EDITORIAL

Frontiers in B-cell immunology

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During the last several decades, significant progress has been made in understanding the roles of B cells in immunity and autoimmunity. B-cell development, occurring in the bone marrow, is a complex dynamic process involving immunoglobulin (Ig) gene rearrangement and B-cell receptor (BCR) expression. Early progenitor B (pro-B) cells initiate DNA rearrangement at their Ig heavy chain loci, resulting in the synthesis of μ -chains in the cytoplasm and the assembly of the precursor B-cell receptor (pre-BCR). Following successful rearrangement of light chain genes, these precursor B (pre-B) cells differentiate into immature B cells when whole IgM molecules are expressed as the functional BCR on the cell surface. Newly formed immature B cells then leave the bone marrow and become mature B lymphocytes in the peripheral lymphoid organs. To generate the functional antibody repertoire, developing B cells in the bone marrow pass through a number of checkpoints to select cells for survival upon their successful Ig gene rearrangements and subsequent functional BCR expression. Although B cells have been well recognized as a major player in adaptive immune responses *via* antibody production and antigen presentation, recent studies have revealed new functional features of various B-cell subsets under both the steady-state and autoimmune conditions.

In this issue, there are five reviews that highlight recent progress in studying the regulation of B-cell development and function, as well as B cell-targeted therapy for autoimmune diseases. Hua and Hou¹ review the role of Toll-like receptor (TLR) signaling in modulating B-cell development and activation. Early studies have revealed functional TLR expression in early hematopoietic progenitors, and activation of TLR signaling in these cells shifts their development potential towards myelopoiesis rather than lymphopoiesis.¹ It has become clear that TLR signaling plays a pivotal role in regulating B-cell lymphopoiesis and shaping the composition of the B-cell repertoire. Moreover, TLR9 signaling has been shown to drive murine common lymphoid progenitors to differentiate into dendritic cells. In addition to its role in B-cell lineage commitment, TLR signaling also plays a role in the negative selection

process during B-cell development, as suggested by findings that reduced TLR signaling may increase the threshold for the elimination of B cells during negative selection. In recent years, increasing evidence has accumulated to indicate that microRNAs (miRNAs) are implicated in normal immune function and autoimmune inflammation. In the review by Li *et al.*,² the authors present an overview of recent advances in elucidating the role of miRNAs in B-cell development, differentiation, apoptosis and function. It is known that miRNAs are first transcribed by RNA polymerase II as primary transcripts and then processed by RNase III-type endonucleases, Drosha and Dicer, into mature miRNAs, which serve as post-transcriptional regulators by binding to complementary sequences on target messenger RNA transcripts, usually resulting in translational repression or target degradation and gene silencing. Dicer ablation in mice results in a B-cell developmental block at the pro- to pre-B-cell transition stage and significantly affects antibody diversity.² To date, several miRNAs including miR-181, miR-150, the miR-17-92 cluster and miR-34a have been identified as important regulators in modulating B-cell development in the bone marrow.² Moreover, several studies have also supported a crucial role played by miRNAs in regulating germinal center B-cell formation during terminal B-cell differentiation in peripheral lymphoid system. There is increasing evidence to indicate that miR-155 is required in normal B-cell function and germinal centre response, whereas miR-181b negatively regulates class-switch recombination.² Although the regulatory mechanisms of miRNAs in controlling and maintaining B-cell development and homeostasis remain largely unclear, future studies on miRNAs and their targets will provide new insights for understanding B-cell development and function.

Although B cells are generally considered to be a positive regulator for their ability to produce antibodies and facilitate optimal CD4⁺ T-cell activation by serving as an antigen-presenting cell, recent studies have characterized various B-cell subsets that can also negatively regulate the immune response by producing regulatory cytokines or directly interacting with pathogenic T cells. Zhang³ has reviewed the latest advance in the field of innate-like B cells (ILBs) with a focus on their regulatory functions in mice and human. ILBs, a heterogeneous population of unconventional B cells with innate-sensing and

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responding properties, are composed of B1 cells, marginal zone B cells and related B cells in mice. ILBs are mainly involved in natural IgM production at the steady state but can rapidly acquire immune regulatory functions through antibody secretion and cytokine production upon activation by innate signals. Recent studies show that B1 and marginal zone B cells rapidly produce IgM concomitantly with the upregulation of Blimp-1 and Xbp-1, following TLR4 agonist LPS or TLR9 agonist CpG stimulations. Newly produced natural IgM plays a critical role in the protection of the host before eliciting an adaptive immune response. Extensive studies have suggested that ILBs exert their regulatory functions in an IL-10-dependent fashion in murine models of various inflammatory and autoimmune diseases.³ Growing evidence also shows that microbes such as parasites and bacteria can directly stimulate ILBs to exert a regulatory function by producing IL-10 during infections. To provide an update on IL-10 producing regulatory B (Breg) cells, Yang *et al.*⁴ have reviewed recent developments in the characterization of Breg cells with a focus on the functional implications of these cells in autoimmune disease. Although the exact origin and molecular identity of Breg cells remain elusive, accumulating evidence suggests that the Breg cell population is heterogeneous and can be derived from all B cells if given the appropriate stimulatory signals and context. Although the existence of Breg cells in various types of mouse disease models including inflammation, autoimmunity and cancer is well established, the phenotypic characterization of Breg cells in humans has only recently been reported. Moreover, dynamic changes of Breg cells have been shown to be associated with the disease progression of human autoimmune diseases. Notably, Breg cells can not only influence the Th1/Th2 balance, but also regulate Treg/Th17 cell functions, which supports the notion that Breg cells may play an important role in modulating T-cell plasticity.⁴ Apart from cytokine-mediated suppression, B cells can also exert their regulatory function by cell–cell interactions, including the promotion of activation-induced cell death. Since recent studies from various mouse models have suggested that B-cell depletion leads to the expansion of the Breg cell subset in reconstituted B-cell populations *in vivo*, further investigations on the effect of adoptive transfer of Breg cells alone or in combination with B-cell depletion may provide a novel and effective treatment for autoimmune diseases.⁵

Autoreactive B cells are one of the key immune cell types that have been implicated in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus (SLE). Chan and colleagues⁶ have reviewed the role of B cells in SLE in animal and human studies and present an update on the clinical trials that have evaluated the therapeutic efficacy and safety of agents that antagonize CD20, CD22 and B-lymphocyte stimulator in human SLE. It has been well recognized that the prominent elevation of auto-antibodies against nuclear antigens is the key pathological factor leading to the formation and deposition of

immune complexes that cause tissue inflammation and multiple organ damage in SLE patients. Current studies have suggested that B cells are critically involved in disease initiation and development. In addition to functioning as antigen-presenting cells for activation of autoreactive T cells, B cells can secrete various pro-inflammatory cytokines, such as lymphotoxin- α , TNF- α and IL-6, which may exacerbate disease progression.⁶ Although the efficacy of B-cell targeted therapies remain to be revealed in more clinical trials, a fuller understanding of the development and functional characteristics of various B-cell subsets is essential for the design of new B-cell therapies in the future.

In view of the rapidly evolving field of B-cell biology, many critical questions await to be addressed, including further characterization of the molecular targets of miRNAs in regulating B-cell development and functional maturation; dissection of the intrinsic signaling pathways in TLR-mediated B-cell activation and function; elucidation of the developmental pathways and functional differentiation of the innate-like lymphocyte subset; identification of the origin and molecular signature of Breg cells; and exploration of the selective targeting of autoreactive B cells without compromising humoral immunity in the treatment of autoimmune disease. Answers to these key questions will enhance our current understanding on the pivotal role of B cells in the immune response and autoimmune development.

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