of HIF1AN led to a hypermetabolic state, characterized by enlarged oxygen consumption and heat production, increased oxidative metabolism, decreased metabolic efficiency in skeletal muscle, hyperventilation and an increased heart rate. Also, HIF1AN knockout mice displayed a reduced body mass, lower blood lipid levels and enhanced insulin sensitivity. Further, they gained less weight and developed less hepatic steatosis when fed a high- fat diet [19,32]. Given that steatosis can eventually develop into liver cirrhosis and cancer [33,34], HIF1AN inhibition may be beneficial as a preventative measure against these liver diseases. Possibly, HIF1AN's impact on metabolism involves asparagine hydroxylation of the deubiquitinase OTUB1 that seems to suppress binding to many proteins related to metabolic processes [35].

Mutations in ANKS6 and INVS can cause nephronophthisis, an autosomal recessive cystic kidney disease. HIF1AN hydroxylates both proteins on asparagine residues and facilitates the formation of protein complexes containing both ANKS6 and INVS. HIF1AN knockdown in Xenopus led to edema and renal tubular shortening, implying that HIF1AN contributes to kidney development through posttranslational modification of ANKS6 and INVS [36]. Nephronophthisis is just one of many ciliopathies [37], implicating that altered HIF1AN activity could contribute to their genesis through modulation of the primary cilia-associated ANKS6 and INVS proteins. In addition, HIF1AN may thereby also affect tumorigenesis, since primary cilia defects are correlated with both pro- and anti-tumor effects [38].

2.2. TYW5

Based on JMJD protein alignments, the closest homolog of HIF1AN is TYW5 (tRNA-yW synthesizing enzyme 5), which also manifests in their highly similar crystal structure [39]. TYW5 binds to $tRNA^{Phe}$, whose guanosine at position 37 is converted through an enzyme cascade into wybutosine or hydroxywybutosine. TYW5 is required for the formation of hydroxywybutosine (Fig. 2I). While it is unknown how the underlying TYW5-mediated hydroxylation affects $tRNA^{Phe}$ function, this expands the role of JMJD proteins to RNA hydroxylases [40,41].

2.3. HSPBAP1

HSPB1 associated protein 1 (HSPBAP1) was identified as an interaction partner of the 27 kDa heat shock protein HSPB1. This interaction appears to suppress the ability of HSPB1 to protect cells from heat shock [42]. Interestingly, HSPBAP1 mRNA levels were found to be

upregulated in the anterior temporal neocortex of patients afflicted with intractable epilepsy, where HSPBAP1 may contribute to disease development by disabling the known neuroprotective function of HSPB1 [43]. Another potential function within the brain may relate to the response to alcohol. In Drosophila, knockout of HSPBAP1 led to slower sedation upon first exposure to low ethanol doses and decreased ethanol tolerance upon repeated exposure [44]. Since we do not know yet of any enzymatic activity of HSPBAP1, it remains unresolved if any of these physiological roles requires HSPBAP1 catalytic activity.

Several reports have linked HSPBAP1 to cancer development. First, a fusion transcript of HSPBAP1 as a consequence of a chromosomal translocation was found in a case of familial renal cell cancer. This fusion transcript is predicted to give rise to a slightly N-terminally truncated HSPBAP1 protein that retains the HSPB1 binding and JmjC domains [45]. Accordingly, dysregulation of expression through placement of a novel promoter upstream of the HSPBAP1 gene rather than an inactivated HSPBAP1 protein may be involved in disease formation. However, functional studies are needed to confirm any function of HSPBAP1 in renal cell cancer, and the same holds true for hepatocellular carcinoma in which HSPBAP1 mRNA is overexpressed [46]. The most convincing relationship of HSPBAP1 with cancer has been found in the prostate. Downregulation of HSPBAP1 in human VCaP prostate cancer cells impaired growth upon androgen deprivation, and HSPBAP1 mRNA and protein are overexpressed in prostate tumors and correlate with worse disease outcome. Mechanistically, HSPBAP1 was shown to coimmunoprecipitate with the androgen receptor, bind to selective androgen- responsive gene promoters and cooperate with the androgen receptor in their activation [47]. While this indicates a nuclear function of HSPBAP1 in promoting prostate cancer, the majority of HSPBAP1 is localized in the cytoplasm [47,48] where it might perform other functions that are (more?) relevant to tumor formation.

2.4. JMJD5

JMJD5 is a mostly nuclear protein that shuttles between the cytoplasm and cell nucleus [49,50]. Varous enzymatic activities have been ascribed to JMJD5: demethylation of H3K36me$_2$ that resulted into the alternate name of KDM8 for JMJD5 [51,52], hydroxylation at the C3 position of arginine residues [53], and proteolysis [54,55]. However, the H3K36me$_2$ demethylation activity has been contested by several laboratories that were unable to reproduce it in vitro and additionally, the crystal structure revealed that the catalytic center of JMJD5 is not conducive to accommodate methylated lysine residues [53,56–59]. Further, the evidence for arginine hydroxylation is weak as this has only been shown with peptide substrates in vitro and no corresponding in vivo evidence provided [53]. Most astonishing was the ability of JMJD5 to act as an endopeptidase that resulted into histone clipping. One group reported that such endoproteolytic activity occurs after monomethylated K4, K9, K27 and K36 on histone H3, with a preference for monomethylated K9 [55], while the second group found histones H2, H3 and H4 as substrates when they were mono- or dimethylated (symmetrically or asymmetrically) on arginine residues [54]. The latter group found an additional exopeptidase activity after the initial endoproteolysis. In support of cleavage after methylated arginine residues, ablation of JMJD5 led to increased H3R2me$_2$ and H4R3me$_2$ levels. Amino acid and structural

alignments revealed similarity of the JMJD5 JmjC domain to cathepsin L-type proteases and additionally a binding pocket for the methylated side chain of an arginine was identified [59]. While the purported JMJD5 lysine demethylase and arginine hydroxylase activities were dependent on 2OG and Fe^{2+}, the role of these cofactors for the peptidase activity is not clear. One report indicated that 2OG had marginal impact on proteolytic activity, while the other showed that mutation of the 2OG binding site within the JmjC domain impaired it [55,59]. Also, although EDTA, a chelator of Fe^{2+} and other metal ions, suppressed catalytic activity, Fe^{2+} may not be the natural divalent ion responsible for JMJD5 proteolytic activity, but rather Zn^{2+} as for other metalloproteinases. And indeed, Fe^{2+}- and Zn^{2+}-loaded JMJD5 displayed the same peptidase activity [59]. Regardless, the likely mechanism for the proteolytic activity predicts that no oxygen is required and 2OG, if it is essential, would not be converted to succinate. A consequence of the potential peptidase activity of JMJD5 could be to produce tailless nucleosomes that may help in transcription elongation by RNA polymerases.

Homozygous JMJD5 knockout mice die around embryonic days 10–11, indicating an essential role of JMJD5 in mammalian development [60,61]. In contrast, JMJD5 knockout in Arabidopsis or Drosophila was not lethal [48,62]. Notably, JMJD5 ablation in Arabidopsis, Drosophila or human U2OS osteosarcoma cells resulted into a short-period circadian phenotype and additionally a reduction in daytime sleep was observed in Drosophila [62,63]. The underlying mechanism may involve the interaction of JMJD5 with cryptochrome 1, a key modulator of circadian rhythm, and subsequent targeting of cryptochrome 1 to the proteasome [64]. This is similar to JMJD5 facilitating the degradation of the NFATC1 transcription factor by promoting its association with the Von Hippel-Lindau tumor suppressor. Interestingly, JMJD5 seems to hydroxylate NFATC1 and catalytic activity of JMJD5 was required for JMJD5 to induce NFATC1 degradation [49]. Albeit the nature of this hydroxylation is unknown, it is tempting to speculate that JMJD5-dependent arginine hydroxylation of NFATC1 is regulating its stability.

Embryonic lethality upon JMJD5 ablation was ameliorated by knockout of the cell cycle inhibitor p21 and even more so by knockout of the p53 tumor suppressor, but respective mouse embryos still died during gestation [60,65]. This can be explained by JMJD5 normally interacting with and inhibiting p53, thereby causing decreased expression of p21, a target gene of p53 [65,66]. Accordingly, JMJD5 bound to the p21 gene promoter and p21 expression in JMJD5 knockout embryos was enhanced [60,61]. Similarly, JMJD5 downregulation in human embryonic stem cells led to p21 upregulation, and p21 shRNA rescued the loss of pluripotency and cell cycle defects caused by JMJD5 shRNA [67]. In human hepatocellular carcinoma cells, JMJD5 also bound to the p21 gene promoter, but JMJD5 downregulation displayed the opposite effect of inhibiting p21 transcription [68]. This suggests that JMJD5 cell type specifically impacts on p21 gene transcription in opposite ways.

Pyruvate kinase M2 (PKM2) is highly expressed in tumor cells and controls the last step of glycolysis. In addition, PKM2 can translocate to the cell nucleus and function as a cofactor for HIF-1α. Thereby, PKM2 is intricately involved in metabolic changes under normoxia and hypoxia [69]. JMJD5 bound to PKM2 and hindered its tetramerization that is required

for cytosolic pyruvate kinase activity, whereas dimerization of PKM2 that is characteristic of its nuclear function was unaffected. Within the cell nucleus, JMJD5 and PKM2 jointly regulated gene transcription in both breast and prostate cancer cells and promoted aerobic glycolysis [70,71]. Another interaction of JMJD5 with the androgen receptor may additionally facilitate prostate tumorigenesis [71]. Consistent with an oncogenic function of JMJD5, it is overexpressed in breast and prostate tumors as well as oral squamous cell carcinomas and promoted growth of respective cancer cell lines [51,61,70–74]. Likewise, JMJD5 shRNA impaired proliferation and invasion of Caco-2 colon cancer cells, and JMJD5 was overexpressed and correlated with lower survival in colorectal cancer patients [75].

On the other hand, JMJD5 expression was downregulated in lung cancer, cholangiocarcinomas and hepatocellular carcinomas [68,76,77]. Further, JMJD5 downregulation led to multipolar spindle formation and spindle assembly defects, and JMJD5 was found to be partially localized to the mitotic spindle [52,78]. Hence, one may imagine that loss of JMJD5 leads to inaccurate mitosis and the development of aneuploidy that is thought to be important for both cancer initiation and evolution [79]. Another potential tumor suppressive role related to DNA repair was revealed in C. elegans and NIH3T3 cells. In C. elegans, feeding with JMJD5 siRNA induced mutations in the germline [80] and genetic ablation of JMJD5 led to hypersensitivity to ionizing radiation and impaired DNA double strand break repair through homologous recombination [81], while JMJD5 downregulation in NIH3T3 cells resulted in defective mismatch repair [82]. Taken together, JMJD5 may context dependently exert pro- or anti-cancer activities.

2.5. JMJD7

Identical to JMJD5, JMJD7 has been identified as a protease that cleaves arginine methylated histones [54,59]. But it is also endowed with the ability to hydroxylate lysine residues at the C3 position [83]. This was shown for DRG1 and 2, two GTPases that have been implicated in ribosome biogenesis [84], and JMJD7 interacted with DRG1\2 in both the cytoplasm and cell nuclei. Hydroxylation of DRG1\2 promoted their binding to RNA, but a corresponding biological relevance has not yet been established. Notably, JMJD7 was present at gene promoters and its promoter occupancy changed upon osteoclast differentiation. Further, JMJD7 downregulation caused more rapid osteoclast differentiation [85], hinting at a role for JMJD7 in bone formation and turnover. JMJD7 downregulation also led to reduced viability of DU145 prostate cancer cells [86] and impaired colony formation in soft agar by MDA-MB-231 breast cancer cells [54], suggesting that JMJD7 may promote cancer development.

The JMJD7 gene is in close proximity to PLA2G4B that encodes a phospholipase. In human head and neck squamous cell carcinoma cell lines and tumor samples, a JMJD7-PLA2G4B read- through transcript has been observed (Fig. 3). Downregulation of this fusion transcript, but not of JMJD7, reduced the proliferation and viability of squamous cell carcinoma cell lines [87]. Given that the JMJD7-PLA2G4B fusion protein does not encompass the full JmjC domain of JMJD7 – predicting absence of any enzymatic activity – but consists of nearly the whole PLA2G4B protein, the functions of JMJD7-PLA2G4B are likely to match those of PLA2G4B. In the same vein, the association of a sequence variant of the JMJD7-

PLA2G4B gene with high-risk autism [88] is unlikely due to dysregulated JMJD7 enzymatic activity.

2.6. RIOX1 and RIOX2

Ribosomal oxygenase (RIOX) 1 and 2 were identified as primarily nucleolar proteins. However, upon serum starvation of MCF7 breast cancer cells, RIOX2 but not RIOX1 dissociated from the nucleolar structures, indicating that the metabolic state of a cell influences RIOX2 localization [89–91]. Consistent with their nucleolar localization, RIOX1 and 2 bind to the 60S ribosomal proteins RPL8 and RPL27A, respectively, and are capable of hydroxylating their interaction partners on specific histidine residues [92,93]. Another activity attributed to RIOX2 is enhancing the recruitment of RNA polymerase I to the rRNA gene promoter and its activation, which was implicated to occur through RIOX2-mediated demethylation of H3K9me$_3$ [94]. Likewise, RIOX1 was reported as capable of demethylating H3K4me$_{3/2/1}$ and H3K36me$_{3/2}$, but not H3K9me$_3$ or H3K27me$_3$ [95]. However, another report was unable to reproduce these histone demethylation activities [92] and the structure of RIOX1\2 can also not easily be reconciled with the use of methylated lysine residues as substrates [93], casting doubt on the reported histone demethylase function of RIOX1\2.

In contrast to RIOX2 that is nearly exclusively a nucleolar protein in growing cells, a significant portion of RIOX1 can be found outside the nucleoli within the nucleoplasm [90]. Accordingly, interactions of RIOX1 with RNA polymerase II connected transcription factors have been observed. This includes complex formation with Osterix, a protein that is crucial for osteoblast differentiation. RIOX1 association with Osterix target genes was inversely correlated with their activation status, suggesting that RIOX1 inhibits Osterix function [95]; the fact that RIOX1 is associated with the polycomb repressive complex 2 [96] may explain how it inhibits Osterix-mediated transcription. Physiologically, RIOX1 downregulation accelerated osteoblast differentiation and maturation in vitro [95]. Consistently, deletion of RIOX1 in mesenchymal cells produced mice with an increased number of preosteoblasts and osteoblasts, a larger skeleton and higher bone mass [97]. On the other hand, overexpression of RIOX1 in mesenchymal cells resulted in mice whose skeletal growth and bone formation were inhibited. This was associated with decreased chondrocyte and osteoblast proliferation and differentiation [98]. Collectively, this indicates an important role for RIOX1 in bone formation.

Genetic models of RIOX2 have implicated this protein as a regulator of the immune system. Transgenic mice overexpressing RIOX2 in lymphocytes displayed decreased levels of interleukin 4 (IL4), an effector cytokine of T helper type 2 (T_H2) cells that also controls their differentiation. Molecular studies revealed that RIOX2 bound to and thereby repressed the IL4 gene promoter [99]. However, there was no altered T_H2 phenotype observable upon differentiation of naïve T cells from RIOX2 knockout mice, which might be due to redundancy provided by RIOX1 [100]. Unexpectedly, IL4 produced in response to house dust mites was less in RIOX2 knockout compared to wild-type mice [101]. These conflicting data about the impact of RIOX2 on IL4 expression could be due to the utilization of different experimental systems or mouse strains. Regardless, RIOX2 knockout mice, which are viable

and fertile, displayed a reduced allergic response in an asthma model [101], while a single-nucleotide polymorphism in the RIOX2 gene was associated with the development of childhood asthma and increased IL4 levels [102]. Moreover, analysis of RIOX2 knockout mice provided evidence that RIOX2 promotes the differentiation of T_H17 cells that are implicated in defending against extracellular pathogens and the development of autoimmune diseases [100]. Together, these data imply that inhibition of RIOX2 might be beneficial in the treatment of asthma and autoimmune diseases.

Many reports have associated RIOX2 with colon cancer, esophageal squamous cell carcinoma, lung cancer, renal cell carcinoma, gastric adenocarcinoma, hepatocellular carcinoma, cholangiocarcinoma, pancreatic cancer or glioblastoma, demonstrating that RIOX2 is overexpressed in tumor specimens compared to normal tissue, that high RIOX2 expression correlates with an adverse prognosis, and/or that RIOX2 downregulation impairs proliferation or survival of cancer cells [103–114]. In part, upregulation of RIOX2 transcription by the MYC oncoprotein [89] may account for the overexpression of RIOX2 in cancer. Less is known about RIOX1 and its role in cancer, although it is also overexpressed in colorectal cancer and associated with increased metastasis. In RKO and HT29 colorectal cancer cells, downregulation of RIOX1 impaired proliferation, survival and migration, while its overexpression in HCT116 cells had the opposite effects [115]. Although unproven, this may involve the reported binding of RIOX1 to the MYC oncoprotein and their joint activation of gene promoters [116]. Altogether, these data strongly suggest that RIOX1 and 2 can stimulate tumorigenesis.

2.7. JMJD4

The only currently known enzymatic activity of JMJD4 is its ability to hydroxylate the eukaryotic release factor 1 (eRF1) on the C4 carbon of its lysine residue 63. A stable interaction between JMJD4 and eRF1 was observed, while catalytically inactive JMJD4 did not noticeably bind to eRF1, suggesting that hydroxylated eRF1 has a high affinity towards its modifying enzyme. Preventing hydroxylation of eRF1 resulted in reduced efficiency of transcriptional termination, but no physiological consequences were examined [117]. Notably, JMJD4 was essentially unaffected in its catalytic activity at 1% oxygen compared to normoxia, implying that JMJD4 is not a biologically relevant oxygen sensor. Further, similar to eRF1, JMJD4 is a predominantly cytoplasmic protein in HEK293T cells [117], which also holds true for Drosophila and human colon cells [48,118].

In human colon adenocarcinomas, JMJD4 protein was overexpressed in respective tumors compared to normal tissue. Further, high JMJD4 mRNA and protein levels were significantly correlated with reduced survival. This suggests, but does not prove, that JMJD4 promotes colon cancer formation. Similar to colon, JMJD4 overexpression was also found in tumors of the liver, but not breast, esophagus, kidney, lung or stomach [118]. Consistent with a potential pro-growth function of JMJD4, its downregulation in mouse NIH3T3 fibroblasts reduced cell proliferation [119]. But contrasting this, there were no obvious growth defects in vivo, since JMJD4 ablation did not affect embryogenesis or postnatal development in mice or Drosophila [48,120]. Altogether, more experimental data are needed to delineate the role of JMJD4 in cell proliferation and cancer.

2.8. JMJD6

JMJD6 was originally cloned as a receptor for phosphatidylserine [121] and hence first named PSR (phosphatidylserine receptor). Phosphatidylserine is displayed on the outer membrane leaflet of apoptotic cells and serves as an engulfment signal to clear out such cells by phagocytosis. However, it was subsequently shown that JMJD6 is a nuclear protein [122,123], which is incompatible with a function as a phosphatidylserine receptor, and later reports further discredited this function of JMJD6 [124]. Rather, JMJD6 displayed various developmental functions. In particular, JMJD6 knockout mice die perinatally, most likely because of lung defects resulting in an inability to breathe; multiple other defects were noted in a mouse strain- specific manner, including severe anemia, thymus atrophy, brain and cardiac malformations, and abnormal eye development [125–128].

In 2007, it was reported that JMJD6 demethylates histone H3 on arginine 2 and histone H4 on arginine 3. Both di- and monomethylated versions of these arginine residues were substrates and the reaction mechanism was proposed to be identical to JMJD-mediated lysine demethylation [129]. Demethylation of H4R3me$_2$ by JMJD6 was likewise shown in another report [130], but JMJD6-mediated histone arginine demethylation was also reported to be not reproducible [131–133]. Additionally, in 2009, JMJD6 was shown to mediate lysine hydroxylation at the C5 position on U2AF65 [134], and crystallographic studies supported such lysine hydroxylation over arginine demethylation [135]. Consistent with a role of U2AF65 in RNA splicing, JMJD6 downregulation affected the alternative splicing of some, but not all tested genes [134]; moreover, JMJD6 cooperated with U2AF65 in splicing of the vascular endothelial growth factor receptor 1, which may explain how JMJD6 facilitates angiogenic sprouting [136]. Subsequently, JMJD6-mediated lysine hydroxylation was also found in histones and the tumor suppressor p53 [133,137,138]. JMJD6 even hydroxylated itself, which may be a prerequisite for establishing intermolecular covalent bonds causing its homo-oligomerization [133]. JMJD6 was also suggested to demethylate arginine residues in non-histone proteins, including estrogen receptorα, heat shock protein HSP70, tumor necrosis factor receptor-associated factor 6, transcription factor STAT1, and the stress granule nucleating protein G3BP1 [139–143]. However, evidence for the direct demethylation of these proteins by JMJD6 is either missing or underwhelming, thereby not ruling out that JMJD6 may indirectly affect their demethylation. Another enzymatic activity of JMJD6 pertains to 7SK snRNA. This small nuclear RNA that is involved in transcription elongation is stabilized by the addition of a methyl group onto the gamma-phosphate at its 5’-end. JMJD6 was capable to remove this methyl cap [130], and the ability of JMJD6 to bind to ssRNA [131] might facilitate this activity. Lastly, JMJD6 has been suggested to be a novel tyrosine kinase that phosphorylates histone H2A.X. Although the JmjC domain was required for tyrosine kinase activity of JMJD6, it was not sufficient and in vitro kinase reactions with JMJD6 did not require 2OG and Fe^{2+}, but rather ATP or GTP [144]. Taken together, these data highlight a plethora of potential catalytic activities, but lingering controversies about JMJD6’s enzymatic spectrum should be resolved through independent corroborative experiments.

Aside from binding to U2AF65, JMJD6 interacts with other factors involved in RNA splicing [145]. It has become clear that JMJD6’s regulation of RNA splicing is one

important mechanism by which it can potentially affect various processes, including angiogenesis, autoimmunity, preeclampsia or melanoma formation [136,146–149]. A second function of JMJD6 is related to its binding and regulation of gene promoters and enhancers, where interaction of JMJD6 with known transcriptional regulators (e.g., BRD4, MED12) facilitates its recruitment [130,150–154]. A provocative recent report [155] hinted at a third function of JMJD6 that relates to its secretion into the extracellular space and binding to collagen type I. No signal peptide is present in JMJD6 and it does not significantly co-purify with exosomes, suggesting that JMJD6 utilizes an unconventional pathway of protein secretion [156]. Further, the binding of JMJD6 to collagen seems to be independent of its catalytic activity. Of note, interruption of this interaction with a monoclonal antibody reduced fibrosis at the primary tumor site and lung metastasis in a mouse mammary tumor model [155].

In general, JMJD6 appears to be a tumor promoter. Overexpression of JMJD6 in various cancers and its correlation with decreased patient survival has been found, and JMJD6 reportedly enhanced tumor cell proliferation in vitro and in xenografts, increased cell invasion and metastasis, and promoted cancer stemness. Thereby, JMJD6 has been implicated in breast cancer, colon tumors, oral squamous cell carcinomas, melanomas, glioblastomas and hepatocellular carcinomas [138,149,151–154,157–159].

2.9. JMJD8

Currently, no enzymatic activity has been reported for JMJD8; in fact, it may not possess any because the JmjC domain of JMJD8 displays a $HXHX_nH$ motif instead of $HX(D/E)X_nH$. Furthermore, JMJD8 is an outlier with regard to the presence of an N-terminal signal peptide. This allows it to translocate to the endoplasmic reticulum, where it can interact with factors involved in protein folding and complex formation. However, upon deletion of this signal peptide, JMJD8 can reside within the cytosol and the cell nucleus [160,161]. Furthermore, an ectopically expressed N-terminal truncation was found at gene promoters and repressed their activity [161]. But there is currently no evidence that an endogenous N-terminal truncation of JMJD8 naturally exists, raising doubts about such JMJD8 nuclear activity.

JMJD8 knockout mice are viable and display no gross phenotype. Yet, the number of capillaries in muscle tissue was reduced, suggesting an angiogenic function of JMJD8. And indeed, JMJD8 became upregulated during in vitro endothelial cell differentiation and stimulated angiogenic sprouting, which could involve JMJD8-dependent increased oxygen consumption and glycolytic capacity [162]. The authors speculated that the latter is due to the regulation of PKM2 by JMJD8, since they found these proteins to interact. However, to detect complex formation with PKM2, a JMJD8 construct with an N-terminal tag, which presumably interferes with the function of the signal peptide and led to (artificial) cytoplasmic localization of JMJD8, was used [162]. Hence, this interaction with PKM2 may not be biologically relevant.

JMJD8 downregulation in DU145 prostate cancer cells led to reduced viability [86] Similarly, JMJD8 downregulation aggravated tumor necrosis factor-induced apoptosis in HEK293T cells [163]. Thus, JMJD8 overexpression may promote cell viability that would

be beneficial to tumor cells. In addition, JMJD8 was shown to be required for invasion of squamous cell carcinoma cells [164], suggesting that JMJD8 stimulates metastasis. Hence, it appears that JMJD8 exerts pro-tumorigenic functions.

3. Regulation of JMJD activity through metabolic cues

Like other oxygenases, small JMJD proteins are dependent on 2OG, oxygen and Fe^{2+} in order to hydroxylate substrates. These cofactors are intricately linked to cellular metabolism, raising the possibility that small JMJD proteins are metabolic sensors. This predicts that their enzymatic activity becomes altered upon neoplastic transformation or development of other pathologies and corresponding changes in metabolism. Further, it is conceivable that these changes in JMJD activity contribute to disease progression.

3.1. 2OG and oncometabolites

The intracellular concentration of 2OG is influenced by many factors. In cancer cells, aerobic glycolysis (Warburg effect) decreases the regeneration of citrate from acetyl-CoA and oxaloacetate within the Krebs cycle [165], which potentially lowers 2OG levels. On the other hand, cancer cells often become addicted to glutamine as a carbon and nitrogen source and for energy production [166], and glutamine – after conversion to glutamate – can replenish 2OG (Fig. 4). Unfortunately, we have no quantitative knowledge (K_m constants) about the dependencyof JMJD activities on 2OG and hence cannot gauge how changes of the 2OG concentration in cancer cells (the degree of which is also mostly unknown) will affect JMJD catalytic activity.

Metabolites can be present at abnormally high levels in cancer cells and thereby potentially contribute to tumor formation. Such oncometabolites include 2-hydroxyglutarate, succinate and fumarate [167,168] that are all related to the Krebs cycle (Fig. 4). There are two enantiomers of 2-hydroxyglutarate. *L*-2-hydroxyglutarate can be produced from 2OG by malate dehydrogenase (MDH), but with a much lower efficiency than conversion of malate into oxaloacetate by this enzyme in the Krebs cycle [169], and high levels of *L*-2-hydroxyglutarate have been associated with renal cell carcinoma [170]. In contrast, *D*-2-hydroxyglutarate generation from 2OG is catalyzed by neomorphic mutants of isocitrate dehydrogenase (IDH) [171,172]. Both enantiomers of 2-hydroxyglutarate are capable of inhibiting 2OG-dependent enzymes, including JMJD proteins, by competing with 2OG for binding to the catalytic center [173,174]. In the same manner, succinate and fumarate repress JMJD catalytic activity [175,176], and enhanced levels of these molecules are observable upon mutation of succinate dehydrogenase (SDH) and fumarate hydratase (FH). Gain-of-function mutations in IDH were discovered in low-grade glioma, glioblastoma, chondrosarcoma, cholangiocarcinoma or acute myeloid leukemia, while loss-of-function mutations in SDH were found in paraganglioma, pheochromocytoma, renal cell carcinoma, thyroid cancer or gastrointestinal stromal tumors, and mutated FH was detected in leiomyomatosis, renal cell cancer, paraganglioma, pheochromocytoma or neuroblastoma [167,168]. Interestingly, mutations in MDH were also found in paraganglioma and pheochromocytoma patients [177,178]. Although it is presently not proven that malate directly inhibits JMJD proteins, malate accumulation upon MDH mutation was accompanied

by elevated fumarate levels, possibly due to end product inhibition of FH. Hence, malate may at least indirectly inhibit JMJD proteins through inducing fumarate accumulation. On the other hand, MDH inactivating mutations should lead to less production of *L*-2-hydroxyglutarate and in that way to less inhibition of JMJD proteins. How these opposing consequences of MDH mutation are integrated into a net effect needs further study. Regardless, mutations in Krebs cycle enzymes can profoundly affect JMJD activity, but in what way this precisely impinges on each of the small JMJD proteins and if this is crucial for the function of oncometabolites are open questions.

3.2. Oxygen and reactive oxygen species

Hydroxylation mediated by JMJD proteins requires oxygen. Accordingly, high oxygen concentrations should lead to increased catalytic activity, while hypoxia – as often observed in tumors – may decrease JMJD activity. And indeed, HIF1AN activity is lessened under hypoxic conditions and can thereby fine-tune HIF function [12,13]. In contrast, JMJD4 appears to be insensitive to hypoxia [117], indicating that not all JMJD proteins will display differences of activity in hypoxia compared to normoxia. Unfortunately, we presently do not know the impact of changing oxygen levels on the enzymatic activity of most of the small JMJD proteins.

Levels of reactive oxygen species (ROS) are in general increased in tumor cells and contribute to various stages of tumorigenesis [179]. It is thought that their action is concentration dependent: at low concentrations, ROS are pro-tumorigenic whereas high concentrations result into cell death and are therefore tumor-suppressive [180]. Notably, many chemotherapeutics are believed to cause elevated ROS levels and thereby kill cancer cells [181]. Within cancer cells, mitochondrial electron transport chain complexes and NADPH oxidases are main sources of ROS, but they may also be imported through diffusion from cancer-associated fibroblasts, endothelial or immune cells [182]. ROS can induce the oxidation of macromolecules and Fe^{2+}, which is predicted to reduce JMJD enzymatic activity. And indeed, peroxide was shown to inhibit HIF1AN and thereby the hydroxylation of several substrates, including HIF-1α. Currently, it is unknown whether this inhibition is caused by oxidation of the catalytic iron center or on crucial amino acids within HIF1AN [183]. Further, ROS seem to target cysteine within RIOX1, although the consequence of this cysteine oxidation remains to be elucidated [184]. Altogether, these data indicate that oxygen and ROS may antagonistically affect the catalytic activity of small JMJD proteins.

3.3. Ascorbate

A positive role of ascorbate (vitamin C) for the activity of hydroxylases has been firmly established ever since it was shown how lack of ascorbate causes scurvy through impaired collagen hydroxylation. Ascorbate has also been described as a cofactor of many JMJD proteins, but its mechanism of action is still not quite understood [185]. It helps to reduce Fe^{3+} to Fe^{2+}, which is a necessary cofactor for the hydroxylase activity of JMJD proteins. Yet, does this occur in solution or within the active catalytic site where uncoupled reaction cycles may lead to the oxidation of Fe^{2+}? Some support for the latter comes from computer modeling, indicating that ascorbate can complex iron within catalytic sites [186], and from the fact that other antioxidants cannot readily replace ascorbate [185,187]. Evidence is

accruing that ascorbate has an anti- cancer effect, in part via epigenetic regulators like the KDM group of JMJD proteins or via the PHD/HIF1AN-HIF axis [187,188]. While ascorbate is predicted to impact on the small JMJD proteins and their hydroxylation activities, in how far that is related to cancer development is in need of future studies.

3.4. Iron and other heavy metals

Fe^{2+} is present in the catalytic center of JMJD proteins and required for their hydroxylation activity. Accordingly, changes in Fe^{2+} should influence JMJD function, but in vivo evidence is acutely missing. Cancer cells are in high demand of iron and in general display elevated iron levels. Further, some studies link increased iron levels to enhanced tumorigenesis in humans [189,190]. In part, iron's pro-tumorigenic role could be explained by increasing the levels of damaging and mutation-inducing hydroxyl radicals through the Fenton reaction. On the other hand, too much iron can also kill cancer cells through ferroptosis, an iron-dependent, non- apoptotic regulated cell death pathway that is triggered through excessive lipid peroxidation [191]. Lastly, high iron levels may dampen the repressive effect of 2-hydroxyglutarate on JMJD proteins, since $Fe^{2+/3+}$ ions, in conjunction with reducing agents such as ascorbate or glutathione, are capable of oxidizing both *D*- and *L*-2-hydroxyglutarate to 2OG [192].

Several heavy metals, including arsenic, cadmium, chromium and nickel, are carcinogenic and also induce other pathologies like allergies, hypertension, pulmonary disease, renal dysfunction, diabetes, paralysis, osteoporosis, ulcer formation and mental retardation [193,194]. A major mechanism by which heavy metals induce these diseases is increased oxidative stress, and this may lead to ROS-mediated inactivation of small JMJD proteins as discussed above. Yet, heavy metals may also act by competing with Fe^{2+} for binding to the catalytic center of JMJD proteins. And indeed, some JMJD lysine demethylases were shown to be inhibited upon replacement of Fe^{2+} by Ni^{2+} [195,196]. This suggests that also other heavy metals are capable of replacing Fe^{2+} in the catalytic center and thereby cause inactivation of the small JMJD proteins. Whether this is important for heavy metal-induced diseases remains to be examined.

4. Conclusion

The small JMJD proteins are reportedly localized to the cytoplasm, nucleoplasm, nucleoli, endoplasmic reticulum and extracellular space where they perform various, sometimes essential functions. They are evolutionarily separated from the >100 kDa JMJD proteins, which is reflected in their different enzymatic activities. While the large JMJD proteins are mostly histone demethylases and thus epigenetic regulators, the small JMJD proteins mainly hydroxylate various amino acid residues and evidence for their histone demethylase activity is highly controversial. In addition, proteolytic (JMJD5 and JMJD7) and, perhaps more mind-bogglingly, tyrosine kinase activity (JMJD6) has been reported, setting the small JMJD proteins further apart from the other JMJD family members. However, more rigorous and systematic investigations are needed to resolve the true enzymatic capacities of the small JMJD proteins. Also in need of study is how the metabolic milieu affects their function and in that way the biology of normal and diseased cells. Specifically, sensitivity to hypoxia,

ROS, carcinogenic heavy metals and oncometabolites could result into altered enzymatic activity of the small JMJD proteins during tumor initiation and progression, which may be an underlying mechanism by which small JMJD proteins modulate tumor formation.

Indeed, cell culture and xenograft studies provided strong evidence that small JMJD proteins are affecting cancer cell function. They can promote tumorigenesis, and hence their overexpression or stimulation of their enzymatic activity may represent a jinx in many cancers. But not always, since context-dependent tumor suppressive functions have also been implicated for HIF1AN and JMJD5. More in vitro and in vivo investigations are needed to uncover cancer- related roles and mechanisms of action. In particular, transgenic and knockout mouse models would be instrumental to decipher the biological functions of the small JMJD proteins in relevant tumor models. Further, development of specific JMJD inhibitors should help in this pursuit. In fact, since the small JMJD proteins are enzymes, small molecule inhibitors could be developed to ameliorate cancer therapy. And the utility of such inhibitors will not be limited to controlling malignancies; for instance, inhibition of HIF1AN or RIOX2 may also be useful to treat metabolic syndrome or asthma, respectively.

In summary, the small JMJD proteins are involved in a myriad of physiological processes related to development, homeostasis and disease that highlights their wide-ranging biological importance. Yet there remain a lot of unanswered questions about the small JMJD proteins, but we predict that intensified research in the coming years will reveal sparkling new features of these enzymatic jewels especially within the cancer research arena.

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Abbreviations

FH	fumarate hydratase
HIF	hypoxia inducible factor
HIF1AN	hypoxia inducible factor 1 subunit alpha inhibitor
HSPBAP1	HSPB1 associated protein 1
IDH	isocitrate dehydrogenase
IL4	interleukin 4
JmjC	Jumonji C
JMJD	Jumonji C domain-containing
KDM	lysine demethylase
MDH	malate dehydrogenase

2OG	2-oxoglutarate
PKM2	pyruvate kinase M2
PSR	phosphatidylserine receptor
RIOX	ribosomal oxygenase
ROS	reactive oxygen species
SDH	succinate dehydrogenase
T_H2	T helper type 2
TYW5	tRNA-yW synthesizing enzyme 5

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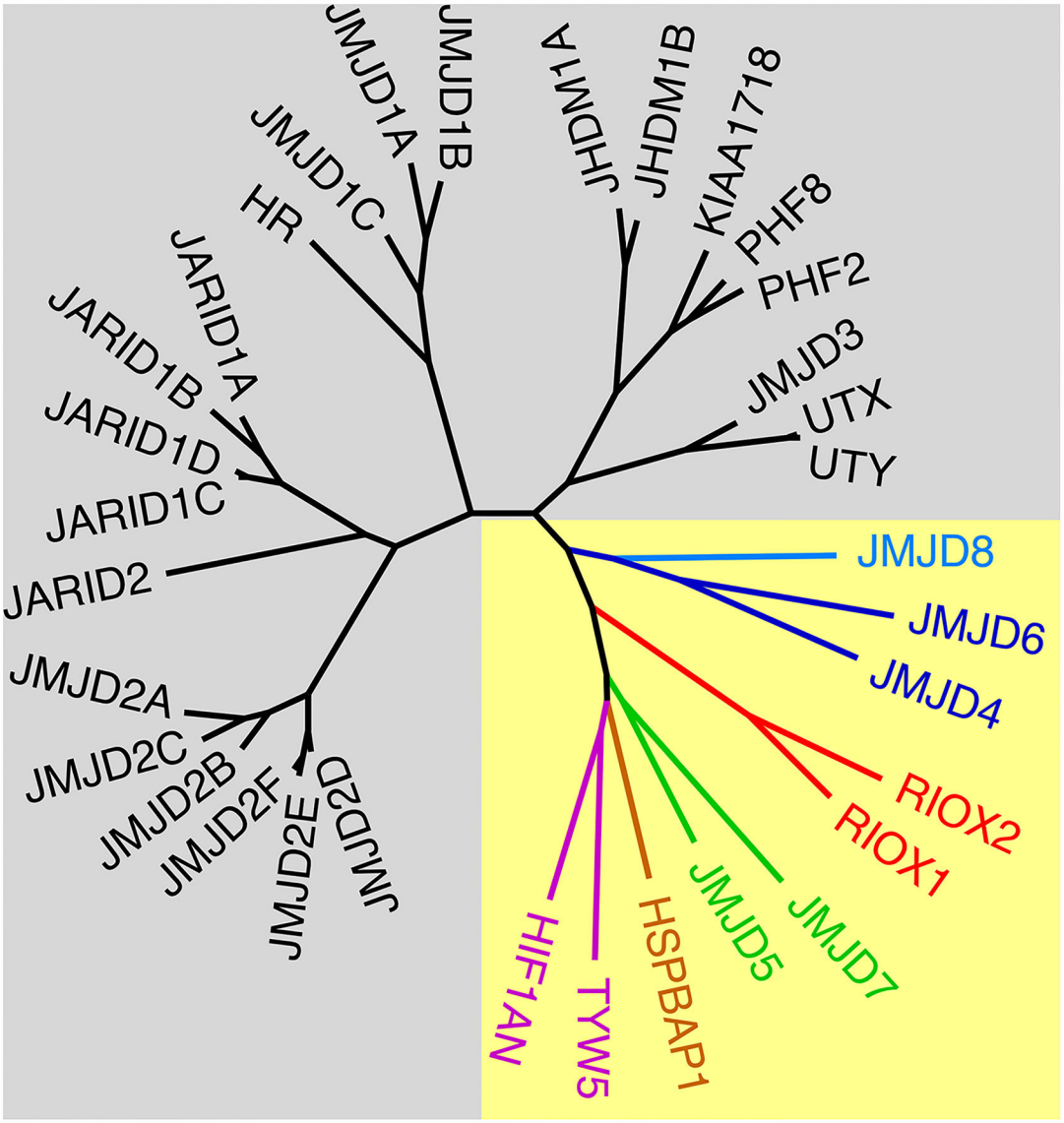

Fig. 1.

Phylogenetic relationship amongst the 33 human JMJD proteins. Whole protein sequences (see Table 1) were aligned with the Clustal Omega algorithm and a phylogenetic tree generated with PhyML, using the JTT amino acid substitution model as implemented in SeaView version 4 [197]. The yellow quadrant highlights the evolutionarily separated small JMJD proteins. All other proteins marked in black color have a calculated molecular weight in excess of 100 kDa (except for JMJD2D-F), have been reported to demethylate histone lysine residues (except for JARID2 and JMJD2F), and are not discussed in this review.

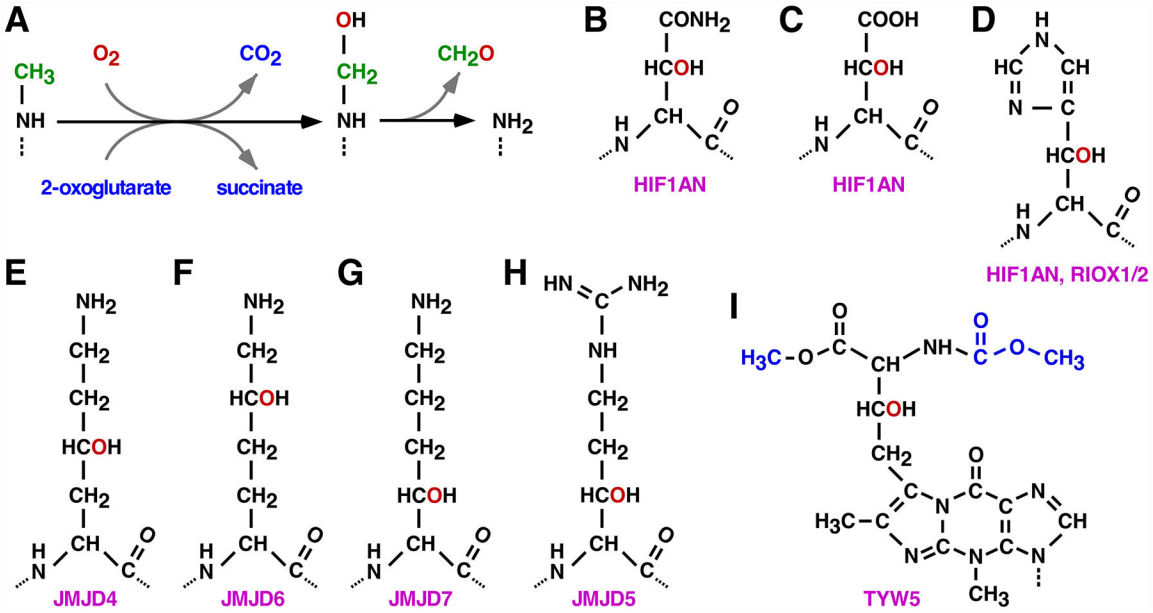

Fig. 2.

Oxygen- and 2OG-dependent catalytic activities displayed by JMJD proteins. (**A**) Demethylation of a monomethylated lysine residue. The first step is the hydroxylation of the methyl moiety, leading to a labile carbinolamine that spontaneously releases formaldehyde. Di- and trimethylated lysine residues are also utilized as substrates by several JMJD proteins. (**B, C**) Hydroxylation of an asparagine or aspartate residue by HIF1AN. (**D**) Hydroxylated histidine residue as a consequence of HIF1AN or RIOX1\2 catalytic activity. (**E-G**) Hydroxylation of lysine at the C4, C5 or C3 position by JMJD4, JMJD6 or JMJD7, respectively. (**H**) JMJD5- mediated hydroxylation at the C3 position of an arginine residue. (**I**) Hydroxywybutosine. Please note that TYW5 hydroxylates a precursor of wybutosine, after which TYW4 catalyzes the addition of further modifications (marked in blue color). In all panels, red color highlights the oxygen added upon JMJD catalytic activity.

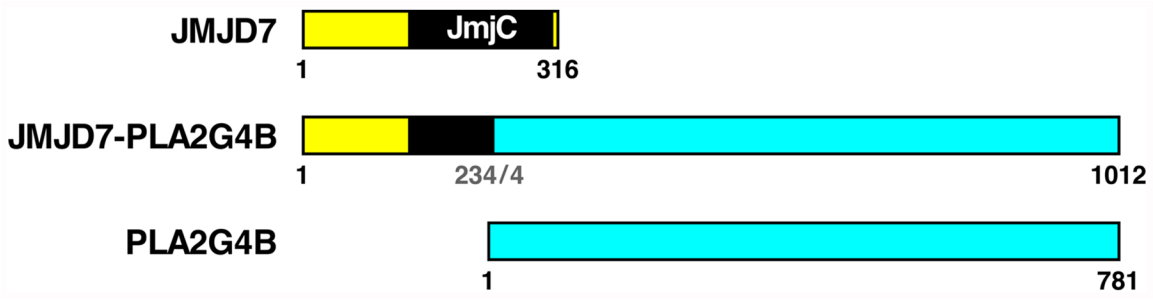

Fig. 3.

The human JMJD7-PLA2G4B fusion protein that is composed of JMJD7 amino acids 1–234 and PLA2G4B amino acids 4–781. Protein sequences for JMJD7 (NP_001108104.1), JMJD7-PLA2G4B (NP_005081.1) and PLA2G4B (NP_001108105.1) were derived from NCBI.

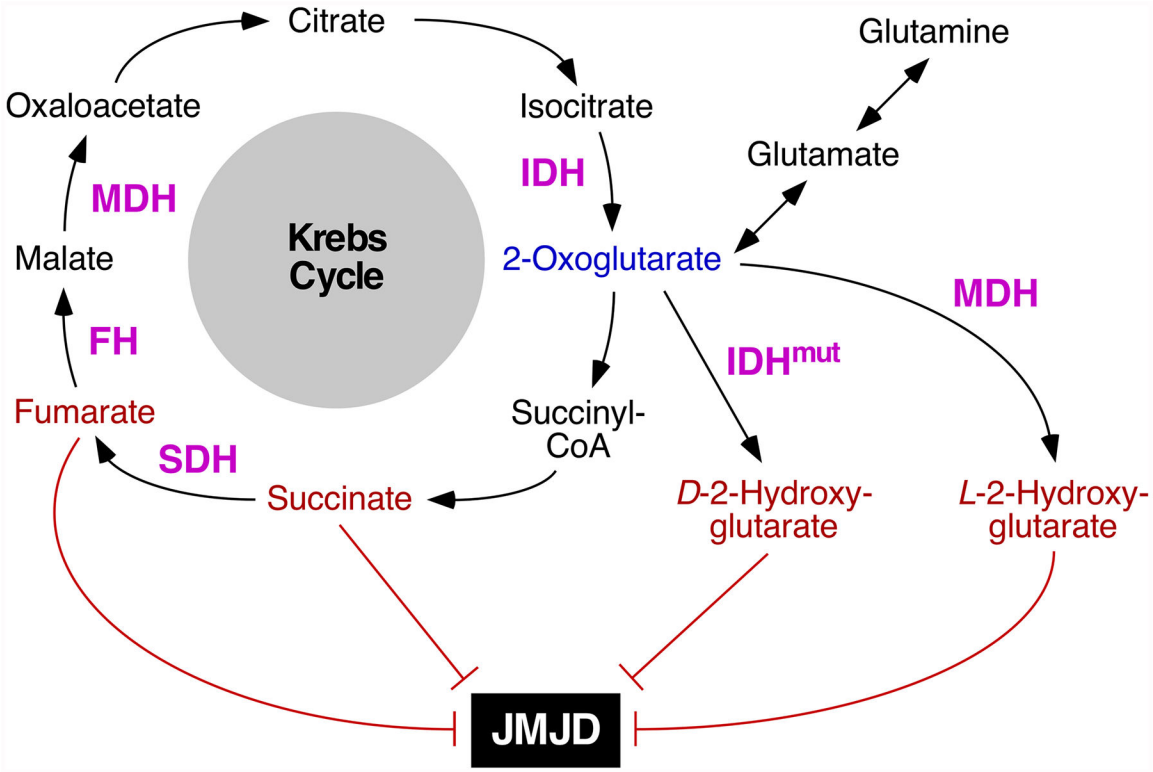

Fig. 4.

Oncometabolites (fumarate, succinate, 2-hydroxyglutarate) and their negative impact on 2OG-dependent activities of JMJD proteins. Inactivating mutations of the Krebs cycle enzymes SDH, FH and MDH have been found in various tumors; likewise, neomorphic mutants of IDH (IDH^{mut}) have been associated with cancer.

Table 1.

The 33 human JMJD proteins shown in Figure 1. The 10 small JMJD proteins discussed in this review are highlighted by boldface. The utilized protein sequences were derived from the indicated NCBI entries. Please note that due to alternative splicing or utilization of alternate start codons, many protein isoforms with a mostly shorter amino acid length exist. Since JMJD2F is currently listed only as a pseudogene (NCBI accession NG_012275.2), the encoded longest open reading frame comprising of 638 amino acids was used for phylogenetic analyses.

Protein	Alternate Name(s)	NCBI Accession Number	Amino Acids
HIF1AN	FIH-1, FIH	NP_060372.2	349
HSPBAP1	PASS1	NP_078886.2	488
JMJD4		NP_075383.2	463
JMJD5	FLJ13798, KDM8	NP_001138820.1	454
JMJD6	PSR, PTDSR	NP_001074930.1	414
JMJD7		NP_001108104.1	316
JMJD8		NP_001005920.3	264
RIOX1	NO66, JMJD9	NP_078920.2	641
RIOX2	MINA, MINA53, NO52, JMJD10	NP_694822.2	465
TYW5	C2orf60	NP_001034782.1	315
HR		NP_005135.2	1189
JARID1A	RBP2, KDM5A	NP_001036068.1	1690
JARID1B	PLU-1, KDM5B	NP_001300971.1	1580
JARID1C	SMCX, KDM5C	NP_004178.2	1560
JARID1D	SMCY, KDM5D	NP_001140177.1	1570
JARID2	JMJ	NP_004964.2	1246
JHDM1A	FBXL11, KDM2A	NP_036440.1	1162
JHDM1B	FBXL10, KDM2B	NP_115979.3	1336
JMJD1A	TSGA, JHDM2A, KDM3A	NP_060903.2	1321
JMJD1B	5qNCA, JHDM2B, KDM3B	NP_057688.3	1761
JMJD1C	TRIP8, JHDM2C, KDM3C	NP_116165.1	2540
JMJD2A	JHDM3A, KDM4A	NP_055478.2	1064
JMJD2B	JHDM3B, KDM4B	NP_055830.1	1096
JMJD2C	GASC1, JHDM3C, KDM4C	NP_055876.2	1056
JMJD2D	JHDM3D, KDM4D	NP_060509.2	523
JMJD2E	KDM4E	NP_001155102.1	506
JMJD2F	KDM4F	-	638
JMJD3	KDM6B	NP_001073893.1	1682
KIAA1718	KDM7A	NP_085150.1	941
PHF2	KDM7C	NP_005383.3	1096
PHF8	KDM7B	NP_001171825.1	1060
UTX	KDM6A	NP_001278344.1	1453

Protein	Alternate Name(s)	NCBI Accession Number	Amino Acids
UTY	KDM6C	NP_001245178.1	1444

Table 2.

Synopsis of enzymatic activities and suspected roles in disease for the ten human small JMJD proteins. Disputed enzymatic activities are highlighted in red color. As a further cautionary note, many other listed enzymatic activities have been reported by just one research group and thus await independent confirmation.

	Enzymatic Activity	Role in Cancer	Role in Other Diseases
HIF1AN	- Hydroxylation of asparagine, aspartate and histidine	Pro cancer: breast cancer, colon adenocarcinoma, melanoma Anti cancer: ovarian cancer	- Hepatic steatosis - Nephronophthisis
HSPBAP1	- unknown	Pro cancer: hepatocellular carcinoma, prostate cancer, renal cell cancer	- Epilepsy
JMJD4	- C4 lysine hydroxylation	Pro cancer: colon adenocarcinoma, liver cancer	
JMJD5	- H3K36me$_2$ demethylation - C3 arginine hydroxylation - Endo-/exopeptidase at arginine-methylated and endopeptidase at lysine- methylated histones	Pro cancer: breast cancer, colorectal cancer, oral squamous cell carcinoma, prostate cancer Anti cancer: cholangiocarcinoma, hepatocellular carcinoma, lung cancer	
JMJD6	- H3R2me$_{2/1}$ and H4R3me$_{2/1}$ demethylation - Arginine demethylation in non-histone proteins - Removal of methyl cap on 7SK snRNA - C5 lysine hydroxylation - H2A.X tyrosine kinase	Pro cancer: breast cancer, colon cancer, glioblastoma, hepatocellular carcinoma, melanoma, oral squamous cell carcinoma	- Autoimmunity - Preeclampsia
JMJD7	- C3 lysine hydroxylation - Endo-/exopeptidase targeting arginine-methylated histones	Pro cancer: breast cancer, prostate cancer	
JMJD8	- unknown	Pro cancer: prostate cancer, squamous cell carcinoma	
RIOX1	- H3K4me$_{3/2/1}$ and H3K36me$_{3/2}$ demethylation - Histidine hydroxylation	Pro cancer: colorectal cancer	
RIOX2	- H3K9me$_3$ demethylation - Histidine hydroxylation	Pro cancer: cholangiocarcinoma, colon cancer, esophageal squamous cell carcinoma, gastric adenocarcinoma, glioblastoma, hepatocellular carcinoma, lung cancer, pancreatic cancer, renal cell carcinoma	- Asthma
TYW5	- tRNA^{Phe} hydroxylation		