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Histone demethylases in physiology and cancer: A tale of two enzymes, JMJD3 and UTX

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Abstract

Gene regulation is fine-tuned by a dynamic balance between transcriptionally activating and repressive modifications of histone tails. It has been well-established that lysine and arginine methylation can be reversed by two groups of evolutionarily conserved enzymes known as histone demethylases, which have been shown to play critical roles in development, differentiation and diseases like cancer. Recent work has demonstrated demethylase-independent functions of these proteins, highlighting the complex mechanisms by which these proteins exert their effects on gene expression. Here we discuss the roles of lysine 27 demethylases, JMJD3 and UTX, in cancer and potential therapeutic avenues targeting these enzymes. Despite a high degree of sequence similarity in the catalytic domain between JMJD3 and UTX, numerous studies revealed surprisingly contrasting roles in cellular reprogramming and cancer, particularly leukemia. Understanding the demethylase-dependent and – independent functions of the enzymes affecting histone methylation, their posttranslational modifications and participation in different complexes as well as in vivo modeling of the mutations affecting those enzymes in cancer can shed light on their unique physiological roles. This information cumulated in the future will aid in the development of improved inhibitors to treat cancers affected by demethylase mutations and aberrant gene activation.

Introduction

The N-terminal tail of histones[1,2] can be post-translationally modified in numerous ways, including acetylation[3] and methylation[4]. The outcome of methylation is a context-dependent modification. For example, methylation of histone H3 lysines 27 (H3K27me2/3) [5,6] and 9 (H3K9me3)[7] are hallmarks of silenced chromatin. In contrast, methylation of lysine 4 on histone 3 (H3K4me3) is an activating histone mark[8,9] and methylation of

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H3K79[10] or H3K36[11] regulates transcriptional elongation. Moreover co-existence of activating and repressive histone marks is found on the control elements of bivalent promoters (see Box 1), which contain both H3K4me3 and H3K27me3[12,13], like the *Homeotic (HOX)* locus. These genes exist in a poised intermediate state in embryonic stem (ES) cells and resolve to become activated (mixed-lineage leukemia (MLL)/Trithorax-associated H3K4me3-enriched, Box 1) or repressed (Polycomb-associated H3K27me3-enriched, Box 1) during differentiation[14–16]. As the expression levels of genes like *Hox* are stable over long periods of time[17–19], it was initially thought that methylation marks were only passively removed through cell division, leading to dilution of their nucleosomal concentration. Despite this notion, two families of demethylases have been identified since 2004, encompassing different mechanisms to remove methylation marks. Biology of those enzymes is more complex than initially thought as they participate in protein complexes implicated in different stages of gene transcription and they play multifaceted roles in physiology and diseases, like cancer. These aspects of demethylase biology have started being characterized over the last 3–4 years and are discussed in this review using lysine 27 demethylases as a proof-of-principle.

The discovery and functions of histone demethylases

In the early 2000s, it was suggested by the Kouzarides group that oxidases can act as demethylases[20] based on published experimental evidence[21–23] and, in 2004, LSD1[24] (also known as KDM1 or AOF)[25] was characterized as the first histone demethylase for H3K4me1/2 and later as a H3K9me1/2 demethylase. LSD1/2 proteins comprise one family of FAD-dependent amine oxidases that exclusively demethylate mono- and di-methylated lysine residues. LSDs are part of co-repressor complexes and play important roles in cancer[26]. The demethylase field rapidly expanded with the identification of the Jumonji family of Fe(II)- and 2-oxoglutarate(2OG)-dependent dioxygenases that demethylate trimethylated lysine residues in addition to mono and di-methyl groups[11,27–29].

There are 30 proteins containing the Jumonji C (JmjC) catalytic domain, and 18 of them have known histone demethylase activity (for an extensive overview see Kooistra and Helin, 2012[30]). The two H3K27me3 demethylases[31], UTX (or KDM6A) and JMJD3 (or KDM6B), were discovered in 2007[32–37] (Fig. 1A). *UTX* escapes X chromosome inactivation and is ubiquitously expressed, whereas *JMJD3* is inducibly expressed upon inflammation, viral and oncogenic stimuli[33,38–40]. UTX consists of 1401 amino acids and contains the JmjC catalytic domain and 6 protein interaction-mediating tetratricopeptide repeat (TPR) domains[37]. JMJD3 consists of 1679 amino acids, but does not contain any characterized domains other than the JmjC domain[41]. Of note, JMJD3 and UTX have 84% sequence similarity in the JmjC domain[37]. The *UTX* paralog, *UTY* (Fig. 1A), is located on the Y chromosome and partially compensates for UTX functions, as it was demonstrated using knockout mouse models[42]. UTY, once considered enzymatically inactive[34], demonstrates minimal demethylase activity [43] due to a mutation in the JmjC catalytic domain.

In vitro and *in vivo* studies showed that both demethylases are critical for development and differentiation[33,42,44–57]. JMJD3 was initially discovered to control H3K27me3 in

macrophage trans-differentiation in response to inflammatory stimuli[33,44] (Fig. 1B). JMJD3 also contributes to cellular differentiation through Smad2/3-mediated regulation of the *Brachyury* locus, and to neural differentiation via activation of *Pax6* and *Sox1*[45–47]. Moreover, JMJD3 activates genes important for epidermal differentiation and wound healing during skin repair[48,49]. UTX promotes myogenesis through activation of *myogenin* and *creatine kinase* genes[50]. Germline homozygous loss of *Jmjd3* in mice results in perinatal death due to respiratory defects, despite intact hematopoiesis[46,51,52] (Table 1). *Utx*-deficient males were smaller in size and born at reduced ratios [42,53,54],[55], in concert with the documented role of *Utx1* in the control of the *Hox* locus and control of body posterior development in animals[34]. Female homozygous *Utx* knockout mice die before birth between days E11.5 and E13.5[42,53,54]. At E9.5–10.5, homozygous *Utx*-deleted females and compound *Utx/Uty*-deficient male embryos showed significant growth, neural and cardiac defects, and anemia[42,55] (Table 1). These results show that UTY can partially compensate for UTX, as some UTX functions are demethylase-independent.

Molecular roles of H3K27me3 demethylases: not only demethylation

Initial studies using mouse macrophages[44] showed that a small fraction of *Jmjd3*-occupied genes exhibited reduced levels of H3K27me. Similar studies of other demethylases[58–60] suggest that histone demethylases play subtle roles in gene expression by maintaining the methylation equilibrium on chromatin to safeguard transcription-accessible chromatin states[30] and potential three-dimensional interactions[61]. Moreover, cumulative evidence supports the importance of nondemethylase activities of JMJD3 and UTX (Fig. 1B). The two enzymes play an architectural role in the T-bet-orchestrated Brg1-containing Switch/Sucrose nonfermentable (Swi/Snf) chromatin remodeling complex (Box 1). Additionally, UTX and the chromatin remodeler BRM control acetylation of lysine 27 (H3K27ac)[62]. Given its significantly reduced enzymatic activity, it would be interesting to study potential roles of UTY in these complexes.

UTX also occupies promoters of the *HOX* cluster, demethylating H3K27 and modulating recruitment of polycomb repressive complex 1 and monoubiquitination of histone H2A[32,34,35]. UTX is part of the mixed-lineage leukemia 3/4 (MLL3/4) complexes responsible for H3K4me3[63], whereas JMJD3 also interacts with the MLL complex proteins WDR5, ASH2L and RBBP5[33]. Chromatin immunoprecipitation coupled to next generation sequencing (ChIP-Seq) for JMJD3 in macrophages confirmed that JMJD3 binding is enriched at H3K4me3 loci[44]. In this way, MLL-demethylase complexes demethylate H3K27 and methylate H3K4 to activate genes. Mass spectrometry and cell physiology analysis showed that JMJD3 contributes to 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced HL-60 (myeloid) cell differentiation[64–67] via interaction with the SPT6 and SPT16 elongation factors as well as KIAA1718 (KDM7A, Fig. 1A), the demethylase for H3K27me1/2 and H3K9me1/2[68]. UTX, in turn, interacts with the transcriptional elongating form of RNA polymerase[69]. Thus, H3K27me3 demethylases control chromatin ubiquitylation, acetylation and remodeling in addition to demethylation. The biological interaction between JMJD3, UTX and KIAA1718 should be further studied in steady-state condition in normal physiology and cancer to better understand the interplay between these three demethylases.

Roles in reprogramming and tumorigenesis

JMJD3 and UTX play opposite roles in reprogramming of somatic cells to induced pluripotent cells. Murine Utx promotes reprogramming through interaction with the transcription factors Oct4 and Nanog[56], whereas JMJD3 inhibits reprogramming through regulation of the Ink/Arf (*Cdkn2a*) locus and PHF20 ubiquitination via (demethylase-independent) recruitment of the Trim26 ubiquitin ligase[57]. Such contrasting roles are also observed in certain malignancies. UTX is a tumor suppressor[39,40,70] and was initially characterized as a repressor of dNotch- and retinoblastoma (dRb)-induced tumors in *Drosophila*[71]. Interaction between RB and UTX was further demonstrated in human cells[72]. UTX is mutated in a number of cancers, including acute lymphoblastic leukemia (ALL)[39,73], chronic myelomonocytic leukemia (CMML)[74], colorectal adenocarcinoma, renal cell carcinoma, multiple myeloma[70] and bladder cancer[75]. Furthermore, UTX is part of the MLL4 complex that is also frequently mutated in cancer[76]. In CMML, UTX mutations co-occurred with ASXL1, TET2, or CBL mutations, and in bladder cancer with somatic BAP1 mutations[75] and enhance *in vitro* proliferation, *in vivo* tumor growth and cell migration[75]. Nevertheless, UTX cannot be perceived solely as a tumor suppressor, as there are documented cases in breast cancer where it might enhance tumor cell proliferation and invasiveness[77].

JMJD3 serves as a tumor suppressor by binding to and activating the INK4A-ARF locus in human diploid fibroblasts[78]. When cells are exposed to oncogenic stress, the locus becomes demethylated and expressed, leading to cell cycle arrest and senescence[79–81]. JMJD3 expression is reduced in cancers, such as lung, liver carcinomas and hematologic malignancies. *JMJD3* is located on chromosome 17 in close proximity to the tumor suppressor *TP53*, and deletions targeting both genes are commonly found in human cancers[82]. Functional interaction between JMJD3 and p53 has also been documented[83,84].

Biological roles of JMJD3 and UTX have best been studied in T cell acute lymphoblastic leukemia (T-ALL). UTX[85] plays a male-specific tumor suppressor role and mutational distribution in this NOTCH1 overexpression-induced disease[40], suggesting that UTX cannot compensate for certain demethylase-dependent activities of UTX. Additionally, most UTX mutations target the JmjC domain of the protein (Fig. 2). In T-ALL, UTX mutations co-occur with aberrant expression of the TLX3 oncogene, activating NOTCH1 mutations, and mutations or deletions targeting the putative chromatin reading factor PHF6[40]. NOTCH1- and UTX-driven tumors are heterogeneous and include early developmental populations. Knockdown or knockout of *Utx* leads to accelerated leukemia development in Notch1-driven mouse models and accumulation of H3K27me3 at the promoters of putative tumor suppressor genes, like Rbbp6 and Fbxw7[39], in contrast to JMJD3, which controls oncogenes[39]. Importantly, loss of UTX increases sensitivity of cancer cells to EZH2 inhibitor 3-DZNep, further emphasizing the clinical importance of H3K27me3[40]. In contrast to its tumor suppressor role in fibroblasts, JMJD3 functions as an oncogene in T-ALL, where it is required for leukemia initiation and maintenance[39]. ChIP studies showed that JMJD3 and UTX have both overlapping and unique targets[34,39]. It is currently unknown what determines this differential target recognition, but the tetratricopeptide

repeats in UTX and/or participation in different complexes might contribute to this unique specificity. Strikingly, there are no documented JMJD3 mutations in leukemia, which further emphasizes that these two demethylases exert different roles, despite the high degree of sequence similarity in their catalytic domains.

Targeting UTX and JMJD3 for inhibition

Due to the role of demethylases in cancer, viral infection, and inflammation, there has been an active effort to identify specific inhibitors for these enzymes (for an in depth review see[86,87]). To date, the only described selective inhibitor of UTX and JMJD3 is GSK-J1, with the cell-active prodrug being the ethyl ester GSK-J4[88]. This inhibitor shows remarkable specificity to UTX and JMJD3, though it also appears to bind with low affinity to JARID1B/C [89]. The mechanism of action of GSK-J4 is chelation of the Fe(II) active site and binding of a propanoic acid side-chain to the 2OG binding site. Inhibition of H3K27me3 demethylases via GSK-J4 reduces Toll-like receptor-mediated proinflammatory cytokine production by human primary macrophages[33]. GSK-J4 reduced the production of herpes simplex virus 1 from its latent state, which is associated with repressive marks[90]. GSK-J4 was also shown to be a potent antitumor drug against pediatric brainstem gliomas harboring the oncogenic K27M mutation of histone H3.3[91]. Treatment of T-ALL cells with GSK-J4 resulted in cell cycle arrest and increased apoptosis[39]. These effects were mediated through the demethylase activity of JMJD3, since H3K27me3 levels were altered and overexpression of catalytically inactive JMJD3 did not rescue the phenotype[39]. Moreover, other potential targets of GSKJ1 (like JARID1B/C)[89] do not seem to be necessary for T-ALL progression (Ntziachristos and Aifantis, unpublished data). As JMJD3 and UTX are not required for the early stages of T cell development (up to double positive (DP, for CD4/CD8) stage)[39,52,92–94], these results might pave the way for targeted therapy in T-ALL though targeting of the JMJD3 demethylase alone or in combination with other oncogenic pathways, like NOTCH1.

There are other inhibitors of 2OG oxygenase enzymes; however, they are not specific and belong to a class of broad-spectrum inhibitors that act on other members of the JmjC domain-containing family. Some of these inhibitors include N-oxalylglycine and catechols[95][96] [95,97–100]. Moreover the 2,2'-bipyridine metal-binding pharmacophore (MBP, Box 1) utilized by GSK-J1 is a very strong metal chelator that interacts with many other metalloproteins, including the Jumonji demethylases JARID1B and JMJD2C[89]. The strength of metal coordination by 2,2'-bipyridine depends on the planar orientation with respect to the Fe²⁺ ion, limiting the flexibility of the MBP for additional chemical modifications. Additional approaches to design selective inhibitors have utilized mimetics of the α -ketoglutarate co-substrate joined to a strong metal chelator. While this strategy has generated relatively potent compounds, these inhibitors do not exhibit sufficient selectivity or synthetic tractability. A persistent obstacle in the development of metalloprotein inhibitors has been the identification of diverse MBPs. Companies are currently using alternative approaches to overcome these issues[101].

Conclusions

Histone demethylases act as fine balancers of gene expression through demethylase-dependent and -independent functions. What determines the balance between demethylase-related and -unrelated functions of JMJD3 and UTX might be pertinent to their relative expression, post-translational modifications and complex formation. Improved tools, including antibodies for the endogenous proteins, are needed to better study the roles of these two enzymes, including delineation of complex formation in pluripotency, differentiation and cancer. Similar studies should be performed to characterize the molecular underpinnings for the other two understudied demethylases KDM7 and UTY. Moreover, the crystal structure of the enzymes and recognition of methyl-lysines, with the exception of UTX[102], have not been resolved. Protein and structural analysis, together with alternative methods of MBP inhibition, will lead to more efficient targeting of demethylases. Currently, GSKJ1 and similar drugs can only be used in preclinical mouse models of leukemia in combination with classic chemotherapy and radiation therapy to evaluate the effects of demethylase inhibition in cancer. Finally, we tend to broadly cluster mutations as loss- or gain-of-function, but mutations might have different effects in cancer progression depending on whether they affect the catalytic or other domains of the demethylases, like UTX. Modeling of the human mutations in mice will help us understand the tumor suppressor roles of UTX.

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*Special Interest

**Outstanding Interest

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- **These papers [39, 40] collectively show that Jmjd3 and Utx play opposite roles in cancer. UTX escapes X-chromosome inactivation and functions as a tumor suppressor in T-ALL. They also show that UTX-driven T-ALL exhibits collateral sensitivity to H3K27me3 inhibition.
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Box 1**Bivalent genes**

Genes containing both the activating H3K4me3 and repressive H3K27me3 mark at their promoters. They are found poised for transcription in embryonic stem cells, and become activated or repressed during differentiation.

Homeotic (HOX) genes

These transcription factors play critical roles in body formation in early development. In ES cells, they exist in a bivalent state, and their activation is regulated through the balance between activating (MLL- associated) H3K4me3 and repressive (PRC- associated) H3K27me3 mark at their promoters.

MLL/Trithorax complexes

In addition to several other proteins, these complexes consist of mixed-lineage leukemia (MLL) methyltransferases responsible for placing the gene activating methyl marks at H3K4. UTX is part of the MLL3/4 complexes, while JMJD3 associates with the common MLL complex proteins WDR5, ASH2L, and RBBP5.

Polycomb repressive complexes (PRC)

There are two classes of these multi-protein complexes: PRC1, which facilitates H2A monoubiquitination, and PRC2, which tri-methylates H3K27 to promote gene silencing. UTX plays a role in the recruitment of PRC1 to H2A.

Chromatin remodeling

In the context of this review, it is the restructuring or repositioning of nucleosomes carried out by SWI/SNF complexes. These complexes contain one of two ATPases, BRG1 or BRM. JMJD3 and UTX associate with BRG1-containing complexes, and UTX also associates with BRM-containing complexes.

Metal-binding pharmacophore (MBP)

A component of the GSK-J1 inhibitor, this metal chelator binds to metalloproteins, including JmjC demethylases.

Fig. 1.

Main enzymes with demethylase activity against lysine 27 methylation and other non-demethylase functions. A) JMJD3 and UTX are the two best-characterized H3K27me3 demethylases. The UTX paralog, UTY, has very weak, albeit detectable, demethylase activity due to a point mutation in the JmjC catalytic domain. KIAA1718 has demethylase activity against multiple lysine residues, including lysine 9 and 27 on histone H3. JmjC: Jumonji C domain, TPR: tetratricopeptide repeats, PHD: plant homeodomain, aa: amino acids. B) Apart from direct histone demethylation, H3K27 demethylases can also participate

in complexes or interact with enzymes that affect histone lysine methylation, chromatin remodeling, transcriptional elongation and protein ubiquitination. Lysine methylation levels can also affect genomic interactions and gene expression programs in a three-dimensional fashion. MLL: mixed-lineage leukemia, SWI/SNF: switch/sucrose non-fermentable, AR: androgen receptor, PRC1: polycomb repressor complex 1, TRIM26: tripartite motif (family) 26, PHF20: plant homeodomain factor 20.

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Fig. 2. Schematic diagram of the protein UTX showing loss-of-function mutations in different cancer types. Red squares denote mutations identified in acute lymphoblastic leukemia, blue circles correspond to bladder cancer mutations, and black triangles denote chronic myelomonocytic leukemia (CMML) cases. del: deletion, fs: frameshift, sj: splice junction, X: stop codon.

Table 1

Animal models and their phenotypes associated with alteration of lysine 27 demethylases

Model Organism	Demethylase	Phenotypes	References
<i>C. elegans</i>	utx-1	Loss results in embryonic lethality, reduced fertility, posterior developmental defects, and aberrant gonad migration and oocyte organization Knockdown in adults leads to increased lifespan and stress resistance	<i>Jin et al, Maures et al, Vandamme et al.</i>
	XJ193 (JMJD3 homolog)	Required for proper gonad development and organization	<i>Agger et al.</i>
<i>Drosophila</i>	dUtx	Required for adult viability and normal salivary gland cell death at larval stage Loss results in architectural defects in testes, rough eyes, wing abnormalities, and homeotic transformation	<i>Copur et al, Denton et al, Herz et al, Tarayrah et al, Zhang et al 2013.</i>
Mouse	Utx	Homozygous loss in females results in embryonic lethality – growth, neuronal, cardiac, and yolk sac defects Inducible knockout in females leads to weight loss, anemia, splenomegaly, and bone marrow dysplasia Deficient males survive to adulthood and are fertile, but are smaller in size and born at reduced frequency Required for proper T cell subset development/differentiation and thymic egress	<i>Dobenecker et al, Lee et al, Manna et al, Shpargel et al 2012, Thieme et al, Wang et al, Welstead et al.</i>
	Jmjd3	Homozygous loss results in perinatal lethality due to respiratory defects Required for osteoblast differentiation, endochondral ossification, neurogenesis, proper T cell subset development, differentiation, and thymic egress, and the regulation of adipogenesis and white fat cell plasticity	<i>Burgold et al, Dobenecker et al, Li et al, Q Li et al, Liu et al, Manna et al, Pan et al, Park et al, Shpargel et al 2014, Zhang et al 2015, F Zhang et al.</i>
Zebrafish	Utx1, Utx2	Required for posterior development and primordial germ cell migration	<i>Lan et al, Thieme et al.</i>

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