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Review Article

B cells responses and cytokine production are regulated by their immune microenvironment

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ABSTRACT

The adaptive immune system consists of two types of lymphocytes: T and B cells. These two lymphocytes originate from a common precursor, yet are fundamentally different with B cells mediating humoral immunity while T cells mediate cell mediated immunity. In cytokine production, naïve T cells produce multiple cytokines upon activation while naïve activated B cells do not. B cells are capable of producing cytokines, but their cytokine production depends on their differentiation state and activation conditions. Hence, unlike T cells that can produce a large amount of cytokines upon activation, B cells require specific differentiation and activation conditions to produce cytokines. Many cytokines act on B cells as well. Here, we discuss several cytokines and their effects on B cells including: Interleukins, IL-7, IL-4, IL-6, IL-10, and Interferons, IFN-α, IFN-β, IFN-γ. These cytokines play important roles in the development, survival, differentiation and/or proliferation of B cells. Certain chemokines also play important roles in B cell function, namely antibody production. As an example, we discuss CCL28, a chemokine that directs the migration of plasma cells to mucosal sites. We conclude with a brief overview of B cells as cytokine producers and their likely functional consequences on the immune response.

1. Introduction

The immune system is a highly evolved mechanism designed to protect us from pathogens present in our environment. If a pathogen breaches our primary defense mechanisms, represented by barrier tissues such as the skin and mucosal epithelia, we are equipped with an arsenal of molecular and cellular weaponry that has adapted over millions of years of host-pathogen interactions. In its earliest stages, the immune system consisted of a group of generic receptors capable of recognizing conserved pathogen patterns that could elicit a host response [1–3]. The ability to recognize conserved pathogen associated molecular patterns or "PAMP's" is a fundamental characteristic of the innate immune system. Despite the capacity to recognize conserved patterns present on pathogens, the innate system lacks the ability to remember a previous assailant and respond with a larger and more rapid response against that insult.

The adaptive immune system includes of two main types of lymphocytes: T and B cells. Each of these originate from different lymphoid organs: the thymus and bone marrow, respectively. The ability to generate diverse antigen receptors, a key feature associated with the adaptive immune system, is driven by the gene *AID*, which encodes an activation-induced deaminase. This gene plays a crucial role in the recombination process that generates a variable T or B cell receptor (TCR/BCR) [4,5]. The two main types of lymphocytes work in concert to produce an adaptive immune response.

We begin this review with an overview of B cell development and differentiation. Given the large number of cytokines that act on B cells we have chosen to focus on several that play significant roles in the development, survival, differentiation and proliferation of B cells. Interleukins IL-7, IL-4, IL-6, and IL-10 are discussed because of their role in B cell development, B cell proliferation and isotype secretion, and the ability of B cells to regulate the immune response, respectively. The interferons: IFN-α, IFN-β, and IFN-γ, also play important roles in the development of B cell responses. Next, we discuss CCL28, a chemotactic cytokine (chemokine) that recruits IgA^+ plasma cells to the mucosal tissues. For a list of the cytokines discussed and their functions see Table 1. Finally, we conclude with a brief overview of B cells as cytokine producers and their effects on the immune system.

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Table 1
Effects of cytokines on B cells.

Cytokine	Function	Refs.
IL-7	B cell development, Ig gene rearrangement	[31–36,38,41–43,47]
IL-4	B cell proliferation, isotype switching	[10,48,50–54,56,57,59]
IL-6	B cell proliferation, isotype switching	[62–66,70]
IL-10	Regulate response	[73,77,81–85]
IFN-α	B cell development, increased BCR sensitivity	[95–97]
IFN-β	B cell development, increased BCR sensitivity	[95,96]
IFN-γ	Inhibit/stimulate B cell proliferation, isotype switching	[99–102]
CCL28	Recruitment of IgA^+ plasma cells to mucosa	[107–109,112]

2. B cell development, differentiation, and their role in adaptive immunity

B cells undergo a molecular process to rearrange the heavy and light chains of their immunoglobulin genes. This is known as V–D–J and V–J recombination [6] and it applies to the heavy and light chains, respectively. It occurs in the fetal liver and bone marrow and is supported by stromal cell-derived IL-7 [7]. Upon completion of this rearrangement, B cells express a unique BCR [8]. The BCR is required for further B cell development and survival [9]. Upon exiting the bone marrow a B cell is considered 'immature' or "transitional". This name is based on cell surface markers expressed at this particular stage in the differentiation program of the B cell, which includes membrane-bound IgM and IgD. Although technically immature, a B cell can respond to type-I antigens including lipopolysaccharide (LPS) which can induce a rapid antibody response.

Upon migration to secondary lymphoid organs (spleen or lymph nodes) B cells may encounter antigen through interactions with other immune cells such as dendritic cells or macrophages. The B cell can either differentiate into a short lived plasma cell or enter a germinal center (GC). Within the GC, B cells undergo clonal expansion, class switch recombination (CSR), and somatic hypermutation [10]. This process results in the production of high affinity antibody-producing plasma and memory B cells [11].

B cells, like T cells, can also be divided into subsets based on location and function. Some subsets include: Marginal Zone (MZ) B cells, Follicular (FO) B cells, and B-1 cells. Like their name implies, MZ B cells are sessile cells found in the marginal zone of the spleen. This location allows them to capture blood borne pathogens and respond with a rapid antibody response [12]. However, most of the data available on MZ B cells comes from murine models, likely a result of anatomical differences in the marginal zone of the spleen between humans and mice. FO B cells circulate throughout the periphery, but upon encountering their cognate antigen they enter a GC [13]. Memory B cells, generated during the GC reaction, persist and differentiate into plasma cells in a secondary immune response to provide rapid antibody production [14]. B-1 B cells are different from conventional B-2 cells in their location, phenotype, and self-renewing capacity. B-1 cells can be further subdivided into B-1a and B-1b cells based on the expression of CD5 [15]. B-1a are fetal B cell progenitors and are known as "innate B cells" because of their ability to produce natural antibodies without T cells help [16]. While B-1b cells are involved with clearance of specific pathogens such as *Borrelia hermsii* and are therefore considered to be involved in adaptive immune responses [16–18]. B-1 cells can respond to T-independent antigens by secreting natural IgM antibodies which they produce without T cell help [19,20]. Unfortunately, most information on B-1 cells has been obtained in the mouse, and little information is available on human B-1 cells. This is probably because B-1 cells reside in the peritoneal cavity. Their peritoneal location makes it challenging to study them in humans. Interestingly, B-1-like cells have been implicated in human diseases, for example, endometriosis [21].

Since their discovery in the mid-1960s, B cells were recognized for their ability to produce antibodies [8,22]. More recently, it has been recognized that B cells are more than antibody factories. For example, B cells are required for optimal T cell activation to certain antigens including low dose foreign proteins, pathogen challenge, and auto-antigens [23]. Furthermore, their presence facilitates the genesis of the immune system, and maintains its integrity. Mice that develop without B cells exhibit a dramatic decrease in thymocyte numbers and diversity, and also show defects in the spleen, dendritic cells (DC), [24] and T cell compartments, lack of Peyer's Patches (PP), organogenesis and follicular DC networks, have a paucity of MZ macrophages, and reduced chemokine expression [8,25,26]. The importance of B cells in immune system homeostasis is apparent in the function of T and DC functions, regulation of lymphoid tissue organization, wound healing, tissue rejection, and tumor immunity [8,27]. This information indicates that B cells are linked to the development and maintenance of the immune system.

3. Cytokines that act on B cells

Cytokines are proteins produced and secreted by a variety of cells including stromal cells, fibroblasts, and endothelial cells. In the immune system they are produced by leukocytes and exert their function on other leukocytes or tissues that express the cytokine receptor [28]. Some of them are called interleukins (between leukocytes). The term interleukin (IL) was first used in 1979 to describe two different molecules secreted by leukocytes with a similar molecular weight. These two early interleukins are now known as IL-1 and IL-2 [29]. Since the introduction of the term, and concurrent identification of the first two interleukins, 37 more interleukins have been described [30,31]. Our laboratory has contributed to the discovery and characterization of interleukins and recently described IL-39 (meteorin-like) [32]. Many of the new additions are members of the IL-1 superfamily [30,33]. Here, we review IL-7, IL-4, IL-6, and IL-10. These interleukins play important roles in B cell development (IL-7), survival/proliferation of B cells, and isotype switching (IL-4 and IL-6), and regulation of the immune response (IL-10).

3.1. IL-7

IL-7 is essential to B cell development in mice [34–36]. Mice deficient in IL-7, IL-7R or treated with anti-IL-7 antibodies exhibit the same phenotype: B cell development arrest [37–39]. The developmental arrest occurs at different stages: pro-B to pre-B cell transition and the earlier stage of pre-pro B cells for IL-7 deficient mice and IL-7Rα deficient mice, respectively.

In developing B cells, IL-7 acts as a survival factor. This effect may be due to its ability to regulate Bcl-2 family members [40]. Other extrinsic signaling can synergize with IL-7 signaling. IL-7 drives expansion of developing B cells [41]; this activity originally established IL-7 as a pro-B cell growth factor. IL-7 and IL-7Rα are critical for the development of B cells in mice, but this may not apply to humans. In humans, mutations to the IL-7Rα gene result in SCID (Severe Combined Immune Deficiency), making IL-7 indispensable for T cell development; yet SCID patients have normal B cell populations [42]. Therefore, while IL-7 is not strictly required for the development of normal human B cells. However, numerous reports have documented that IL-7 can influence B cell develop-