Novel arginine demethylase function of JMJD1B gene controls cell fate decision of blood progenitors

Epigenetic modifications such as post-translational modifications (PTMs) of histone proteins and DNA methylation dynamically changes in cells to fine-tune the expression of genes required for normal cellular function. These epigenetic modifications involve in nearly all cell fate and development processes. The enzymes that deposit and remove these PTMs of histone proteins and DNA methylation are primary drug targets to alter specific pathways or gene expression to treat certain diseases such as cancer.

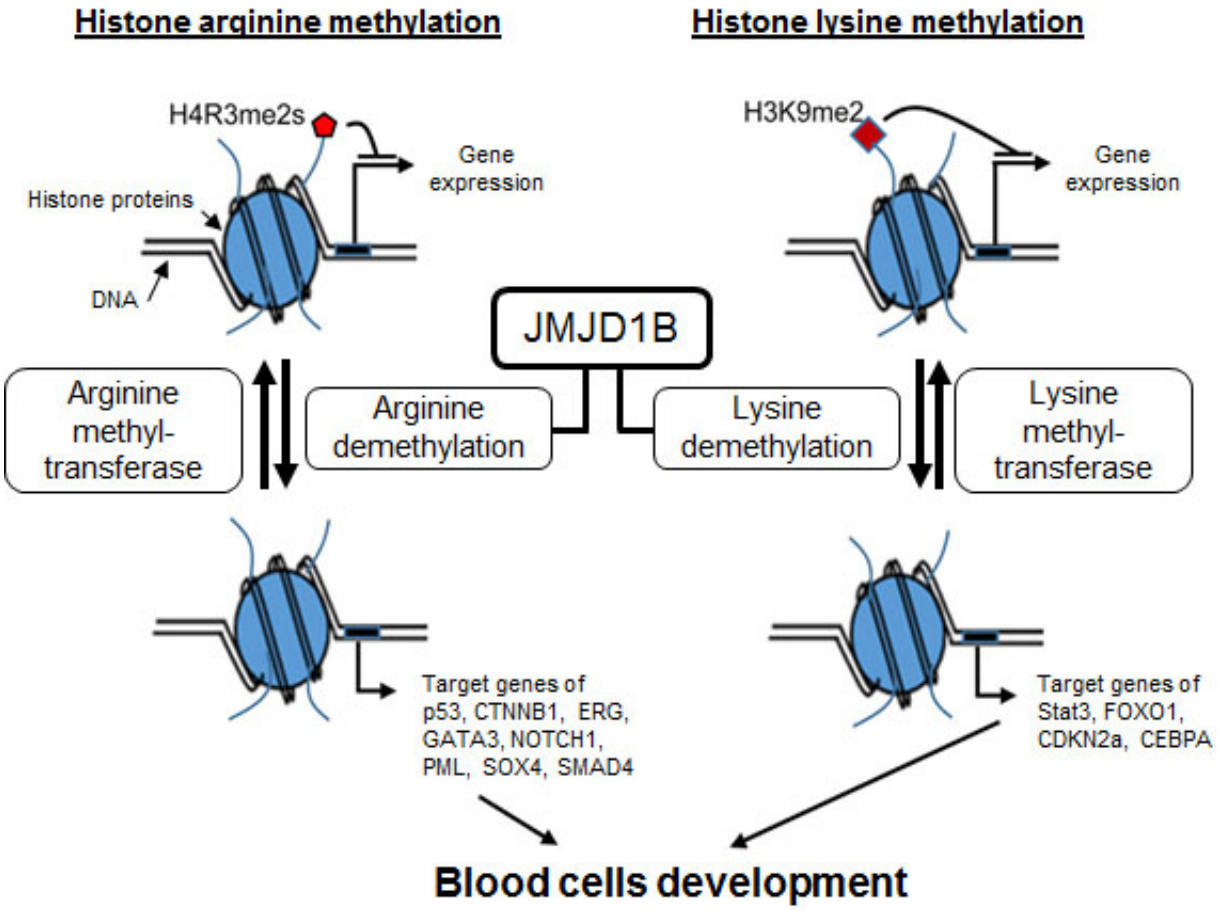

Fig. 1.

Arginine methylation is a common post-translational modification of histones and its role has been identified in embryonic and hematopoietic stem cell development. Arginine methylation of histone like other PTMs (such as acetylation, phosphorylation, lysine methylation etc) also dynamically

changes in the cell to regulate expression of genes. The dysregulation of arginine methylation level on histone has been linked to many human diseases, including neurological disorders, autoimmunity, and cancer. Arginine methyltransferases, the enzymes that deposit methyl marks on histone arginine residue, have been identified and their function in cells has been well documented. However, arginine demethylases, the enzymes that remove methyl marks from histone arginine residue, have not yet been identified. Recently a study, using methylated histone-peptide model substrates, provided compelling evidences that certain lysine demethylase enzymes possess arginine demethylase activity. However, an arginine demethylase with a biological role has not been reported yet.

The research group, Li et al., in Beckman Research Institute of City of Hope published a study in April 2018 edition of "*Cell Reports*" a Cell press journal and reported first-time that JMJD1B gene is able to remove methyl marks from histone arginine residue, H4R3me2s/H4R3me1. JMJD1B previously been identified to remove methyl mark from histone lysine residue, H3K9me2, and uses almost similar reaction conditions to catalyze demethylation. They further identified that these histone methyl-arginine and methyl-lysine modifications act as suppressive markers for gene expression and removal of methyl marks from histone residue at gene promoter regions enhances expression of the gene.

Loss of JMJD1B gene function in mouse model causes accumulation of these methyl-marks (H4R3me2s and/or H3K9me2) at distinct cluster of the genes and impairs activation of pathways of genes important for blood progenitor-cells development and differentiation. As a consequence, JMJD1B deficient mice develop blood cells disorder such as increase in white blood cells (lymphocytosis) and also slight decrease in red blood cells (mild anemia), phenotypes of myelodysplastic syndrome. Particularly these mice displayed a distinct blood cell lineage distribution, with an increase of neutrophils cell population. The most outstanding deduced transcription factors signaling affected by loss of JMJD1B gene and deregulated arginine-methylation level on histones include p53 and CTNNB1 and the gene expression level of corresponding affected genes. These signaling pathways are closely relevant to blood progenitor cell proliferation and differentiation. Figure illustrated the schematic representations of arginine-/lysine-demethylase function of JMJD1B gene and affected corresponding target genes which are involve in blood cell development and differentiation.

This study emphasizes that active arginine demethylation process exists in eukaryotes and that JMJD1B demethylates both methylated arginine/lysine residue of histones for epigenetic programming of gene expression during blood cells development and differentiation. Identification of the arginine demethylase not only fills a fundamental gap for understanding the dynamic regulation of arginine methylation level at histones but also provides therapeutic target for associated disorder.

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Li S, Ali S, Duan X, Liu S, Du J, Liu C, Dai H, Zhou M, Zhou L, Yang L, Chu P, Li L, Bhatia R, Schones DE, Wu X, Xu H, Hua Y, Guo Z, Yang Y, Zheng L, Shen B
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