International Immunology, Vol. 27, No. 10, pp. 513–519
doi:10.1093/intimm/dxv037
Advance Access publication 10 June 2015

Suppressive functions of B cells in infectious diseases

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Received 9 February 2015, *accepted* 8 June 2015

Abstract

B lymphocytes are often essential to successfully control invading pathogens and play a primary role in the protection afforded by successful vaccines through the production of specific antibodies. However, recent studies have highlighted the complex roles of B cells in infectious diseases, showing unexpectedly that some activated B cells limited host defense towards pathogens. This B-cell function involves production of regulatory cytokines including IL-10 and IL-35 and is reminiscent of the regulatory functions of B cells initially defined in autoimmune diseases. It is now known that various types of microbes including bacteria, helminths and viruses can induce IL-10-expressing B cells with inhibitory functions, indicating that this response is a general component of anti-microbial immunity. Interestingly, IL-10-producing B cells induced in the course of some microbial infections can inhibit concurrent immune responses directed towards unrelated antigens in a bystander manner and as a consequence ameliorate the course of autoimmune or allergic diseases. This could explain how some micro-organisms might provide protection from these pathologies, as formulated in the 'hygiene hypothesis'. In this review, we discuss the regulatory functions of B cells in bacterial, parasitic and viral infections, taking into account the phenotype of the B cells implicated, the signals controlling their induction and the cell types targeted by their suppressive activities.

Keywords: autoimmunity, B cells, infection, IL-10, IL-35

Introduction

B cells are primarily known for their positive contribution to immunity through antibody production, a function they acquire during the course of their differentiation into plasmablasts or plasma cells. Antibodies are essential for protection against infectious diseases, and antibody deficiencies are associated with an increased susceptibility to infections by microbes such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and by Gram-negative bacteria such as pseudomonas (1).

Remarkably, B cells can also suppress immunity, a function initially identified in autoimmune diseases, and mediated in large part through production of IL-10 (2, 3). Thus, in experimental autoimmune encephalomyelitis (EAE), the primary animal model for multiple sclerosis (MS), mice with wild-type B cells rapidly recover from disease after a short episode of paralysis, whereas mice with a deficiency in IL-10 production restricted to B cells develop a severe, chronic disease (3). In naive mice, distinct B-cell subsets sharing, as a cardinal feature, high-level CD1d expression have a superior capacity to produce IL-10 upon activation *in vitro* and to inhibit immunity in an IL-10-dependent manner in recipient mice upon adoptive transfer (4, 5). The B cells producing IL-10 in a suppressive manner *in vivo* are however mostly found among $CD19^{+}CD138^{hi}MHC\text{-}II^{+}$ antibody-secreting cells (ASC) (6–8). The inhibitory activity of B cells is therefore not a function of resting but of activated cells.

The induction of immunosuppressive IL-10-expressing B cells critically depends on intrinsic Toll-like receptor (TLR) signaling. TLR agonists have a unique capacity to initiate IL-10 secretion by naive B cells *in vitro*, and mice with a deficiency in *Myd88* (which encodes an adaptor molecule essential for signaling via most TLRs except TLR3), or a deficiency in both *Tlr2* and *Tlr4*, restricted to B cells develop a chronic EAE, like mice with *Il10*-deficient B cells do, implicating that the suppressive function of B cells is linked to receptors with key roles in sensing microbial invasion (9). It is therefore natural to ask whether B cells are triggered to express IL-10 and perform regulatory functions during infectious diseases. Here, we review the regulatory functions of B cells during infections by bacteria, helminths or viruses.

Regulatory functions of B cells in bacterial infections

Infections by intracellular bacterial pathogens of the genus *Salmonella spp.* and *Listeria spp.* remain important causes

of foodborne illnesses. *Salmonella typhi* can cause typhoid fever, a disease affecting ~16 million people and causing 500 000 to 600 000 deaths each year (10). *Listeria* infection can cause severe diseases in pregnant women, the elderly and immunocompromised patients (11). Although B cells are usually thought of secondary importance for host defense against these infections, compared with phagocytes and T cells, recent studies have revealed their complex contributions.

B cells contribute positively to immunity against *Salmonella*, as indicated by the fact that B cell-deficient mice are less resistant to a primary oral infection by this pathogen than wild-type mice (12). The beneficial role of B cells is even clearer upon re-challenge of vaccinated mice (12, 13), which reflects their importance for optimal memory T_h1 responses (13, 14). This B-cell function is independent of antibody production, is reduced when all B cells express an identical B-cell receptor (BCR) of irrelevant antigen specificity and requires their expression of MHC-II, altogether suggesting that *Salmonella*-reactive B cells are essential antigen-presenting cells (APC) for the development of a protective T_h1 response (15). *Salmonella* directly stimulates the APC function of B cells by up-regulating their expression of CD80 and CD86 (16). In addition, B cells contribute to protective T_h1 immunity through IFN-γ production (15).

However, B cells also exert suppressive functions during *Salmonella* infection. *Salmonella* induces B cells to secrete IL-10 in a TLR2/TLR4 and MyD88-dependent manner *in vitro* and promotes the rapid appearance of IL-10-expressing B cells in the spleen of infected mice *in vivo* (6). Using IL-10-eGFP reporter knock-in mice, it was found that in infected mice all IL-10-expressing B cells have a $CD19^+CD138^{hi}$ phenotype characteristic of ASC, a finding confirmed by quantitative PCR showing *Il10* mRNA up-regulation exclusively in $CD19^+CD138^{hi}$ but not $CD19^+CD138^-$ cells (6). IL-10 expression was also not detected in splenic $CD19^-$ cells, highlighting ASC as an exclusive source of IL-10 in the spleen of infected mice early after infection (6). The IL-10 produced by these ASC suppressed host defense against *Salmonella* because mice with a B-cell-specific deficiency in *Il10* had a prolonged survival compared with control mice with wild-type B cells, which correlated with a stronger activation of neutrophils and NK cells (6).

Thus, ASC can inhibit innate host defense mechanisms to *Salmonella* through IL-10 production. This function is dependent on intrinsic MyD88 signaling in B cells (6). Indeed, mice with a deficiency in *Myd88* restricted to B cells similarly displayed improved resistance to *Salmonella* infection, which correlated with a stronger activation of neutrophils and NK cells (6). It is noteworthy that these mice also displayed a markedly increased neutrophil activation and survival rate during secondary challenge after vaccination (6). Intrinsic MyD88 signaling in B cells was required for the rapid accumulation of IL-10-producing $CD19^+CD138^{hi}$ ASC in the spleen of infected mice after challenge with *Salmonella* (6).

In addition to IL-10 secretion, B cells also suppress immunity to *Salmonella* via IL-35 production (7). IL-35 is a heterodimer of IL-12p35 and Epstein–Barr-induced gene 3 (EBi3) that was initially identified in trophoblast extracts from human placenta (17). Mice with B-cell-specific deficiency in IL-35 subunits displayed an improved control of the bacteria and a prolonged survival compared with control mice, both during primary infection and upon secondary challenge, which was associated with an increased activation of macrophages and specific T_h1 responses (7) that provide protection from *Salmonella* (10).

The characterization of IL-35-expressing B cells showed that they were also $CD19^+CD138^{hi}$ ASC, like IL-10-expressing B cells are (7). More specifically, IL-10-expressing B cells or IL-35-expressing B cells corresponded to distinct sets of ASC, sharing a surface-$IgM^+CD138^{hi}CD44^{hi}CD69^+TACI^+CXCR4^+CD1d^{int}TIM\text{-}1^{int}MHC\text{-}II^+CD80^+CD86^+$ phenotype and expressing the transcription factors Blimp1 and IRF4 (7). These ASC could not produce IL-6 (7), a mediator of the pro-inflammatory functions of B cells (18). Based on their expression of anti- but not pro-inflammatory cytokines, it was proposed that they represent two distinct subsets of 'regulatory plasma cells' (19). These regulatory plasma cells can inhibit immunity independently of $CD4^+CD25^+Foxp3^+$ T regulatory (T_{reg}) cells (6).

B cells might have other deleterious functions during *Salmonella* infection, for instance, by acting as a reservoir facilitating bacteria persistence and dissemination (20, 21). This might be facilitated by the fact that *Salmonella* modifies the properties of the B cells it infects to promote their survival and limit their immune stimulating properties (22, 23).

B cells similarly have positive and negative roles during *Listeria* infection. Indeed, B-cell depletion with anti-CD20 impaired the activation of anti-bacterial $CD4^+$ T-cell responses (24), yet B-cell-deficient mice displayed reduced bacterial load and improved survival at early time points after intravenous *Listeria* injection compared with control mice (25). Splenic marginal-zone $CD19^+CD1d^{hi}$ B cells play a key role in this inhibitory process (20, 26). They produce IL-10 in a TLR2- and TLR4-dependent manner upon activation with heat-killed *Listeria in vitro* (20) and inhibit the control of the infection in an IL-10-dependent manner in recipient mice upon adoptive transfer, whereas $CD19^+CD1d^{lo}$ cells have no effect (20, 26).

Moreover, mice lacking marginal-zone B cells because of a deficiency in *Cd19* or a deletion of the gene coding for the Notch signaling component RBP-J in B cells survive longer than control mice and have a lower bacterial burden after infection (20, 26). The suppressive effect of marginal-zone B cells is already apparent on day 1.5 after challenge, indicating that they inhibit innate defense mechanisms (20). Supporting this notion, $CD19^+CD1d^{hi}$ B cells impair control of *Listeria* in *Rag*-deficient mice upon adoptive transfer (20). Their suppressive effect probably operates directly rather than via the induction of IL-10-producing T cells, since they can also suppress anti-*Listeria* immunity in *Il10*-deficient mice upon transfer (20). Marginal-zone B cells can therefore differentiate into regulatory IL-10-producing B cells in the absence of T cells. However, $CD4^+$ T cells can help this process, as indicated by the fact that $CD19^+CD1d^{hi}$ B cells required expression of MHC-II and IL-21 receptor (IL-21R) to suppress anti-*Listeria* immunity in a different study (26).

It is tempting to integrate in a single model the data available on the regulatory functions of B cells during *Listeria* and *Salmonella* infection, which respectively identified the B-cell subsets implicated in this effect, and the phenotype of cells

mediating this function *in vivo*. Accordingly, we speculate that upon infection, CD19^{+}CD1d^{hi} B cells rapidly differentiate into IL-10-producing CD19^{+}CD138^{hi} ASC that inhibit innate immune cells. In both *Salmonella* and *Listeria* infection, the suppression becomes evident within less than 2 days after challenge. The frequency of ASC expressing IL-10 peaked on day 1 post-challenge and was proportional to the amount of bacteria administered upon *Salmonella* infection (6). The rapidity of this regulatory response is typical of an innate reaction, in line with its dependence on intrinsic TLR signaling in B cells. Indeed, this response can develop in a T-cell-independent manner, yet can be amplified by IL-21-producing T cells in a cognate manner (Fig. 1).

Regulatory functions of B cells in helminth infections

Helminths infect over 2 billion individuals worldwide, usually causing chronic infections. The persistence of helminths in the host is facilitated by their capacity to dampen host immune defenses (27). It has been proposed that the low incidence of such infections, which trigger potent immune-regulatory mechanisms, in western countries, and more recently in

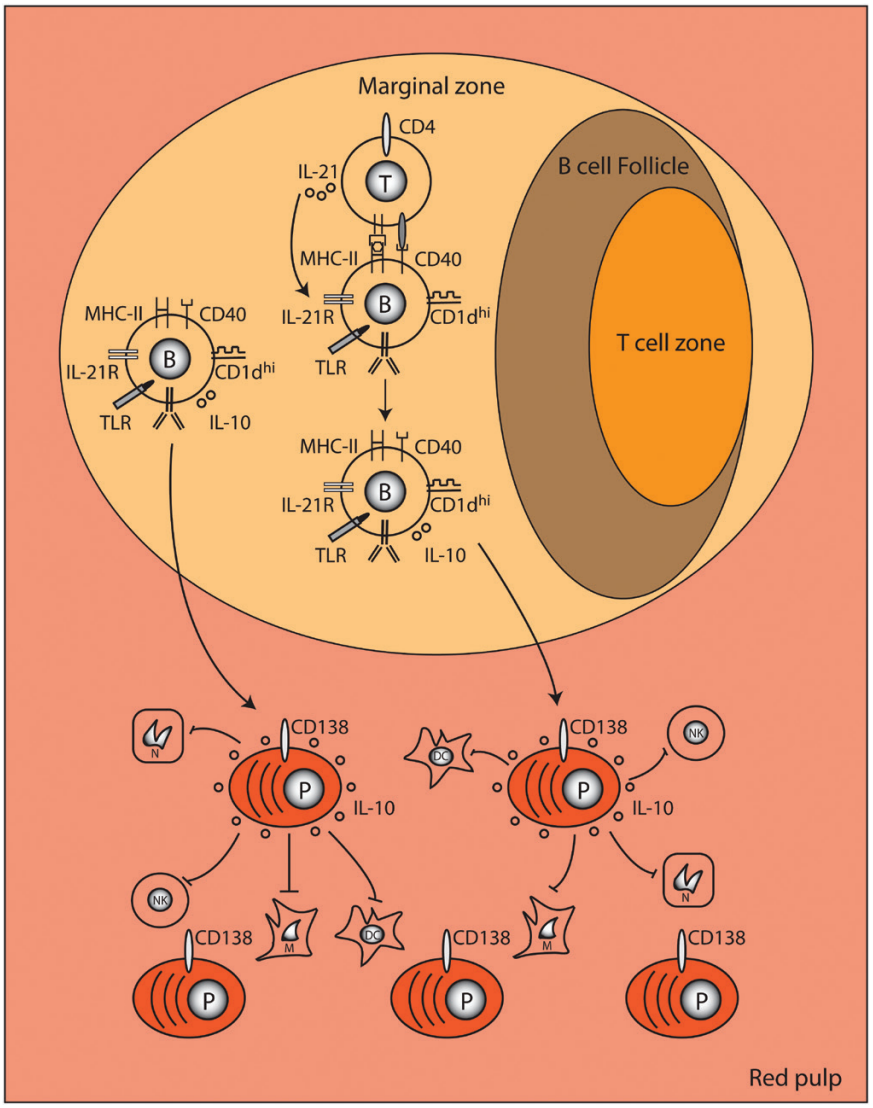

Fig. 1. Schematic model illustrating the generation and function of IL-10-producing ASC from CD1d^{hi} B cells during *Salmonella* and *Listeria* infection. CD19^{+}CD1d^{hi} B cells reside primarily in the splenic marginal zone in naive mice. We propose that upon bacterial infection, these cells can rapidly develop into IL-10-producing CD19^{+}CD138^{hi} ASC. This might be associated with their re-localization in the proximal red pulp where dendritic cells (DC), NK cells (NK), macrophages (M) and neutrophils (N) are involved in the innate reaction that controls the bacterial dissemination. Through IL-10 production, CD19^{+}CD138^{hi} ASC (P) inhibit this innate response. These ASC are rapidly generated after immune challenge and might therefore qualify as plasmablasts rather than long-lived plasma cells. Although this B-cell response can occur in a T-cell-independent manner, possibly under the control of TLR signaling, it can also be stimulated by cognate CD4^{+} T cells producing IL-21. Please note that the respective sizes of the splenic T-cell zones, B-cell follicle, and marginal zone have not been respected in this schematic representation. It is noteworthy that B cells can also give rise to a distinct set of CD19^{+}CD138^{hi} ASC in the spleen of immune mice, which complement IL-10-producing ASC to regulate immunity. We think that IL-35-producing ASC also localize in ASC foci in the splenic red pulp, probably close to the marginal zone area.

developing countries, is at the origin of the increased incidence of allergies and autoimmune disorders in these societies, a concept defining the so-called "hygiene hypothesis" (28). Understanding the suppressive networks elicited by helminth infections might therefore shed light on how to treat diseases driven by unwanted immune responses including allergic and autoimmune diseases. Several mechanisms have already been identified that are involved in the protective effects of some microbes against allergy and autoimmunity, including immune deviation, immune competition and induction of various subsets of regulatory T cells (29). Recent evidence indicates that B cells also contribute to these effects.

B cells contribute positively to host defense against helminths. B-cell-deficient mice less efficiently control primary infections with *Brugia pahangi* and *Brugia malayi* (30), as well as secondary challenges with *Strongyloides stercoralis* (31) and *Schistosoma mansoni*, than wild-type mice (32). Several mechanisms of B-cell-mediated protection have been identified, depending on the parasite, including production of antibodies (33), presentation of antigen to T cells (34) and secretion of cytokines (35).

It is noteworthy that helminths can also induce mouse B cells to express suppressive cytokines such as IL-10 (36, 37). Several helminth-derived molecules can directly trigger IL-10 production by B cells including the sugar lacto-N-fucopentaose III from *Schistosoma* egg antigens and phosphorylcholine from *Brugia malayi* (38–40). The underlying mechanism might involve TLR signaling since lacto-N-fucopentaose III and phosphorylcholine can both trigger TLR4 (39, 41). It however remains unclear whether B-cell-derived IL-10 impacts on the course of diseases caused by helminths.

In contrast, several studies demonstrated that IL-10-producing B cells elicited by *Schistosoma* infection could suppress concurrent immune responses towards irrelevant antigens such as allergens (36, 42, 43). Thus, *Schistosoma* infection can protect mice with wild-type B cells from ovalbumin-induced allergic airway inflammation (AAI), yet mice with an *Il10* deficiency restricted to B cells are not protected from AAI by such infection (42). In keeping with this, depletion of B cells erased the protection afforded by *Schistosoma* against an allergic reaction towards penicillin in wild-type mice, while T-cell depletion had no effect (43). The fact that T cells are dispensable suggests that B cells provided protection from allergy independently of $CD4^+Foxp3^+$ T_{reg} cells (43). The protection afforded by *Schistosoma* infection can be recapitulated by adoptive transfer of B cells into mice sensitized with allergen, indicating that B cells are necessary and sufficient to achieve this effect (36, 42).

Such adoptive transfer experiments permitted an identification of the B-cell subsets implicated in this protection. Moreover, several mechanisms were identified depending on the organ from where the B cells were isolated. For spleen, $CD1d^{hi}$ (but not $CD1d^{lo}$ or $CD21^+$-depleted) B cells from *Schistosoma*-infected mice reduced the severity of AAI in recipient mice upon adoptive transfer, which correlated with an enhanced accumulation of T_{reg} cells in the lungs of recipient mice (36, 42). In one study, T_{reg} cell depletion completely ablated the protection provided by the transferred B cells (36), whereas it only partially abrogated the B-cell-mediated protection in a different study (42).

The fact that B cells use other mechanisms than T_{reg} cells to suppress AAI was clearly shown when B cells were isolated from the lungs of mice that had been infected with *Schistosoma* and challenged with an allergen (42). Indeed, although these B cells produced elevated amounts of IL-10 upon stimulation with *Schistosoma* antigen *in vitro*, they protected recipient mice from AAI in an IL-10-independent manner and without inducing any noticeable T_{reg} cell expansion in the lungs of recipient mice (42). B cells from mesenteric lymph nodes of mice infected with *Heligmosomoides polygyrus*, which expressed high levels of CD23, also suppressed AAI and EAE in an IL-10-independent manner in recipient mice (44). The mechanisms implicated in these B-cell-mediated suppressive effects remain to be determined.

There is evidence that chronic infection by helminths might also suppress allergic and autoimmune responses in humans. Gabonese school children infected with *Schistosoma spp.* have reduced skin allergy reaction test results compared with controls, which were normalized upon anti-helminth drug treatment (45, 46). IL-10-producing B cells might be involved in this process since infection with *Schistosoma spp.* was associated with an accumulation in blood of $CD1d^{hi}$ B cells having a strong capacity to produce IL-10 upon activation *ex vivo*, and the abundance of these cells was reduced after treatment with the anti-helminth drug praziquantel (42).

Helminth infections were also associated with an increased capacity of B cells to produce IL-10 in MS patients (47). Indeed, B cells from non-infected MS patients show a decreased capacity to secrete IL-10 compared with B cells from healthy individuals, suggesting that MS is facilitated by a defect in this regulatory circuit (48). This defective IL-10 production was subsequently confirmed by an independent study, which also highlighted that B cells from MS patients infected by helminths produced normal IL-10 levels, which correlated with an improvement of the disease course compared with non-infected patients (47, 49). This effect was specific to helminth infections, because infections with other parasites such as *Trypanosoma cruzi* rather reduced the capacity of blood B cells to express IL-10 after *ex vivo* stimulation (47). It is possible that TLR2 is involved in the up-regulated capacity of B cells from helminth-infected individuals to produce IL-10 (50), suggesting that, as in mice, intrinsic signalling via TLR might be involved in the regulatory function of human B cells.

Regulatory functions of B cells in viral infections

Viruses can also trigger IL-10 expression in B cells. In mice, B cells up-regulate IL-10 expression after infection with murine cytomegalovirus (MCMV) (51). IL-10 plays a suppressive role in this disease, limiting the $CD8^+$ T-cell response responsible for the elimination of infected cells (52, 53). B cells are a relevant source of this IL-10 because mice with an *Il10* deficiency restricted to B cells display a 2-fold increase in IFN-γ-producing MCMV-specific $CD8^+$ T cells on day 7 after infection compared with controls (51).

Using an IL-10 reporter mouse strain, it was found that several B-cell subsets produced IL-10 after MCMV infection, including $CD138^+$ plasmablasts/plasma cells, which represented ~30% of the cells expressing the fluorescent protein

used as the reporter of IL-10 expression (51). However, this study did not define which of these B-cell subsets actually provided IL-10 in a suppressive manner in this disease. Intriguingly, the reporter mice used in this study already contained fluorescent cells at steady state, but IL-10 is only secreted by stimulated cells, which suggests that the reporter protein was possibly also produced in cells that did not secrete IL-10. This emphasizes the importance of confirming data obtained using reporter mice by measuring IL-10 expression in sorted B-cell subsets from wild-type mice, for instance, by quantifying *Il10* mRNA expression in sorted B-cell subpopulations or by single-cell PCR.

Some viruses encode molecules that directly promote the differentiation of IL-10-producing B cells, as shown for the murine gammaherpesvirus 68 (MHV68) (54). After intranasal infection, this virus produces an acute disease that is controlled within 10–12 days and is followed by the establishment of a latent reservoir that persists primarily in splenic memory B cells (55). The viral protein M2 plays an important role in the establishment of, and the reactivation from, this latency (56). The role of M2 in reactivation of latent virus is linked to its capacity to stimulate IRF4 expression in B cells, and subsequently to promote their differentiation into ASC and production of IL-10 (54, 57, 58). Thus, mice in which *Irf4* was selectively deleted in infected cells, which were generated by infecting $Irf4^{fl/fl}$ conditional mutant mice with a Cre recombinase-expressing MHV68 strain, displayed a defect in establishment of, and reactivation from, latency in the spleen compared with controls (54).

Viral reactivation is intimately linked to plasma cell differentiation, and most reactivation takes place in ASC (58). It is plausible that the induction of IL-10 expression in ASC, concomitant to the viral reactivation, might facilitate the virus replication by transiently suppressing host immune defense mechanisms. In keeping with this possibility, inoculation with an M2-deficient MHV68 resulted in lower IL-10 levels in infected mice and in enhanced antiviral $CD8^+$ T-cell responses in comparison with mice infected with a wild-type MHV68 virus (57).

Remarkably, reactivation of EBV and Kaposi's sarcoma-associated herpes virus (KSHV), two other gammaherpesviruses, in latently infected human B cells is also linked to the plasma cell differentiation program since expression of the key transactivation viral genes driving viral replication (BZLF1 and BRLF1 gene 50 for EBV, and gene 50 for KSHV) is directly induced by the transcription factor XPB1s, which is induced in B cells during their differentiation into ASC (59–61). It therefore seems that the link between viral reactivation and induction of plasma cell differentiation is a general feature of gammaherpesvirus infections, including in humans. The remarkable capacity of ASC to synthesize proteins might provide a unique platform for ensuring efficient viral replication, while production of IL-10 by these cells might facilitate virus dissemination through inhibition of immunity.

Some human viral infections have also been associated with increased IL-10 expression in B cells. Peripheral blood B cells from HIV-infected individuals contain increased *IL10* mRNA levels (62), and a higher frequency of B cells from peripheral blood of untreated HIV patients expresses IL-10 after *ex vivo* stimulation with mitogen compared with non-infected controls (63, 64). This enhanced capacity to produce IL-10 is noticeable already at early disease stages and correlates positively with the HIV viral load (63, 64). B cells might therefore contribute to the suppression of immunity against HIV through IL-10 production. Consistent with this possibility, the capacity to produce IL-10 after *ex vivo* stimulation was particularly strong in B cells expressing high levels of TIM-1 (63), and $TIM\text{-}1^+$ B cells suppressed the activation of HIV-reactive $CD4^+$ and $CD8^+$ T cells *in vitro* in an IL-10-dependent manner (63).

Increased expression of IL-10 by B cells in this disease might be related to the elevated amounts of TLR agonists present in HIV-infected individuals, caused at least in part by the enhanced translocation of microbes through the damaged gut mucosal barrier in this disease (65). Supporting this notion, the frequency of IL-10-producing B cells was higher in sigmoid colon biopsies from HIV patients compared with control individuals (63).

The induction of an increased capacity of B cells to produce IL-10 has also been documented in hepatitis B virus (HBV)-infected individuals (66). In a cohort of patients undergoing liver disease flares during chronic HBV infection, the capacity of B cells to express IL-10 increased concomitantly to the hepatic flares, which were also associated with increases in serum IL-10 levels (66). B cells from these patients could suppress HBV-specific $CD8^+$ T-cell activation in an IL-10-dependent manner *in vitro* (66). It might therefore be possible to improve host defense against chronic viral infections by targeting the suppressive functions of IL-10-expressing B cells.

Conclusion

The notion that B cells can negatively regulate immunity through production of IL-10 is now well accepted. This regulatory pathway is induced and plays important roles during infectious diseases caused by bacteria, helminths and viruses, underlining its general relevance. It is noteworthy that B cells can exert potent inhibitory effects, even in diseases during which they have essential roles in host defense. It is therefore important to now identify the molecular mechanisms and B-cell subsets implicated in these various effects. Novel mechanisms implicated in the suppressive function of B cells are emerging, such as the production of IL-35, possibly explaining why B cells can exert suppressive functions in an IL-10-independent manner.

Remarkably, some infections such as chronic helminth infection can induce regulatory B-cell responses capable of suppressing concomitant immune responses directed towards allergens or self-antigens, providing a cellular and molecular mechanism to explain the epidemiological data summarized in the "hygiene hypothesis".

Over the last few years, the identification of the B-cell subsets implicated in this regulatory circuit has become more precise. There is now convincing evidence that B-cell subsets characterized by high levels of surface CD1d expression are an important source of IL-10-producing B cells and that they acquire this cytokine-mediated suppressive activity upon differentiation into ASC *in vivo*. This is coherent with the fact that intrinsic TLR signaling in B cells, which is a strong

potentiator of ASC differentiation, is critical for the regulatory function of B cells. Supporting the concept that ASC are a major mediator of the regulatory function of B cells *in vivo*, certain microbes such as gammaherpesviruses manipulate or make use of the processes implicated in B-cell differentiation into ASC to achieve superior infections.

Altogether, this knowledge now provides a renewed framework to understand the roles of B cells during infectious diseases, which may offer novel opportunities for targeting these cells therapeutically.

Acknowledgements

The laboratory of S.F. is supported by grants from the Deutsche Forschungsgemeinschaft (SFB-650, TRR-130 and FI-1238/02), Hertie Stiftung and an advanced grant from the Merieux Institute.

Conflict of interest statement: The authors declared no conflict of interests.

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