Short Communication
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IL-10 producing regulatory b cells: where are we?

Abstract

B cells have long been only considered as effector cells during the specific immune response because of antibody production and antigen presentation to T cells. Recently growing evidence has shown that B cells are also able to secrete proinflammatory cytokines as well as the anti-inflammatory cytokine IL-10. IL-10-producing regulatory B cells (Bregs) and more recently IL-10 producing plasma cells have been undoubtedly identified in mice and shown to down-regulate inflammation. Several recent works have also identified IL-10 producing regulatory B cells in humans and have begun to unravel their phenotype and mode of suppression. Future work should explore whether a specific transcriptional factor drives the natural fate of Bregs or whether IL-10 producing B cells only emerge from any B cell subset in response to specific inflammatory signals.

Keywords: B cell, Plasma cell, Interleukin-10, Tolerance

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B cells were first recognized for their role as positive regulators of immune responses in immunity, because they can give rise to antibody-producing plasma cells and contribute to CD4+ T cell responses. The B cells carrying these functions can be commonly designated as effector B cells. Recent studies have indicated that B cells also play a role as negative regulators of immune response in autoimmunity, these properties being mainly attributed to the latterly described interleukin 10 (IL-10) regulatory B cell (Breg) compartment.[1,2] Bregs play key roles in immune tolerance and their absence results in exacerbation of auto-immunity,[3-7] graft-versus-host disease[8] and impaired anti-tumor immune response.[9] The first assumption that B cells may have a suppressive role wass made in the early seventies in a contact dermatitis mouse model. In this study, adoptively transferred whole splenocytes but not adoptively transferred B cell depleted splenocytes had a suppressive effect *in vivo*.[10] In mouse models of inflammation key experiments demonstrated the negative regulatory role of IL-10 producing B cells. Janeway et al.[5] have shown that B cells had regulatory properties in a mouse model of experimental autoimmune encephalomyelitis (EAE).[5] Later, the regulatory properties of these B cells were linked to their ability to produce IL-10:[3] bone marrow chimeras with IL-10 deficient B cells have more severe autoimmune encephalomyelitis (EAE) ("B cells regulate autoimmunity by provision of IL-10"). Mizoguchi et al.[11] demonstrated that chronic intestinal inflammation generates IL-10 producing B cells in mesenteric lymph nodes and that these IL-10 producing B cells suppressed inflammatory bowel disease.[11] Mauri et al.[7] described that repeated adoptive transfer of CD40-activated B cells (IL-10 producing B cells) reduced the severity of collagen-induced arthritis in mice.[7] Finally, Tedder group showed in several publications that adoptive transfer of IL-10 producing B cells that displayed a $CD5^{+}CD1d^{hi}$ phenotype (called "B10" cells) could diminish inflammation in mouse models of contact dermatitis,[6] EAE[12] and lupus.[13] The most recent findings about the biology of Bregs in mice include: i/ the crucial role of interleukin 21 in the *in vitro* generation of IL-10 producing B cells,[14] ii/ the emerging concept that plasma cells derived from B cells play a key role *in vivo* in the regulatory function of the B cell lineage through IL-10 and IL-35 cytokine production.[15] We and others have also identified IL-10 producing regulatory B cells in humans and have begun to unravel their phenotype and mode of suppression. Cell surface phenotype of human Bregs mainly includes $CD24^{high}CD27^{+}$ B cell subset.[16,17] and $CD24^{high}CD38^{high}$ transitional blood B cell subset.[18] Mechanisms of suppression may imply inhibition of CD4+ T proliferation, inhibition of Th1 differentiation, induction of regulatory T cells and suppression of monocyte activation. Recently diminished frequency and/or a diminished suppressive capacity of Bregs have been demonstrated in patients with lupus,[18] immune thrombocytopenia,[19] rheumatoid arthritis[20] and ANCA-associated vasculitis.[21] However the exact mechanism of how human Bregs exert their regulatory functions *in vivo* remains unclear. Future work should explore whether a specific transcriptional factor drives the natural fate of Bregs or whether IL-10 producing B cells only emerge from any B cell subset in response to specific inflammatory signals.

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Conflicts of interest

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