

## Multiple Roles for Blimp-1 in Lymphocytes

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B lymphocyte induced maturation protein-1 (Blimp-1) has previously been shown to be both required and sufficient for terminal differentiation of activated B cells to become immunoglobulin (Ig)-secreting, non-dividing plasma cells. To enforce plasmacytic differentiation Blimp-1 regulates several critical programs of gene expression. First, Blimp-1 represses an activated B cell phenotype. Repression of both Bcl-6 and Pax5 are involved in this function. Other repressed genes include those encoding proteins necessary for BCR signaling, interaction with T cells, follicular homing, somatic hypermutation and isotype class switching. Second, it represses cell proliferation. This involves direct repression of c-myc, as well as repression of many other genes required for cell cycle entry, DNA replication and cell division. Third, it induces Ig secretion. Direct repression of Pax5 by Blimp-1 leads to derepression of IgH, J chain and XBP-1. Blimp-1 is also required for formation of mu-secreted mRNA. XBP-1 is then the proximal inducer of many genes involved in endoplasmic reticulum function and protein secretion. [1-3]. More recently we have shown that Blimp-1 is also required for secretion of Ig by B-1 cells. In B-1 cells lacking Blimp-1, Pax5 fails to be repressed and muS and XBP-1 fail to be induced, showing that B-1 and B-2 cells share these components of the program regulating Ig secretion.

Long-lived plasma cells in the bone marrow provide one form of humoral memory; however they can be pathogenic in certain autoimmune diseases. We have shown that once plasma cells are formed and home to the bone marrow, they continue to require Blimp-1 for their maintenance. This requirement demonstrates that the changes in histone covalent modification and chromatin structure that are thought to be important for Blimp-1 to repress its target genes are not stable, even in the absence of cell division [4].

However, Blimp-1 is not a B-cell specific protein. In the T-cell lineage, Blimp-1 mRNA is present in thymocytes and naïve T cells. It is approximately 30X higher in effector T cells and in regulatory T cells. Highest levels are found in Th2 cells. Memory cells have levels intermediate between naïve and effector T cells. When Blimp-1 is deleted in a T-lineage specific way using LckCre, conditional knockout (CKO) mice develop severe colitis at an early age. They have reduced numbers of thymocytes due to increased apoptosis and hyperactivated peripheral T cells. Naïve CD4<sup>+</sup> T cells in CKO mice are hyperproliferative and make more IL-2 following TCR stimulation. CKO cells also make more IFN $\gamma$  and less IL-10 when stimulated under non-polarizing conditions. In vivo models support the idea that defects in both naïve/effector and Tregs are involved in colitis in the CKO mice. We are continuing to study both the regulation and molecular mechanisms of action of Blimp-1 in thymocytes and T cells.

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3. Shapiro-Shelef, M., et al., *Blimp-1 Is Required for the Formation of Immunoglobulin Secreting Plasma Cells and Pre-Plasma Memory Cells*. *Immunity*, 2003. **19**: p. 607-620.
4. Shapiro-Shelef, M., et al., *Blimp-1 is required for maintenance of long-lived plasma cells in the bone marrow*. *J Exp Med*, 2005.