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Innate B Cells: the Archetype of Protective Immune Cells

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Abstract
The innate B cell (IBC) population is heterogeneous and involved in the primary immune response. IBC functions include a high ability to produce natural antibodies with IgM isotype, the elimination of apoptotic cells, and a capacity to be cognate help to T cells. Among IBC subsets, B-1 cells and marginal zone B cells are the main producers of IgM, act as rapid immune responders that may relocate to follicular lymphoid and differentiate to cytokine and antibody-secreting cells shortly after infection. IBCs functions are highly dependent on their localization site and the nature of their B cell receptor repertoire, suggesting a high plasticity range of different immune responses. In this review, we will describe the nature and functions of the different innate-like B cell subsets, first in mice and then in humans. Besides this, we will emphasize the strong ability of these cells to undertake different protective functions from the first line of defense against pathogens to the regulatory role of the broader immune response.

Keywords Innate B cells · Effector functions · IgM · Autoreactivity · Regulatory B cells

Introduction

The immune system is classically divided into two separate branches. The more fundamental one, and referred to as innate immunity, is present in all eukaryote organisms. Its main function is to sense infections through germline molecular recognition in order to generate a protective response. The second branch is referred to as the acquired immunity or adaptive immunity and has appeared with jawed and jawless vertebrates during the evolution [1]. The main characteristic of the acquired immunity is to harbor a clonal antigen (Ag) receptor that is generated from a specific mechanism involving chromosomal DNA rearrangements to specifically recognize the pathogen [2]. Jawless fishes (lampreys) possess primary lymphoid organs including a thymus, but they lack secondary lymphoid organs (spleen and lymph nodes) explaining why T and B cell–like cells harbor clonally variable lymphoid receptors (VLR) generated through DNA rearrangement during the lymphocyte ontogeny. The VLR B protein is expressed on the surface of the B cell–like cells from lampreys and can be secreted following stimulation [2], evoking the ancestor of the B cell receptor (BCR). The VLB protein is secreted as a pentamer, which suggests that IgM might be the primordial antibody class. Later on, during evolution, acquired immunity gained in specificity due to elaboration of its selection and memory programs within secondary lymphoid organs. B cells from the ectotherm family (e.g., lizards, snakes) have conserved their capacity to phagocytize different pathogens underlining the common origin of B cells and myeloid cells, whereas this capacity is lost in mammals [3, 4]. Innate functions are provided by specialized immune cells such as cells from the myeloid-derived lineage, which have not acquired the memory capacity. Myeloid functions include rapid and localized responses in tissues, the ability to clean up dead cells in a process known as efferocytosis, an elevated phagocytotic capacity, and the ability to provide cognate help to T cells.

Growing over the past decade, new insights regarding the functional heterogeneity of the two systems have allowed rethinking of how the multi-layered immune responses are articulated. The recent description of innate lymphoid cells (ILCs) has further contributed to provide substantial pieces of evidence showing that different lymphoid cells participate in the time-sequential shift from an innate to acquired immune response. As a consequence,

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this modifies the dogma of functioning of the two systems. Together, new insights from comparative and developmental immunology bring us new perspectives for understanding the complexity of the immune response; through the observation of the compartmentalization of the immune system into components that change rapidly or disappear during evolution and those with a strong selective advantage that were conserved throughout the evolution.

Among lymphoid cells, arguments are accumulating to consider that B cells have conserved innate functions during their evolution. To this end, this review will describe the characteristics and functions of innate-like B cells (IBCs) first in mice and then in humans. In addition, we will highlight new insights into the biology of this subset shedding light on the strong plasticity of these cells to undertake different protective functions at the crossroad between innate and adaptive immunity.

Mice IBCs Family

B1 and MZB

Among the IBC family, two major B cell subsets have emerged and have been extensively described in mice. The first subset is referred to as B1 cells that reside in the serous cavities and can be dichotomized into B1a and B1b cells based on the expression of the plasma-membrane molecules CD5 and CD45RA [1]. The second subset, called marginal-zone B cells (MZB), was first described in the marginal zone of the spleen. Both subsets possess unique and shared properties and play a crucial role in the primary immune response.

One of the characteristics of B1 and MZB from mice is their expression of invariant or semi-invariant BCR [5]. Those receptors recognize mostly non-protein antigens, such as phospholipids, or carbohydrates shared by many pathogens as well as by the host [6, 7].

IBCs repertoire appears to be not only restricted to autoreactive germline-encoded elements but arise also from a selection process. Such an assertion came from the observation that BCR of IBCs producing antibodies directed against blood-group antigens are not germline-encoded immunoglobulins but result from a selection process in response to commensal bacteria [2]. More recently, a subset of IgM^+ naïve B cells that recognizes the algal protein phycoerythrin (PE) was described in the spleen of Igh^b mice. Those PE-specific B cells were restricted to a single expression of the immunoglobulin variable heavy chain (V_H1-81) and these cells have conserved their capacity to differentiate into IgM^+ producing plasma cells, which supports the possibility that exo-antigen could also participate to the selection process of the pre-immune repertoire of IBCs [8]. As a consequence, IBCs constitute a strong and protective local defense against infection. However, the counterpart to the use of germline-encoded V segments is their potential self-reactivity as demonstrated for anti-type II collagen-specific IBCs in autoimmunity [9]. These autoreactive B cell clones are associated with a pathogenic response in patients with rheumatoid arthritis [10, 11] uncovering the ambiguous role of IBCs in the immune system.

Nevertheless, in most cases, IBCs possess a unique BCR recognition signature, which suggests that a positive selection step is critical during IBC development. In this regard and when forcing expression of different canonical BCR during the B cell ontogeny, IBCs are able to differentiate into new lineages from which the BCR has been generated [12–15]. These observations raise fascinating questions about the control of central and peripheral tolerance. In other words, the selection of IBCs for self-reactivity seems contrary to the dogma of the strict discrimination between self and non-self. One major challenge to the persistence of those autoreactive clones is their potential to increase their BCR affinity through somatic hypermutation (SHM) and class switching by recombination. However, murine B1 and MZB do not seem to undergo extensive SHM and the main reason is related to the fact that the antigen sequestration occurs away from the T cell area and germinal center [16]. Again, such an assertion is not absolute as recent studies have clearly demonstrated that a single clone of autoreactive B cells can generate autoreactive and peripheral germinal center producing clones of B cells targeting other self and non-self-antigens [17].

How are autoreactive IBCs restricted? Such a question is based on the broad observation that IBCs express a large panel of inhibitory receptors that may fine-tune the threshold of antigen-BCR signaling necessary for selection. B1 cells express the T cell marker CD5, while B1b and MZB express the myeloid marker CD11b and Fc receptor-like (FcRL)-5 known to restrict the BCR response through the recruitment of the Src homology protein tyrosine phosphatase (SHP-1) and may serve as a gatekeeper to an exacerbated response [18]. Although B1 cells are suspected to be anergic based on the expression of the CD5 molecule [19], B1 and MZB are not intrinsically anergic and one of the main arguments for that is the reported high level of cell surface IgM and the low level of cell surface IgD. Furthermore, it is hardly expected that natural autoreactive IBCs are anergic cells since different studies have demonstrated that those cells are able to respond rapidly and efficiently to foreign pathogens [20]. B1 cells and MZB are both activated following several types of infections through both Ag-specific and non Ag-specific processes suggesting that IBCs activation is not restricted to the engagement of BCR but may occur from BCR-independent signals such as Toll-like receptors (TLR) and cytokines receptors [21–23]. The strong inter-dependence between IBCs and their microenvironment supports an important role of the extracellular factors to control IBC survival and activation. In this regard,

B1 cells have the capacity to adapt to tissue-specific signals inducing a unique phenotypic and functional imprint [24, 25]. Nevertheless, the interconnection between IBC ontogeny and the natural B cell autoreactivity remains to be solved, probing which specific mechanisms of selection and activation are required to confer a broad natural response without triggering acute autoimmune responses.

The Protective Functions of IBCs

Natural IgM Production

The Nature of the IgM-Producing Cells One and if not the main contribution of IBCs in the immune system is to produce and secrete natural non-switched IgM antibodies. Expression and secretion of IgM is one of the most ancestral attributes of B cells. This capacity has been highly conserved during the evolution and this can be explained by the fact that natural IgM is particularly effective in removing auto-antigens from the circulation [26]. Both polyclonal and some monoclonal IgM Abs enhance the clearance of apoptotic components from dying cells [27] mainly through a complement-dependent mechanism. When bound, IgM is an early recruiter of C1q that activates the classical complement pathway and promotes opsonization by phagocytes. This was demonstrated in mice deficient in serum (s)IgM, as these mice showed reduced apoptotic cell clearance and C3 cellular deposition, similar to C1q deficient mice [28]. It has been recently proposed that B1a and MZB are the two main B cell actors involved in the clearance of apoptotic cells and participate in the elimination of a significant source of neoantigens [29].

B1 cells produce polyreactive and low avidity IgM antibody during infections including respiratory viral infections explaining why they are locally distributed within the respiratory tract epithelium but also present in the lymph nodes within regional and non T cell areas [20]. B1 cell development is auto-regulated by the production and secretion of natural IgM as mice unable to secrete IgM develop an impairment of B1 cell generation in the body cavities [30]. The accumulation of B1 clones in lymph nodes but outside T cell areas supports a role for these cells to the generation of high-specific response in germinal centers by providing antigen accessibility to T cells or to specific B cells, referred to as B2 cells.

Although B1 cells are the primary source of natural IgM, this fundamental function is not restricted to this particular subset of B cells [31]. Some authors have proposed that B1b (CD5 neg, CD45 low) rather than B1a (CD5 pos, CD45RA intermediate) are more critical for natural IgM production [32]. Furthermore, the contributions of other tissue-localized IBCs (MZB and B1 cells from the spleens) have also been incriminated. This increases the complexity of defining a unique natural IgM-producing B cell population. Such diversity is retrieved at the molecular level as splenic B2 cells, B1 cells, and B1-derived plasma cells are all dependent on the transcription factor B lymphocyte–induced maturation protein 1 (Blimp-1) expression for IgM and IgG3 production [33], while natural IgM production by B1 cells can occur independently of Blimp-1 in both bone marrow and in the peritoneal cavity.

During *Ehrlichia muris* infection, in the mantle zone of the spleen and in the bone marrow, MZB elicits the generation of IgM memory B cells harboring the myeloid integrin CD11c and expressing the T cell–associated transcription factor (T-bet) (Fig. 1, Table 1) [36, 37, 39]. In addition, the spleen $CD11c^+$ $T\text{-}bet^+$ IgM memory B cell subset expresses at its plasma-membrane the C-X-C chemokine receptor type 4 (CXCR-4) for CXCL12 (also known as SDF1), the transmembrane activator and CAML interactor (TACI, also known as tumor necrosis factor receptor superfamily member 13B [TNFRSF13B]), and CD73 an ecto-5′-nucleotidase. For the IgG antibody response, the $CD11c^+$ $T\text{-}bet^+$ IgM memory B cell subset needs contact with T cells and IL-21 signaling as reported upon antigen challenge in lymph nodes [38]. In addition to the secretion of antibodies, $CD11c^+$ $T\text{-}bet^+$ B cells are potent antigen presenting cells to T cells and this is possible due to their localization at the T/B cell border in the spleen and the expression of the chemokine receptor CCR7 [40]. This observation is consistent with several reports suggesting that CD11c and T-bet expressing B cells may be a decisive subset in autoimmunity in mice [41] and also in humans [42].

Molecular Mechanism Controlling the IBC-Dependent Ig Production One major question arising is: What is related to the molecular mechanisms controlling T cell–independent activation and antibody production in IBCs? To this end, cytokines, as well as direct cellular interactions, could provide classical and alternative pathways leading to rapid production of antibodies associated or not with class-switching recombination. Using Blimp-1-GFP mice, in-depth sequencing analysis of the transcriptional program of antibody-secreting cells from distinct B cell subsets, including IBCs, based on their location and maturity stage has revealed a tissue-specific program necessary for the B cell differentiation [43]. Although a core transcriptional signaling is conserved between plasmablast and plasmocytes (PC) from the spleen and bone marrow-resident PC, a specific network has been underlined between the different compartments showing the key role played by chemokine receptors and cell adhesion molecules. However, the common and natural IgM antibody-secreting cell signature from IBCs remains to be defined, challenged by the complexity of the different origins of natural Ab-producing cells.

Collectively, the different steps involved in the generation of IgM^+ memory B cells or IgM-producing cells from IBCs is still an open question and may be highly dependent on (1) the

Table 1 Extended phenotypes of innate B cells in mice to complete Fig. 1

	Reference	B220	CD19	CD5	IgM	IgD	CD21	CD23	CD43	CD1d	CD11b	CD11c	CD73	CD38	CD138	TACI	CXCR4	CXCR3	PD-L2
$CD5^{+}CD1d^{hi}$ $IL10^{+}$	[34]	lo	+	+	+	lo	lo	lo	+	hi	±								
$CD5^{+}$ $CD1d^{lo}$ $IL10^{+}$	[29]	lo	+	+	+	lo	lo	lo	+	lo	++								
LAG-3^{+} $CD138^{hi}$	[35]	lo	+		+				lo	hi					hi		+		
$CD11c^{lo}$	[36]	lo	+	–	hi	lo	+	+	+	hi	lo	lo		hi	–				+
$CD11c^{+}$ T-Bet	[37]	+	hi	–	hi	lo	lo	lo	hi	+	+	lo	+	hi	++	+	hi		+
IgM memory $CD11c^{+}$ T-Bet	[38]	+	hi		hi	±	lo	+			hi	+	hi	hi	–	+	+		+

stimulatory antigen; (2) the tissue localization of the activation; (3) the interplay with other immune cells; and (4) canonical and non-canonical intrinsic molecular mechanisms.

Initiation of a Class Switch-Specific Immune Response

In addition to their capacity to promote an effective and protective response to infection by a steady-state production of polyreactive IgM antibodies, IBCs are also able to develop specific class-switched responses in secondary lymphoid organs. This is particularly true for MZB that could undergo class-switching through a strict metabolic program [44] [45]. MZB produce IgM but also class-switched IgG and IgA antibodies mainly in response to commensal antigens [21]. It is the chemical nature of the antigen that locally regulates the immunoglobulin production and drives the T-dependent or T-independent pathway for antibody production [46]. Some antigens could induce MZB activation and CXCR5 upregulation, necessary for MZB relocalization into the follicular area rich in T cells [47]; [48]. One general explanation may, on one hand, be that T cell–independent antigens stimulate MZB to proliferate and produce IgM and class-switched antibodies without forming germinal centers whereas, and on the other, T cell–dependent antigens most likely induce MZB cell migration into the follicles [49]. However, the exact role of MZB in generating a GC reaction is still under investigation.

Additionally, MZB possess a strong propensity to interact with other immune cells and, in particular, to promote T cell–dependent responses within the spleen. It was demonstrated that dendritic cells expressing CLE4A4 selectively stimulate rapid IgG1 but not IgM production from MZB [50]. In humans, the newly described neutrophil and B cell helper subset (NBH) promotes MZB activation by presenting a higher expression of B cell stimulating molecules such as BAFF, APRIL, IL-21, and CD40L, than do classical neutrophils, leading to IgM production but also allowing class-switching recombination to IgG2 or IgA [51]. MZB have been demonstrated to closely interact with natural killer (NK)-T cells through the expression of CD1d [52]. CD1d-restricted glycolipid antigen ligands are present on the surface of *Streptococcus pneumonia*, *Borrelia burgdorferi*, and *Sphingomonas species* [53, 54]. This interaction promotes an early wave of response to bacterial and viral pathogens [55]. The relationship between MZB and innate lymphoid cells (ILC) has been recently explored and it was demonstrated that mouse ILC3 express APRIL enhancing a T cell–independent IgG3 response from MZB [56].

Regulatory Functions of IBCs

The link between IBCs and B cell regulatory functions has been continuously suggested since the first appreciation of the B cell capacity to control the immune response (Fig. 1, Table 1) [57].

One of the primary functions of IBCs was related to the control of the immune response by different means. First, IBCs possess intrinsic regulatory functions mediated by their natural capacity to produce IgM at a steady state or following activation. Second, IBCs can exercise regulatory functions through the release of anti-inflammatory cytokines such as IL-10 upon stimulation. Third, IBCs are also able to control the inflammatory response [58].

Regulatory Functions of IBCs: Activation Pathways One crucial question remains related to the necessity or not of a BCR engagement in the natural regulatory functions of IBCs is not well understood. Indeed, there are arguments to consider that part of the regulatory functions of IBCs is not strictly dependent on antigen stimulation via an engagement of the BCR. Accordingly, some studies have related a TLR pathway rather than an antigen-specific BCR activation pathway of IBCs leading to their redistribution in secondary lymphoid organs in order to regulate polyreactive IgM IBC production at the site of infection [22]. Support for such an assertion was observed during influenza infection in mice with IBCs that can rapidly migrate from local niches to secondary lymphoid organs following a type-I interferon stimulation and CD11b integrin cell surface expression in response to a TLR pathway activation [25]. This observation has also been reported during *tetanus toxoid* (*tet*) vaccination in humans. It was shown that specific staining of circulating antigen-specific B cells following *tet* vaccination revealed 6 days after vaccination the induction of two distinct plasmablast subsets. Indeed and along with the increase of the antigen-selected *tet*-positive CD38 high plasmablast, the authors have demonstrated the emergence of a second and non-specific (tet^- IgM^+) plasmablast subset, which represents more than 60% of the entire plasmablast population. A complex phenotypic signature characterizes this bystander subset with moderate expression of CD138 (syndecan-I), HLA-DR, and CD126 (IL-6 α Receptor) but an increased expression of CXCR4 (C-X-C chemokine receptor type 4). Although this study did not formally identify the nature of this non-specific plasmablast subset, the authors highlighted that those cells expressed a reduced expression of Blimp-1 suggests an innate origin [59].

On the other hand, different types of infections have demonstrated the induction of Breg cells arising mostly from IBCs that suppress harmful Th1 or Th2 responses in an antigenic non-specific manner [34, 60, 61]. Although the final phenotype of this Breg subset differs from one experimental model to another, and this is continually debated, such studies have, however, demonstrated that the greater part of the initial B cell origin is related to IBCs. As an example using IL-10-EGFP reporter mice, the dominant IL-10 producing B cell subset in the spleen of infected mice with *Schistosoma mansoni* is composed of MZB [61] whereas others have suggested that B1 cells were involved [62]. It is highly likely that these two IBC subsets are crucial in the control of infection in mouse models [63]. This raises the possibility that innate Bregs could emerge from distinct IBC subsets (e.g., B1 and MZB) and perhaps from all of them during an immune response with specific attributes depending on (1) the nature of the antigen, (2) the localization of the response, and somehow (3) genetic and epigenetic factors that have not yet been elucidated. To summarize, we can consider that IBCs exert their regulatory functions at the crossroad of promoting a protective response in order to preserve the organism from exacerbating responses, and through recruitment activation and control of the antigen-specific response.

Innate Versus Regulatory Functions of IBCs Innate B cell functions and regulatory functions of IBCs are often examined separately but they represent the two sides of the same coin. Infectious models represent a robust and pertinent approach to evaluate the interplay between innate and regulatory functions in IBCs. Among them, the mouse model infected with the *Salmonella enterica serovar typhimurium* (STm) gram-negative bacterium infection has been well studied and provides interesting information regarding the innate properties of IBCs. STm has the capacity to introduce a specific bacterial effector protein into the host cytosol via a specific system, the Salmonella type III secretion system (TTSS) that can infect most immune cell types. In this model, IBCs were described as a significant partner in the generation of a protective response against Stm and this response depends on the nature of the bacteria (virulent or attenuated). Recently, a study demonstrated that a STm-attenuated infection induces rapid plasmablast production independent of the formation of germinal centers, supporting a T cell–independent activation of germline B cell clones. The authors demonstrated that the IgM-producing cells were present at 4 days post-infection, while IgG reaches a maximum 18 days post-infection. One interesting finding is that almost 95% of plasmablasts generated during the primary response possess a very poor ability to bind Salmonella antigens, suggesting no or a very low affinity for the antigen [64]. In this study, the authors propose an exciting concept where first an innate signal was generated leading to a burst of low-specific IBC expansion in response to Salmonella infection. This initial response is followed by a second and more-specific response dependent on germinal center-dependent somatic hypermutations taking place at extra-follicular sites in specific patches. This finding supports the view that engaging extremely low affinity or polyreactive IBC cells in early and primary response achieves a high potential of generating a rapid protective response that perfectly fits with the IBCs' fate. Another key conceptual observation involving regulatory IBC functions and performed in *Salmonella* infection mouse models comes from the ability of the pathogen to subvert the regulatory IBC response to its

advantage. This was demonstrated in mice lacking the capacity to produce IL-10 as these mice are significantly more resistant to death after infection as compared with wild type mice, supporting the notion that IL-10 production from lymphoid cells including regulatory IBCs may be a critical process for the survival of bacteria [65]. The IL-10 immunosuppressive role of B cells in infection was thus confirmed to be dependent on TLR signaling since mice lacking MyD88, the canonical adaptor for inflammatory signaling pathways downstream of TLR, in B cells became resistant to lethal infection [66] while B cells have conserved their capacity to produce a normal antibody response [67]. This paradoxical observation is due to the absence of the MyD88 signaling pathway in B cells leading to a defect in the IL-10-dependent B cell regulatory function of controlling neutrophil, NK cell, and inflammatory T cell accumulation at the site of bacterial replication. From additional studies, this group formally identified surface IgM^+ $CD138^+$ $TACI^+$ $CXCR4^+$ $LAG3^+$ plasmablasts as the critical player inhibiting anti-*Salmonella* immunity during the early course of the infection through the release of two anti-inflammatory cytokines, IL-10 and IL-35 [35, 68]. In this latter study, the authors demonstrated that an intense burst of $IL10^+$ IgM^+ plasmablasts was generated several hours after infection, and decreased after 8 days reflecting the archetype of the primary humoral response. Epigenome-wide and repertoire analyses have further established the origin of these regulatory plasmablasts in this model to be B1a cells and B1b cells but not MZB [35].

The ability of pathogens to manipulate the suppressive functions of B cells to counteract the anti-bacterial response is not unique to the *Salmonella* infection as other intercellular bacteria such as *Chlamydia abortus* and also viruses such as CMV (cytomegalovirus), HIV (human immunodeficiency virus), and HBV (human hepatitis B virus) have the capacity to induce suppressive functions in B cells [69–73]. These models uncover the intrinsic dual function of IBCs, initiating protective immunity while promoting regulatory mechanisms against uncontrolled inflammation. Such feedback is a common feature in the homeostatic system but allows us to extend our point of view of IBCs and the general function of B cells such as immunoglobulin production or suppressive functions. Reconciling different observations, IBCs are a fair representative of the plasticity and the adaptability of immune cells to their microenvironment [74]. IBCs can differently respond to stimulation, change their identity, differentiate, and relocate throughout the body adapting their function to their new location (Fig. 1, Table 1).

Other Innate B Cell Populations

Atypical IBCs

Growing evidence during the past decade points toward the atypical capacity of IBCs to differentiate into other lymphoid or myeloid lineages. This incredible cellular plasticity represents a reliable tool to offer the best range of responses against organism aggression. In this regard, B cells have continuously been described as a very plastic lineage. Interestingly, studies have demonstrated the conversion of B cells to other immune cell types by modification of lineage key transcription factors. Indeed, ectopic expression of C/EBP (CCAAT/enhancer binding protein) in primary progenitor B cells and mature B cells induces transdifferentiation of B cells toward a distinct myeloid cell fate including granulocytes macrophages and dendritic cells [75–77].). In vivo, this relevance seems restricted the ability of transdifferentiation from the pro-B cell population and can occur during the inflammation process [78]. A new study has highlighted the transcription factor Hoxb5 (Homeobox B5) as a master regulatory factor involved in the lineage conversion of B cell precursors into fully functional T cells [79]. A CD11c or CD11b B cell subset with myeloid or dendritic attributes and T cell regulatory functions has been described in mice [80]. These CD19 + $CD11c^+$ B cells (discussed above) are present in mouse spleen, expressing Pax5 and the T cell regulatory enzyme IDO (indoleamine 2, 3-dioxygenase), and develop from stem cell progenitors in B cell-deficient mice (μMT knockout) but not from CD19-knockout mice.

Are myeloid and non-B cell–restricted identity attributes such as CD5, CD11b, and CD11c a hallmark of IBCs? Do those characteristics represent different functional subsets? Does it represent alternatively, a conserved evolutionary function from a common progenitor? Although these questions remain to be solved, their investigation might bring us new insights into the function of these populations and how these populations could be conserved in humans.

Natural Killer B Cells

Three years ago, a study described a new innate B cell population with NK (natural killer) attributes emerging from bone marrow pro-B cells. These NK B cells (NKB) are present in the marginal zone of the spleen and mesenteric lymph nodes in both mice and humans. Murine NKB express the NK1-1 marker plus CD19 and a cell surface IgM with a limited repertoire. NKB cells exhibit a critical role in the control of microbial infection since NKB-depleted mice were more prone to *Listeria monocytogen* and STm infections [81]. NKB show a great potential to produce IL-18 and IL-12 leading to activation of NK and ILC1 against bacterial infection. The description of this population was completed in an additional study showing that $NK1\text{-}1^+$ $CD19^+$ cells have the capacity to differentiate into $CD138^+$ $Blimp1^+$ plasmablasts upon LPS (lipopolysaccharide) stimulation. This has motivated the authors to propose that $NK1\text{-}1^+$ or $NKp46^+$ B cells represent a phenotypic attribute of MZB [82].

Although discrepancies exist in the characterization of IBCs, one significant aspect to keep in mind is the capacity of IBCs to express atypical B cell markers. Expression of CD11b, CD11c, NK1.1, PDCA, and other atypical phenotypic attributes in IBCs underline that the necessity that the dogma of the strict stable phenotypic identity of B cells has to be re-evaluated. This idea is already accepted in T cell biology where phenotypic attributes could be transitory and related to a functional program in many different T cell "subsets" establishing the foundation of inhibitory blockade molecules in some cancers [83, 84] and recently providing new therapeutic consideration in autoimmune diseases [85].

IBCs in Humans

Although an extensive amount of literature has provided evidence for the high diversity of IBCs in rodent models, the study of human IBC (hIBCs) is more challenging. One crucial feature of hIBCs is their tissue-dependent localization and functions that complicate experimental approaches in humans. From an evolutionary point of view, B cell subsets become diversified. Mouse IBCs represent a conserved B cell subset with functions close to the myeloid lineage supporting a substantial advantage against infections. Nevertheless, transposition to human is more speculative perhaps because most of the tissues housing IBCs are structurally very different (Table 2) [86].

Human B1 Cells

Characterization of the B1 cell population is the best illustration of the complexity of studying IBCs in humans. In 2011, the Rothstein's group identified a homolog of the B1 subset (hB1) in cord blood and adult circulating peripheral blood based on their capacity to spontaneously produce IgM secretion, to stimulate T cells, and to possess a tonic intracellular signal [87]. This subset expresses CD27 and CD43 among the $CD19^+$ $CD20^+$ B cell population, and in addition, this population was the only one able to bind phosphoryl-choline (PC), another hallmark of the murine B1 cells [88, 89]. Interestingly, the hB1 subset was distinct from $CD5^+$ B cells since the majority of $CD5^+$ B cells were negative for CD27 and CD43. CD5 expression in humans is mainly an inducible marker that appears upon activation decoupling its expression from a specific subset [90, 91]. Beyond phenotypic considerations, one functional aspect of this intriguing $CD27^+$ $CD43^+$ $CD5^{\pm}$ B cell subset is its ability to spontaneously produce IgM within 3 h. This unique ability has evoked the question of the real nature of this specific subset and has raised the question of a possible contamination with plasmablasts that also express $CD43^+$ and $CD27^+$ [92, 93]. However, one recent study has further confirmed the presence of hB1 cells ($CD20^+CD43^+CD27^+CD70^-$) in the human choriodecidual stroma of women with spontaneous pre-term (PTL) and term (TL) labor [94]. According to these authors, choriodecidual B cells display a unique phenotype that is distinct PTL from TL stroma since B cells from PTL stroma exhibit an hB1 phenotype with altered function promoting spontaneous polyreactive IgM and with a suspected impact on pregnancy outcomes [95].

Human MZ B Cells

Among innate B cell actors, human MZ B cells contribute mainly to a specific antigenic response leading to a rapid production of IgM and IgG3 isotype antibodies. In addition, human MZ B cells have been described as the main humoral actors of systemic anti-bacterial immunity [96]. Since the first description of circulating human MZB [97, 98], some advances have established the existence of two main hMZB subsets according to their localization.

Human Circulating MZ-Like B Cells

The circulating $IgD^+IgM^+CD27^+$ B cell population harboring some shared properties with murine MZB was first observed in healthy children younger than 2 years old with mutations of their immunoglobulin receptor during ontogeny, prior differentiation into T-independent antigen responsive cells and from the formation of a competent germinal center [99, 100]. In adults, the presence of immunoglobulin-mutated V genes in this subset has suggested different interpretations regarding MZ-like B cell origin and in particular with the possibility to have somatic hypermutation events outside of the germinal centers [101] or the possibility that IgM memory B cells are generated during the immune response in germinal centers but without immunoglobulin class switching [102, 103]. Recent assessment of IgM^+CD27^+ subsets in humans reveals the heterogeneity of the MZ-like B cell subset including both "true" innate B cells harboring a unique repertoire and IgM-mutated memory cells (with no or low IgD expression) displaying a clonal relationship with switched memory B cells [104]. Additional evidence has demonstrated that the IgM^+ memory B cell repertoire presents a bias in IgVH family usage and may be affected by age [105]. Furthermore, this study has further underlined that the IgM^+ memory B cell subset is heterogeneous based on the density of IgM^+ expression that could be used to dichotomize between T-dependent and T-independent types of IgM memory cells. There is no doubt that the emergence of single-cell transcriptomic analyses will bring new insights into the biology of human MZB-like and IgM^+ memory cells together with additional traits about their function in the immune system. The ongoing characterization of MZ-like cells in humans rises fascinating questions about how those cells are generated during B cell development and by which mechanisms these cells are regulated coupling tissue localization with specific functional characteristics.

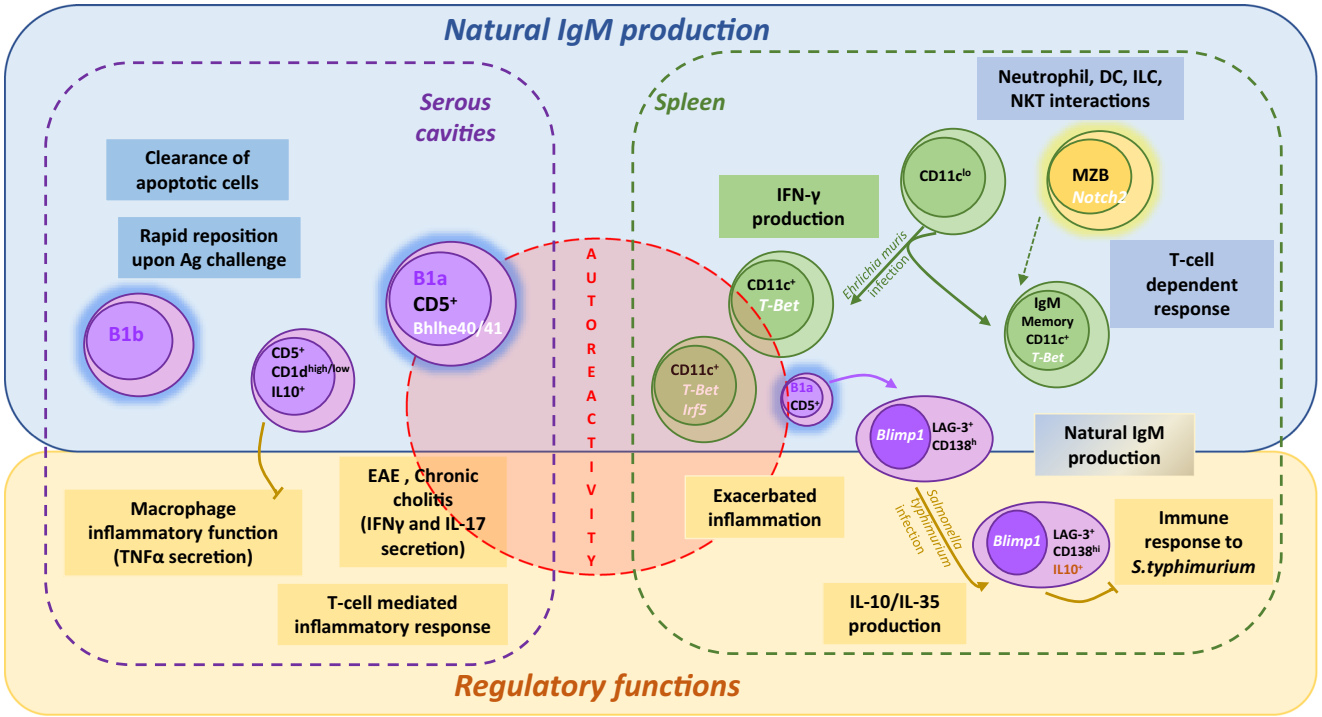

Fig. 1 Versatile sides of innate B cells. EAE (experimental autoimmune encephalomyelitis); MZB (marginal zone B cell), NKT (natural-killer) T cell, ILC (innate lymphoid cell), DC (dendritic cell). B1 cells (purple) and MZB (orange) cells are the two main contributors to natural IgM production. IgM secretion by B1 cells is independent of the transcription factor Blimp-1 in serous cavities and participates in the clearance of apoptotic cells. T-bet expressing B-cells (green) are a heterogeneous subset: 1-T-bet+IgM+ B-cells could arise from MZB cells or unknown progenitors secreting natural IgM. 2-T-bet+ CD11c+ B-cells undergo class-switching and participate in the autoreactive response. In another hand, when activated through the TLR pathway, innate B cells display a regulatory role preventing the organism from an exacerbated inflammation. This function is performed by the production of natural IgM and by the anti-inflammatory cytokines IL-10 and IL-35

In line with these questions, the selection of the reactivity of MZ-like B cells in the unrestricted human repertoire is still under investigation asking how MZ-like B cells are developmentally linked to the selection of autoreactive B cells. Some studies have revealed that autoreactive B cells against proteinase 3 (PR3) are not restricted to autoimmune patients but also found in healthy controls, and in this case, they exhibit an MZ-like phenotype (IgD^+CD27^+) [106]. Intriguingly, a decrease in this subset has been reported in systemic autoimmune diseases and with correction under treatment with immunotherapy [107–111]. How could the proportion of circulating MZ-like B cells reflect the tolerance breach could be asking? Nevertheless, the intricate network established in mice existing between this population and the control of autoreactivity [112] offers promising future tracks for understanding the control of B cell tolerance in humans.

Tissues Resident Innate B Cells

Spleen human B cells located in the mantel zone area around the germinal center are characterized by a specific cell surface phenotype $CD27^+IgD^{low}IgM^{high}$ [99, 113] and this phenotype included the expression of CD45RB (MEM55 epitope) and the absence of positive labeling for the mitotracker green (MTG) fluorescence dye [114]. Transcriptomic analysis has defined the transcription factor SOX7 as significantly involved in the MZ-like B cell fate associated with IL21-R and CCR9 suggesting a strong relationship of MZ-like B cells with their microenvironment. More recently, in-depth phenotypic profiling of human B cells from different tissues coupled with mass cytometry and imaging mass cytometry has revealed a phenotypic alignment between the $IgM^+IgD^+CD27^+$ B cell subset and a precursor $CD45RB^+$ subset distinct from memory B cells, suggesting a separate developmental branch between MZ-like B cells and memory B cells [115]. Interestingly TACI, CD80, and FcRL4 could be used to distinguish IgD^+CD27^+ MZ-like B cells across the spleen, the gut, and the tonsils.

Human IBC Functions

Natural Protection

The molecular pathways that lead to immature B cells to differentiate into either MZB or follicular B cells were extensively studied in mice but remain elusive in humans. In both species, the transmembrane neurogenic locus notch homolog

protein 2 (Notch2) receptor presents an essential role for MZB development through the interaction with one of its ligands, Delta-like 1 (Dll1), that is expressed by fibroblastic reticular stream cell in the spleen [116]. Additionally, BCR engagement on type 1 transitional (T1) B cells via the serine-threonine kinase TAOK3 (TAO kinase 3) is effective to inducing ADAM10 (ADAM metallopeptidase domain 10) expression that is necessary for promoting Notch2 intracellular domain translocation into the nucleus [117]. In addition to the Notch2 pathway, the importance of the signal downstream from the BCR in the choice of MZB and B1 cell fate seems crucial since mutations in genes encoding regulators of the BCR signaling such as CD19 or CD22 result in the profound modification of the IBC compartment (Table 2) [15, 121].

In humans, it was suggested that IBCs are prone to recognize microbial cell-wall fragments from the microbiota protecting against microbial infection. Human splenic MZ-like B cells have the particularity to possess a strong pre-activation state characterized by high metabolic activity coupled with a specific activation gene signature [45]. This gene signature highlights the increase of the mTORC1 (mammalian target of rapamycin complex 1) signaling pathway depending on the cooperative activation of TACI and TLR9. Interestingly, mTORC1 signaling regulates class switch recombination-inducing signaling pathways specifically. This observation was further extended in an additional study [118]. Those authors demonstrated that IgM-secreting cells are present in humans, but in contrast to mouse, small intestine MZB harbor a large repertoire against a high diversity of microbial communities. The study further suggests that IgM-secreting cells reacting to commensal bacterial compounds are clonally related to a specific IgM^+ memory B cell subset expressing a gut-specific gene signature that differs from marginal zone B cells. This tissue-specific memory signature is characterized by an upregulation of *FCRL4*, *IL-10*, *CCR9*, and *CD11c*. This study documented the heterogeneity of human IBCs and supports the possibility of mucosal tissue-resident IgM^+ memory B cells in human, but not in mice.

Conventional IBCs and IgM^+ memory B cells share some protective functions through the provision of rapid immunoglobulin production that may or may not involve class switch recombination. The dichotomization of the peripheral memory B cell compartment into different subsets based on IgM, IgD, IgG, IgA, CD27, CD38, and CD24 expression has suggested three distinct maturation pathways [122]. The first and second memory B cell subsets were local and systemic and independent of the GC reaction. These pathways encompass IgD^+ IgM^+ $CD27^+$ called the natural effector B cell subset and corresponding to MZ-like B cells and the $CD27^-$ IgA cells. Both populations showed limited proliferation and reduced somatic hypermutation levels. IgM^+ $CD27^+$ IgD^- memory B cells present a complex ontogeny as they are suspected arising from IBCs in the primary response but also from the

Table 2 Protective B cell subsets in humans

		CD19	CD20	CD27	CD43	CD5	IgM	IgD	CD21	CD23	CD1c	CD45RB	CD80	fcrl4	CD24	CD38	CD10	Reference	TISSUE
Natural protection	Homolog of B1	+	+	+	+	±												[87]	Cord blood
	IgD^+ IgM^+ $CD27^+$ B cells	+	+	+			hi	lo	+	–	hi	+			+	–		[99] [114]	Blood Spleen
		+	+	+			hi	+	+	+		+	++	+	+	lo	–	[115]	GALT
		+	+	+			hi	+	++	lo		+	lo	lo	+	lo	–		Spleen
		+	+	+			hi	+	+	lo		+	lo	++	+	lo	–		Tonsil
	IgM+ memory B cells	+	+	+	+		+	–	+		hi			+				[118]	Gut
	T1 $CD24^{hi}$ $CD38^{hi}$	+	+	–		+	hi	lo	lo	Lo			–		hi	hi	+	[119]	Blood
Regulatory functions	$CD27^+CD24^{hi}$ $CD38^{hi}$	+	+	+		+	hi	hi	+	+			–		hi	hi	+		
	T2 $CD24^{hi}$ $CD38^{hi}$	+	+	–		+	hi	hi	+	+			–		hi	hi	+		
	T3 $CD24^{hi}$ $CD38^{hi}$	+	+	–		+	lo	lo	+	+			+		hi	hi	+		
	$CD19^+$ $CD24^{hi}$ $CD38^{hi}$	+	+	–		+	hi	hi			hi				hi	hi	+	[120]	Blood

T1, 2 or 3 (transitional type 1, 2 or 3 B cells); GALT (gut-associated lymphoid tissue)

recirculation of germinal center-dependent tissue-resident memory B cells. Although the high complexity of heterogeneity of the human protective response has still not been uncovered, human IBCs may integrate local signals to undergo higher functional activities including local antibody production, commensal bacterial memory B cell generation, and greater capacity to recirculate to provide adequate and broad protection against pathogens.

The Control of the Immune Response

Beyond protection against pathogen, studies in humans have now begun regarding the regulatory functions of IBCs on the immune system begin. Transitional B cells were been first ascribed to possess regulatory B cell functions in humans [120] as the homologous of their T2-marginal zone precursor mouse-counterpart. However, human transitional B cells possess different functional subsets [119] and consequently do not represent an exclusive Breg subset. In addition, IBCs express natural features that may render those cells highly compatible for exerting some regulatory mechanisms. Examining IL-10 secretion, we and others have underlined that, in the human peripheral blood, IgM^+ $CD27^+$ (IgD^+ and IgD^{low}) and transitional type-2 B cells are the major source of IL-10 following innate TLR9 stimulation [119, 123, 124]. Both hIBCs and human Bregs present shared properties including CD5 expression, the rapid capacity to differentiate, and a capacity to produce IgM spontaneously or after activation [120, 125, 126]. Some pathological situations have emphasized the ability of IBCs to exert regulatory functions as highlighted in a longitudinal phenotypic analysis of HIV-1 infected patients [127]. Additional studies demonstrated an increase of IL-10-expressing MZ-like B cells in HIV patients, associated with a high level of lymphotoxin-α [128] that was suggested to be involved in suppression of anti-viral T effector functions.

Studies regarding graft-versus-host diseases (GVHD) have underlined the fact that data in this area are often contradictory and fail to provide a uniform concept of the human Breg. In an initial study, IgM^+ $CD27^+$ $CD38^{low}$ human MZB and transitional B cells were enriched in IL-10 producing B cells when activated by CD40L and could control T cell proliferation as well as IFN-γ production. This population was impaired in patients with chronic GVHD. In another study, IL-10^+ B cells were assessed in controls and patients with active or remitting GVHD. B cells were activated by CpG and CD40 demonstrating that IL-10 production was enriched in the $CD24^+$ $CD27^+$ and in the plasmablast compartment and that this pool was defective in active GVHD patients [129]. Although the first stimulation inducing IL-10 was different in both studies, they underline one of the standard features while examining Breg functions that B cells could undertake regulatory functions depending on the microenvironment. However, some B cell populations may have distinct properties to undertake regulatory abilities. Among them, human and mouse IBCs may represent the most potent B cell subsets able to display regulatory functions in the immune system.

The existing and recurrent link between plasmablast differentiation and acquired regulatory function may represent the missing link between IBCs and Bregs [130]. IBCs are cells poised to differentiate in response to many different signals. IBCs integrate signals from cytokines, TLR, and BCR and from interaction with other cells like DCs, ILCs, or neutrophils. All those interactions have been demonstrated to trigger regulatory functions in B cell. One recent study shows that CpG-stimulated human peripheral B cells gradually induce TNF-receptor R2 (TNFR2) upregulation and develop into IL-10^+ IgM^+ plasmablast. Researchers have shown that IgM^+ $CD27^+$ cells were the primary source of IL-10 positive Ab-secreting cells confirming the appropriate link between IBCs and regulatory functions [131]. What could be the purpose of triggering regulatory mechanisms in B cells dedicated to the protective response? Although more questions than answers remain, IL-10 is a complex actor that may fulfill different roles that could sustain Ab production while controlling exacerbated immune response. Regulatory mechanisms of IBCs may act as a homeostatic counter-regulator of inflammation.

Conclusion

Overall, a great interest has emerged this past decade for better understanding of the heterogeneity of innate mechanisms in humans as reported in this special issue [132–140]. Of particular interest are questions about molecular mechanisms regulating the multiple layers of innate B cells with different functions. Further studies that will focus on delineating cellular and molecular switch programming innate B cells from effector to regulatory cells are bound to yield valuable new insights into the biology of B cells promoting effective Ab protection as well as B cells driving or preventing cancer and autoimmunity.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Ethical Approval Ethical approval is not applicable as this is a review article.

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