Special AT-Rich Sequence-Binding Protein 1 Supports Survival and Maturation of Naive B Cells Stimulated by B Cell Receptors

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Epigenetic mechanisms underpin the elaborate activities of essential transcription factors in lymphocyte development. Special AT-rich sequence-binding protein 1 (SATB1) is a chromatin remodeler that orchestrates the spatial and temporal actions of transcription factors. Previous studies have revealed the significance of SATB1 in T cell lineage. However, whether and how SATB1 controls B cell lineage development is yet to be clarified. In this study, we show that SATB1 is an important factor during splenic B cell maturation. By analyzing SATB1/Tomato reporter mice, we determined the dynamic fluctuation of SATB1 expression in the B cell lineage. Although SATB1 expression decreased to minimal levels during B cell differentiation in the bone marrow, it resurged markedly in naive B cells in the spleen. The expression was dramatically downregulated upon Ag-induced activation. Splenic naive B cells were subdivided into two categories, namely SATB1^{high} and SATB1$^{-/low}$, according to their SATB1 expression levels. SATB1^{high} naive B cells were less susceptible to death and greater proliferative than were SATB1$^{-/low}$ cells during incubation with an anti-IgM Ab. Additionally, SATB1^{high} cells tended to induce the expression of MHC class II, CD86, and CD83. Accordingly, naive B cells from B lineage–specific SATB1 conditional knockout mice were more susceptible to apoptosis than that in the control group upon anti-IgM Ab stimulation in vitro. Furthermore, conditional knockout mice were less capable of producing Ag-specific B cells after immunization. Collectively, our findings suggest that SATB1 expression increases in naive B cells and plays an important role in their survival and maturation. ***The Journal of Immunology*****, 2022, 208: 1–10.**

Numerous studies have shown that transcription factors play essential roles in lymphocyte maturation (1); they directly bind to the promoter elements of key genes, thereby inducing or repressing these expressions. Many recent studies have also focused on epigenetic mechanisms (including DNA methylation, histone modification, and chromatin remodeling) because they work cooperatively with transcription factors in the dynamic control of gene expression (2, 3).

Special AT-rich sequence-binding protein 1 (SATB) functions in the epigenetic remodeling of chromatin architecture, which is indispensable for normal T lymphocyte development (4–6). SATB1 organizes cell type–specific nuclear architecture by binding specific AT-rich motifs of DNA sequences and folding chromatin into loop forms (7, 8). The loop forms combine enhancer or repressor regions with target genes that are separated by long sequence distances, thereby regulating the transcription of target genes elaborately (7, 8). As SATB1 is predominantly expressed in the thymus, it is understandable that T cell development is impaired in SATB1-deficient mice (4).

In addition to its essential roles at the $CD4^+CD8^+$ double-positive stage in T cell development, several reports have shown that SATB1 is also involved in the late stages of T lineage differentiation and that it plays an essential role in establishing immune tolerance (9, 10). Downregulation of the SATB1 expression is required for the generation of $CD4^+CD25^+$ regulatory T cells (9). In mice, T cell–specific SATB1 deletion was found to significantly reduce the number of $Foxp3^+$ regulatory T cells, and they developed lethal autoimmune disease (10). Furthermore, SATB1 has also been found to play a role in preventing premature T cell exhaustion by regulating the expression of programmed cell death protein 1 (*Pdcd1*), which encodes the inhibitory receptor PD-1. PD-1 expression levels increased 40-fold in SATB1-deleted T cells, which impaired their effector response to tumor cells (11).

However, compared with our extensive knowledge of T cells, we have limited knowledge of SATB1 function in B cell lineage. In SATB1-deficient mice, the B lymphocyte numbers were found to decrease, although the developmental defect in the B lineage was less evident than that in the T lineage (4). Our previous studies have shown that SATB1 governs the early differentiation process of hematopoietic stem cells (HSCs) toward both T and B cell lineages (12, 13). Indeed, a high SATB1 expression was found to enhance B lymphocyte production, even from aged HSCs, whereas SATB1

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Received for publication November 17, 2021. Accepted for publication February 9, 2022.

This work was supported by Japan Society for the Promotion of Science KAKENHI Grants 21K08415 and 18K16115.

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The online version of this article contains supplemental material.

Abbreviations used in this article: BM, bone marrow; CGG, chicken γ globulin; cKO, conditional knockout; GCB, germinal center B cell; HSC, hematopoietic stem cell; MHC II, MHC class II; NP, 4-hydroxy-3-nitrophenylacetyl; qRT-PCR, quantitative real-time PCR; SATB1, AT-rich sequence-binding protein 1; T, transitional.

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