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Cells in focus

B cells—Masters of the immunoverse

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ABSTRACT

The immune system involves the complex interplay between many different cell types. Over the last decade, T cells, dendritic cells (DC) and macrophages have all been implicated as the key regulator cells of the immunological response, linking innate and adaptive immunity. The forgotten cell in this discourse has been the B-cell. Long considered as simple antibody production units dictated to by T-cells, recent years have begun to shift this assumption. The discovery that numerous B-cell subsets exist, with specific regulatory functions capable of modulating T-cell and chronic inflammatory responses has revealed a hitherto unappreciated role of B-cells. In particular, these ideas have been developed in light of the surprisingly successful responses delivered in autoimmune settings following depletion of B-cells with the anti-CD20 antibody rituximab. Here we summarise the history of the humble B-cell and discuss some of the key recent findings that lead us to propose it as an important regulator of ongoing immune responses and as such, one of the masters of the immunoverse.

1. Introduction

Bursa-derived or bone marrow-derived (B) cells are central to the adaptive humoral immune system and responsible for mediating the production of antigen-specific immunoglobulin (Ig) directed against invasive microbial agents. They have an unremarkable morphology when viewed by light microscopy, visible as small round lymphocytes with few organelles. The function of B-cells became apparent in the 1960s when Max Cooper demonstrated that antibody production was completely abrogated in irradiated chickens after the bursa of Fabricius (the primary site of B-cell development in birds) was surgically removed (LeBien and Tedder, 2008). Subsequently, discovery of antigen-specific Ig on the surface of B-cells in the early 1970s established Ig as the B-cell receptor (BCR) and validated the one cell–one antibody model of clonal selection forwarded by Frank Burnet in 1957 (Nossal, 2002). By the mid 1970s it was fully accepted that individual B-cells recognise antigen through unique and specific Ig receptors and differentiate into antigen-secreting plasma cells (PCs), usually in conjunction with T-cell help. Several different B-cell subsets have now been defined that have distinct functions in both adaptive and innate humoral immune responses and which also play a role in regulating T-cell immunity.

2. Cell origin and plasticity

B-cells are derived from pluripotent haematopoietic stem cells (HSC) and produced in human foetal liver by 7.5 weeks of gestation and in the bone marrow by weeks 14–17. In mice, B-cell development begins with the differentiation of pluripotent HSC through a series of developmental intermediates with decreasing differentiation potential (Fig. 1). In the bone marrow, Ig heavy chain gene rearrangement begins in the pre-pro-B-cell stage and continues in pro-B-cells. The rearranged heavy chain is then expressed intracellularly in large pre-B-cells along with surrogate light chain. Together these form the pre-BCR that relocates to the cell surface, signalling proliferation and differentiation into small pre-B-cells (Hardy and Hayakawa, 2001). Small pre-B-cells upregulate the genes required for rearrangement of the Ig light chain, allowing the production of a mature BCR with unique specificity that is expressed as IgM on the surface of immature B-cells. Immature B-cells then undergo negative selection to remove cells expressing a self-reactive BCR before exiting the bone marrow as short-lived transitional type 1 (T1) B-cells (Allman and Pillai, 2008). As such, B-cells experience both antigen dependent and independent selection, tightly regulated through key signalling events. Although outside the scope of this review, the key signalling molecules involved downstream are highlighted in Fig. 2.

T1 B-cells migrate into splenic B-cell follicles before differentiating into non-circulatory T2 B-cells. The existence of a developmental T3 B-cell has also been proposed (Allman and Pillai, 2008). However, it is over-expressed in murine models of anergy, suggesting that these are anergic B-cells and not an intermediate stage of development (Merrell et al., 2006), although their exact

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Cell facts

- B-cells are responsible for the production of antibodies.
- B-cells have unique receptors on their cell surface allowing them to respond specifically to different antigens.
- B-cells are able to modulate immune responses independently of antibody production.

function remains uncertain. After passage through the transitional stages, B-cells become long-lived mature follicular cells. Cariappa and coworkers propose that the follicular type II (FO II) phenotype is the first mature B-cell stage to develop. A binary cell fate decision occurs in the FO II stage in which BCR signalling stimulates the majority of cells to differentiate into FO I cells, the conventional mature B2 cell phenotype. Conversely, absent or weaker signalling stimulates cells to differentiate into marginal zone (MZ) B-cells via a MZ precursor (Cariappa et al., 2007). Although the elucidation of developmental B-cell intermediates has been derived mostly from murine studies, many similar phenotypes have been found in humans, suggesting that human B-cells develop along a similar pathway to that illustrated in Fig. 1 (Carsetti et al., 2004).

In addition to B2 and MZ B-cells, mice have B1 B-cells. A lineage$^-$ B220$^-$ CD19$^+$ progenitor cell has been identified in mice that appears prior to pre-pro-B-cells and preferentially forms B1 B-cells upon adoptive transfer into SCID mice. Dorshkind and Montecino-Rodriguez (2007) suggest that this is the B1 progenitor cell, but the intermediate stages between this and mature B1 B-cells have not been elucidated.

3. B-cell functions

The individual mature B-cell subsets that have been described (Fig. 1) were defined based on differences in function and anatomical location. The role of each subset in mediating innate and adaptive humoral immunity is discussed below along with the immunomodulatory effects that B-cells mediate independently of antibody production.

3.1. B2 B-cells

Mature follicular B2 B-cells mediate the majority of T helper cell-dependent humoral immune responses that result in immunological memory (McHeyzer-Williams and McHeyzer-Williams, 2005). During a microbial infection, B2 B-cell recognition of foreign protein via the BCR results in internalisation, processing and presentation of peptide to cognate CD4$^+$ T-cells primed by the same peptides presented by DC. This interaction promotes the rapid generation of PC via an extrafollicular route (MacLennan et al., 2003) and the longer formation of a germinal centre (GC) where somatic recombination increases the affinity of the BCR to antigen, and subsequent isotype switching extends the breadth of antibody effector mechanisms available to clear the infection (McHeyzer-Williams and McHeyzer-Williams, 2005). Affinity-matured, isotype-switched B-cells differentiate into mem-

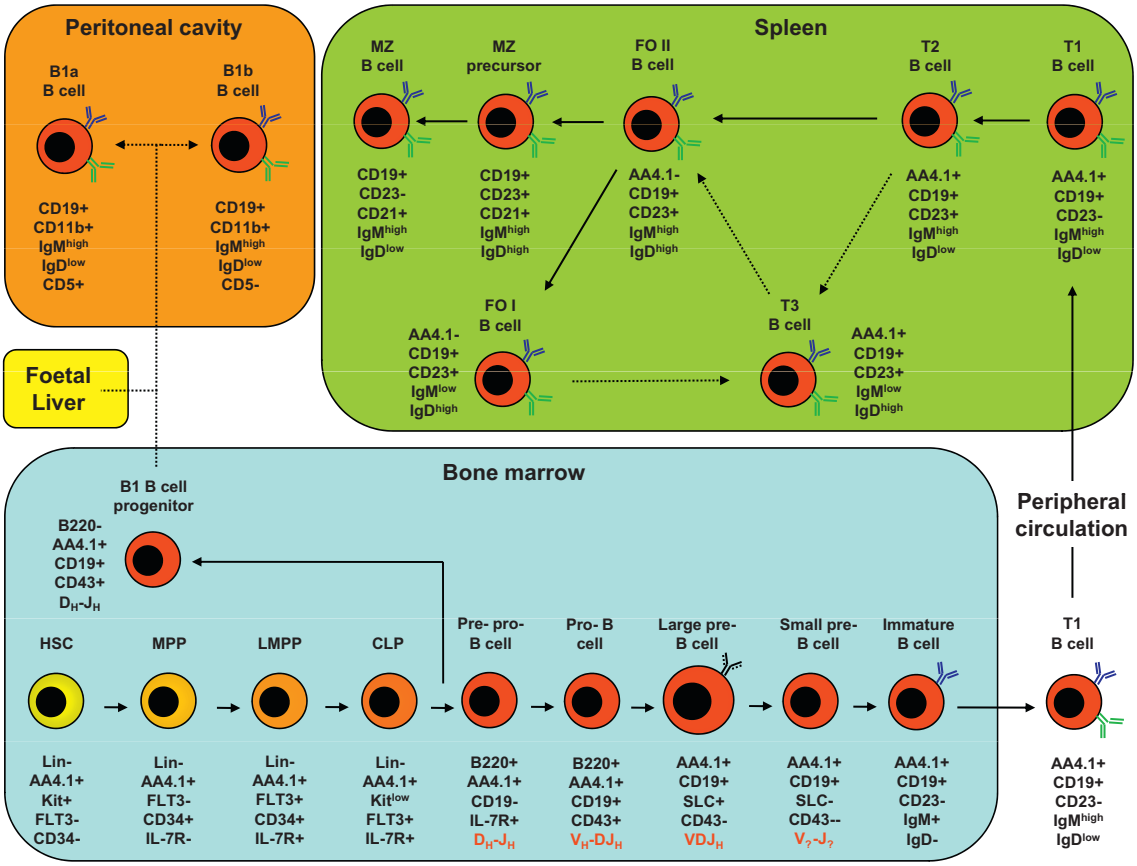

Fig. 1. Murine B-cell development. B-cells differentiate from haematopoietic stem cells (HSC) in the bone marrow and progress through several intermediate stages before egress into the peripheral circulation. Further maturation to follicular and MZ B-cells occurs in the spleen. B1 B-cells mature in the peritoneal cavity. The intermediate developmental stages currently defined are illustrated together with a list of important cell surface markers expressed at each stage (black text) and the status of Ig gene rearrangement (red text). Solid arrows indicate known pathways of differentiation. Dotted arrows indicate hypothetical pathways, which may contain undiscovered intermediates. MPP, multipotent progenitor; LMPP, lymphoid-primed multipotent progenitor; CLP, common lymphoid progenitor; SLC, surrogate light chain.