

Autoreactive Pre-Plasma Cell Regulation

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To determine how autoreactive B cells are regulated to prevent autoimmunity, we have created the 2-12H transgenic (Tg) mouse to study the regulation of anti-Smith (Sm) B cells. Sm is a target of the immune system in systemic lupus erythematosus (SLE) and mouse models of SLE, and anti-Sm is a diagnostic marker of this disease. Approximately 30% of peripheral B cells in 2-12H mice are anti-Sm, yet the anti-Sm titer in these mice is no different from non-Tg, indicating regulation. We have recently defined a tolerance checkpoint at an early pre-plasma cell (PC) stage that is overcome in MRL/*lpr* mice, a mouse model of SLE. Anti-Sm pre-PCs in the 2-12H spleen are present at a high frequency (~20%) and their formation is antigen-dependent, yet they are regulated to prevent antibody-secreting cell (ASC) differentiation. We show here that these cells are highly sensitive to toll-like receptor activation: LPS stimulation induces a ~2-fold increase in anti-Sm ASCs compared to non-pre-PCs and CpG stimulation induces a ~5-fold increase. Moreover, 2-12H pre-PCs become ASCs upon anti-CD40 and IL-4 stimulation, suggesting T cell signals are also capable of activating these cells. Importantly, 2-12H pre-PCs are activated to secrete autoantibody upon transfer to C57BL/6 *Fas^{lpr}* mice, indicating they are able to rapidly become ASCs in this autoimmune environment. Adoptive transfer experiments indicate that both anti-Sm follicular (FO) and marginal zone (MZ) B cells are precursors to pre-PCs. Immunization of 2-12H mice with apoptotic cells, which expose Sm on their surface, induces anti-Sm MZ B cell depletion and promotes anti-Sm pre-PC differentiation. These results are consistent with a relationship between anti-Sm MZ B cells and pre-PCs *in vivo*. These data provide evidence that pre-PCs are functional and poised to secrete, thus a necessary checkpoint for autoreactive B cell regulation.