HDMs demethylate histones

D'Eustachio, P., Hopkinson, J., Jupe, S., Schofield, C.J., Walport, I.J.

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 70

This document contains 1 pathway and 17 reactions (see Table of Contents)
Histone lysine demethylases (KDMs) are able to reverse N-methylations of histones and probably other proteins. To date KDMs have been demonstrated to catalyse demethylation of N-epsilon methylated lysine residues. Biochemically there are two distinct groups of N-epsilon methylated lysine demethylases with different catalytic mechanisms, both of which result in methyl group oxidation to produce formaldehyde. KDM1A, formerly known as Lysine Specific Demethylase 1 (LSD1), belongs to the flavin adenine dinucleotide (FAD)-dependent amino oxidase family. The KDM1A reaction mechanism requires a protonatable lysine epsilon-amine group, not available in trimethylated lysines, which consequently are not KDM1 substrates. Other KDMs belong to the Jumonji C (JmjC) domain containing family. These are members of the Cupin superfamily of mononuclear Fe (II)-dependent oxygenases, which are characterised by the presence of a double-stranded beta-helix core fold. They require 2-oxoglutarate (2OG) and molecular oxygen as co-substrates, producing, in addition to formaldehyde, succinate and carbon dioxide. This hydroxylation-based mechanism does not require a protonatable lysine epsilon-amine group and consequently JmjC-containing demethylases are able to demethylate tri-, di- and monomethylated lysines.

The coordinates of post-translational modifications represented and described here follow UniProt standard practice whereby coordinates refer to the translated protein before any further processing. Histone literature typically refers to coordinates of the protein after the initiating methionine has been removed. Therefore the coordinates of post-translated residues in the Reactome database and described here are frequently +1 when compared with the literature.

In general, methylation at histone H3 lysine-5 (H3K4) and lysine-37 (H3K36), including di- and trimethylation at these sites, has been linked to actively transcribed genes (reviewed in Martin & Zhang 2005). In contrast, lysine-10 (H3K9) promoter methylation is considered a repressive mark for euchromatic genes and is also one of the landmark modifications associated with heterochromatin (Peters et al. 2002).
The first reported JmjC-containing demethylases were KDM2A/B (JHDM1A/B, FBXL11/10). These catalyse demethylation of histone H3 lysine-37 when mono- or di-methylated (H3K36Me1/2) (Tsukada et al. 2006). They were found to contain a JmjC catalytic domain, previously implicated in chromatin-dependent functions (Clissold & Ponting 2001). Subsequently, many other JmjC enzymes have been identified and discovered to have lysine demethylase activities with distinct methylation site and state specificities.


KDM7A (KIAA1718/JHDM1D) catalyses demethylation of mono- or di-methylated lysine-10 of histone H3 (H3K9Me1/2) and mono- and di-methylated lysine-28 of histone H3 (H3K27Me1/2) (Horton et al. 2010, Huang et al. 2010). PHF8 (JHDM1E) catalyses demethylation of mono- or di-methylated lysine-10 of histone H3 (H3K9Me1/2) and mono-methylated lysine-21 of histone H4 (H4K20Me1) (Loenarz et al. 2010, Horton et al. 2010, Feng et al. 2010, Kleine-Kohlbrecher et al. 2010, Fortschegger et al. 2010, Qi et al. 2010, Liu et al. 2010). PHF2 (JHDM1E) catalyses demethylation of mono- or di-methylated lysine-10 of histone H3 (H3K9Me1/2) (Wen et al. 2010, Baba et al. 2011). JMJD6 was initially characterized as an arginine demethylase that catalyses demethylation of mono or di methylated arginine 3 of histone H3 (H3R2Me1/2) and arginine 4 of histone H4 (H4R3Me1/2) (Chang et al. 2007) although it was subsequently also characterized as a lysine hydroxylase (Webby et al. 2009).

N.B. The coordinates of post-translational modifications represented and described here follow UniProt standard practice whereby coordinates refer to the translated protein before any further processing. Histone literature typically refers to coordinates of the protein after the initiating methionine has been removed. Therefore the coordinates of post-translated residues in the Reactome database and described here are frequently +1 when compared with the literature.

**Literature references**

KDM1A, KDM1B demethylate MeK5-histone H3

**Location:** HDMs demethylate histones

**Stable identifier:** R-HSA-3214912

**Type:** transition

**Compartments:** nucleoplasm

Histone demethylases (HDMs) belong to two groups with distinct catalytic mechanisms. KDM1A and KDM1B (formerly known as Lysine Specific Demethylases 1 and 2), belong to the flavin adenine dinucleotide (FAD)-dependent amino oxidase family, releasing formaldehyde. The reaction mechanism requires a protonatable lysine epsilon-amino group, not available in trimethylated lysines (Shi et al. 2004). KDM1A and subsequently KDM1B were shown to catalyse demethylation of monomethyl and dimethyl, but not trimethyl, histone H3 at lysine 5 (H3K4) in vitro (Shi et al. 2004, Ciccone et al. 2009). Subsequently KDM1A was found to be much more proficient at catalysing demethylation of H3K4 when part of a multiprotein complex (Lee et al. 2005) and shown to catalyse demethylation of histone H3 at lysine 10 (H3K9) in vivo when associated with the androgen receptor (Metzger et al. 2007), suggesting that its substrate specificity is modulated by interacting proteins. KDM1A is a subunit of several complexes, including CtBP, Co-REST, NRD and BRAF35 (Lan et al. 2008). It is also able to catalyse demethylation of a number of non-histone proteins (Nicholson & Chen 2009).

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KDM1A, KDM1B demethylate Me2K5-histone H3

**Location:** HDMs demethylate histones

**Stable identifier:** R-HSA-5661123

**Type:** transition

**Compartments:** nucleoplasm

Histone demethylases (HDMs) belong to two groups with distinct catalytic mechanisms. KDM1A and KDM1B (formerly known as Lysine Specific Demethylases 1 and 2), belong to the flavin adenine dinucleotide (FAD)-dependent amino oxidase family, releasing formaldehyde. The reaction mechanism requires a protonatable lysine epsilon-amino group, not available in trimethylated lysines (Shi et al. 2004). KDM1A and subsequently KDM1B were shown to catalyse demethylation of monomethyl and dimethyl, but not trimethyl, histone H3 at lysine 5 (H3K4) in vitro (Shi et al. 2004, Ciccone et al. 2009).

Subsequently KDM1A was found to be much more proficient at catalysing demethylation of H3K4 when part of a multiprotein complex (Lee et al. 2005) and shown to catalyse demethylation of histone H3 at lysine 10 (H3K9) in vivo when associated with the androgen receptor (Metzger et al. 2007), suggesting that its substrate specificity is modulated by interacting proteins. KDM1A is a subunit of several complexes, including CtBP, Co-REST, NRD and BRAF35 (Lan et al. 2008). It is also able to catalyse demethylation of a number of non-histone proteins (Nicholson & Chen 2009).

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KDM2A, KDM2B, KDM4A demethylate MeK37-histone H3

Location: HDMs demethylate histones

Stable identifier: R-HSA-4722133

Type: transition

Compartments: nucleoplasm

All characterised lysine demethylases other than KDM1A belong to the jumonji C-domain (JmjC) containing family, members of the Cupin superfamily of mononuclear Fe (II)-dependent oxygenases. They require 2-oxoglutarate (2-OG) and molecular oxygen as co-substrates, producing succinate and carbon dioxide. This hydroxylation-based mechanism does not require a protonatable lysine epsilon-amine group and consequently JmjC-containing demethylases are able to demethylate tri-, di- and monomethylated lysines.

The first reported JmjC-containing demethylases were KDM2A and KDM2B (JHDM1A/B, FBXL11/10). These demethylate lysine-37 of histone H3 when mono- or di-methylated (H3K36Me1/2) (Tsukada et al. 2006). KDM4A (JHDM3A) can demethylate mono-, di and trimethylated lysine-37 of histone H3 (Klose et al. 2006).

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KDM2A, KDM2B, KDM4A demethylate Me2K37-histone H3

Location: HDMs demethylate histones

Stable identifier: R-HSA-5661114

Type: transition

Compartments: nucleoplasm

All characterised lysine demethylases other than KDM1A belong to the jumonji C-domain (JmjC) containing family, members of the Cupin superfamily of mononuclear Fe (II)-dependent oxygenases. They require 2-oxoglutarate (2-OG) and molecular oxygen as co-substrates, producing succinate and carbon dioxide. This hydroxylation-based mechanism does not require a protonatable lysine epsilon-amine group and consequently JmjC-containing demethylases are able to demethylate tri-, di- and monomethylated lysines.

The first reported JmjC-containing demethylases were KDM2A and KDM2B (JHDM1A/B, FBXL11/10). These demethylate lysine-37 of histone H3 when mono- or di-methylated (H3K36Me1/2) (Tsukada et al. 2006). KDM4A (JHDM3A) can demethylate mono-, di and trimethylated lysine-37 of histone H3 (Klose et al. 2006).

KDM8 was initially thought to demethylate dimethylated lysine-37 of histone H3 (Hsia et al. 2010) but later work indicates that, consistent with its closer structural similarity to JmjC hydroxylases, the enzyme lacks histone demethylase activity and rather hydroxylates arginine residues of proteins RPS6 and RCCD1 (Wilkins et al. 2018).

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KDM3A, KDM3B, KDM7A, PHF2:ARID5B, PHF8 demethylate MeK10-histone H3

**Location:** HDMs demethylate histones

**Stable identifier:** R-HSA-4724284

**Type:** transition

**Compartments:** nucleoplasm

All characterized lysine demethylases other than KDM1A belong to the jumonjiC domain (JmjC) containing family. The JmjC KDMs are members of the Cupin superfamily of mononuclear Fe (II) dependent oxygenases, which are characterized by the presence of a double-stranded beta-helix core fold. The JmjC KDMs require 2 oxoglutarate (2 OG) and molecular oxygen as co substrates, producing, along with formaldehyde, succinate and carbon dioxide. This hydroxylation based mechanism does not require a protonatable lysine epsilon-amine group and consequently JmjC containing demethylases are able to catalyse demethylation of tri-, di- and monomethylated lysines.

KDM3A (JHDM2A), KDM3B (JHDM2B), KDM7A (JHDM1D), PHF8 (JHDM1E) and PHF2 when complexed with ARID5B (Wen et al. 2010, Baba et al. 2011) are specific for mono or di-methylated lysine-10 on histone H3 (H3K9Me1/2) (Yamane et al. 2006, Kim et al. 2012, Horton et al. 2010, Huang et al. 2010, Loenarz et al. 2008, Feng et al. 2010, Fortschegger et al. 2010, Qi et al. 2010).

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KDM3A, KDM3B, KDM7A, PHF2:ARID5B, PHF8 demethylate Me2K10-histone H3

Location: HDMs demethylate histones

Stable identifier: R-HSA-5661115

Type: transition

Compartments: nucleoplasm

All characterized lysine demethylases other than KDM1A belong to the jumonjiC domain (JmjC) containing family. The JmjC KDMs are members of the Cupin superfamily of mononuclear Fe (II) dependent oxygenases, which are characterized by the presence of a double-stranded beta-helix core fold. The JmjC KDMs require 2 oxoglutarate (2 OG) and molecular oxygen as co substrates, producing, along with formaldehyde, succinate and carbon dioxide. This hydroxylation based mechanism does not require a protonatable lysine epsilon-amine group and consequently JmjC containing demethylases are able to catalyse demethylation of tri-, di- and monomethylated lysines.

KDM3A (JHDM2A), KDM3B (JHDM2B), KDM7A (JHDM1D), PHF8 (JHDM1E) and PHF2 when complexed with ARID5B (Wen et al. 2010, Baba et al. 2011) are specific for mono or di-methylated lysine-10 on histone H3 (H3K9Me1/2) (Yamane et al. 2006, Kim et al. 2012, Horton et al. 2010, Huang et al. 2010, Loenarz et al. 2008, Feng et al. 2010, Fortschegger et al. 2010, Qi et al. 2010).

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KDM4A, KDM4B, KDM4C, KDM4D demethylate Me2K10-histone H3

Location: HDMs demethylate histones

Stable identifier: R-HSA-4724279

Type: transition

Compartments: nucleoplasm

All characterized lysine demethylases other than KDM1A belong to the jumonjiC domain (JmjC) containing family. The JmjC KDMs are members of the Cupin superfamily of mononuclear Fe (II) dependent oxygenases, which are characterized by the presence of a double-stranded beta-helix core fold. The JmjC KDMs require 2 oxoglutarate (2 OG) and molecular oxygen as co substrates, producing, along with formaldehyde, succinate and carbon dioxide. This hydroxylation based mechanism does not require a protonatable lysine e amine group and consequently JmjC containing demethylases are able to demethylate tri-, di- and monomethylated lysines.

KDM4A-D (JMJD2A-D/JHDM3A-D) catalyse the demethylation of di- or tri-methylated histone H3 at lysine-10 (H3K9Me2/3) (Cloos et al. 2006, Fodor et al. 2006, Whetstine et al. 2007), with a strong preference for Me3 (Whetstine et al. 2007). MINA, a bifunctional histone lysine demethylase and ribosomal histidine hydroxylase, demethylates trimethylated lysine-10 of histone H3 (Lu et al. 2009).

KDM4A (JHDM3A) can also demethylate lysine-37 of histone H3 (H3K36Me2/3) (Klose et al. 2006).

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KDM4A, KDM4B, KDM4C, KDM4D, MINA demethylate Me3K10-histone H3

Location: HDMs demethylate histones

Stable identifier: R-HSA-5661120

Type: transition

Compartments: nucleoplasm

All characterized lysine demethylases other than KDM1A belong to the jumonjiC domain (JmjC) containing family. The JmjC KDMs are members of the Cupin superfamily of mononuclear Fe (II) dependent oxygenases, which are characterized by the presence of a double-stranded beta-helix core fold. The JmjC KDMs require 2 oxoglutarate (2 OG) and molecular oxygen as co substrates, producing, along with formaldehyde, succinate and carbon dioxide. This hydroxylation based mechanism does not require a protonatable lysine e amine group and consequently JmjC containing demethylases are able to demethylate tri, di and monomethylated lysines.

KDM4A-D (JMJD2A-D/JHDM3A-D) catalyse the demethylation of di- or tri-methylated histone H3 at lysine-10 (H3K9Me2/3) (Cloos et al. 2006, Fodor et al. 2006, Whetstone et al. 2007), with a strong preference for Me3 (Whetstone et al. 2007). MINA, a bifunctional histone lysine demethylase and ribosomal histidine hydroxylase, demethylates trimethylated lysine-10 of histone H3 (Lu et al. 2009).

KDM4A (JHDM3A) can also demethylate lysine-37 of histone H3 (H3K36Me2/3) (Klose et al. 2006).

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KDM5A-D demethylate Me2K5-histone H3

Location: HDMs demethylate histones

Stable identifier: R-HSA-4754181

Type: transition

Compartments: nucleoplasm

All characterized lysine demethylases other than KDM1A belong to the jumonjiC domain (JmjC) containing family. The JmjC KDMs are members of the Cupin superfamily of mononuclear Fe (II) dependent oxygenases, which are characterized by the presence of a double-stranded beta-helix core fold. The JmjC KDMs require 2 oxoglutarate (2 OG) and molecular oxygen as co substrates, producing, along with formaldehyde, succinate and carbon dioxide. This hydroxylation based mechanism does not require a protonatable lysine epsilon-amine group and consequently JmjC containing demethylases are able to demethylate tri-, di- and monomethylated lysines.

KDM5A-D (JARID1A-D) catalyse the demethylation of di- or tri-methylated lysine-5 of histone H3 (H3K4Me2/3) (Christensen et al. 2007, Klose et al. 2007, Lee et al. 2007, Secombe et al. 2007, Seward et al. 2007, Iwase et al. 2007).

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KDM5A-D demethylate Me3K5-histone H3

Location: HDMs demethylate histones

Stable identifier: R-HSA-5661116

Type: transition

Compartments: nucleoplasm

All characterized lysine demethylases other than KDM1A belong to the jumonjiC domain (JmjC) containing family. The JmjC KDMs are members of the Cupin superfamily of mononuclear Fe (II) dependent oxygenases, which are characterized by the presence of a double-stranded beta-helix core fold. The JmjC KDMs require 2 oxoglutarate (2 OG) and molecular oxygen as co substrates, producing, along with formaldehyde, succinate and carbon dioxide. This hydroxylation based mechanism does not require a protonatable lysine epsilon-amino group and consequently JmjC containing demethylases are able to demethylate tri, di and monomethylated lysines.

KDM5A-D (JARID1A-D) catalyse the demethylation of di- or tri-methylated lysine-5 of histone H3 (H3K4Me2/3) (Christensen et al. 2007, Klose et al. 2007, Lee et al. 2007, Secombe et al. 2007, Seward et al. 2007, Iwase et al. 2007).

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KDM6A, KDM6B, KDM7A demethylate Me2K28-histone H3

**Location:** HDMs demethylate histones

**Stable identifier:** R-HSA-4754187

**Type:** transition

**Compartments:** nucleoplasm

All characterized lysine demethylases other than KDM1A belong to the jumonjiC domain (JmjC) containing family. The JmjC KDMs are members of the Cupin superfamily of mononuclear Fe (II) dependent oxygenases, which are characterized by the presence of a double-stranded beta-helix core fold. The JmjC KDMs require 2 oxoglutarate (2 OG) and molecular oxygen as co substrates, producing, along with formaldehyde, succinate and carbon dioxide. This hydroxylation based mechanism does not require a protonatable lysine e amine group and consequently JmjC containing demethylases are able to demethylate tri, di and monomethylated lysines.


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KDM6A, KDM6B, KDM7A demethylate Me3K28-histone H3

Location: HDMs demethylate histones

Stable identifier: R-HSA-5661121

Type: transition

Compartments: nucleoplasm

All characterized lysine demethylases other than KDM1A belong to the jumonjiC domain (JmjC) containing family. The JmjC KDMs are members of the Cupin superfamily of mononuclear Fe (II) dependent oxygenases, which are characterized by the presence of a double-stranded beta-helix core fold. The JmjC KDMs require 2 oxoglutarate (2 OG) and molecular oxygen as co substrates, producing, along with formaldehyde, succinate and carbon dioxide. This hydroxylation based mechanism does not require a protonatable lysine e amine group and consequently JmjC containing demethylases are able to demethylate tri, di and monomethylated lysines.


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https://www.reactome.org
JMJD6 demethylates MeR3-histone H3

Location: HDMs demethylate histones

Stable identifier: R-HSA-4754176

Type: transition

Compartments: nucleoplasm

JMJD6 catalyses demethylation of mono- or di-methylated arginine-3 of histone H3 (H3R2Me1/2) and arginine-4 of histone H4 (H4R3Me1/2) (Chang et al. 2007). Non-histone substrates of JMJD6 arginine demethylation have also been reported (Poulard et al. 2014, Lawrence et al. 2014). Subsequent to its characterization as an arginine demethylase, JMJD6 was reported to be a lysine hydroxylase (Webby et al 2009).

Literature references

JMJD6 demethylates Me2R3-histone H3

Location: HDMs demethylate histones

Stable identifier: R-HSA-5661122

Type: transition

Compartments: nucleoplasm

JMJD6 catalyses demethylation of mono- or di-methylated arginine-3 of histone H3 (H3R2Me1/2) and arginine-4 of histone H4 (H4R3Me1/2) (Chang et al. 2007). Non-histone substrates of JMJD6 arginine demethylation have also been reported (Poulard et al. 2014, Lawrence et al. 2014). Subsequent to its characterization as an arginine demethylase, JMJD6 was reported to be a lysine hydroxylase (Webby et al 2009).

Literature references


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JMJD6 demethylates Me2sR4-HIST1H4

**Location:** HDMs demethylate histones

**Stable identifier:** R-HSA-5661125

**Type:** transition

**Compartments:** nucleoplasm

JMJD6 catalyses demethylation of mono- or di-methylated arginine-3 of histone H3 (H3R2Me1/2) and arginine-4 of histone H4 (H4R3Me1/2) (Chang et al. 2007). Non-histone substrates of JMJD6 arginine demethylation have also been reported (Poulard et al. 2014, Lawrence et al. 2014). Subsequent to its characterization as an arginine demethylase, JMJD6 was reported to be a lysine hydroxylase (Webby et al 2009).

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JMJD6 demethylates MeR4-HIST1H4

Location: HDMs demethylate histones

Stable identifier: R-HSA-5661124

Type: transition

Compartments: nucleoplasm

JMJD6 catalyses demethylation of mono- or di-methylated arginine-3 of histone H3 (H3R2Me1/2) and arginine-4 of histone H4 (H4R3Me1/2) (Chang et al. 2007). Non-histone substrates of JMJD6 arginine demethylation have also been reported (Poulard et al. 2014, Lawrence et al. 2014). Subsequent to its characterization as an arginine demethylase, JMJD6 was reported to be a lysine hydroxylase (Webby et al. 2009).

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**PHF8 demethylates MeK21-histone H4**

**Location:** HDMs demethylate histones

**Stable identifier:** R-HSA-5423117

**Type:** transition

**Compartments:** nucleoplasm

PHF8 (JHDM1E) catalyses demethylation of mono-methylated lysine-21 of histone H4 (H4K20Me1) (Qi et al. 2010, Liu et al. 2010).

**Literature references**


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