trasted with the negative regulatory cells both expressing CD25 (IL-2Rα), was not anticipated. The sparing of the negative regulatory cells from the ADCC process may reflect the lower levels of expression of IL-2Rα on these cells when contrasted with that of fully activated effector T cells. The combined IL-2/Fc, mIL-15/Fc, and rapamycin treatment had a number of desirable effects including the hastening of the expression of IL-2Rα among activated T cells. Furthermore, as just noted, the three element combination therapy exclusively acted upon activated T cells but spared the $CD4^+CD25^+$ T cells that were resistant to the lytic effects of IL-2/Fc. The combination strategy involving IL-2/Fc, mutant IL-15/Fc, and rapamycin treatment was successful in the induction of the indefinite engraftment of MHC mismatched skin and heart allografts and also permitted the long-term engraftment of allogenic islets in nonobese diabetic (NOD) mice (Zheng et al., 2003).

The present study was developed to prevent allograft rejection but the approach may also be applicable to the treatment of autoimmune diseases where the elimination of activated cytotoxic T cells and self-reactive memory T cells with the simultaneous retention of $CD4^+CD25^+$ negative regulatory cells would be desirable. In parallel with receptor directed monoclonal antibody-mediated strategies being used to interdict the interactions of IL-2 and IL-15 with their receptors on activated T cells and memory CD8 cells, the therapeutic approach being proposed by Zheng has successfully translated the emerging insights concerning the roles of IL-2 and IL-15 cytokines and their receptors in the balance between cytopathic and regulatory cells to yield a rational approach for the treatment of autoimmune diseases and for the maintenance of allograft retention (Zheng et al., 2003; Guex-Crosier et al., 1997).

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It's a Good Year for Blimp-1 (and Plasma Cells)

Immunoglobulin secreting plasma cells are critical mediators of an effective humoral immune response. In this issue of *Immunity,* an article by Shapiro-Shelef et al. defines an essential role for the transcription factor Blimp-1 in plasma cell differentiation and preplasma memory B cell formation.

During a primary humoral response, engagement of antigen-specific receptors on naive B cells initiates a series of temporally and spatially regulated events that lead to the differentiation of both memory B cells and antibody-secreting plasma cells. As terminally differentiated effector cells, plasma cells play an essential role in the humoral immune response by producing large amounts of immunoglobulin (Ig). These antibodies act as protective effector molecules in the elimination of invading pathogens. Conversely, production of autoreactive antibodies is pathogenic in autoimmune diseases such as systemic lupus erythematosus. Therefore a better understanding of the molecular mechanisms involved in plasma cell differentiation and Ig secretion are crucial for effective drug design targeting autoimmune diseases and vaccine development.

Currently only two transcriptional regulators, X box protein-1 (XBP-1) and B lymphocyte induced maturation protein 1 (Blimp-1), have been shown to be involved in plasma cell differentiation. Chimeric mice whose lymphoid system lacks XBP-1 have a severe impairment in the production of immunoglobulin of all isotypes despite the presence of normal numbers of T and B cells. Inspection of the peripheral lymphoid tissue revealed an absence of plasma cells, demonstrating an absolute requirement for XBP-1 in B cell terminal differentiation (Reimold et al., 2001). Now an article by Shapiro-Shelef et al. in this issue of *Immunity* provides definitive proof that Blimp-1 is also essential for plasmacytic differentiation.

Blimp-1 (also called PRD1), isolated by Mark Davis' laboratory almost a decade ago, was the first transcription factor described to drive B cell differentiation to the plasma cell stage (Turner et al., 1994). This zinc finger protein is specifically expressed in a subset of germinal center B cells and plasma cells. Overexpression of Blimp-1 in the BCL1 cell line induces plasmacytic differentiation accompanied by J chain expression and Ig secretion (Calame, 2001). Unequivocal proof that Blimp-1 was required for plasma cell differentiation was missing, however, because of the early embryonic lethality of homozygous mutant embryos. Shapiro-Shelef et al. have now solved this problem. They generated mice lacking Blimp-1 in B cells by crossing mice expressing CD19-driven Cre recombinase with mice in which the

prdm1 locus was flanked by *lox*P sites to generate conditional null alleles of *prdm1* in B cells. Although numbers and phenotype of bone marrow and splenic B cell subsets appeared normal, serum Ig levels of all isotypes were significantly reduced both at baseline and upon immunization with T-independent and T-dependent antigens. As for XBP-1, both numbers of IgM secreting cells and $CD138^{+}B220^{+/-}$ plasma cells were shown to be significantly reduced. That the defect was intrinsic to the B cell was evidenced by the failure of LPS stimulated $prdm1^{-/-}$ B cells to produce wild-type levels of IgM and IgG3 and to differentiate into $CD138^{+}$ cells.

Recent microarray analyses have suggested that the mechanism by which Blimp-1 promotes plasma cell generation largely relies on a program of transcriptional repression of genes involved in proliferation and germinal center function (Shaffer et al., 2002). Among the target genes identified were subsets of genes involved in cell cycle (*c- myc, E2F-1,* p18, and p21) and the inhibition of apoptosis *(A1).* The hyperproliferation observed in $prdm1^{-/-}$ B cells is consistent with a role for Blimp-1 as an inhibitor of cell division and ties in nicely with work from Chen-Kiang on the cell cycle regulator p18 (INK4c) that revealed a close link between proliferation, apoptosis, and differentiation in generating the plasma cell lineage (Morse et al., 1997).

One interesting Blimp-1 target gene is XBP-1 itself. Previous work and data from this report showing defective XBP-1 expression in Blimp-$1^{-/-}$ B cells support the idea that Blimp-1 acts upstream of XBP-1. One way by which Blimp-1 could induce XBP-1 transcription is by relieving the repression by BSAP/Pax5, a B cell factor that binds to and suppresses XBP-1 transcription. However, the lack of plasma cells in $prdm1^{-/-}$ B cells was not exclusively due to the absence of XBP-1, since ectopic expression of Blimp-1 but not XBP-1 restored plasmacytic differentiation. This is not surprising as the regulation of XBP-1 is subject to complex transcriptional and posttranscriptional controls that likely stem from additional upstream factors. For example, the immediate and early induction of XBP-1 by both IL-4 and IL-6 argues against a Blimp-1-dependent mechanism (Iwakoshi et al., 2003). Thus, Blimp-1 and XBP-1 must control unique as well as overlapping sets of target genes involved in plasma cell differentiation. Other attractive candidates involved in Ig secretion or plasma cell differentiation such as IRF4, NFATc1, 2, BCL-6, and Ets 1 are poorly understood in relation to Blimp-1 and XBP-1 and important goals for future studies. A comparison of $prdm1^{-/-}$ and $xbp\text{-}1^{-/-}$ target genes should shed light on these issues.

The upstream signals that regulate Blimp-1 remain unclear although XBP-1 does not appear to be one of them, as previous work has shown that Blimp-1 is normally expressed in XBP-$1^{-/-}$ B cells. A better understanding of these signals is critical in allowing the identification of in vivo factors important for plasma cell differentiation. For example, XBP-1 is a vital component of the unfolded protein response (UPR), a signaling pathway evoked by ER stress that is required for the correct folding and transport of proteins from secretory cells such as plasma cells. During the UPR, XBP-1 mRNA is subjected to an unconventional splicing event by the endoribonuclease IRE1 (Calfon et al., 2002; Shen et al., 2001; Turner et al., 1994; Yoshida et al., 2001). The resultant spliced XBP-1 mRNA encodes for a more transcriptionally active form of XBP-1, and it is this spliced form that has been specifically shown to be necessary for plasma cell differentiation and the UPR (Iwakoshi et al., 2003). It is still unclear whether XBP-1 has a distinct role in plasma cell differentiation in addition to its role in the UPR. Analogously, it is not clear whether Blimp-1 is also involved in UPR-related secretory activities independent of XBP-1. The importance of the UPR in the developmental program of plasma cells cell remains an intriguing question.

The authors also examined memory B cell subsets in $prdm1^{-/-}$ mice and discovered that preplasma memory B cell formation is severely defective in the absence of Blimp-1. Thus, immunized $prdm1^{-/-}$ mice display a block in the generation of antigen-specific $B220^{-}$ memory B cells that results in the accumulation of an antigen-specific $B220^{+}$ cell population. This provocative result was perhaps not entirely unexpected given that previous work by this group provided evidence that a preplasma $B220^{-}$ memory B cell population could rapidly differentiate to $CD138^{+}$ plasma cells (McHeyzer-Williams et al., 2000). A more precise, functional characterization of this distinct $B220^{+}$ cell population that accumulates in the absence of Blimp-1 may be difficult since these cells hyperproliferate and fail to produce antibody. Nonetheless, the involvement of Blimp-1 in memory B cell formation is an interesting observation that is certain to provide new insights into a still poorly understood but critical stage of humoral immunity.

It wasn't all that long ago when most discussions about plasma cell differentiation emphasized how little we knew about it. Although this is still true, some major strides have occurred in this field recently, as illustrated by the elegant paper by Shapiro-Shelef in this issue of *Immunity.* It confirms much of what we expected from Blimp-1 but also offers novel insights and valuable tools to pursue further studies in this arena.

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