Poster #24

Synergistic induction of IL-27 in B cells by TLR and CD40 signaling inhibits class switch DNA recombination and plasma cell differentiation.

Wang, R.[1], **Lou, Z.**[1], **Rivera, C.**[1], **Kulp, D.**[1], **Heredia, D.**[2], **Casali, P.**[1] **and Xu, Z.**[1]

[1]*The Antibody Laboratory, Department of Microbiology and Immunology, School of Medicine, University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229.*
[2]*School of Science, Engineering and Technology, St. Mary's University, San Antonio, TX.*

During host immune responses to microbial pathogens and allergens, a B cell is exposed to T-independent (e.g., a ligand of Toll-like receptor, TLR) and T-dependent (i.e., CD40 ligand, CD154) stimuli and integrates different signals for effective antibody responses. We have previously shown that engagement of a TLR (e.g., TLR4 by LPS) or CD40 in B cells induces immunoglobulin (Ig) class switch DNA recombination (CSR) and B cell differentiation into plasma cells. Here, we showed that co-stimulation of TLR4 and CD40, unexpectedly, inhibited CSR to IgG1, IgG2b, IgG3, IgA and IgE as well as plasma cell differentiation. The inhibition was associated with normal IgH germline I_H-C_H transcription and AID induction (as critical for CSR) and expression of Blimp-1 (a master transcription factor in plasma cell differentiation), but much upregulated B cell expression of IL-27, an immunosuppressive cytokine. Knockout (KO) of the IL-27 receptor gene (*Il27ra*$^{-/-}$) in co-stimulated B cells effectively, albeit not fully, restored significant levels of CSR and plasma cell differentiation; so did an antibody that blocked the activity of the p28 subunit of IL-27. Indeed, induction of these two B cell differentiation processes by TLR4 or CD40 alone was enhanced in *Il27ra*$^{-/-}$ B cells and, conversely, inhibited by recombinant IL-27. These findings indicate an autocrine role of IL-27 in negatively regulating B cell functions. They also suggest a B cell-intrinsic role of IL-27 in shaping T cell-dependent antibody responses to microbial components that also engage TLRs and in controlling autoimmunity underpinned by aberrant T helper cell and dysregulated TLR activities.

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