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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.

Keywords

B cells; cytokines; interleukins; interferon; chemokines; autoimmunity

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

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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, 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

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-la 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-1960’s, 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 development in humans [43]. We conclude that the exact effects of IL-7 in human B cell development remain to be defined.

IL-7-mediated induction of BCR rearrangement in animal models has been difficult to study. An IL-7Rα$^{-/-}$ mouse exhibits impaired immunoglobulin gene rearrangements [44]; while the IL-7 deficient mouse does not show impaired V-D-J or V-J gene rearrangements [45]. These discrepancies were recently resolved using mutated constructs of the IL-7Rα that were transferred into IL-7Rα$^{-/-}$ mice. This experimental approach demonstrated that the IL-7Rα has a direct role in promoting immunoglobulin gene rearrangement [46]. The previously reported data may not necessarily be contradictory; instead, the discrepancy may be explained by a second ligand of IL-7Rα called thymic stromal lymphopoietin (TSLP). TSLP is a cytokine that has stimulatory effects on B cells under *in vitro* culture conditions and plays a role in early B cell development [47].

Generally, only developing B cells respond to IL-7 signaling [48]. However, FO B cells that enter GC's undergo various reactions that result in the production of higher affinity antibodies. The events that lead to the production of higher affinity antibodies require the reactivation of certain genes including: RAG (recombination activating genes), responsible for the GC's reactions [49, 50] and IL-7Rα [51], which, as discussed above, plays a direct role in immunoglobulin gene rearrangement.

3.2. IL-4

IL-4 was discovered over thirty years ago, but remains a topic that deserves further research. It is mainly produced by activated $CD4^+$ Th2 cells and can act on a wide array of cells of hematopoietic origin [52]. The IL-4 receptor (IL-4R) is expressed on diverse cells including hematopoetic, endothelial, epithelial, muscle, fibroblast, hepatocyte, and brain cells [53]; the expression of IL-4R on these widely diverse cells reflects the pleiotropic effects of IL-4.

IL-4 was initially described as a B cell growth factor, due to its ability to co-stimulate B cell proliferation [54]. It acts on both resting B cells (by increasing their volume and homotypic aggregation) [55] and activated B cells by acting synergistically with CD40 ligation to enable division, survival, and differentiation [56]. Hence, it is a potent survival factor for B cells [10, 57, 58]. IL-4 stimulates the preferential secretion of certain immunoglobulin isotypes, such as IgG1 and IgE [52]; thereby driving the immune response towards a Type 2 reaction. IL-4 also induces the expression of class II MHC (major histocompatibility complex), in B cells [59].

STAT6, a latent component of IL-4 signaling, is essential for the IL-4 response [60]. STAT6 deficient mice have B cells that are unresponsive to IL-4 stimulation, reduced T cell proliferative ability (likely a result of B cell unresponsiveness), a severe reduction in Th2 cytokines, and lack of IgE and IgG1 production during parasitic infection [61, 62]. IL-4 is produced by activated $CD4^+$ Th2 cells [63] and it promotes Th2 responses by inducing the differentiation of naïve T cells to the Th2 phenotype. This leads to the production of other anti-inflammatory cytokines and inhibits pro-inflammatory conditions thereby serving as a cross-regulator of the immune response [64].

3.3. IL-6

IL-6 is produced by a variety of cells including lymphocytes, fibroblasts, and peripheral blood mononuclear cells (PBMC) [65]. Although there is low homology between human and mouse IL-6 (65% and 42% at the DNA and protein level, respectively) there are four conserved cysteine residues, reflecting an evolutionary relationship between these molecules [66]. Moreover, the genes encoding mouse and human IL-6 are located in syntenic regions. This indicates that the IL-6 gene is conserved and that its function is similar in both species.

IL-6 is expressed under inflammatory conditions including viral infections [67, 68] and LPS stimulation [69, 70]. Initially, IL-6 was named BSF-2, or B cell stimulation factor 2, due to its ability to increase immunoglobulin secretion, IgM and IgG, in either freshly stimulated B cells or EBV, Epstein-Barr virus, immortalized cells [71].

IL-6-producing B cells exacerbate inflammatory conditions and autoimmune pathologies. Conversely, lack of IL-6 can lead to immune defects. For example, an IL-6 deficient mouse is resistant to myelin oligodendrocyte glycoprotein (MOG)-induced experimental autoimmune encephalomyelitis (EAE). This phenotype is a consequence of poor lymphocyte proliferation that leads to reduced inflammation and demyelination in the central nervous system [72–75]. Furthermore, mouse studies have demonstrated that IL-6-deficient B cells do not support the polarization of T cells to Th17, a cell type linked to various inflammatory conditions [75]. In humans, IL-6 is elevated in both Systemic lupus erythematosus (SLE)

and Castleman's disease patients [75–77]. However, the exact origin of IL-6 producing B cells remains unknown. Overall, IL-6 over-production by B cells promotes inflammation through the generation of pathogenic antibodies and increased proliferation of pathogenic T cells.

3.4. IL-10

IL-10 is best known for its anti-inflammatory properties. It was identified as an inhibitor of type 1 (pro-inflammatory) cytokines including: IL-1, TNF-α, and IL-12 [78–81]. It can also down-regulate MHC class II expression on immune cells [78].

An IL-$10^{-/-}$ mouse exhibits an exaggerated inflammatory response to microbial challenges; however, other pathogens are better cleared in absence of IL-10 [82]. This dichotomy is illustrated by the spontaneous development of irritable bowel disease (IBD) observed in IL-$10^{-/-}$ mice [83] as a consequence of their gut being colonized with enteric bacteria [84]. This *in vivo* phenotype mirrors *in vitro* data and indicates that IL-10 is a non-redundant cytokine, that is, there is no alternative regulatory mechanism to compensate for its ablation [85].

Despite the fact that an early study documented IL-10 production by a B cell lymphoma [86], the ability of B cells to produce IL-10 remained unrecognized. Recently, a unique B cell subpopulation, identified by its ability to secrete IL-10, has been characterized in mice. These B cells are phenotypically $CD1d^{hi}CD5^{+}$ and represent only 1–2% of splenic $B220^{+}$ cells in wild-type (WT) mice. Furthermore, adoptive transfer these IL-10-producing B cells can reverse inflammation in mice lacking $CD20^{+}$ B cells and $CD19^{-/-}$ mice. The negative regulation of inflammation is mediated by IL-10, a cytokine strongly produced by this B cell subpopulation. These cells are now known as B regulatory or B10 cells [87].

In the mouse, B10 cells are also found in the peritoneal cavity and are similar to their spleen counterparts: same surface marker phenotype and both secrete IL-10. However, can peritoneal B10 cells modulate inflammation? To investigate this, a $RAG2^{-/-}$ mouse (a mouse that lacks both B and T cells), received $CD25^{-}CD45RB^{hi}CD4^{+}$ T cells, and either IL-$10^{-/-}$ $CD19^{+}$ B cells or WT $CD19^{+}$ B cells [24]. The $RAG2^{-/-}$ mice that received the IL-$10^{-/-}$ $CD19^{+}$ B cells developed higher colitis scores [88]. Taken together, these results suggest that peritoneal B10 cells are important in gut homeostasis and can modulate T cell function during inflammatory conditions such as colitis.

In 2010, a human B cell subset with the ability to produce IL-10 and capacity to suppress the differentiation of Th1 cells was described [89]. This regulatory capacity was IL-10 dependent and ablated by the addition of either anti-CD80 or anti-CD86 antibodies suggesting that T cell help is required for Breg function. This regulatory B cell subset is phenotypically defined as $CD19^{+}CD24^{hi}CD38^{hi}$ and was found in both normal and SLE patients; however, the suppressive capacity of these cells was diminished in cells from SLE patients [89]. Taken together, this indicates that a breach in the interplay of between T and B cells may lead to autoimmunity.

In humans, the inflamed gut leads to the differentiation of Breg cells that negatively regulate inflammation via the release of IL-10 [90]. Although the mechanism behind the differentiation of the Breg cells has not been completely elucidated, IL-1β and IL-6 are important cytokines in the induction of these regulatory B cells. Interestingly, both IL-1β and IL-6 are pro-inflammatory cytokines; hence overt immune responses would be regulated through the production of IL-10. These data are reminiscent of animal studies where Breg cells have been shown to lead to the resolution of colitis in mice [88].

While there are cell surface markers that define the B10 population, (for example, $CD1d^{hi}CD5^{+}$), a specific transcription factor has yet to be associated to this cell subset. However, Blimp1 and IRF4 are upregulated while pax5 and Bcl6 are down-regulated [91]. Given that these transcription factors are linked to plasma cells, these observations suggest that B10 cells have the ability to differentiate into plasma cells capable of secreting polyreactive IgM and IgG antibodies. This may reflect their ability to dampen inflammation through the clearance of potentially threatening antigens. The B10 cell lineage has yet to be well defined. B10 cells share some phenotypic characteristics with B1a cells of the peritoneal cavity, T2-MZ, transitional-2, precursors and MZ B cells [92–94].

4. Interferons that act on B cells

Several interferons, including IFN-α, IFN-β, IFN-γ have interesting effects on B cells [95]. Both type I and type II IFN's are involved in generating an antiviral state. They accomplish this by regulating both branches of the immune system. However, sustained antiviral responses are dependent on IFN-γ [96–98]. Beyond their ability to interfere with the replication of viruses they also have a role in the type of response produced. For example, both types of interferons up-regulate peptides associated with class I MHC, but only IFN-γ can induce the expression of class II MHC molecules in macrophages [99]

4.1. Type I IFN's: IFN-α and IFN-β

Type I IFN's (IFN-α/β) are constitutively produced in the bone marrow and promote the generation and selection of normal B cell populations [100]. Treatment of mature B cells with IFN-α/β results in partial activation that is associated with increased sensitivity to BCR engagement [101]. This increased sensitivity has been proposed to be a link between innate and acquired immune responses because IFN-α/β (associated with innate responses) leads to the amplification of B cell responses (associated with acquired immune responses) [101]. Similar results were obtained using plasmacytoid DC-derived IFN-α [24] or recombinant IFN-α [102]. Moreover, IFN-α, regardless of the source (endogenous or exogenous), results in increased B cell activation. This renders B cells more receptive to T cells; thus, IFN-α promotes B cell proliferation and their differentiation to antibody secreting cells [102].

4.2. Type II IFN: IFN-γ

IFN-γ is produced by Th1, natural killer T cells (NKT), and natural killer (NK) cells. Its production is induced by IL-12 and IL-18, and inhibited by IL-4, IL-10, and TGF-β [95]. This regulation reflects its strong association with type 1 responses driven by Th1 polarized cells, which produce of large amounts of IFN-γ [103].

IFN-γ was initially reported as an inhibitor of B cell responses [104] due to inhibition of IgM production as a result of a reduction in IgM precursor cells. However, its inhibitory effects are limited to pre-activated B cells and do not affect resting B cells. This suggests that IFN-γ may play a role in the control of polyclonal B cell responses [104].

IFN-γ can also induce B cell proliferation when used with anti-CD40 antibody [105]. This suggests that the manner in which B cells are activated, i.e. LPS, anti-IgM or CD40 ligation, is a critical factor in the fate of B cells treated with IFN-γ. Moreover, it reveals a finely-tuned adaptation of the humoral immune response to IFN-γ

Immunoglobulin secretion by B cells is a direct consequence of the cytokines shaping the response (Table 2). IFN-γ, a Th1 cytokine, is involved in the induction/repression of various immunoglobulin classes. In humans, IFN-γ reduces total IgG production, and it specifically inhibits IgG1, a major component of total IgG, while increasing IgG2, with no notable effects on either IgG3 or IgG4 production levels [106]. This phenotype is also observed in the mouse. LPS-activated B cells treated with IFN-γ produced increased levels of IgG2a and IgG3 while IgG1, IgM, and IgE were inhibited [107]. These data indicate that IFN-γ has similar functions in both humans and mice and that it is involved in the humoral response by directly controlling the immunoglobulin isotypes produced by B cells.

5. Chemokines and B cells

Chemokines are small secreted chemotactic cytokines that control both the innate and adaptive branches of the immune system. In the immune system, their primary function is to direct the migration of cells of the immune system in the body; hence they are often considered the ‘traffic directors’ of the immune system because they guide different leukocyte subsets to a given destination. Here we will discuss CCL28 as an example, because of its important role in directing B cells, specifically IgA^+ plasma cells, to mucosal sites.

5.1. CCL28

CCL28, a β-chemokine, is expressed by epithelial cells that line the mucosa, and has a high level of homology with another chemokine (CCL27) [108]. This homology explains their shared receptor, CCR10, and suggests that these two genes arose through a gene duplication event. CCL27 is expressed in the skin and directs T cell homing to cutaneous sites; therefore the gene duplication event that occurred led to selective chemokine differentiation and specialized tissue/cell type expression [109]. We should note that both the mucosa and skin are barrier tissues, an observation that may account for the specialization of their functions and may explain their expression patterns.

The highest site of human CCL28 expression is the salivary gland. Other mucosal sites including small intestine and colon [110] also express CCL28. Deregulated levels of CCL28 have been correlated to various pathologies including salivary gland tumors and [110] Hodgkin’s disease (HD) [111], and Sjögren’s syndrome [112]

The CCL28/CCR10 axis strongly correlates with CCL28 function, namely the recruitment of IgA^+ plasma cells to mucosal sites [113–115]. The mammary gland, an exocrine gland responsible for the production and secretion of milk, is unlike other mucosal immune organs because it develops in stages [116]. Importantly, the ductal epithelia in mammary gland express CCL28 upon the onset of lactation. Expression of CCL28 in the mammary gland parallels the accumulation of IgA antibody secreting cells in the mammary gland, a process that can be inhibited by anti-CCL28 antibodies [113]. Taken together, these results indicate that the CCL28/CCR10 axis regulates the recruitment of IgA secreting plasma cells to the mammary gland (Figure 1).

CCL28 has also been reported to bind CCR3 [109]. However, CCR3 is not the primary physiological receptor under healthy conditions [109, 117]. During pathological conditions, the ability of CCL28 to bind CCR3 may become relevant. For example, levels CCL28 levels increase in patients with atopic asthma and this leads to the accumulation of IgE-producing plasma cells. This effect is likely due to the CCL28/CCR3 axis [118].

6. B cells as cytokine producers

Naïve B cells do not secrete many cytokines upon activation. In contrast, naïve T cells initiate cytokine production almost immediately after activation. This inherent difference between T and B cells reflects the fact that B cells require additional signaling beyond activation to become cytokine producers. The additional signaling can be provided by the immune microenvironment and specific differentiation stages of the B cell. For example, the main cytokines produced by naïve B cells upon activation are the chemokines CCL22 and CCLl7 [119–121]. These two chemokines share the same receptor (CCR4), which is strongly expressed in $CD4^+$ Th2 type T cells. Therefore, the production of CCL17 and CCL22 by naïve B cells reflects the ability of activated B cells to recruit Th2 cells. In turn, the recruited Th2 cells produce cytokines, such as IL-4, that shape the B cell response and induce the differentiation of B cells towards cytokine producing B cells (Figure 2). Thus, cytokine secretion by B cells is regulated by extrinsic signaling provided by other immune cell types. Once B cells acquire the capacity to produce cytokines, they become capable of cross-regulating responses via polarization/inhibition and can even negatively regulate the entire immune system.

The first report of B cells as cytokine producers described ROHA-9, an EBV transformed human B cell line that constitutively produces IL-1 and leads to enhanced T cell proliferation [122, 123]. These findings have been replicated using mouse B cells. For example, EBV transformed mouse B cells secrete IL-5, which promotes proliferation of eosinophil precursors, B cell proliferation, and antibody production [124]. This set the stage for B cells as effectors of the immune response and suggested that B cells are able to modulate the magnitude of the immune response by both antigen-presentation and cytokine production (Figure 3).

B cells are classified into effector subtypes depending on the cytokines they secrete. There are two main B effector (Be) populations: Be1 and Be2, which either drive Th1/Th2 responses and cross-regulate the other [125, 126]. In a recent study, it was demonstrated that

cytokine secretion by human B cells depends on the stimuli they encounter [127]. B cells stimulated with CD40L and BCR signaling proliferated and produced pro-inflammatory cytokines including TNF-α, lymphotoxin, and IL-6; however, stimulation through CD40 alone led to a significant production of IL-10 which down-regulates 'unnecessary' responses [127]. In the presence of autoimmunity this "cytokine network" becomes deregulated. For example, cells collected from multiple sclerosis (MS) patients have a reduced capacity to secrete IL-10 [128]. Naïve B cells from patients with MS retain the ability to be polarized *in vitro* to Be1 cells which produce pro-inflammatory cytokines, or Be2 cells which produce anti-inflammatory cytokines. Treatment with Mitoxantrone, a therapeutic agent used for MS, recapitulated these results *in vivo* suggesting an *in vivo* "cytokine network" switch [128]. Taken together, these studies demonstrate that in addition to receiving activation signaling, B cells require further cues from their immune microenvironment to produce cytokines.

As the list of cytokines produced by B cells expands, we must reconsider the function of B cells. B cells ultimately become plasma cells; yet throughout their journey to their final differentiated state, they are active immune response modulators with the ability to either augment, suppress or skew a given immune response depending on the cytokines they secrete. Furthermore, the identified effector subtypes, Be1 and Be2, are of critical importance to the initiation and propagation of either type I or type II responses because their products not only stimulate either response, but also participate in cross regulation mechanisms that inhibit opposite responses [129]. Overall, we conclude that B cells should be considered an integral component of the adaptive immune system. Their ability to produce cytokines likely reflects their increasingly important role as regulatory cells of the immune system. Given the therapeutic success of B cell ablation (using anti-CD20 antibodies) in the treatment of human autoimmune diseases [130], we predict that the potential role of cytokine-producing B cells in human disease is a field that will yield many future surprises.

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Highlights

- Cytokines drive the differentiation of B cells
- Differentiation and immune microenvironment determine B cell cytokine production
- Cytokines produced by B cells can modulate the adaptive immune response

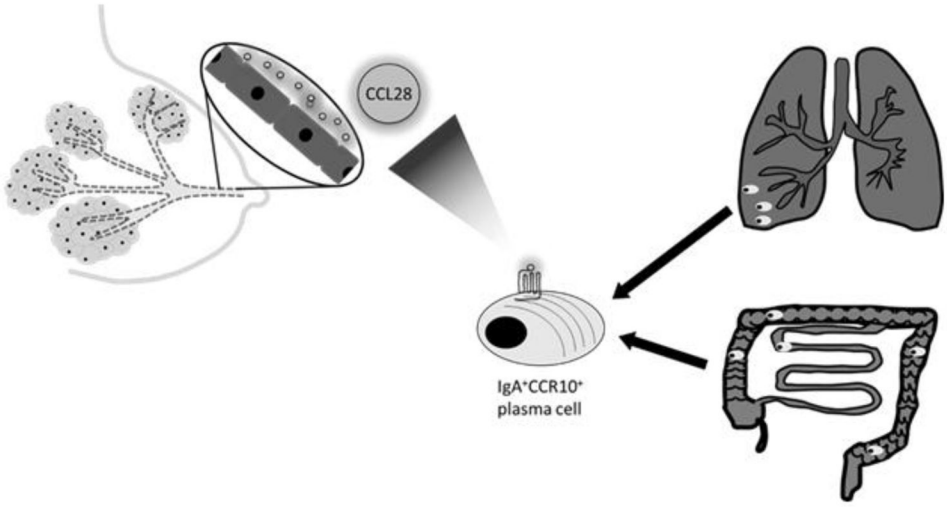

Figure 1. CCL28 expression is induced upon lactation

This results in the recruitment of IgA^+ $CCR10^+$ plasma cells from the respiratory and gastrointestinal tract. Hence, neonates receive passive immunity against respiratory and gut pathogens via breast milk.

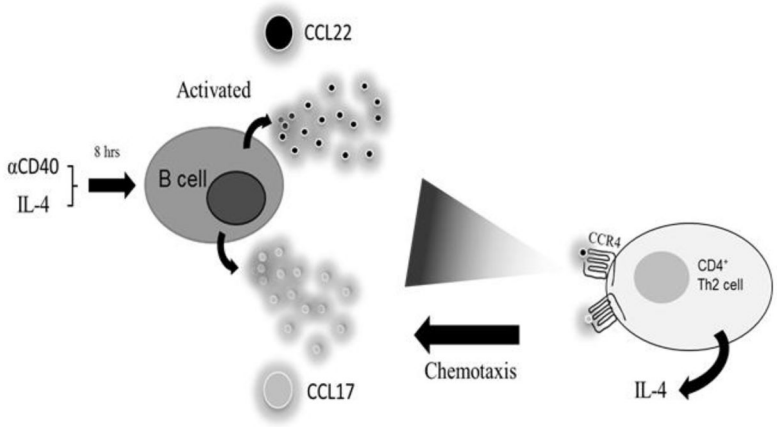

Figure 2. B cells recruit Th2 cells to receive stimuli

Upon activation, naïve B cells express CCL17 and CCL22. These chemokines recruit $CD4^{+}CCR4^{+}$ Th2 T cells that provide B cells with appropriate cues to differentiate and produce cytokines.

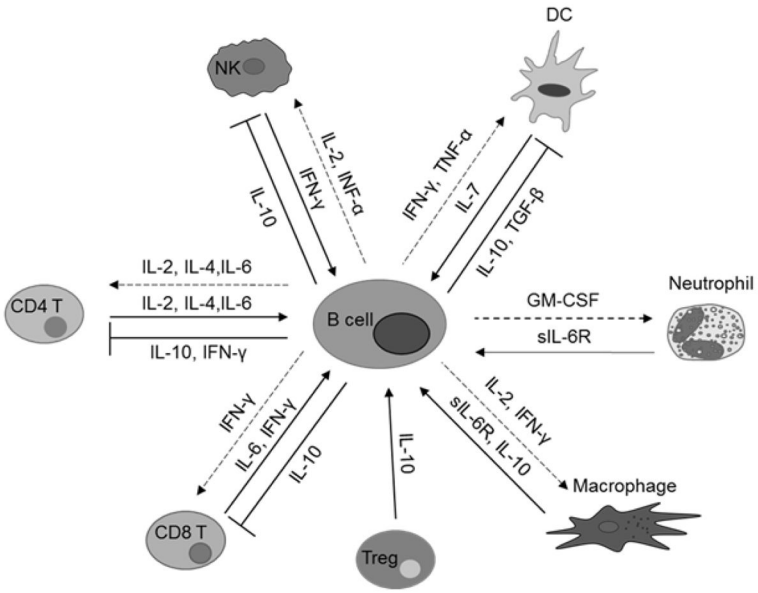

Figure 3. Cytokine production by B cells

Arrows are cytokines produced by an immune cells that act on B cells. Inhibition lines are cytokines that B cells produce that have a regulatory effect on immune cells. Dashed arrows are cytokines produced by B cells that propagate/magnify effects on immune cells

Table 1

Effects of cytokines on B cells.

Cytokine	Function	Reference
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

Table 2

Role of cytokines in murine isotype class switching.

	IgM	IgG1	IgG2a	IgG2b	IgG3	IgA	IgE
IL-4	Inhibits	Induces			Inhibits		Induces
IL-6	Induces						
IFN-γ	Inhibits	Inhibits	Induces		Induces		Inhibits
TGF-β	Inhibits		Induces		Inhibits	Induces	