Review

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The emerging roles for histone demethylases in the modulation of signaling pathways

Abstract: Since their discovery in 2004, histone demethylases have emerged as key regulators of chromatin. Recent studies have started to reveal the interconnections between histone demethylases and signaling pathways, suggesting that this interplay drives fundamental biological processes. Here, we summarize the different families and subfamilies of histone demethylases and the insights into the biological roles of these enzymes that have been provided by the analysis of mutant animals. We then review recent work linking demethylases and signaling pathways. These studies suggest that demethylase activities are a component of the critical connections that enable environmental signals to modulate the epigenetic landscape of a cell. A greater mechanistic understanding of the network of signals that control chromatin states during normal cellular processes, together with a better understanding of the ways that epigenetic alterations lead to uncontrolled cell proliferation, might help in the design of effective tools for cancer therapy.

Keywords: chromatin; histone demethylation; signaling pathways; transcription.

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Introduction

Each cell within an organism contains the same genetic information; however, only a specific subset of genes is transcribed in a given cell at a given time. This cell/stage-specific transcription is controlled by the coordinated action of signaling pathways, chromatin-associated proteins and transcription factors. Modulation of chromatin through covalent modifications of histones is instrumental for the control of gene expression. In particular, strict regulation of epigenetic modifications is critical for normal development. Furthermore, defects in chromatin organization and gene expression due to aberrant activity of chromatin-modifying enzymes can contribute to diseases such as cancer. Traditionally, epigenetics is defined as a set of stable molecular phenomena that lead to heritable changes in gene expression without any change in the coding capacity of the genetic material (1). Currently, however, many scientists use the term 'epigenetics' to refer to mechanisms that acutely or persisently modify transcription in cells irrespective of cell division (1, 2). This broader definition includes the biology of covalent modifications of histones in post-mitotic cells.

Histones are subject to numerous post-translational modifications, including acetylation, phosphorylation, ubiquitination, methylation and sumoylation. Modifications such as acetylation and phosphorylation alter the charge of histones; methylation, instead, serves as a binding site for factors that recognize specific methyl residues. These chromatin readers mediate the assembly of protein complexes involved in DNA-templated processes, such as transcriptional regulation (3). Histone methylation can poise genes for transcriptional activation or repression depending on the types of proteins that recognize the modification. Histones can be methylated on lysine (K) and arginine residues. The most widely studied methyl marks occur on histone H3 lysines and include K4, K9, K27, K36 and K79. Up to three methyl groups can be added to each lysine, producing a total of four methyl states: unmethylated, monomethylated (me1), dimethylated (me2) or trimethylated (me3). These states exhibit distinct distribution patterns in the genome. For example, trimethylation of lysine 4 of histone H3 (H3K4me3) is frequently found at active promoter regions, whereas H3K4me1 is prevalent at enhancer regions. Modifications such as H3K27me3 and H3K9me3 are frequently mapped to regions where transcription is repressed (4). To add further complexity to the system, modifications are often interdependent, as one mark can either promote or prevent the establishment of other modifications. Methylation of histones was known

since the 1960s, yet for a long time it was believed that histone methylation was an irreversible modification that could only be removed by histone exchange or by dilution during DNA replication. In 2004, the landmark discovery of the first histone lysine demethylase showed that histone methylation is reversible (5). More recent studies suggest that dynamic regulation of histone methylation is used to integrate upstream cellular and environmental signals and establish cellular identity.

In this review, we will focus on the interplay between histone demethylases and signaling pathways. Here, we describe the different histone demethylases that have been discovered to date and summarize information about the biological roles of these enzymes that has been gleaned from studies of mutant animals. We then review recent findings that show an involvement of histone demethylases in the modulation of signaling pathways and discuss the idea that these connections may be altered in cancer.

Histone demethylases

The first histone lysine demethylase to be identified was LSD1/KDM1A (lysine-specific demethylase 1) (5). LSD1 demethylates H3K4me1/me2 methyl residues, marks that are associated with active gene transcription. Consistent with this, LSD1 binds corepressor complexes such as the coREST and NuRD (Mi-2/nucleosome remodeling and deacetylase) complexes and contributes to transcriptional repression (6–8). However, LSD1 has also been found in association with coactivating complexes [such as androgen receptor (AR) and estrogen receptor (ER)-containing complexes] and contributes to gene activation by demethylating H3K9me, a repressive mark (9). A closely related enzyme, LSD2/KDM1B was also shown to possess H3K4me2/1 histone demethylase activity (10). LSD1 and LSD2 remove histone marks in a reaction that utilizes flavin adenine dinucleotide as a cofactor and requires a protonated nitrogen, which limits activity to mono- and dimethyl substrates (6).

The discovery of LSD1 was followed by the identification of a separate and much larger family of proteins: the Jumonji C (JmjC) domain-containing histone demethylating enzymes. The JmjC family uses an alternative oxidation-reduction mechanism for histone demethylation that depends on Fe(II) and α-ketoglutarate. To date, 19 JmjC domain-containing proteins have been shown to have histone demethylase activity (Table 1) (11). This family of proteins can be clustered into seven subfamilies (KDM2–KDM8) (12).

KDM2A/JHDM1A was the first JmjC domain-containing protein shown to possess histone demethylase activity (13). The KDM2 cluster catalyzes H3K36me2/me1 demethylation; in addition, KDM2B/JHDM1B has been suggested to catalyze demethylation of H3K4me3 (14). KDM2A and KDM2B repress ribosomal RNA transcription in a demethylase activity-dependent manner (14, 15). KDM2A is also recruited to unmethylated CpG islands, thus conferring an H3K36me-depleted state at these loci (16).

The KDM3 family proteins KDM3A, KDM3B and KDM3C are histone demethylases that are specific for H3K9me2/me1. They are generally thought to promote gene activation through their H3K9 demethylase activity (17–22).

The KDM4 proteins were the first demethylases described that can act on trimethylated lysines, specifically H3K9me3/me2 and H3K36me3/me2, marks linked to transcriptional repression and to elongation, respectively (23–25). More recently, the KDM4 proteins have been shown to demethylate K26me3/me2 on H1.4, an H1 isotype implicated in transcriptional repression (26). The KDM4 family has been linked to activation of androgen receptor (AR) target genes and genes involved in muscle differentiation (27–29). In pluripotent embryonic stem cells, Kdm4c/Jmjd2c positively regulates the expression of the transcription factor Nanog, a key regulator of self-renewal (30). KDM4A has also been proposed to act as a corepressor when associated with nuclear receptor-corepressor (N-CoR) (31) or the retinoblastoma protein (pRB) (32).

The KDM5 proteins catalyze the demethylation of H3K4me2/me3 residues (33–38). The four members of the KDM5 cluster (KDM5A to KDM5D) are distinct from the other JmjC-containing proteins because, in addition to the Jmj catalytic motif, the PHD and the zinc finger interacting domain, they possess an ARID domain, which allows them to bind the DNA in a sequence-specific manner. KDM5A/RBP2 was originally described as a protein that binds to pRB (39, 40), and only later was it recognized as a histone H3K4 demethylating enzyme (33, 38). Genome-wide analysis of KDM5A targets revealed that KDM5 regulates genes involved in differentiation, cell cycle progression and mitochondrial function (41–43). KDM5 family members have been shown to repress gene transcription and to be associated with repressive complexes (37, 42, 44, 45). However, by interacting with Myc and steroid receptors, they are also thought to participate in transcriptional activation (46, 47).

In mice and humans, the KDM6 cluster consists of three members, two of which, KDM6A/UTX and KDM6B/JMJD3, are histone demethylases specific for H3K27me2/me3 (48–50). H3K27me3 is the prototypical mark of Polycomb repression, and it is frequently found in the promoters of

Name	Substrate	*D. melanogaster*	*C. elegans*
KDM1A/LSD1/AOF2	H3K4me2/1 H3K9me2/1	dLSD1/SU(VAR)3-3	SPR5
KDM1B/LSD2/AOF1	H3K4me2/me1		
KDM2A/JHDM1A/FBXL11	H3K36me2/me1	dKDM2	3H549
KDM2B/JHDM1b/FBXL10	H3K36me2/me1 H3K4me3		T26A5.5
KDM3A/JMJD1A/JHDM2A KDM3B/JMJD1B/JHDM2B KDM3C/JMJD1C/JHDM2C	H3K9me1/2	CG8165	
KDM4A/JMJD2A/JHDM3A	H3K9me2/3	dKDM4A	JMJD-2
KDM4B/JMJD2B/JHDM3B KDM4C/JMJD2C/GASC1	H3K36me2/3	dKDM4B	
KDM4D/JMJD2D/ JHDM3D	H3K9me3		
KDM5A/JARID1A/RBP2 KDM5B/JARID1B/PLU-1 KDM5C/JARID1C/SMCX KDM5D/JARID1D/SMCY	H3K4me2/3	LID	RBR-2
KDM6A/UTX	H3K27me2/3	dUTX	UTX-1
KDM6B/JMJD3			F18E9.5
KDM6C/UTY	None described		
KDM7A/KIAA1718	H3K9me1/2 H3K27me1/2		F29B9.2
KDM7B/PHF8	H3K9me1/2 H3K27me1/2 H4K20me1		
KDM7C/PHF2	H3K9me1/2		
KDM8/JMJD5	H3K36me2		

Table 1 List of human histone lysine demethylases, their substrate specificities and their orthologs in *Drosophila melanogaster* and *Caenorhabditis elegans*.

repressed genes, including the HOX genes. Accordingly, KDM6A and KDM6B are described as transcriptional coactivators of HOX genes (48–51). Furthermore, both KDM6A and KDM6B have been involved in the regulation of cell cycle genes. Genome-wide studies showed that KDM6A/UTX binds to multiple genes belonging to the pRB pathway (52), and KDM6B/JMJD3 regulates the INK4a-ARF locus (53–55). KDM6A has also been involved in transcriptional activation of muscle-specific genes during myogenesis (56), whereas KDM6B is essential for macrophage differentiation and activates IRF4, a transcription factor important for inflammatory response (57).

The PHF cluster demethylates H3K9me2/me1 and H3K27me2/me1 (58–63), and more recently, KDM7B/PHF8 was shown to demethylate H4K20me1, a mark implicated in cell cycle regulation (64, 65). The PHF cluster is generally thought to promote gene activation. PHF8 is recruited to target genes of the retinoic acid receptor (RAR), where it functions as a RAR coactivator during neuronal cell differentiation (66). PHF8 and its homolog PHF2 activate ribosomal RNA transcription by demethylating H3K9me2 (67, 68). Furthermore, by demethylating H4K20me1, PHF8 participates in activation of cell cycle genes, including several E2F1 targets (64).

KDM8/JMJD5 has been implicated in the regulation of circadian clocks in *Arabidopsis* and in human cells (69). Furthermore, it was proposed to regulate the expression of cell cycle genes such as *Cdkn1a/p21* and *Cyclin A* (70, 71). Misregulation of Cyclin A by KDM8 was linked to increased proliferation of breast cancer cell lines (71). KDM8/JMJD5 was reported to be a H3K36me2 demethylase; however, very recent experimental evidence and an analysis of the crystal structure of the KDM8 catalytic domain suggest that KDM8 might instead function as a protein hydroxylase (72, 73).

Some lysine methylation sites, such as H3K79, still lack a known demethylase. It is not yet clear whether these residues are targeted by one of the known histone demethylases or if there are more histone demethylases yet to be discovered. If new demethylases exist, it will be interesting to discover whether they use the same chemical

mechanisms as the known demethylases or if there are alternative mechanisms of histone demethylation.

Furthermore, it is becoming increasingly clear that histone demethylase functions are not restricted to regulation of gene expression, as many of them have been implicated in other processes such as DNA double-strand break repair (74, 75), DNA repair by nonhomologous end-joining (76), DNA replication (77) and regulation of euchromatin-heterochromatin boundaries (14, 78–84). For example, LSD1 has been shown to promote heterochromatin spreading in *Drosophila* (78, 80). In mammalian cells, JMJD2B and JMJD2C have been shown to antagonize H3K9 trimethylation at pericentric heterochromatin (23, 24). An exciting challenge for scientists is to understand the mechanisms by which histone demethylases contribute to these processes in various biological contexts.

Intriguingly, there is evidence that demethylase substrates are not limited to lysines on the histone tails. For example, LSD1 has been shown to demethylate nonhistone substrates, such as p53, E2F1 and DNMT1 (85). It is likely that additional nonhistone targets will be discovered, and a significant topic for future studies will include the challenge of dissecting the relative importance to demethylase function of demethylation of histone tails vs. nonhistone substrates.

Biological roles of demethylases

Histone demethylases have important and diverse biological roles during development, and they have been implicated in many diseases, including cancer. Genetic studies in model organisms have shown that deletion or mutation of many demethylases causes developmental defects. For example, deletion of mouse *LSD1* results in embryonic lethality, and conditional knockdown of its activity in the pituitary gland causes defects in late-cell lineage differentiation (86). Mice deficient for *LSD2* have a maternal effect lethal phenotype associated with defects in DNA methylation at specific imprinted genes (87). We and others have shown that mutation of the *Drosophila melanogaster* ortholog of *LSD1, dLsd1*, results in oogenesis and wing defects (78), whereas mutation of the *Caenorhabditis elegans* ortholog, *SPR-5*, causes a transgenerational accumulation of H3K4me2, which correlates with loss of fertility (88).

In *Drosophila*, P-element insertions in the *dKdm2* gene, when homozygous, result in lethality (89), and in mouse, *Kdm2b* gene targeting causes defects in neuronal tube closure, resulting in exencephaly and partial peri- and postnatal lethality (90).

Kdm3a knockouts display phenotypes such as obesity and male infertility (21, 22, 91). The male infertility defect was proposed to be due to KDM3A's role in activating the expression of genes involved in sperm chromatin condensation and maturation through its H3K9 demethylase activity (21, 22, 92). The obesity phenotype was suggested to be due to KDM3A's role in controlling the expression of metabolic genes in muscle and adipose tissues (91, 93).

In the case of *Kdm4d* knockout, no detectable phenotype was found (94); however, heart-specific deletion and overexpression of *Kdm4a* resulted in altered response to cardiac stresses (95). In *C. elegans*, depletion of the KDM4 ortholog results in genomic instability, apoptosis and defects in meiosis in the germ line (96). In *Drosophila*, mutation of *Kdm4* causes a reduction in the lifespan of males (97).

Kdm5b knockout mice are embryonic lethal (98–100); however, only mild phenotypic abnormalities, such as hematological defects and aberrant behavior, were observed in *Kdm5a* knockout mice (38). This could be due to functional compensation by other Jmj family members. In *Drosophila*, only one KDM5 member exists, Lid (little imaginal disc), and it was shown to be required for normal development (101). The *C. elegans* KDM5 ortholog, RBR-2 (retinoblastoma binding protein related 2), is required for normal vulva formation (33) and is potentially involved in regulating lifespan (102). Mutations in *Kdm5c/Jarid1c* are frequently found in patients with X-linked mental retardation (103), and depletion of its ortholog in zebrafish causes brain-patterning defects and neuronal cell death (34).

In mice, *Utx* deletion causes heart defects and embryonic lethality in females, which were proposed to be the result of a failure to properly activate cardiac expression programs (104). *dUtx* mutation in *Drosophila* affects viability and causes defects in wings, eyes and sex combs (105). In *C. elegans*, mutation of the *UTX* ortholog *F18E9.5* disrupts gonadal development (48), and depletion of a zebrafish ortholog resulted in posterior developmental defects and misregulation of HOX genes, key regulators of body patterning (49).

PHF family members are highly expressed in the brains of zebrafish, mice and worms (59, 62). Mutation of the *C. elegans* ortholog of the human PHF family, *F29B9.2*, results in locomotion defects (59). In zebrafish, KDM7/PHF8 regulates neuronal cell survival and craniofacial development (62, 65). Intriguingly, both deletions and point mutations of the human *PHF8* gene have been found in patients with X-linked mental retardation and craniofacial deformities (106–108). Thus, PHF family members

seem to have an important and conserved role in neuronal development.

Kdm8/Jmjd5-null embryos display severe growth retardation and die at the mid-gestation stage, suggesting that Jmjd5 is essential for mouse development (70, 109). *Cdkn1a/p21* deficiency can partially rescue the growth retardation defect (70), suggesting that this defect might be at least partly due to the elevated Cdkn1a/p21 levels observed in *Jmjd5*-null embryos (70, 109).

The analysis of the available knockout animals demonstrates the importance of histone demethylases during development. However, in many cases, despite tremendous progress, the molecular and cellular mechanisms by which they control specific developmental processes remain to be determined. Understanding how demethylases are recruited to specific targets or to regions of chromatin is likely to be a key element in the regulation of their function. Furthermore, it is already evident that the biological activities of histone demethylases *in vivo* do not always require an intact histone demethylase domain (110). Experiments that investigate the contribution of the catalytic activity of each of these enzymes, for each aspect of their biological function, likely will be needed before the roles that these enzymes play *in vivo* are fully understood. Perhaps the biggest challenge, however, will be to understand the roles that demethylases play in the processes that allow context-specific signaling pathways to be integrated into epigenetic information. As we discuss in the next section, to understand the biological consequences of demethylase action, it will be essential to know which signaling pathways are required in a specific context, to determine how histone demethylase are regulated based on changes in signaling pathways and, conversely, to know how the activity of signaling pathways is regulated by demethylase function.

Interplay of demethylases with signaling pathways

Signaling pathways mediate context-dependent responses to the various cues that direct developmental events. Disorganization of these networks has been linked to diseases, including cancer (111). Understanding the links between signaling pathways and chromatin is not only crucial for understanding normal developmental processes, but it is also a key element in the altered cellular responses that occur during disease. Changes in epigenetic states enable programs of gene expression to be coordinatedly regulated. In some instances, altered demethylase activity may contribute to the pathology of disease. Demethylases also have value as potential therapeutic targets because they may provide an opportunity to control extensive programs of gene expression.

Even before one examines the data, it is easy to imagine several different ways in which demethylases and signaling pathways might be interconnected. Perhaps the simplest connection would be one in which histone demethylases act downstream of signaling pathways as components of coactivator or corepressor complexes. By targeting specific histone methyl residues in response to a signal, demethylases may contribute to either the activation or the repression of genes that are crucial for a response to the stimuli. Alternatively, a different functional relationship might occur if histone demethylases directly activate (or repress) the expression of genes encoding master regulators of signaling pathways. In this situation, changes in demethylase activity could potentiate, or weaken, the signaling response. A converse model is also possible, in which a signaling pathway might control the expression of a histone demethylase. Furthermore, histone demethylases could be directly modified (e.g., phosphorylated) by a signaling pathway. Such a modification might directly alter the activity of a histone demethylase, its stability, or possibly its specificity toward different histone residues. In a more complex model, one could imagine that components of signaling pathways might directly alter the accessibility of histone demethylases to specific histone residues by phosphorylating residues within the histone tails or other chromatin components. Given that demethylases can have nonhistone substrates, it is also possible that signaling proteins might be direct targets for histone demethylases, resulting in their altered stability and/or activity. Clearly, the interplay between demethylases and signaling pathways can be anticipated to occur in several different ways. In the following section, we will describe some examples of known interplay between histone demethylases and various components of signaling pathways.

Regulation of signaling target genes by histone demethylation

The literature contains several instances in which important targets of signaling pathways are directly regulated by histone demethylases. For example, it was shown that in *Drosophila* the H3K4me3 demethylase Lid in association with complexes containing ASF1 and NAP1 histone chaperones contribute to the silencing of E(spl) Notch target

genes (112). This function is conserved in mammals, as the mice ortholog of Lid, KDM5A, was shown to be a component of the RBP-J corepressor complex and to demethylate H3K4me3 at Notch target genes (44). The involvement of another H3K4 demethylase, KDM1/LSD1 in the regulation of Notch target genes was also shown in *Drosophila*, where dLsd1 is recruited to a subset of Notch target genes, and dLsd1 depletion results in an upregulation of gene expression and increased levels of H3K4me1/me2 at their promoters and enhancers (79). In mice, LSD1 has been shown to repress the Notch target *Hey1* in late stages of pituitary development (86). Furthermore, a recent study shows the presence of a SIRT1-LSD1 corepressor complex at Notch target genes in human cell lines (113). Taken together, these studies suggest that histone H3K4 demethylases play an important role in the transcriptional regulation of the Notch target genes in many species.

Histone demethylases have also been shown to be part of steroid receptor coactivating complexes and to contribute to the activation of target genes. Transcriptional regulation by AR involves interaction with multiple factors that modify chromatin, including the histone demethylase LSD1, which was shown to activate the expression of AR target genes (114). This was surprising, given that LSD1 had been originally described as an H3K4me2/me1-specific demethylase and as a component of corepressive complexes (5, 115). The authors propose that, when bound to AR, LSD1 preferentially demethylates H3K9me2/1, thus promoting transcriptional activation (114). The change in specificity might be due to phosphorylation of H3T6 by protein kinase C β1 (PKCβ1) during AR-dependent gene activation, which prevents LSD1 from demethylating H3K4 (116) as discussed later in this review. Also, the histone demethylase KDM3A/JHDM2A was shown to bind AR-responsive genes and to promote gene transcription by demethylating H3K9me2/1 residues (17). Therefore, the relative contribution of LSD1 and JHDM2A to gene activation through H3K9 demethylation remains to be determined. Ligand-dependent activation of AR target genes requires the removal of trimethyl H3K9 marks from the regulatory regions of target genes, a task that is performed by KDM4C/JMJD2C. Wissmann et al. showed that JMJD2C binds AR and stimulates AR-dependent transcription (28). Of note, two other histone H3K9me3 demethylases, KDM4A/JMJD2A and KDM4A/JMJD2D, were also shown to interact with AR (29), suggesting functional redundancy between JMJD2 family members. Taken together, these data suggest that cooperative demethylation of repressive H3K9 methyl marks by the coordinated activity of histone demethylase is an important determinant of AR-dependent gene activation (Figure 1A), which could potentially be exploited to treat prostate tumors. AR is central to the normal development of the prostate gland and has a pivotal role in prostate cancer. Accordingly, LSD1 and JMJD2A were found to be highly expressed in prostate cancers (29, 117), and LSD1 inhibition resulted in impaired proliferation of prostate cancer cells (118).

Garcia-Bassets and colleagues showed that LSD1 interacts with another nuclear receptor, ERα (119). ER signaling plays a key role in breast cancer progression. The biological effects of estrogen are mediated by its binding to two members of the nuclear receptor family, ERα and ERβ. ER regulates transcription by binding to estrogen-responsive elements and by recruiting several cofactors, including acetyltransferases, deacetylases, methyltransferases and demethylases (120). LSD1 is recruited to a significant fraction of ERα target genes, and its depletion prevents activation of ER targets (119). LSD1 was suggested to reverse the inhibitory effect of H3K9 methyltransferases at ER-regulated genes. Interestingly, in the absence of ligand, ERα binds LSD1 and promotes H3K4 demethylation, and only when bound to ligand, ERα promotes demethylation of H3K9me2 by LSD1 (121). It was suggested that LSD1's change of specificity, in this case, is due to ERα-mediated recruitment of the cofactor Pelp1 upon ligand binding (122). However, the precise structural changes at the basis of this switch are yet to be determined. Another ER-binding protein is KDM4B/JMJD2B, which demethylates H3K9me3 at ER target genes and facilitates gene transcription (123, 124).

A very recent study illustrates how the action of histone demethylases in response to a developmental signal can provide the plasticity required during development (125). Specifically, this study reveals that KDM6B/JMJD3 in association with Smad3 regulates the expression of genes crucial for neuronal differentiation in response to transforming growth factor β (TGFβ) and that this interplay is required for TGFβ-induced neurogenesis in chick embryos (125).

In some cases, blocking the activity of histone demethylase has been shown to affect the expression of specific targets of signaling pathways crucial for oncogenesis. For example, KDM6B/JMJD3 is induced in response to the RAS/RAF pathway and contributes to the activation of the INK4a-ARF locus (53–55). Activation of the INK4a-ARF locus is a key event in the induction of Ras oncogene-induced senescence, suggesting a tumor-suppressive role for JMJD3. Notably, JMJD3 expression is lower in various primary tumors relative to normal tissues (53). However, the mechanisms by which JMJD3 is induced by the RAS/RAF pathway and is recruited to the INK4a-ARF locus still remain to be elucidated.

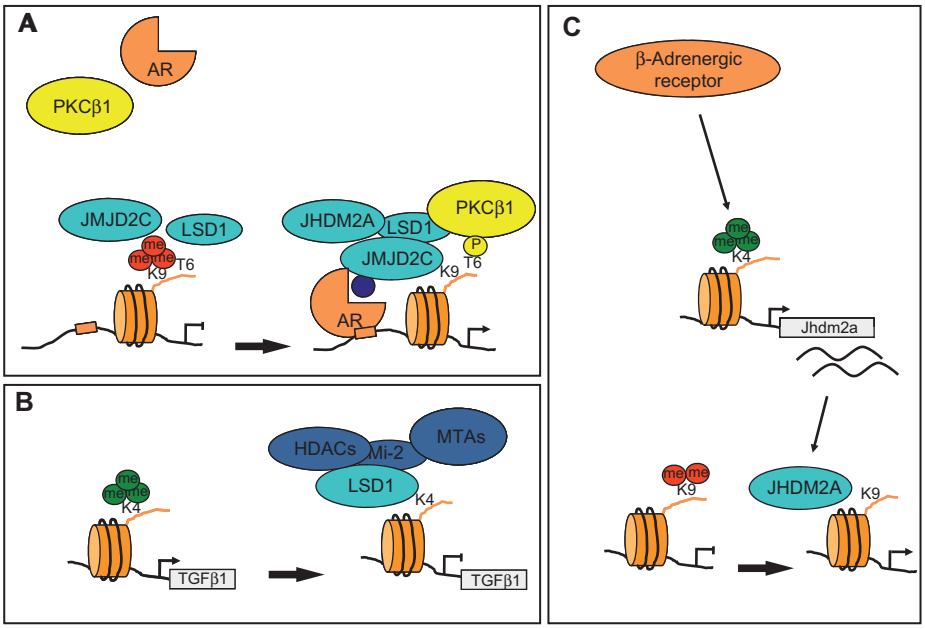

Figure 1 Examples of interplay of demethylases with signaling pathways resulting in transcriptional changes.
(A) An example of regulation of signaling target genes by histone demethylases. The AR activates its targets through recruitment of histone demethylases LSD1, JMJD2C, JHDM2A. (B) An example of regulation of components of signaling pathways by histone demethylases. LSD1 in association with the NuRD complex contributes to the repression of TGFβ1 by demethylating H3K4me2/1. (C) Histone demethylases as targets of signaling pathways. β-Adrenergic stimulation induces the expression of JHDM2A, which in turn regulates genes involved in the control of energy balance.

Additionally, histone demethylases have been shown to directly regulate the expression of master regulators of signaling pathways. This could result in a feed-forward loop of regulation in which activation of a signaling pathway by external signals can be potentiated by further activation of the components of the signaling machinery by the histone demethylases. Direct activation of master regulators of signaling can be particularly relevant in tumorigenesis, where for example, overexpression of an histone demethylase in tumors could potentially lead to aberrant activation of a component of a signaling pathway, thus favoring tumor progression. This would be particularly deleterious in the case of a mutant activated form. It has been shown that histone modifications control the expression of key regulators of the Wnt signaling pathway in cancer leading to aberrant activation of Wnt signaling (126). Downregulation of extracellular WNT antagonists, including members of the SFRP (secreted frizzled-related protein) family, correlates with constitutive activation of Wnt signaling in several tumors (126). Recently, LSD1-inhibiting oligoamines, in combination with the ornithine decarboxylase inhibitor 2-difluoromethylornithine, were shown to result in increased expression of the tumor suppressor gene *SFRP2* in colon cancer cell lines. The reactivation of SFRP2 correlated with increased H3K4me2 and decreased LSD1 binding at the promoter (127). These genes are often aberrantly silenced in colon cancer; thus, their reactivation by modulation of histone methylation may represent a novel epigenetic form of therapy with significant therapeutic potential.

Chromatin immunoprecipitation experiments showed that the the TGFβ1 promoter is bound and repressed by LSD1 (Figure 1B) (7). Given the well-documented role of TGFβ1 in breast cancer metastasis (128), Wang and colleagues hypothesized that by repressing TGFβ1 transcription, LSD1 might inhibit the metastatic potential of cells. LSD1 gain-of-function and loss-of-function experiments in breast cancer cell lines and in severe combined immunodeficient mice suggested that LSD1 inhibits breast cancer cell invasion *in vitro* and suppresses the metastatic potential of breast cancer cells *in vivo* (7).

Evidence for Notch signaling modulation by H3K27 demethylation of Notch regulators was proposed by Herz and colleagues. These investigators observed increased H3K27 methylation of Notch target genes in *dUtx Drosophila* mutants (105). Herz et al. propose that this leads to downregulation of negative regulators of Notch, which is prevalent over the silencing of Notch activators, resulting in a net increase of Notch activity. They suggest

that increased Notch signaling might at least partly explain the excessive proliferation observed in *dUtx* mutants (105).

Histone demethylases as transcriptional targets of signaling pathways

To implement their program, signaling pathways must activate a specific set of downstream targets. There are examples where histone demethylase expression is directly induced by a signaling pathway to in turn allow the implementation of these programs. For example, in mice, β-adrenergic stimulation induces the expression of KDM3A/JHDM2A, which in turn regulates genes involved in the control of energy balance (Figure 1C). The authors suggest that β-adrenergic signaling controls energy homeostasis at least in part by inducing JHDM2A, which is consistent with the obesity defect observed in *Jhdm2a* knockout mice (91). In another study, the demethylase KDM4B/JMJD2B was shown to be a direct target of ER. Interestingly, JMJD2B is highly expressed in ER-positive primary breast cancer, and loss of JMJD2B results in decreased proliferation of ER-positive breast cancer cell lines (123, 124). Other examples include vitamin D-dependent induction of KDM6B/JMJD3 (129) and induction of JMJD1A expression by HIF-1α in hypoxic conditions (130–132) to facilitate the expression of hypoxic genes (133).

Modification of histone demethylases by signaling pathways

An example of modulation of histone demethylase activity by phosphorylation was provided by Baba and colleagues. These authors show that KDM7C/PHF2 is enzymatically inactive by itself and becomes an active demethylase following protein kinase A (PKA)-mediated phosphorylation (134). Phosphorylation induces demethylation of ARID5A, which in turn allows association of the ARID5A-PHF2 complex to target promoters and H3K9 demethylation (Figure 2A). There is evidence that also LSD1 can be phosphorylated, although the enzyme responsible for this event and the functional consequences are currently unknown (135). It would be important to determine whether this mechanism of regulation can be extended to other demethylases.

Finally, it has been reported that phosphorylation of adjacent histone residues can affect the accessibility of

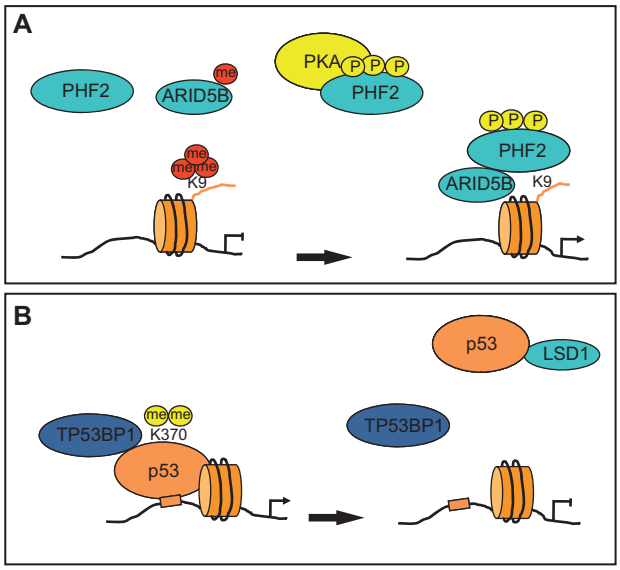

Figure 2 Examples of post-translational modification of components of signaling pathways and histone demethylases. (A) Modification of histone demethylases by signaling pathways. PHF2 demethylase activity is induced by PKA-mediated phosphorylation. Active PHF2 demethylases ARID5B and the two associate to chromatin, where PHF2 promotes gene transcription by demethylating H3K9me2. (B) Demethylation of components of signaling pathways. Demethylation of p53 at K370 by LSD1 results in dissociation of the p53-TF53BP1 complex and inhibits p53-mediated activation of transcription.

histone demethylase activity to their substrate. For example, Metzger et al. found that androgen-dependent phosphorylation of H3T6 by PKCβ1 prevents LSD1 from demethylating H3K4 during AR-dependent gene activation (116).

Demethylation of components of signaling pathways

It is becoming evident that demethylase targets are not limited to histones and include important effectors of signaling pathways such as the transcription factors p53, E2F1, and nuclear factor κB (NF-κB). p53 is subject to various post-translational modifications, including acetylation and methylation. It was shown that demethylation of p53 at K370 by LSD1 prevents p53 from interacting with 53BP1, thus inhibiting p53 pro-apoptotic activity (Figure 2B) (136). LSD1 has been shown to demethylate another transcription factor, E2F1. By demethylating E2F1 at K180, LSD1 stabilizes E2F1 protein, allowing accumulation of E2F1 upon DNA damage stimuli and promoting apoptosis (137). Thus, LSD1 might have pro-apoptotic or anti-apoptotic roles depending on the context.

The mechanism by which LSD1 recognizes and demethylates so many different substrates and the context in which it does so still need to be elucidated. LSD1 has a large catalytic pocket, which could presumably accommodate different molecules. It has been proposed that binding to specific protein complexes confers on LSD1 the ability to recognize and demethylate specific residues. Potentially, post-translational modification of LSD1 could modulate its specificity (85, 122).

NF-κB signaling is regulated at multiple levels. Recent studies have added a new layer to NF-κB regulation, showing that demethylation of lysines 218 and 221 of its p65 subunit by KDM2A/FBXL11 results in negative regulation of NF-κB (138). Moreover, expression of FBXL11 is induced upon NF-κB activation, suggesting that FBXL11 participates in a negative feedback loop to modulate NF-κB activity (138).

The ways in which lysine demethylation regulates transcription factor activity as well as their substrate specificity, the recruitment mechanisms and the consequences of the demethylation events on the transcription factors stability and/or regulation of specific target genes are important issues for future research. One could hypothesize that demethylation of specific residues within transcription factors might confer selectivity toward a subset of target genes, leading to signal-specific changes in gene expression.

Summary and outlook

Accumulating evidence has indicated that aberrant expression and/or activity of histone demethylases contributes to cancer (9). However, in most instances, the precise mechanisms underlying the oncogenic potential of these enzymes have yet to be elucidated. There are several possible ways in which histone demethylases can contribute to or even drive cancer. First, aberrant activity due to mutation, deletion or amplification of genes coding for histone demethylases can cause changes in gene expression patterns that lead to cancer formation or maintenance. Alternatively, they can modulate the activity of pathologically activated transcription factors or signaling proteins (139). For example, inhibition or activation of histone demethylases by aberrant signaling pathways might act synergistically to reprogram gene expression signatures that underlie the malignant phenotype of tumor cells. Deregulation of signaling pathways is usually directly linked to cancer development. An exciting opportunity, derived from studies of the links between signaling pathways and histone demethylases, is the possibility that demethylases may be exploited to prevent the consequences of aberrant signaling in cancer.

There is experimental evidence that histone demethylases can be easily targeted by small-molecule inhibitors (139). Several molecules have been found to inhibit LSD1 activity *in vitro* and to inhibit proliferation of cancer cell lines (140). They can be classified into different classes, which include the classical monoamine oxidase (MAO) inhibitors such as pargyline, tranylcypromine and their derivatives as well as peptides and polyamine-based LSD1 inhibitors (140). Preclinical studies in mice showed that MAO inhibitors, such as tranylcypromine, have antitumor activity in xenografts (141, 142). Inhibition of xenograft tumor growth in nude mice was also observed using a combination of polyamine analogs and DNA methyltransferase inhibitors (143).

Given the high degree of identity between JmjC proteins, the development of selective inhibitors for JmjC demethylase is more challenging; however, on the basis of the crystal structure and catalytic mechanism of JmjC family members, a first generation of compounds has been identified that represent good leads for further optimization. They include succinate, Ni(II) ions, analogs of α-ketoglutarate, hydroxamate-based and pyridine-based inhibitors. Two of them, NCDM-32 and methylstat, were shown to inhibit the growth of cancer cells (140). Although further studies are required to develop more potent and specific inhibitors, these initial studies suggest that demethylase inhibitors can potentially be used clinically to target cancer cells either alone or in combination with other chromatin-modifying agents.

As more potent and selective inhibitors of demethylases are being identified, a complete understanding of demethylase function and their interplay with signaling pathways is necessary to achieve their clinical potential. However, apart from a few examples, a full characterization of the links between histone demethylases and signaling pathway is still lacking and some fundamental questions still need to be answered, such as: Which signaling pathways control the recruitment of histone demethylases to specific loci and in what context? Which sequence-specific transcription factors or chromatin-binding proteins direct their targeting? How are histone demethylase expression patterns and activities regulated by signaling pathways? Do histone demethylases directly regulate signaling pathways, and is this a common mechanism of regulation?

We anticipate that the use of animal model systems will be essential in answering these questions. *In vivo* models are crucial because the function of histone demethylases

seems to be highly context-dependent, and the signals that normally provide these contexts are often lost when cells are placed in tissue culture. Genome-wide analysis of histone demethylase targets in differentiated cells, and throughout development, will be necessary to understand the consequences of altered histone demethylase function. Furthermore, biochemichal analysis of demethylase function will help in understanding their mechanisms of action. Such studies will illuminate the mechanisms by which histone demethylases act in conjunction with signaling pathways to control gene transcription and chromatin architecture.

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