Histone-lysine N-methyltransferase Subclass Complexes

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KMT2 (histone-lysine N-methyltransferase subclass 2) complexes methylate lysine 4 on the histone H3 tail at gene promoters and gene enhancers. H3K4 methylation mark allows to control gene transcription. The KMT2s function in large multi-subunit complexes, which, in vertebrates, are often referred to as COMPASS or COMPASS-like complexes (COMplex of Proteins ASsociated with Set1). These complexes contain an enzyme (KMT2A or KMT2B, KMT2C or KMT2D, KMT2F or KMT2G), common core subunits (WDR5, RBBP5, ASH2L, DPY30) and unique interacting proteins, which are different for each of the three KMT2 groups (A/B, C/D and F/G). Also, the KMT2 complexes dynamically interact with many transcription factors.

histone-lysine N-methyltransferase subclass 2 | gene transcription | normal development | aberrant growth

1. Introduction

KMT2 (histone-lysine N-methyltransferase subclass 2) complexes methylate lysine 4 on the histone H3 tail at gene promoters and gene enhancers and, thus, control the process of gene transcription. These complexes not only play an essential role in normal development but have also been described as involved in the aberrant growth of tissues.

2. Structure of the KMT2 Complexes

KMT2s are the main H3K4 methyltransferases that regulate gene transcription. The KMT2 family is highly conserved in eukaryotes. While three subgroups of KMT2s, each with a single representative, are present in *Drosophila melanogaster*—trithorax (Trx), trithorax-related (Trr), and Set1—two paralogs of each subgroup appeared in humans during evolution. Human cells contain two Trx-related KMT2s (KMT2A and KMT2B), two Trr-related KMT2s (KMT2C and KMT2D), and two Set1-related KMT2s (KMT2F and KMT2G) (Figure 1). Although KMT2E was initially classified under the KMT2 family, it was identified to be more homologous to yeast SET3 (SET domain-containing protein 3) and SET4 (SET domain-containing protein 4) and *Drosophila* CG9007 (encoding the protein “UpSET”) [1][2][3]. Moreover, unlike the other KMT2s present in humans, KMT2E does not exhibit intrinsic methyltransferase activity toward histone substrates [3].

Figure 1. (**a**) Domain structure of the KMT2 family and core subunits of the KMT2 complexes. The numbers indicate the number of amino acids. KMT, histone–lysine N-methyltransferase; ASH2L, absent, small, or homeotic 2-like; DPY30, Dumpy-30; RBBP5, retinoblastoma-binding protein 5; WDR5, WD repeat-containing protein 5; AT-hook, adenosine-thymidine-hook; CXXC, Zinc finger-CXXC domain; FYRN/FYRC, phenylalanine and tyrosine-rich region (N- and C-terminal); HMG, high mobility group; HWH, helix-wing-helix domain; N-SET, N-terminal of SET; PHD, plant homeodomain; Post-SET, C-terminal of SET; RRM, RNA recognition motif; SDI, Sdc1-Dpy-30 interaction; SET, Su(var)3-9, Enhancer-of-zeste and Trithorax; SPRY, SPla and the ryanodine receptor domain; and WD repeat, tryptophan-aspartic acid repeat. (**b**) The structure of the KMT2 complex. The enzyme and the core subunits of the complex are shown in the diagram. The interactions between individual subunits are marked with blue lines. Subunits specific to individual KMT2 complexes, not shown in the figure, interact with the amino terminus of the KMT2s. WIN motif, WDR5 interaction motif.

The KMT2s function in large multi-subunit complexes, which, in vertebrates, are often referred to as COMPASS or COMPASS-like complexes (COMplex of Proteins ASsociated with Set1). While there is one COMPASS complex in yeast, there are three in *Drosophila* and six closely related complexes in vertebrates, which contain one KMT2 methyltransferase unique to each complex, four core subunits commonly found in all KMT2 complexes, and additional complex-specific proteins (Table 1).

Table 1. Subunit composition of the mammalian KMT2 complexes.

	KMT2A or KMT2B	KMT2C or KMT2D	KMT2F or KMT2G

	Complex	Complex	Complex
Enzyme	KMT2A or KMT2B	KMT2C or KMT2D	KMT2F or KMT2G
Core subunits	ASH2L RBBP5 WDR5 DPY30	ASH2L RBBP5 WDR5 DPY30	ASH2L RBBP5 WDR5 DPY30
Unique subunits	Menin HCF1 or HCF2	PTIP PA1 NCOA6 UTX	CFP1 WDR82 HCF1

KMT, histone–lysine N-methyltransferase; ASH2L, absent, small, or homeotic 2-like; RBBP5, retinoblastoma-binding protein 5; WDR5, WD repeat-containing protein 5; DPY30, Dumpy-30; HCF1, host cell factor 1; PTIP, PAX transactivation-domain interacting protein; PA1, PTIP-associated 1; NCOA6, nuclear receptor coactivator 6; UTX, ubiquitously transcribed tetratricopeptide repeat, X chromosome; CFP1, CXXC finger protein 1; and WDR82, WD repeat-containing protein 82.

The four core subunits—WDR5 (WD repeat domain 5), RBBP5 (retinoblastoma-binding protein 5), ASH2L (absent, small or homeotic 2-like), and DPY30 (Dumpy-30)—form a subcomplex that stably interacts with the KMT2 enzymes and stimulates KMT2 catalytic activity up to several hundred-fold [4][5]. A crystal structure analysis of the KMT2A complex has shown that the interaction of KMT2A with the core subunits (WDR5, RBBP5, and ASH2L) forces a conformational change in the SET domain of KMT2A, which is necessary to achieve a catalytically efficient form [5][6][7][8]. Biochemical and structural studies have demonstrated that the KMT2A complex is stabilized by direct interactions between KMT2A and WDR5 that bridges KMT2A to RBBP5. Furthermore, RBBP5 interacts with ASH2L, which binds the DPY30 protein. Although WDR5 is essential for regulating the activity of KMT2A, it is not responsible for the regulation of other KMT2s, and these KMT2s have been shown to be stimulated by the stable ASH2L-RBBP5 heterodimer that directly interacts with them [4]. The structure of the KMT2 complex is presented in Figure 1b.

In addition to their role in stabilizing and regulating KMT2 complexes, the core subunits of the WRAD subcomplex participate in the recruitment of these complexes to chromatin. The recruitment of KMT2 complexes to the genomic loci is also regulated by the unique complex-specific subunits that determine the functional diversity of these complexes. The three KMT2 groups of complexes differ in their sets of interacting proteins (Table 1). The additional subunits associated with the KMT2A/KMT2B complexes are Menin and HCF1/2 (host cell factors 1/2) [9][10]. Another protein that interacts with the KMT2A/KMT2B complexes is LEDGF (lens epithelium-derived growth factor, also known as PSIP1/p75). However, LEDGF is a substoichiometric component in these complexes and exhibits only a weak interaction with them through Menin [10][11][12]. PTIP (PAX transactivation domain-interacting protein), PA1 (PTIP-associated 1), NCOA6 (nuclear receptor coactivator 6), and UTX (ubiquitously transcribed tetratricopeptide repeat, X chromosome) interact specifically with KMT2C and KMT2D [13][14][15], while CFP1 (CXXC finger protein 1), WDR82 (WD repeat domain 82), and HCF1 (host cell factor 1) interact only with KMT2G and KMT2F [10][16].

In addition to the stable interaction with the complex-specific subunits, the KMT2 complexes dynamically interact with many transcription factors, including NFE2 (nuclear factor, erythroid 2) [17], USF1 (upstream transcription factor 1) [18], MEF2D (myocyte enhancer factor 2D) [19], NF-Y (nuclear transcription factor Y) [20], NF-E2 (nuclear transcription factor erythroid 2) [17][21], AP2δ (activating protein 2δ) [22], MYC [23], OCT4 (octamer-binding transcription factor 4, also known as POU5F1) [24], NANOG [25], p53 [26][27][28], E2Fs [26][29][30], and PAX7 (Paired Box 7) [31]. These interactions of the KMT2 complexes are important for their context-dependent roles.

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