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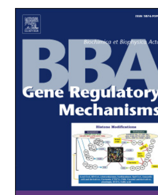

1 Review

2 Targeting histone lysine demethylases — Progress, challenges, 3 and the future ☆

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ABSTRACT

N-Methylation of lysine and arginine residues has emerged as a major mechanism of transcriptional regulation in 20 eukaryotes. In humans, N^{ε}-methyllysine residue demethylation is catalysed by two distinct subfamilies of 21 demethylases (KDMs), the flavin-dependent KDM1 subfamily and the 2-oxoglutarate- (2OG) dependent JmjC 22 KDM2-7 subfamily, which both employ oxidative mechanisms. Modulation of histone methylation status is pro- 23 posed to be important in epigenetic regulation and has substantial medicinal potential for the treatment of dis- 24 eases including cancer and genetic disorders. This article provides an introduction to the enzymology of the 25 KDMs and the therapeutic possibilities and challenges associated with targeting them, followed by a review of 26 reported KDM inhibitors and their mechanisms of action from kinetic and structural perspectives. This article 27 is part of a Special Issue entitled: Methylation Multifaceted Modification — looking at transcription and beyond. 28

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34 1. Introduction

35 Post-oligomerisation modifications to the nucleic acid and protein 36 components of chromatin are of central importance in eukaryotic tran- 37 scriptional regulation. Established modifications to chromatin include 38 methylation of DNA and histones, and further modifications to histones 39 include acetylation, phosphorylation, and ubiquitination, with the 40 *N*-terminal tail of histone H3 being subjected to a particularly complex 41 set of modifications. These modifications, together with other factors, 42 are proposed to substantially contribute to the regulation of gene expres- 43 sion in a context-dependent manner in part by affecting the accessibility 44 of DNA sequences for transcription [1–3]. The post-translational modifica- 45 tions affect chromatin structure and dynamics, the lifetimes of chromatin 46 components, and mediate chromatin binding interactions. Aberrant mod- 47 ification patterns to chromatin have been associated with the onset and 48 progression of both germline and somatic diseases, ranging from mental 49 disorders to many cancers [4–6]. Presently, it seems quite possible that 50 most, if not all, major human diseases (including at least some infectious 51 diseases) will be linked to changes in post-oligomerisation modifications 52 to chromatin. Consequently, many of the enzymes that catalyse these 53 modifications and their removal (sometimes referred to as 'writers' and 54 'erasers', respectively), as well as the multiple binding domains that inter- 55 act with them, are being pursued as small-molecule targets for therapeu- 56 tic benefit. Small molecules targeting chromatin-modifying enzymes for 57 cancer treatment are already in clinical use (e.g. DNA methyltransferase 58 inhibitors (Azacitidine, Decitabine) and histone deacetylase inhibitors 59 (Vorinostat, Romidepsin)), and others are in trials [7–9].

60 *N*-Methylations of both DNA and histones are chromatin modifica- 61 tions of central importance in (epi)genetics. Due to the strength of the 62 C–N bond, *N*-methylation was once thought to be irreversible, at 63 least via direct enzymatic catalysis; however, it is now clear that 64 *N*-methylation of DNA (and RNA) is both common and can be directly 65 reversed by the action of demethylases (note that indirect methods of 66 repair of methylated DNA, for example base excision repair, are well- 67 established, but beyond the scope of this article).

68 The available evidence is that protein *N*-methylation occurs princi- 69 pally, but not exclusively, on the histone lysyl and arginyl side chains 70 of histones H3 and H4. There is also evidence, both from 'global' prote- 71 omic as well as focused studies, that many other proteins are 72 *N*-methylated (and likely demethylated), including some associated 73 with transcriptional regulation (e.g. methylation of p53 [10] and 74 NF-κB [11,12]). In contrast to histone lysine acetylation, which results 75 in transcriptional activation, histone methylation can either enable 76 context-dependent activation or repression of transcription. In general, 77 methylation of histone H3 at Lys9 or Lys27 (H3K9 or H3K27) or histone 78 H4 at Lys20 (H4K20) correlates with transcriptional repression, where- 79 as methylation of H3K4, H3K36 and H3K79 correlates with enhanced

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transcription [13]. The outcomes of methylation depend on its site and extent, the presence of other chromatin modifications, and many other regulatory factors.

The available evidence is that lysine is one of, if not the, most diversely and extensively modified component monomer of any biological polymer [14,15]. Lysine residues can be altered by modifications including acetylation, crotonylation, ubiquitination (multiple forms), hydroxylation (at least several types), and by N^{ε}-methylation. Lysine and arginine residues can each exist in four biologically identified methylation states (unmodified, mono-, di- and tri-N^{ε}-methylation for lysine and unmodified, mono-, di-(symmetric)- and di-(asymmetric)-methylation for arginine) (Fig. 1A). The possibility of combinations of modifications both on the same residue and on other histone residues enables an enormity of potential complexity that is proposed to be a central factor in the regulation of gene expression. Defining how the combinations of post-oligomerisation modifications to chromatin, and associated other variables (e.g. association of binding partner proteins) regulate context-dependent transcription of individual open reading frames is a major current biological challenge. Substantial difficulties arise in epigenetic regulation, including with inhibition, due to the context-dependent nature of effects, linked, at least in higher organisms, to redundancy and adaptation. The precise mechanisms of how N-methylation and other modifications regulate the transcription of individual open reading frames are complex and may take a long time, possibly decades, to be unravelled in detailed chemical terms. Whilst such an understanding is desirable, one would hope that it is not essential for therapeutic benefit to occur based on existing, or soon to be acquired, knowledge. Many enzymes catalysing chromatin modifications and their reversal, e.g. methylation/demethylation, have been identified; along with non-catalytic binding proteins, some are being pursued as therapeutic targets. Currently, the main therapeutic focus regarding methyltransferases and demethylases is cancer, but in the longer term the complexity of transcriptional regulation, and in particular methylation, suggests that the possibilities for selective treatment of many diseases involving transcriptional regulation are very substantial.

Histone methylation is catalysed by *S*-adenosylmethionine- (SAM) dependent histone lysine methyltransferases (KMTs) and protein arginine methyltransferases (PRMTs). Over-expression as well as both activating and inactivating mutations of many KMTs correlate with cancer [16]. In several acute leukaemias, the mixed lineage leukaemia (*MLL*) gene undergoes chromosomal translocation resulting in an oncogenic MLL fusion protein, which recruits DOT1L, an H3K79 KMT, causing aberrant methylation and transcription of leukaemeogenic genes [17,18]. EZH2, an H3K27 KMT which is a catalytic component of

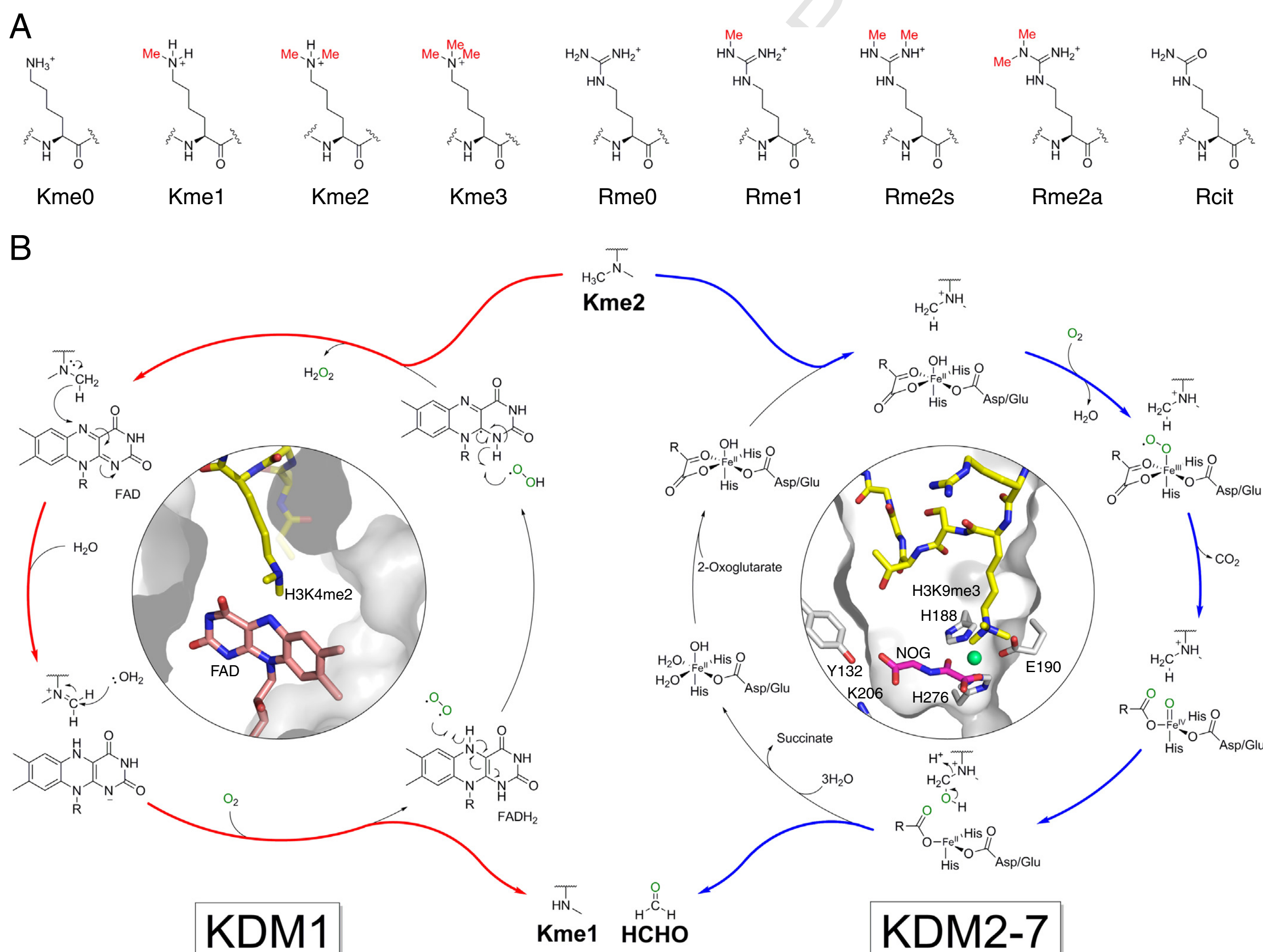

Fig. 1. Histone lysyl demethylation is catalysed by histone demethylases (KDMs). (A) Methylation states of lysine and arginine residues in histones. Lysine residues may be mono-, di- or trimethylated on their N^{ε}-amino groups (Kme1, Kme2 and Kme3 respectively), whereas arginine residues may be either mono- or dimethylated on their N^{ω}-guanidino nitrogens (Rme1 and Rme2 respectively). Dimethylated arginine exists in either symmetric (Rme2s) or asymmetric (Rme2a) forms, depending upon the positions of methylation. Arginine may also be deaminated to form citrulline (Rcit), as catalysed by peptidylarginine deiminase activity. (B) Mechanisms of lysyl demethylation catalysed by the KDM1 and JmjC (KDM2-7) subfamilies. The KDM1 subfamily only accepts mono- and dimethylated lysines as substrates.

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