ELSEVIER

Blood 142 (2023) 155

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

203.LYMPHOCYTES AND ACQUIRED OR CONGENITAL IMMUNODEFICIENCY DISORDERS

Epigenetic Control of B Cell Autoimmunity By Jmjd1c

Yongguang Zhang, PhD[1], *Mei Yu, PhD*[1], *Yongwei Zheng, PhD*[1], *Yuhong Chen*[1], *Jesus Izaguirre-Carbonell*[2], *Nan Zhu, PhD*[3], *Renren Wen, PhD*[1,4], *Demin Wang, PhD*[5,4]

[1] Versiti Blood Research Institute, Milwaukee, WI
[2] Blood Research Institute, Versiti Inc., Milwaukee, WI
[3] Versiti Blood Research Institute Milwaukee, Milwaukee, WI
[4] Department of Microbiology and Immunology, Medical College of Wisconsin, Milwaukee, WI
[5] The Blood Research Institute, Milwaukee, WI

Emerging evidence underscores the importance of e *pigenetic modifications* in controlling B-cell development and function. While Jmjd1c, a member of the l *ysine - specific histone demethylase 3* subfamily, is known to regulate the self-renewal of normal hematopoietic stem cells and leukemia stem cells, its impact on B cell biology is unknown. To explore Jmjd1c's role in B cells, we developed B-cell-specific Jmjd1c-deficient mice through crossbreeding Jmjd1c "floxed" mice with B cell-specific Mb1-Cre mice. The absence of Jmjd1c did not impact B-cell development, but it did lead to significant alterations in basal B cell antibody production. Specifically, we observed skewed isotypes from IgG2c and IgG3 to IgG1 and IgG2b. Additionally, Jmjd1c deficiency affected antigen-specific immune responses upon T-dependent and T-independent antigen challenges, implying a crucial role of Jmjd1c in B cell function. Furthermore, auto-antibody array assays revealed increased self-reactive antibody production in Jmjd1c-deficient animals, indicating the role of Jmjd1c in regulating self-reactive B cells. At a cellular level, Jmjd1c-deficient B cells showed elevated expression of CD86, a canonical marker of B cell activation. Moreover, these B cells exhibited increased BCR-induced cell proliferation, suggesting hyperactivity to antigens, including self-antigens. Notably, Jmjd1c deficiency induced systemic autoimmune disorder in a BM12-induced systemic lupus erythematosus (SLE) animal model, resulting in amplified auto-antibody production and CD86 expression.

To investigate the underlying molecular mechanisms, RNA sequencing analysis demonstrated upregulation of B cell receptor signaling related genes, NF-κB pathway signature genes, and cell cycle-related genes in Jmjd1c-deficient B cells upon anti-IgM stimulation, consistent with their hyperresponsiveness. Of particular interest, we observed upregulation of genes encoding the 26S proteasome complex, a pivotal regulator of diverse cellular processes including NF-κB pathway activation and self-antigen presentation. To explore the epigenetic aspect of these genes, we employed CUT&Tag sequencing and found that Jmjd1c deficiency correlated with increased levels of H3K36me1, a marker of active chromatin and gene transcription. Moreover, the H3K36me1 levels of B cell receptor signaling related genes, NF-κB pathway signature genes, and cell cycle-related genes were significantly augmented in Jmjd1c-deficient B cells upon anti-IgM stimulation. Notably, 26S proteasome subunit genes that were upregulated in Jmjd1c-deficient B cells exhibited higher H3K36me1 modification at the promoter regions.

Collectively, our study provides valuable insights into the epigenetic control of B cell autoimmunity through the regulation of H3K36 mono-methylation by Jmjd1c. This mechanism plays a critical role in B cell activation and function, including the regulation of key genes such as those encoding the 26S proteasome complex.

Disclosures No relevant conflicts of interest to declare.

https://doi.org/10.1182/blood-2023-182034