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Histone H3K4 Methyltransferases; Emerging Roles in Nuclear Receptor-Mediated Transcription

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Epigenetic regulation of transcription is one of the mechanisms of gene regulation in eukaryotes. Methylation of histones on lysine residues is one such epigenetic mechanism. The hallmark of proteins possessing lysine methyltransferase activity is the evolutionary conserved catalytic SET domain [1]. The SET domain methyltransferases can be divided into six main families in mammals: SETD1A, SETD1B and four MLLs (Mixed Lineage Leukemia families, also known as KMT2), including MLL1, MLL2, MLL3 and MLL4. Members of the MLL family work by forming multi-subunit complexes composed of unique sets of proteins [2-8]. The common components of MLL complex are RbBP5, Ash2L and WDR5. Those proteins are stably associated with the MLLs and facilitate enzyme-substrate interaction. Especially WDR5 interacts with MLL-C terminal region and helps stabilize other core components [9-11].

MLLs, containing a conserved SET domain, have histone H3 on lysine 4 (H3K4) methyltransferase function and regulate specific gene expression through it [2,9,12-14]. For instance, MLLs target SET domain methyltransferase activity to the *Hox* gene promoters [14]. In the case of Hox13, MLLs play critical roles in estrogen-mediated regulation as a methyltransferase [15]. Also, MLL1 fusion proteins activate the HoxA9 gene expression which causes aggressive leukemia. Specific recruitment of MLL1 requires multiple interactions which is a precondition for the stable recruitment of MLL1 fusion proteins to HoxA9 in leukemogenesis [16]. Furthermore, each member of the MLL family regulates gene expression in various ways. When NF-κB pathway is activated by tumor necrosis factor (TNF-α) and lipopolysaccharide, MLL1 is translocated onto the promoters of NF-κB target genes in a p65-dependent manner [17]. On the other hand, H3K4 trimethylation by MLL3 is critical for the activation of bile acid transporter genes through Farnesoid X receptor (FXR) and Glucocorticoid receptor (GR) signaling in hepatoma cells [18].

The function of MLLs as co-activators for nuclear receptor-mediated activationhas also been proposed by several groups [19-22]. Most recently, we found that MLL1 is critically involved in the transcriptional regulation of endogenous estrogen receptor(ER) α target genes, (e.g. *TFF1* and *GREB1*) in MCF-7 cells [23]. MLL1 has a high occupancy at estrogen response element3 (ERE3) of the TFF1 gene after estradiol (E2) treatment. After MLL1 is recruited at the enhancer region (ERE3), it makes H3K4 mono-methylation, facilitating the recruitment of histone acetyltransferase (e.g. TIP60) which plays a critical role for the *TFF1* gene transcription. Interestingly, the depletion of brahma-related gene 1 (BRG1) which is a key component of SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin remodeling complex eliminates E2-enhanced MLL1 occupancy, indicating that BRG1 is required for the hormonal enhancement of the MLL1 occupancy. Thus, it appears that MLL1 acts as a co-activator in ERα-mediated gene expression.

Interestingly, our research indicated that the enhancer region of *TFF1* gene is already occupied with MLL1 even before ERα binding. In this case, depletion of BRG1 does not affect the pre-hormonal occupancy level of MLL1(24). Thus, we conducted another research to investigate the potential role of MLL1 in maintaining the local chromatin structure in the enhancer region. Further intensive study revealed that MLL1 binds to the unmethylated CpG-rich enhancer region of target genes through the interaction with the CXXC motif. Importantly, MLL1 is required for the binding of Forkhead box protein A1 (FOXA1) and ERα to ERα target genes. FOXA1, a pioneer factor which is a transcription factor binding with chromosome and initiating the relaxation of chromatin (25-27), is known to bind with the genomic region that has high level of H3K4me1/2(28,29), and ERα binding [30]. When FOXA1 is recruited, FOXA1 aids chromosome binding of ERα, thus the depletion of FOXA1 almost eliminate ERα binding at EREs while it did not affect at MLL1 occupancy. However, depletion of MLL1 results in not only a decrease of the pre-existing FOXA1 occupancy but also a dramatic inhibition of E2-induced ERα recruitment, confirming the absolute requirement of MLL1 for the estrogen-mediated transcription process. Under the absence of E2 stimulation, estrogen binding sites are partially opened. However, when MLL1 is depleted, chromatin accessibility to EREs is dramatically reduced. Also, enhancer region of ERα-target genes in MLL1-depleted cell shows remarkably reduced chromatin accessibility regardless being under E2 stimulation and not [23]. Thus, it appears that MLL1 maintains an active chromatin state by nucleosome positioning. CXXC motif of MLL1 binds to the unmethylated CpG region and facilitates the binding of FOXA1, and eventually ERα. Together, these results indicate that MLL1 plays a critical role in maintaining nucleosome positioning and chromatin configurations, which allows for establishment of active chromatin states required for gene activation (Figure 1).

Histone H3K4 specific methyltransferases (HMTs) play a critical role in maintaining nucleosome positioning as well as chromatin configurations by H3K4 methylation, thus facilitating the establishment of active chromatin states of ERα target genes.

MLL family proteins are also involved in aryl hydrocarbon receptor (AHR)-mediated transcription. AHR is a ligand dependent transcription factor and a member of bHLH (basic helix-loop-helix)-

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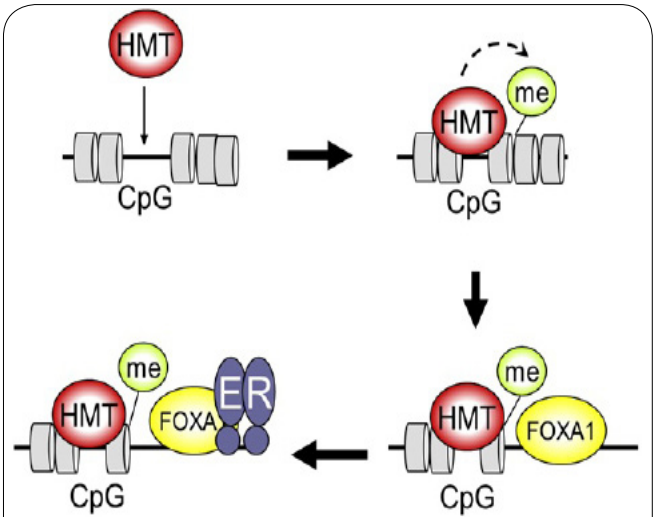

Figure 1. Chromatin accessibility to the enhancer is regulated by histone methyltransferases. Histone H3K4 specific methyltransferases (HMTs) play a critical role in maintaining nucleosome positioning as well as chromatin configurations by H3K4 methylation, thus facilitating the establishment of active chromatin states of ERα target genes.

PAS (Per-ARNT-Sim) family [31]. In the absence of the ligand, it resides in the cytosol associated with heat-shock protein 90 and hepatitis B virus X-associated protein (XAP2) as an inactive protein complex [32]. Upon ligand binding (e.g. TCDD) to AHR, it is dimerized with the AHR nuclear translocator (ARNT). The AHR/ARNT heterodimer interacts with xenobiotic responsive element (XRE) and facilitates the expression of multiple target genes, mostly encoding drug metabolism enzymes (e.g. cytochrome P450(*CYP*)1A1, B1) [33]. Binding of AhR/ARNT heterodimer to XREs in the promoter regions induces the recruitment of various coregulators of transcription(34). In our recent study, depletion of MLLs in hepatocytes caused the change of transcription of AHR target genes, suggesting that MLLmight be a key regulator of aryl hydrocarbon receptor target gene expression (unpublished data).

Similarly, MLL2 (also known as KMT2D or ALR) plays a critical role in the expression of GR target genes. Upon dexamethasone stimulation, GR induces the gene expression in such a manner as to recruit co-activators after binding to the GR-target genes. We found that the expression of GR-target genes increase after dexamethasone treatment in cell-type specific manner at the transcription level. However, the expression of those genes is significantly decreased by depletion of MLL2 (unpublished data). Further research must be conducted to determine how MLL family proteins are involved in cell-type specific or pathway specific transcription of target gene.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Author Contributions

All authors substantially contributed to the drafting of the manuscript.

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References

1. Issaeva I, Zonis Y, Rozovskaia T, Orlovsky K, Croce CM, et al. (2007) Knockdown of ALR (MLL2) reveals ALR target genes and leads to alterations in cell adhesion and growth. Mol Cell Biol 27: 1889-1903.
2. Dou Y, Milne TA, Tackett AJ, Smith ER, Fukuda A, et al. (2005) Physical association and coordinate function of the H3 K4 methyltransferase MLL1 and the H4 K16 acetyltransferase MOF. Cell 121: 873-885.
3. Nakamura T Mori T, Tada S, Krajewski W, Rozovskaia T, et al. (2002) ALL-1 is a histone methyltransferase that assembles a supercomplex of proteins involved in transcriptional regulation. Mol Cell 10: 1119-1128.
4. Goo YH, Sohn YC, Kim DH, Kim SW, Kang MJ, et al. (2003) Activating signal cointegrator 2 belongs to a novel steady-state complex that contains a subset of trithorax group proteins. Mol Cell Biol 23: 140-149.
5. Hughes CM, Rozenblatt-Rosen O, Milne TA, Copeland TD, et al. (2004) Menin associates with a trithorax family histone methyltransferase complex and with the hoxc8 locus. Mol Cell 13: 587-597.
6. Cho YW, Hong T, Hong S, Guo H, Yu H, et al. (2007) PTIP associates with MLL3- and MLL4-containing histone H3 lysine 4 methyltransferase complex. The Journal of biological chemistry 282: 20395-20406.
7. Lee JH, Skalnik DG (2005) CpG-binding protein (CXXC finger protein 1) is a component of the mammalian Set1 histone H3-Lys4 methyltransferase complex, the analogue of the yeast Set1/COMPASS complex. J Biol Chem 280: 41725-41731.
8. Lee JH, Tate CM, You JS, Skalnik DG (2007) Identification and characterization of the human Set1B histone H3-Lys4 methyltransferase complex. J Biol Chem 282: 13419-13428.
9. Dou Y, Milne TA, Ruthenburg AJ, Lee S, Lee JW, et al. (2006) Regulation of MLL1 H3K4 methyltransferase activity by its core components. Nat Struct Mol Biol 13: 713-719.
10. Patel A, Dharmarajan V, Vought VE, Cosgrove MS (2009) On the mechanism of multiple lysine methylation by the human mixed lineage leukemia protein-1 (MLL1) core complex. J Biol Chem 284: 24242-24256.
11. Rao RC, Dou Y (2015) Hijacked in cancer: the KMT2 (MLL) family of methyltransferases. Nat Rev Cancer 15: 334-346.
12. Crawford BD, Hess JL (2006) MLL core components give the green light to histone methylation. ACS Chem Biol 1: 495-498.
13. Steward MM, Lee JS, O'Donovan A, Wyatt M, Bernstein BE, et al. (2006) Molecular regulation of H3K4 trimethylation by ASH2L, a shared subunit of MLL complexes. Nat Struct Mol Biol 13: 852-854.
14. Milne TA, Briggs SD, Brock HW, Martin ME, Gibbs D, et al. (2002) MLL targets SET domain methyltransferase activity to Hox gene promoters. Mol Cell 10: 1107-1117.
15. Ansari KI, Kasiri S, Hussain I, Mandal SS (2009) Mixed lineage leukemia histone methylases play critical roles in estrogen-mediated regulation of HOXC13. FEBS J 276: 7400-7411.
16. Milne TA, Kim J, Wang GG, Stadler SC, Basrur V, et al. (2010) Multiple interactions recruit MLL1 and MLL1 fusion proteins to the HOXA9 locus in leukemogenesis. Mol Cell 38: 853-863.
17. Wang X, Zhu K, Li S, Liao Y, Du R, et al. (2012) MLL1, a H3K4 methyltransferase, regulates the TNFalpha-stimulated activation of genes downstream of NF-kappB. J Cell Sci 125: 4058-4066.
18. Ananthanarayanan M, Li Y, Surapureddi S, Balasubramaniyan N, Ahn J, et al. (2011) Histone H3K4 trimethylation by MLL3 as part of ASCOM complex is critical for NR activation of bile acid transporter genes and is downregulated in cholestasis. American journal of physiology. Am J Physiol Gastrointest Liver Physiol 300: G771-G781.
19. Dreijerink KM, Mulder KW, Winkler GS, Höppener JW, Lips CJ, et al. (2006) Menin links estrogen receptor activation to histone H3K4 trimethylation. Cancer Res 66: 4929-4935.
20. Lee S, Kim DH, Goo YH, Lee YC, Lee SK, et al. (2009) Crucial roles for interactions between MLL3/4 and INI1 in nuclear receptor transactivation. Mol Endocrinol 23: 610-619.

21. Mo R, Rao SM, Zhu YJ (2006) Identification of the MLL2 complex as a coactivator for estrogen receptor alpha. J Biol Chem 281: 15714-15720.

22. Ansari KI, Hussain I, Shrestha B, Kasiri S, Mandal SS (2011) HOXC6 Is transcriptionally regulated via coordination of MLL histone methylase and estrogen receptor in an estrogen environment. J Mol Biol 411: 334-349.

23. Jeong KW, Andreu-Vieyra C, You JS, Jones PA, Stallcup MR (2014) Establishment of active chromatin structure at enhancer elements by mixed-lineage leukemia 1 to initiate estrogen-dependent gene expression. Nucleic Acids Res 42: 2245-2256.

24. Jeong KW, Kim K, Situ AJ, Ulmer TS, An W, et al. (2011) Recognition of enhancer element-specific histone methylation by TIP60 in transcriptional activation. Nat Struct Mol Biol 18: 1358-1365.

25. Zaret K (1999) Developmental competence of the gut endoderm: genetic potentiation by GATA and HNF3/fork head proteins. Dev Biol 209: 1-10.

26. Eeckhoute J, Carroll JS, Geistlinger TR, Torres-Arzayus MI, Brown M (2006) A cell-type-specific transcriptional network required for estrogen regulation of cyclin D1 and cell cycle progression in breast cancer. Genes Dev 20: 2513-2526.

27. Sekiya T, Muthurajan UM, Luger K, Tulin AV, Zaret KS (2009) Nucleosome-binding affinity as a primary determinant of the nuclear mobility of the pioneer transcription factor FoxA. Genes Dev 23: 804-809

28. Lupien M, Eeckhoute J, Meyer CA, Wang Q, Zhang Y, et al. (2008) FoxA1 translates epigenetic signatures into enhancer-driven lineage-specific transcription. Cell 132: 958-970.

29. Serandour AA, Avner S, Percevault F, Demay F, Bizot M, et al. (2011) Epigenetic switch involved in activation of pioneer factor FOXA1-dependent enhancers. Genome research 21: 555-565.

30. Hurtado A, Holmes KA, Ross-Innes CS, Schmidt D, Carroll JS (2011) FOXA1 is a key determinant of estrogen receptor function and endocrine response. Nat Genet 43: 27-33.

31. Karchner SI, Powell WH, Hahn ME (1999) Identification and functional characterization of two highly divergent aryl hydrocarbon receptors (AHR1 and AHR2) in the teleost Fundulus heteroclitus. Evidence for a novel subfamily of ligand-binding basic helix loop helix-Per-ARNT-Sim (bHLH-PAS) factors. J Biol Chem 274: 33814-33824.

32. Brokken L, Giwercman YL (2014) Gene-environment interactions in male reproductive health: special reference to the aryl hydrocarbon receptor signaling pathway. Asian J Androl16: 89-96.

33. Nebert DW, Dalton TP, Okey AB, Gonzalez FJ (2004) Role of aryl hydrocarbon receptor-mediated induction of the CYP1 enzymes in environmental toxicity and cancer. J Biol Chem 279: 23847-23850.

34. Matthews J, Wihlén B, Thomsen J, Gustafsson JA (2005) Aryl hydrocarbon receptor-mediated transcription: ligand-dependent recruitment of estrogen receptor a to 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin-responsive promoters. Molecular and cellular biology 25: 5317-5328