

## **IL-6 regulates antigen-experienced B cells via an Erk-dependent mechanism**

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A robust immune response to polyclonal activators such as LPS is essential for a rapid clearance of pathogens. Interestingly, polyclonal activation does not trigger autoantibody secretion, suggesting that autoreactive B cells are regulated during innate immune responses. We recently described that B cell tolerance to Smith antigen (Sm) is maintained during activation of innate immune responses by dendritic cell secretion of IL-6. IL-6 repressed immunoglobulin (Ig) secretion by antigen-experienced B cells during polyclonal activation. In contrast, IL-6 did not diminish Ig secretion by naïve cells, supporting previous studies that IL-6 acts as a positive regulator of B cell differentiation. Repression of Ig secretion by IL-6 was not limited to Sm-specific B cells (2-12H/Vk8) as hen egg lysozyme- (HEL), and *p*-azophenylarsonate-(Ars) specific B cells also failed to secrete Ig when exposed to IL-6. This indicates that chronic exposure to self-antigen reprograms the IL-6 receptor to repress Ig secretion. To investigate the molecular basis for this differential response to IL-6 in naïve and chronically antigen-experienced B cells, we examined IgM and Blimp-1 mRNA in naïve and antigen-experienced B cells following IL-6 receptor ligation. In antigen-experienced cells, IL-6 stimulation resulted in decreased IgM protein and mRNA levels, as well as decreased Blimp-1 mRNA levels. This suggests that regulation occurs at the level of IL-6-mediated signal transduction. IL-6 signaling proceeds through two distinct pathways: the Ras-MAPK pathway and the Jak-Stat3 pathway. To establish the molecular basis of IL-6-mediated repression we examined the role of Erk since it has been implicated in regulating TLR9-induced Ig secretion. Pharmacological inhibition of Erk resulted in a loss of IL-6-mediated repression: IgM secretion was restored and the levels of IgM and Blimp-1 mRNA were comparable to those observed in LPS-stimulated cells. These data indicate that IL-6-induced Erk activation represses Ig secretion and the synthesis of upstream transcriptional regulators such as Blimp-1. We are currently evaluating targets of Erk to elucidate the central effector that regulates IL-6 Ig secretion in antigen-experienced, and naïve B cells.