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Editorial Note: Special Edition

Development of humoral immunity

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This issue of *Biomedical Journal* contains four review articles describing our current understanding of the development and biology of B lymphocytes.

The first review article, by Dr. Ana Cumano and her colleagues [1], describes how the B lymphocyte compartment develops during embryogenesis, and analyzes the contribution of successive waves of progenitors from the yolk sac, aorta-gonads-mesonephros, fetal liver and bone marrow in the production of different B cell subsets. The complexity of these developmental processes is well documented and the fundamental role of several key transcriptional regulators in the establishment of B lymphocyte identity is emphasized in the review. This interesting review provides insights from a very productive scientist who has made major contributions to the field of B lymphocyte development over the past few decades.

The second article, by Dr. Matthew Macauley and his colleagues [2], presents an exhaustive review of the literature on CD22, and analyzes the role of this inhibitory co-receptor in tuning down signaling via the B cell receptor (BCR). The authors describe the structure of sialic acid ligands of CD22 and critically analyze the interactions between CD22 and glycan ligands on the same cell surface (cis-interaction) or on another cell (trans-interaction). They also describe experimental evidence indicating that cis-interactions trigger the formation of nanoclusters of CD22 molecules, which express sialic acid and thus can form homomultimers. These cis-interactions maintain CD22 nanoclusters at a distance from the BCR, while trans-interactions recruit CD22 into the immunological synapse, where the association of CD22 clusters with the BCR leads to a decrease in BCR signaling [Fig. 1]. In addition, the review mentions the potential role of CD22 in maintaining B cell tolerance to self-antigens and the ability of CD22 to downmodulate Toll-like receptor (TLR) signaling. This review provides a thorough summary of current views of CD22 function, and its eight figures are very useful in helping the reader to understand the subtleties of the complex interactions between CD22 and its ligands and the role of CD22 in modulating BCR signaling.

The third article, by Dr. Simon Fillatreau [3], describes the different immunosuppressive B lymphocyte subsets in various autoimmune, infectious and malignant diseases. The immunosuppression is mediated by IL-10-producing B lymphocytes and antibody-producing plasma cells. Importantly, several surface receptors on B cells, such as the tetraspanin CD9, the T cell Ig domain and mucin domain protein 1, and the tumor necrosis factor receptor 2 are associated with the production of IL-10 by B lymphocytes. Several signals involved in the development of suppressive B cells *in vivo* and the principal transcription factors regulating the expression of IL-10 by B lymphocytes are presented in the review. Experimental

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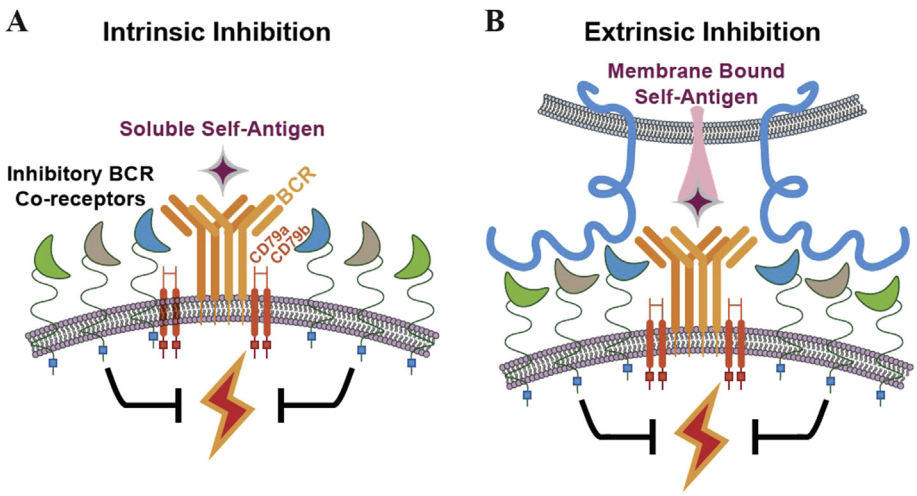

Fig. 1 Intrinsic and extrinsic models for BCR inhibitory co-receptors. (A) Intrinsic inhibitory co-receptors dampen B cell activation by antagonizing BCR signaling. (B) Extrinsic inhibitory co-receptors antagonize BCR signaling and are dependent on how the antigens are displayed. For example, co-expression of self-associated molecular recognition patterns with membrane-bound antigens on another cell have the potential to draw the inhibitory receptor into an immunological synapse and prevent B cell activation. Source: Enterina et al. [2].

evidence is also provided to show that IL-10-producing plasma cells are major players in the immunosuppressive function of B lymphocytes *in vivo*. An interesting model of hepatocellular carcinoma is described in which IgA^+ plasma cells expressing PD-L1 and secreting IL-10 inhibit the natural anti-tumor activity of $CD8^+$ T lymphocytes. Finally, in the last paragraph of this stimulating review, Dr Fillatreau summarizes the functional characteristics of an unusual population of regulatory plasma cells expressing several surface markers ($LAG\text{-}3^+$, $CD200^+$, $PD\text{-}L1^+$, $PD\text{-}L2^+$, $CD19^+$ $CD138^{high}$). This cell subset down-modulates the early innate immune response of neutrophils and NK cells against infectious agents and produces IL-10. Interestingly, these $IL\text{-}10^+$ natural plasma cells express a unique BCR repertoire and molecules such as LAG-3, which correlate with IL-10 expression.

The last review article, by Drs. Meryem Aloulou and Nicolas Fazilleau [4], analyzes the role of different T lymphocyte sub-populations involved in the selection and differentiation of germinal center B lymphocytes. Development and differentiation of follicular helper T cells (Tfh) are stimulated by interactions with antigen-presenting cells, which also involve multiple co-stimulatory molecules. In addition, after antigen priming, Tfh cells express the master transcription factor Bcl-6 which is mediated by IL-6 and IL-21. All these complex molecular mechanisms are presented and discussed in the review. A section of the review is devoted to the topic of circulating and memory Tfh cells, and describes their phenotypes and functions. The last section analyzes the differentiation and roles of follicular regulatory T cells (Tfr), which are implicated in the control of immune self-tolerance and homeostasis. The review provides a thorough comparison of Tfr and Tfh lymphocytes, which can be helpful for experts and novices alike. Overall, this stimulating review of many recent findings helps the reader to understand the complexity of the mechanisms involved in affinity maturation of antibodies, class switch, and generation of long-lived plasma cells and memory B cells.

In conclusion, this collection of timely reviews should interest a broad spectrum of immunologists who study the biology and development of humoral immunity.

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