Fly 9:1, 36–44; January/February/March 2015; Published with license by Taylor & Francis Group, LLC

Histone lysine demethylases in *Drosophila melanogaster*

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Keywords: chromatin, cancer, demethylase, *Drosophila*, Epigenetics, histone, JmjC domain, KDM, modifications, tumorigenesis

Abbreviations: JmjC, Jumonji-C; JmjN, Jumonji-N; JNK, Jun-NH2 terminal kinase; K, lysine; KDM, lysine demethylase; NAD, nicotinamide adenine dinucleotide; PHD, plant homeo domain; R, arginine; Su(var), suppressor of variegation; TPR, tetratricopeptide.

Epigenetic regulation of chromatin structure is a fundamental process for eukaryotes. Regulators include DNA methylation, microRNAs and chromatin modifications. Within the chromatin modifiers, one class of enzymes that can functionally bind and modify chromatin, through the removal of methyl marks, is the histone lysine demethylases. Here, we summarize the current findings of the 13 known histone lysine demethylases in *Drosophila melanogaster*, and discuss the critical role of these histone-modifying enzymes in the maintenance of genomic functions. Additionally, as histone demethylase dysregulation has been identified in cancer, we discuss the advantages for using *Drosophila* as a model system to study tumorigenesis.

Introduction

The basic unit of chromatin is formed by nucleosome building blocks, comprised of 146 base pairs of DNA wrapped around a histone octamer. Assembly of the H2A, H2B, H3, and H4 histone proteins forms the core octamer, and these proteins often undergo modifications on their N-terminal tail. The covalent modification of histones performs essential roles in the organization of chromatin and regulation of genes, and these modifications can be identified by key proteins that regulate chromatin binding and alter functionality.[1-3] Histones can be post-translationally modified through covalent addition of a number of distinct chemical moieties such as methylation, acetylation, ubiquitination, phosphorylation, and sumoylation.[1-3] Changes on the N-tail of histones can interrupt nucleosomal arrangement and interactions, affecting chromatin packaging into higher order structures. Binding of chromatin modifiers onto the tail also facilitates the function of these proteins.

The covalent modification of methylation at particular lysine (K) and arginine (R) residues is the result of the addition or removal of methyl marks by 2 antagonizing enzyme groups, termed "writers" and "erasers."[4] In particular, lysine methylation is substrate specific, and can occur on both the histone H3 and H4 tails. Specific amino acid residues include H3K4, H3K9, H3K27, H3K36, H3K79 and H4K20, where each lysine residue can be un-, mono-, di-, or trimethylated (me0/me1/me2/me3, respectively).[1,5,6] Modifications of these residues can be associated with distinct functional outcomes. It has been shown that H3K4, H3K36 and H3K79 marks associate with transcriptional activation, whereas H3K9, H3K27, and H4K20 are linked to transcriptional repression.[1,5,7] Lysine methylation has been confirmed to play a critical role in the regulation of a variety of important processes, including gene expression, heterochromatin formation, and dosage compensation.[6,8] Here, we review the current findings on the 13 predicted *Drosophila* histone demethylases (**Fig. 1**). These proteins are classified as demethylases based on known sequences and domain structure. Further, we address the dysregulation of histone lysine demethylases in cancer and present the advantages for using *Drosophila* as a model system for studying tumorigenesis.

Amine Oxidase Demethylases

The known or predicted 13 histone lysine demethylases in *Drosophila* can be subdivided into 2 distinct subgroups based on their mechanism of demethylation. Amine oxidase demethylases, the first group, can oxidize their substrate by FAD to generate an imine that gets hydrolyzed (**Fig. 2A**).[5] Suppressor of variegation 3–3, Su(var)3–3, is a histone lysine demethylase that belongs to the flavin monoamine oxidase family, and is the only amine oxidase demethylase in *Drosophila*.[9] Su(var)3–3 is comprised of SWIRM (derived from Swi3p, Rsc8p, and Moira) and nicotinamide adenine dinucleotide-binding (NAD-binding) domains (**Fig. 1**, **Table 1**). It is predicted that the SWIRM domain is involved in protein-protein and DNA-protein interactions, in addition to enzyme catalysis.[10] Su(var)3–3 has been identified to

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Submitted: 05/22/2015; Revised: 07/02/2015; Accepted: 07/10/2015
http://dx.doi.org/10.1080/19336934.2015.1074787

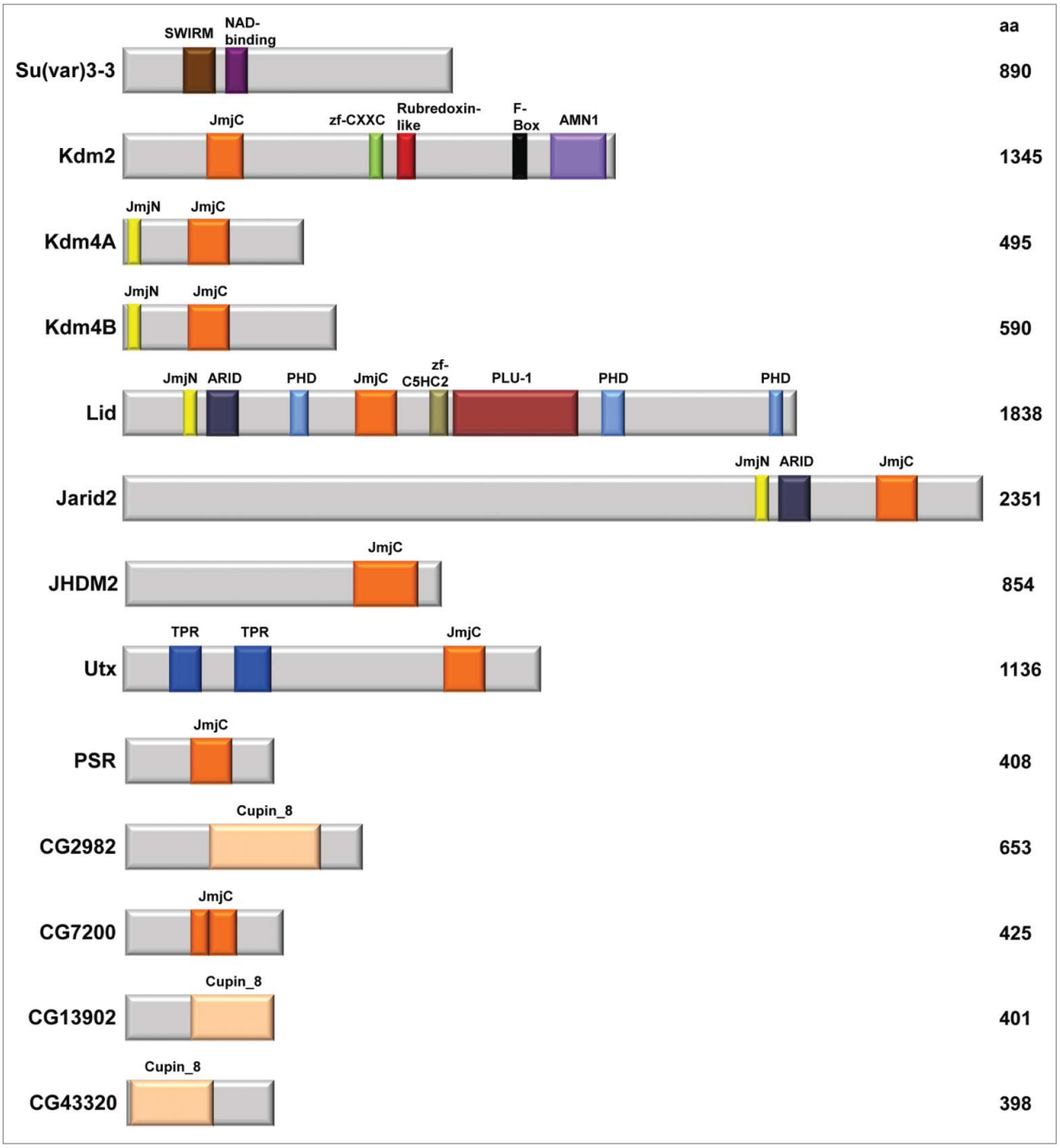

Figure 1. Detailed structures of the 13 histone lysine demethylases in *Drosophila melanogaster*.

act as a corepressor by reducing mono- and dimethylated H3K4 (H3K4me1/me2) marks, with no known activity at any other sites of methylation.[9,11]

Suppressor of variegation, Su(var), genes were originally found to associate with heterochromatin or to prevent heterochromatin spreading into euchromatin.[12] While the mechanism to initiate the formation of heterochromatin is unclear, it is noted that a large portion of the eukaryotic genome remains in a heterochromatic, inaccessible state. The role of Su(var)3–3 in heterochromatin formation involves maintenance during embryonic development, and in the establishment of transcriptional silencing in the germline pole cells.[11] In that same study, the investigators found that Su(var)3–3 associates with RPD3, heterochromatin protein 1 (HP1) and Su(var)3–9, which controls heterochromatin spreading in position-effect variegation. Further, association of Su(var)3–3 with Su(var)3–9 in this silencing complex established that Su(var)3–3 H3K4 demethylase activity is a requirement for subsequent H3K9 methylation in euchromatic regions.

Su(var)3–3 has also been identified as a protein in the Brahma (Brm) complex, physically associating through its SWIRM domain and functioning as a coregulator.[13] The Brm complex is

responsible for chromatin remodeling activities during development, involving both gene transcription activation and repression.[14] As a member of the Brm complex, Su(var)3–3 represses wing vein formation in inter vein cells.[13] Additionally, Su(var)3–3 has been found to functionally interact with the histone demethylase Little imaginal discs (Lid), where together these proteins play a role in Notch pathway-specific control of gene expression in euchromatin.[15] Interestingly, while both Su(var)3–3 and Lid demethylate the H3K4 active mark, each is essential for viability (**Table 2**), suggesting that they are not functionally redundant during development. In fact, phenotypes due to mutation of *Su(var)3–3* can be suppressed by a mutation in *lid*, indicating that these enzymes can act in opposition.[15] In the *Drosophila* ovary, Su(var)3–3 is responsible for regulating the size of the germline stem cell (GSC) niche.[16] Overall, results from multiple research groups suggest that Su(var)3–3 could regulate gene transcription in a stage or cell-type dependent manner. Data derived from studies on the enzymatic activity have further shown that Su(var)3–3 and its mammalian homolog, LSD1, are functionally conserved demethylases (**Table 1**). However, LSD1, unlike Su(var)3–3, is able to demethylate the repressive H3K9 mark.[9,11,17]

JmjC-Domain Containing Demethylases

The other 12 histone lysine demethylases in *Drosophila* belong to the JmjC (JumonjiC)-domain containing group. These demethylases are all characterized by a JmjC domain that has defined enzymatic activity,

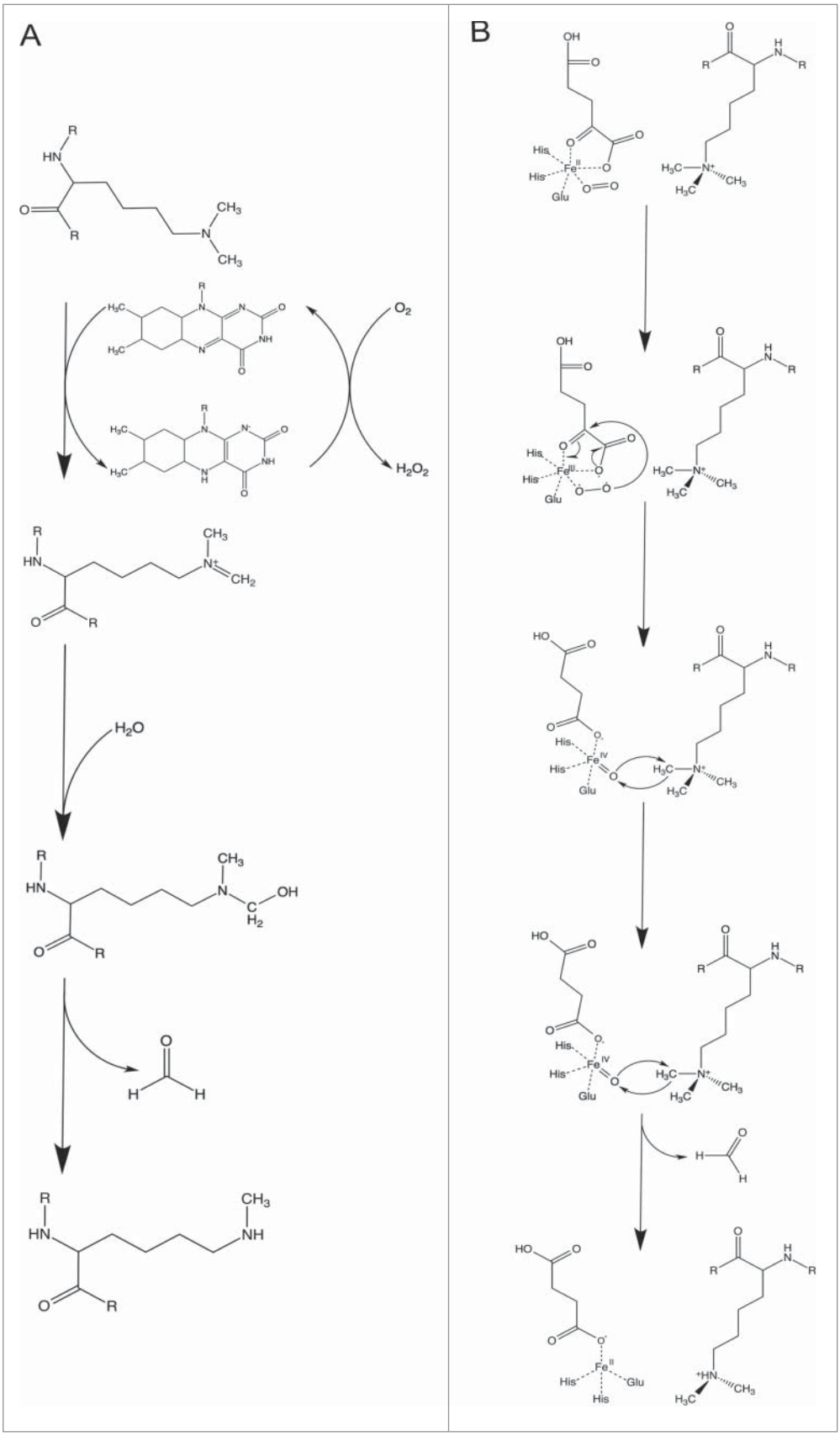

Figure 2. Mechanisms of lysine demethylation. (**A**) Mechanism of LSD1 demethylation via an amine oxidation reaction. (**B**) Mechanism of JmjC protein demethylation via a hydroxylation reaction. Adapted from Cloos et al.[68]

Table 1. Summary of the known 13 histone lysine demethylases in *Drosophila melanogaster*, including: alternate names, molecular functions, histone demethylase activity, biological processes and lysine demethylase human homologues

Symbol	Alternate Names	Molecular Functions[§]	Histone Demethylase Activity	Biological Processes[§]	Human Homolog[ν]
Su(var)3–3	dLsd1, Lsd1, CG17149	Histone demethylase activity; DNA binding[*]; flavin adenine dinucleotide binding[*]; oxidoreductase activity[*].	H3K4	Oogenesis; gene silencing; heterochromatin organization; histone demethylation; wing vein specification; chromatin organization; regulation of Notch signaling pathway; oxidation-reduction process[*]; DNA-templated transcriptional regulation[*].	KDM1/LSD1
Kdm2	dKDM2, dRAF1, FBXL19, JHDM1, CG11033	Histone demethylase activity; DNA binding[*]; ubiquitin-protein transferase activity[*]; zinc ion binding[*].	H3K4, H3K36	Segment specification; histone ubiquitination; histone demethylation; SCF-dependent proteasomal ubiquitin-dependent protein catabolic process[*].	KDM2/ JHDM1; KDM7
Kdm4A	dKDM4A, dJMJD2(1), CG15835	Histone demethylase activity.	H3K9,H3K36	Histone demethylation; positive regulation of gene expression; DNA-templated transcriptional regulation[*].	KDM4
Kdm4B	dKDM4B, dJMJD2(2), CG4037, CG33182	Histone demethylase activity.	H3K9,H3K36	Histone demethylation; DNA-templated transcriptional regulation[*].	KDM4
Lid	dJARID1, dKDM5, CG9088	Histone demethylase activity; histone acetyltransferase activity; protein binding; DNA binding[*], oxidoreductase activity[*], zinc ion binding[*].	H3K4	Histone demethylation; histone acetylation; locomotor rhythm; histone demethylation; chromatin organization; larval somatic muscle development; oxidation-reduction process[*].	KDM5
Jarid2	dJARID2, dJmj, CG3654	Histone demethylase activity; DNA binding[*].	H3K27	Regulation of histone methylation.	JARID2
JHDM2	CG31123, CG8165	Histone demethylase activity.	H3K9	Regulation of response to DNA damage stimulus; positive regulation of chromatin silencing; histone demethylation.	KDM3
UTX	dUTX, anon-31BCa, CG5640	Histone demethylase activity; core promoter binding; protein binding.	H3K27	Histone demethylation; histone methylation; regulation of cell proliferation; regulation of Notch signaling pathway; autophagy regulation; DNA-templated transcriptional regulation; sex comb development; wound healing; transcription regulation in response to DNA damage; cellular response to ecdysone; cellular response to gamma radiation.	KDM6
PSR	dPSR, BEST:LD22859, L0022859, CG5383	Peptidyl-lysine 5-dioxygenase activity[*].		Cell competition in a multicellular organism; negative regulation of the JNK cascade; negative regulation of the apoptotic process; peptidyl-lysine hydroxylation to 5-hydroxy-L-lysine[*].	JMJD6
CG2982	anon-4Bd	Histone demethylase activity[*]; iron ion binding[*]; oxidoreductase activity[*].		Histone demethylation[*]; DNA-templated transcriptional regulation[*].	NO66
CG7200					JMJD4
CG13902					KDM8/JMJD5
CG43320	CG12879				HSPBAP1

[§]Molecular functions and biological processes information was obtained from the listing for individual genes on FlyBase (FB2015_02 Release).[69]
[*]Prediction.
[ν]Homolog represents the human histone demethylase subfamily.

where residues within predicted cofactor binding sites are conserved.[5] The mechanism of demethylation requires 5 residues within the JmjC domain that bind to both the α-ketoglutarate (α-KG) and iron cofactors to undergo a hydroxylation reaction, which allow for removal of a methyl mark (**Fig. 2B**). Often, the JmjC domain can be found in combination with other protein domains, which function in substrate specificity.[5,8]

Lysine-specific demethylase 2, Kdm2, belongs to the group of JmjC-domain containing histone demethylases and is homologous to histone demethylases KDM2 and KDM7 in the mammalian system (**Table 1**). In addition to the JmjC domain, Kdm2 contains zf-CXXC (CXXC-type zinc finger), Rubredoxin-like, F-Box, and AMN1 (Antagonist of mitotic exit network protein 1) domains (**Fig. 1**). In particular, the F-Box, named for this motif being present in cyclin F, is a protein-protein interaction domain associated with ubiquitylation target selection.[18] It was found that Kdm2 is required for efficient H2A ubiquitylation, but has also been shown to mediate demethylation of H3K4me3

Table 2. Summary of the phenotypes resulting from mutation of histone lysine demethylases in *Drosophila melanogaster*

Symbol	Phenotype of mutant allele(s)[§]	Lethality of putative null
Su(var)3–3	Wing vein; anterior crossvein; egg; oviariole; follicle cell; wing; female germline cell; female germline stem cell.	Lethal
Kdm2	Nucleolus; embryonic/larval somatic muscle.	Lethal
Kdm4A	Wing.	Semi-lethal
Kdm4B	Embryonic/larval hemocyte.	ND
Lid	Embryonic/larval optic lobe; mesothoracic tergum; macrochaeta; embryonic/larval somatic muscle; imaginal disc.	Lethal
Jarid2	Embryonic/larval hemocyte; wing vein; polytene chromosome; leg.	Lethal
JHDM2	Eye-antennal disc; adult salivary gland.	ND
UTX	Abdominal tergite 5; eye; wing margin; embryonic/larval salivary gland; haltere; wing vein; wing; eye-antennal disc; mesothoracic tergum.	Lethal
PSR	Male genitalia; ommatidium; eye disc; trichogen cell; wing.	Viable
CG2982	NR	ND
CG7200	NR	ND
CG13902	NR	ND
CG43320	NR	ND

[§]Phenotype information was obtained from the listing for individual genes on FlyBase (FB2015_02 Release).[69]
NR: Not reported. ND: Not determined.

and H3K36me2 (**Table 1**).[19-21] The observed effects on methylation levels were quite small, suggesting that Kdm2 is redundant with other KDMs. Kdm2 has also been implicated as an enhancer of Polycomb silencing and can act as a suppressor of the Trithorax (Trx) and Absent, small or homeotic discs 1 (Ash1) histone methyltransferases.[20] Thus far, Kdm2 has been established to regulate multiple chromatin modifications and linked to factors critical for development.

Histone demethylase 4A, Kdm4A, as well as its homolog Kdm4B, contain both JmjC and JmjN (JumonjiN) domains (**Fig. 1**). JmjN is a highly conserved domain that is essential for enzymatic activity.[5] Proteins that contain both JmjN and JmjC domains, of which there are 4 in *Drosophila*, serve key roles in regulating development and cell cycle progression. Kdm4A affects the organization of heterochromatin, and overexpression of Kdm4 can induce spreading of HP1 into euchromatin.[22] Additionally, it was established that the H3K36me3 activation mark may behave as a barrier to prevent HP1 from spreading into euchromatin, as Kdm4A and HP1 were shown to physically associate.[8,22] At particular heterochromatic genes, the Kdm4A-HP1a interaction is required for demethylation of the H3K36me3 mark.[23] Kdm4A localizes to sites of euchromatin where it regulates the H3K36 mark, as well as H3K9 to a lesser degree.[8,22] Additionally, Kdm4A has been demonstrated to colocalize and physically interact with the Ecdysone Receptor (EcR).[24] Those investigators determined that both Kdm4A and Kdm4B regulate ecdysteroid pathway genes through promoter H3K9 demethylation, highlighting overlapping functions between these histone demethylase homologues. Kdm4B, like Kdm4A, demethylates both H3K9 and H3K36 marks.[8] Unique to Kdm4B is upregulation of this demethylase by p53 upon ultraviolet irradiation.[25] Further, Kdm4B mediates a response to nucleotide excision repair through demethylation of the H3K9 trimethyl mark in heterochromatin. Both Kdm4A and Kdm4B share homology with the mammalian histone demethylase KDM4D (**Table 1**). Mammalian KDM4D, however, is unable to demethylate the H3K36 mark.[26]

Lid is the third protein that belongs to the subgroup of JmjN and JmjC-domain containing histone demethylases. Lid contains 8 protein domains, which include JmjN, ARID, 3 PHD, JmjC, zf-C5HC2 and PLU-1 (**Fig. 1**). Lid demethylates the H3K4 mark, specifically H3K4me3.[8,27-29] Overexpression of Lid in the wing disc was demonstrated to reduce levels of H3K4me3.[27] As mentioned above, Lid activity is not equivalent to that of Su(var) 3–3, the other major H3K4 demethylase in flies.[15] Lid and KDM2, however, may have some redundant functions as double hypomorph mutants die at an earlier stage in development compared to flies carrying the single mutant alleles.[30]

Lid localizes at transcription start sites (TSS) of developmental genes.[31] Association of Lid with genes that are actively transcribed indicates positive contributions to transcription. In fact, data from recent expression profiling experiments comparing Lid deficient cells to wild type indicate that Lid is required for both gene activation and repression, though the majority of genes were activated by Lid.[32] Interestingly, Lid has been found to interact, through its catalytic JmjC domain, with the dMyc oncoprotein, and Lid is required for the expression of a growth regulatory gene.[27] dMyc has been shown to inhibit the demethylase activity of Lid. Notably, the interaction of Lid with dMyc is evolutionarily conserved, even in humans.

Additional functions of Lid include its requirement for the correct regulation of homeotic genes during development.[8] Lid antagonizes silencing of Ultrabithorax (Ubx) in addition to heterochromatin-dependent gene silencing. It has also been suggested that Lid may function in wing vein development in *Drosophila*, through interactions with SWI/SNF remodelers.[13] Recent genetic and transcriptome studies implicate Lid in appropriate mediation of a response to oxidative stress.[32] Lid has also been shown to regulate histone acetylation of polytene chromosomes,[8] but not in S2 cells.[28] Lid was discovered as a factor in the SIN3 histone deacetylase complex, where it was found to interact with the largest SIN3 isoform, SIN3 220.[33,34] KDM5 is the mammalian histone demethylase family with members homologous to Lid (**Table 1**).

Jumonji, AT rich interactive domain 2, Jarid2, is the last JmjN and JmjC-domain containing protein, and is also the largest known histone demethylase in *Drosophila*. Jarid2 contains JmjN, ARID, and JmjC protein domains (**Fig. 1**). At present, no demethylase activity on trimethylated H3K4, H3K9, H3K36 and H4K20 have been associated with Jarid2, and speculations have been made that its JmjC domain is not evolutionarily conserved and thus the amino acid changes at the active site may compromise any enzymatic activity.[8,35] Instead, it has been suggested that Jarid2 may regulate the presence of the H3K27me3 mark by binding to chromatin.[36,37] In addition, Jarid2 interacts with members of the Polycomb repressive complex 2 (PRC2) complex and is thought to control PRC2-dependent transcription.[36] Together these proteins may play a role in gene repression as well as function in transcriptional activation of elongation.[26,36] Jarid2 also promotes gene activation that is required to block vein differentiation in *Drosophila*.[13] Additional work will be required to fully understand the diverse functional roles of this demethylase. Jarid2 is homologous to the mammalian histone demethylase JARID2 (**Table 1**).

JmjC domain-containing histone demethylase 2, JHDM2, is another known histone lysine demethylase in *Drosophila* that is homologous to the mammalian KDM3 demethylase (**Fig. 1**, **Table 1**). JHDM2 is predicted to play a role in regulating responses to DNA damage stimuli, by contributing to gene expression changes in Chk2 downstream signaling.[38] Through overexpression or depletion of this histone demethylase, it has recently been demonstrated to have activity against H3K9 methylation.[39] In that study, the investigators found that JHDM2 is a suppressor of position effect variegation, consistent with its role in removal of the repressive H3K9me3 mark.

Histone demethylase UTX, ubiquitously transcribed TPR gene on the X chromosome, contains a JmjC domain as well as 2 Tetratricopeptide repeat (TPR) structural domains, involved in protein-protein interactions (**Fig. 1**). Similar to the mammalian homolog KDM6, UTX targets the H3K27 repressive mark (**Table 1**).[40,41] Initially, UTX was found to demethylate only H3K27me3/me2 marks, with no activity on H3K27me1.[40] A subsequent study found that the mono methyl H3K4 mark could also be affected, though the influence there is likely indirect.[41] In that study, UTX was found to suppress Notch-dependent and Retinoblastoma-dependent tumors.[41] UTX was also found in complex with acetyltransferase CREB-binding protein (CBP) and chromatin remodeler Brm, where they antagonize Polycomb silencing.[42] It is interesting to note that Jarid2, which also influences H3K27 methylation levels, copurifies with Polycomb group proteins and localizes to silent chromatin.[35] Additional studies are required to dissect the distinct functions of the 2 H3K27 demethylases. Further, UTX was shown to bind to the nuclear hormone receptor EcR complex, and to be recruited to promoter regions for apoptotic and autophagic genes.[43] Through mediation of the H3K27 repressive histone mark, UTX was shown to be required for p53-dependent expression of *ku80* when *Drosophila* Kc cells were exposed to ionizing radiation.[44] UTX physically associates with p53, but is not a requirement for expression of other genes involved in DNA damage response. UTX was also identified in a genetic screen to find factors necessary during wound healing response to induce a repair transcriptome.[45] Together, these studies reveal that UTX plays a critical role to maintain genomic stability.

The phosphatidylserine receptor, PSR, belongs to the JmjC-domain containing subgroup of demethylases (**Fig. 1**). At present, PSR is predicted to catalyze peptidyl-lysine 5-dioxygenase activity, and is known to play a role in cell competition and negative regulation of both the c-Jun-NH2 terminal kinase, JNK, cascade and apoptotic process (**Table 1**).[46,47] PSR plays a role in protection from apoptosis by suppressing the apoptosis regulator Head involution defective, Hid, or Wrinkled. Additionally, activation of the JNK pathway has been shown to suppress phenotypes resulting from PSR overexpression.[46] JMJD6 is the mammalian homolog of PSR and a known histone demethylase (**Table 1**).

CG2982, CG7200, CG13902, and CG43320 are all JmjC-domain containing histone demethylases that can be uniquely characterized by a Cupin 8 domain (**Fig. 1**). Similarities between sequences, secondary structures, and active-sites have led to the identification of JmjC domains as a branch of the cupin family.[48] Currently, only CG2982 has predicted histone demethylation, iron ion binding and oxidoreductase activity. NO66, JMJD4, KDM8, and HSPBAP1 are the respective mammalian homologues to these proteins in *Drosophila* (**Table 1**). The enzymatic activity of these proteins has potential for further studies.

Dysregulation of Histone Lysine Demethylases in Cancer

Histone demethylases play essential roles in dynamically regulating gene expression and chromatin architecture through histone lysine methylation, and are thus implicated in developmental processes, stem cell biology, and tumorigenesis.[49-52] Epigenetic alterations, including chromatin modifications, have been shown to play fundamental roles in cancer initiation and progression. Recently, meta-analyses have uncovered that genes encoding histone lysine demethylases have a high frequency of genetic alterations in tumor types, including breast cancer.[53,54] Amplification and overexpression of histone demethylases, such as the KDM4 subfamily, has been observed in various tumor tissues,[55-58] and histone demethylases, including KDM2A, hold a critical role in preserving aggressive cancer phenotypes.[54] A connection has also been established linking histone demethylases, such as KDM5A, to drug resistance in cancer cells.[59] Thus, it is critical to understand the mechanisms of how histone lysine demethylases contribute to cancer initiation and progression. The use of a whole organism model system, such as *Drosophila melanogaster*, in which development and cell and tissue interaction occur, can facilitate and support mechanistic studies of tumorigenesis.

Drosophila Model System in Tumorigenesis

While *Drosophila* do not typically develop cancer due to their short lifespans, it has been shown that upon perturbation of

cancer-related genes, cells can evade apoptosis, sustain proliferative abilities, exhibit metastasis and tissue invasion, have a loss of differentiation, and show genome instability; all proven hallmarks of cancer.[60] The reduced redundancy of the fruit fly genome and ability to perform large-scale genetic screens in this organism has contributed to the elucidation and characterization of processes for development and signaling cascades.[61] As noted in the sections above and summarized in **Table 2**, mutations in many of the *Drosophila* KDMs result in distinct developmental phenotypes. Relevant to cancer studies, critical signaling pathways such as Hedgehog and Notch, highly implicated in tumorigenesis,[62,63] were first discovered in the fruit fly.[60] Additionally, the potential to identify novel tumor suppressors and oncogenes through the use of new molecular technologies, including CRISPR/Cas-9, in this system highlight the promising direction of this field. Thus, there exists potential to expand tumorigenic studies utilizing *Drosophila*.

One advantage of the *Drosophila* system is in the ability to model context dependency, as different tissues and organs, including muscle, brain, ovaries, eye discs, wings and hemocytes, can model various cancer hallmarks.[60] Flies can allow for *in vivo* study of cell invasion. Evidence has shown that *Drosophila* cells can metastasize and spread through epithelial tissue, colonizing in distant new sites of the organism.[61] Additionally, studies have been able to utilize mutations and generate neoplastic tumors in the fruit fly. Such tumors can develop quickly and when allografted, can metastasize.[64] Thus, there exists the potential to allow for modeling of metastases in *Drosophila* and expanding tumor mass for further analysis. Additionally, through the capacity to generate clones of mutant tissue for specific genes during development, tumor microenvironment analysis can be facilitated.[61]

In addition to modeling molecular mechanisms for tumor progression, several findings have begun to show that *Drosophila* could be used as an *in vivo* system to screen for cancer drug therapies.[65] Advantages to this approach include cost-effectiveness and speed as key advantages for means of drug discovery.[61] To date, *Drosophila* has begun to be utilized to test combination treatments as means for cancer therapy.[65-67] For instance, *Drosophila* were used to perform a small molecule screen to identify drugs that could increase radiation effects to apply these inhibitors to human cancers for novel combination therapy.[67] Additional pharmacological approaches to discover cancer drugs took into account *Drosophila* genetics and profiling of novel compounds to mechanistically investigate drug efficacy.[66] These studies highlight the potential and advantages for performing cancer studies using *Drosophila* as a model system.

Conclusion

Histone lysine demethylases are conserved in organisms from *Drosophila* to humans (**Table 1**). Modifications of histones on the N-terminal tail can prevent higher order assembly of structures in addition to being binding sites for histone-modifying enzymes. Dysregulation of these histone-modifying enzymes has been implicated in human carcinogenesis. Because histone-modifying enzymes are potential drug targets and epigenetic alterations are reversible, pharmacologic targeting of histone-modifying enzymes is a therapeutic strategy to correct the alteration of histone demethylases, and block cancer progression. Recent evidence has demonstrated that *Drosophila* can model tumor progression and be screened to identify novel cancer drugs. Taken together, there is promising potential to investigate the dysregulation of histone lysine demethylases in tumorigenesis using the *Drosophila* model system.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgment

We thank Dr. Ambikai Gajan for critical reading of the manuscript.

Funding

This work was partially supported by funding from the Cancer Biology Graduate Program, Wayne State University School of Medicine, to AH; by grants from the NIH/NCI (R21CA175244) and the Office of Research on Women's Health (OWRH), the Mary Kay Foundation Cancer Research Grant Program, and the Karmanos Cancer Institute-SRIG to Z-QY; and by a grant from the NIH/NIGMS (R01GM088886–01A2) to LAP.

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