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Memory B cells: total recall

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Immunological memory is a cornerstone of adaptive immune responses in higher vertebrates. The remarkable ability to generate memory cells following Ag exposure, in the context of natural infection or immunization, provides long-lived protection against infectious diseases, often for the hosts' lifetime. Indeed, the generation of memory B cells and long-lived plasma cells underpins the success of most vaccines. The concept of immunological memory is not new—it was first proposed nearly 2500 years ago. While our understanding of the complexities of humoral and cell-mediated memory continues to evolve, important aspects of this process remain unresolved. Here, we will provide an overview of recent advances in B-cell memory in mice and humans, and in health and disease.

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Introduction

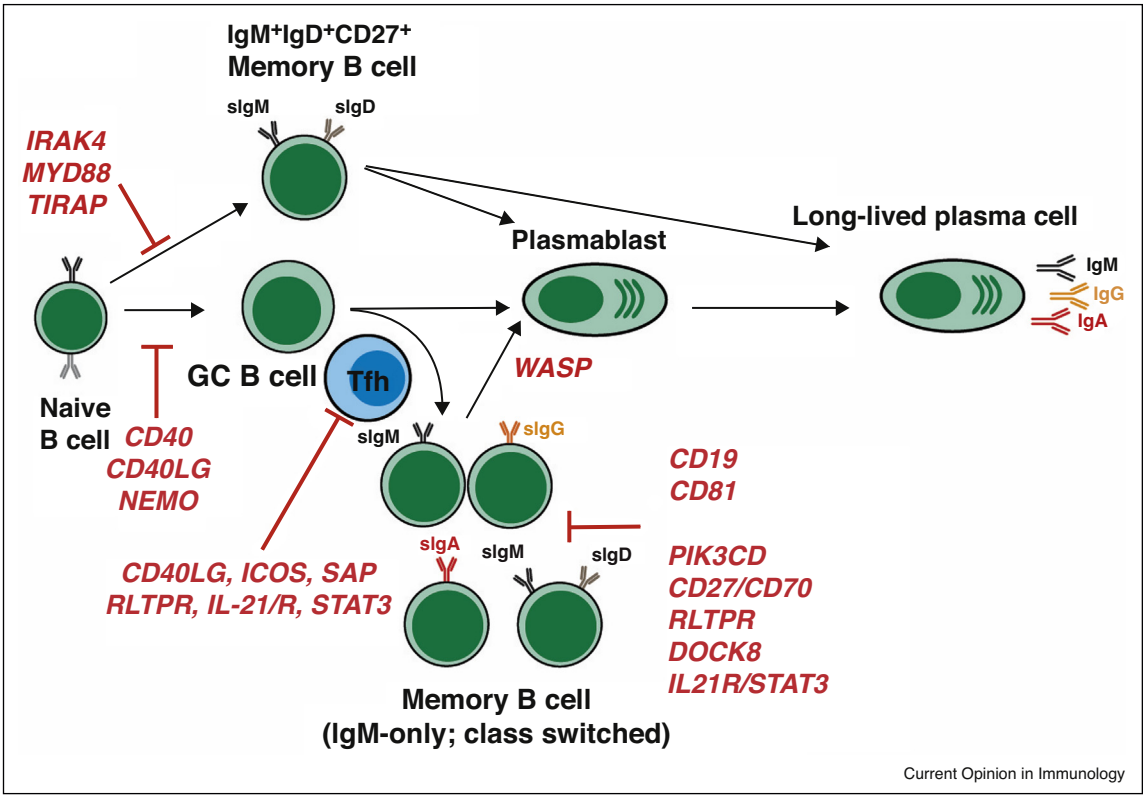
T-dependent memory B cells (MBCs) are generated following interactions between naïve B cells, cognate Ag, and T follicular helper (Tfh) cells within B-cell follicles of secondary lymphoid tissues [1–3]. Within germinal centres (GCs), Ag-specific B cells are re-wired into MBCs that have improved affinity for Ag, elevated expression of co-stimulatory molecules, increased survival, and greater capacity to rapidly proliferate and differentiate into Ab-secreting cells compared to naïve B cells [1,2]. All of these features, together with the increased precursor frequency and anatomical localisation of MBCs, co-operate to facilitate their hyperresponsiveness following re-exposure to Ag, resulting in the efficient generation of high titres of neutralising Ab and Ag clearance [1,2].

Dynamics and differences in MBC subsets

Not all MBCs are equal and multiple subsets have been described. Classic studies in humans inferred that Ag-experienced B cells that had undergone class switching to express IgG or IgA were MBCs; this was supported by the acquisition of somatic hypermutations (SHM) in their Ig V genes [2,4]. However, subsequent studies also detected somatically mutated Ig V genes in human IgM^+ B cells [5]. The ability to delineate the human B-cell compartment based on the differential expression of CD27 clarified the existence of putative IgM^+ MBCs, and also led to the identification of both $IgM^+IgD^{-/lo}$ (or IgM-only) and IgM^+IgD^+ MBC subsets [2,4,6]. These IgM-expressing MBCs exhibit phenotypic, molecular and functional features of class-switched MBCs [4,7,8•]. Despite these findings, the biology of IgM^+CD27^+ MBCs is complex and contentious.

Numerous lines of evidence generally concur that $IgM^+IgD^+CD27^+$ B cells are not strictly MBCs because they: arise early in life in response to TLR signals; develop and diversify their BCR repertoire independently of GCs; and provide protection against polysaccharide/T-independent Ags. In contrast, the generation of $IgM^+IgD^-CD27^+$ B cells (*i.e.* IgM-only MBCs) and class-switched MBCs is GC-dependent and thus these cells correspond to classical MBCs. Evidence for this is as follows: (1) Only $IgM^+IgD^+CD27^+$ B cells are reduced in individuals with inactivating mutations in *MYD88*, *IRAK4* or *TIRAP*, but not those with *TLR3*, *UNC93B* or *TRIF* mutations [9,10]. This reveals a requirement for MYD88/IRAK4/TIRAP signalling downstream of several Toll-like receptors, most likely TLR1, TLR2, TLR6 and/or TLR10 (Figure 1); (2) Class-switched and IgM-only, but not $IgM^+IgD^+CD27^+$, MBCs are absent from individuals unable to form GCs due to inactivating mutations in *CD40*, *CD40LG*, *ICOS* or *SH2D1A*/*SAP* [2,4,11,12••]. This establishes the GC-dependent nature of class-switched and IgM-only memory B cells, and GC-independent nature of $IgM^+IgD^+CD27^+$ B cells (Figure 1); (3) Analysis of the molecular architecture of Ig V genes revealed similarities between IgM-only and class-switched MBCs, and marked differences with $IgM^+IgD^+CD27^+$ B cells [13,14•]; and (4) $IgM^+IgD^+CD27^+$ B cells are reduced in conditions associated with heightened susceptibility to infection with encapsulated bacterial pathogens. This includes individuals with congenital asplenia [9,15], autoimmune lymphoproliferative syndrome due to mutations in *CD95* [16], and impaired immunity against invasive

Figure 1



Pathways for the generation of human memory B-cell subsets. Naïve B cells can yield IgM-only or Ig class switched memory B cells in a GC-dependent manner. In contrast, $IgM^+IgD^+CD27^+$ B cells arise early in life independently of GCs. However, these B cells undergo subsequent 'remodelling' of their Ig V genes (further SHM, affinity selection); this requires $CD4^+$ T cells and GCs. Specific mutations that underlie distinct primary immunodeficiencies have identified molecular requirements for the generation of IgM-only/class switched vs. $IgM^+IgD^+CD27^+$ MBCs.

bacterial infections due to mutations in *IRAK4* or *MYD88* [9,10]. Furthermore, IgM Abs specific for polysaccharide Ags correlated with frequencies of $IgM^+IgD^+CD27^+$ B cells [9], suggesting a role for these cells in frontline protection against infection by invasive encapsulated bacteria.

Despite these results, other findings indicate that $IgM^+IgD^+CD27^+$ B cells may also be derived from GCs, and that other memory subsets contribute to immunity against diverse bacterial Ags. First, while $IgM^+IgD^+CD27^+$ B cells are detected in humans unable to form GCs, the absolute number of these cells is substantially reduced, suggesting a large proportion of $IgM^+IgD^+CD27^+$ B cells require a GC for their generation [4]. Second, IgM^+CD27^+ B cells, including IgD^+ and IgD^{lo} subsets, harbour molecular traits of a GC, namely acquired mutations in *BCL6*, and clonal relatedness to class-switched MBCs [17,18•]. Third, $IgM^+IgD^+CD27^+$ B cells can class switch and secrete multiple downstream Ig isotypes [8•,19], and the proportions of these cells correlate with IgG titers against some bacterial Ags [9], inferring they comprise an important component of the human MBC compartment. This is consistent with previous findings that Ig expressed by IgM^+ MBCs are not enriched for bacterial/polysaccharide Ags [20]. Fourth, class-switched MBCs are also reduced in asplenic individuals vulnerable to infection with encapsulated bacteria [15,16]. Thus, susceptibility to these infections probably results from the combined effect of a deficiency in all MBC subsets, rather than exclusively the $IgM^+IgD^+CD27^+$ subset.

Athough IgM^+ MBCs in neonates have very few mutations, it was recently shown that the level of SHM, including evidence of Ag selection, increases with age and is dependent on the presence of an intact spleen, GCs and $CD4^+$ T cell help [21•]. In contrast, class-switched MBCs exhibit a greater level of SHM than IgM^+ memory B cells at all time points, and this is not affected by asplenia [21•]. Thus, some discrepancies regarding the molecular features and GC-dependence of IgM^+ memory B cells may reflect temporal remodelling of their Ig V genes. Collectively, class-switched memory, IgM-only

memory, and the majority of $IgM^+IgD^+CD27^+$ B cells in humans appear to arise from T-dependent GC responses, while some $IgM^+IgD^+CD27^+$ B cells form independently of GCs. However, this latter population does require innate signalling via some TLRs (Figure 1). This provides the human immune system with layers of memory-type capabilities.

Functional layering of memory by Ig subclass and affinity

IgM^+ MBCs have also been identified in mouse models. As such, murine MBCs are also functionally layered according to their Ig isotype. IgM^+ MBCs proliferate more and re-enter secondary GCs to class switch and further mutate their BCR, whereas IgG^+ MBCs preferentially differentiate into plasmablasts [22,23]. This may be due to intrinsic differences in chemokine responsiveness of IgM^+ and IgG^+ MBCs [8•]. FOXP1 represses *PRDMI*, *IRF4* and *XBP1* and restrains plasma cell differentiation [24•]. Interestingly, human IgM^+ MBCs express higher levels of FOXP1 than IgG^+ MBCs [24•]. This may contribute to the divergent fates of IgM^+ versus IgG^+ MBCs (*i.e.* GC vs. plasmablast). Moreover, IgM^+ MBCs are longer lived and may mediate late memory, when most class-switched MBCs have disappeared [23]. These divergent fates of IgM^+ and IgG^+ MBCs appear to track with expression of CD80 and PDL2, as well as Ig isotype [25]. It is also worth noting that these are generalisations, and class-switched MBCs can also re-enter GCs and further mutate their BCR [26]. Furthermore, the memory response to malaria appears to be dominated by multifunctional IgM^+ MBCs that rapidly proliferate and generate both T-independent IgM^+ plasma cells and T-dependent IgM^+ and IgG^+ plasmablasts [27].

The contribution of Ig isotype vs. affinity to the MBC fate has recently been addressed using an elegant system that uncouples isotype switching from affinity maturation [28••]. It was found that $IgG1^+$ GC B cells are biased towards differentiating into plasma cells rather than towards MBCs, and that polyreactive MBCs generated early in the response were progressively purged from the MBC pool [28••]. Thus, it appears that the Ig isotype imprints the subsequent fate of the GC B cell.

Class-switched MBCs arise to serve specific effector functions and these properties may be imprinted during their ontogeny. Indeed, anti-viral immunity provided by $IgG2a^+$ MBCs is dependent on the transcription factor T-bet, while mucosal immunity provided by IgA^+ MBCs depends on RORα [29]. Moreover, T-bet upregulated CXCR3, promoting migration of $IgG2a^+$ MBCs to inflammatory sites where there is increased expression of CXCR3 ligands (CXCL9, CXCL10, CXCL11). Similarly, RORα upregulated expression of α4β7 on IgA^+ MBCs thereby facilitating binding to $MAdCAM\text{-}1^+$ mucosal vascular endothelial cells (Figure 2).

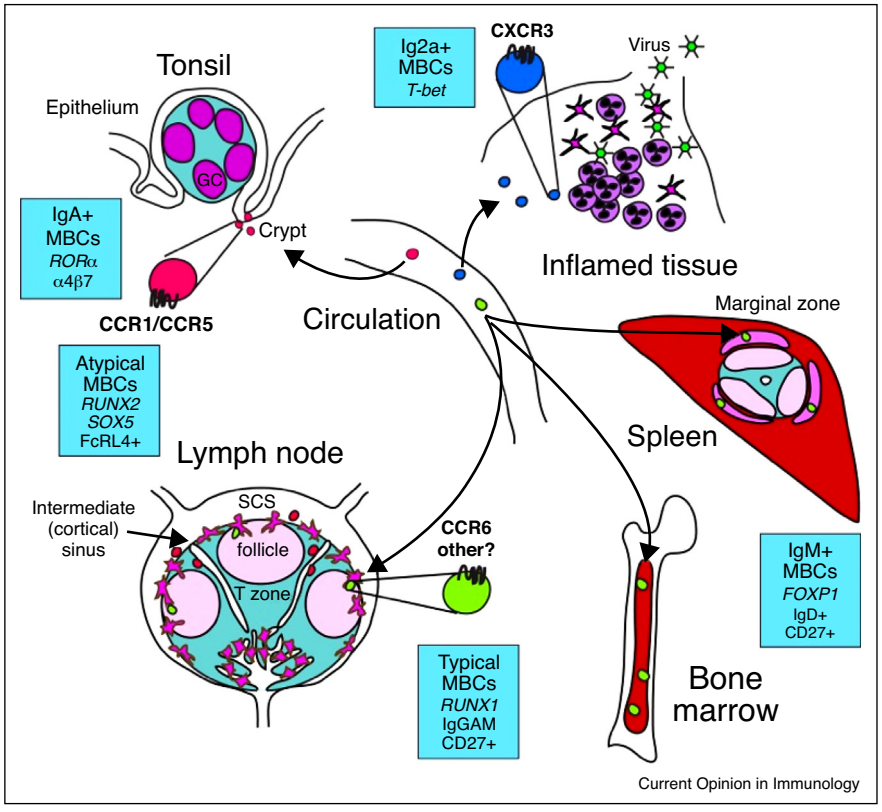
Molecular requirements for the formation and function of MBCs

Monogenic mutations underlying primary immunodeficiencies (PIDs) provide opportunities to identify molecules and signalling pathways required for the generation, maintenance and function of MBCs. Mutations in genes predominantly expressed by T cells – *CD40LG*, *ICOS*, *SH2D1A/SAP* – dramatically reduce the numbers of circulating MBCs [2,4,11,12••]. Notably, these genes are most highly expressed by Tfh cells [3], underscoring their critical role cells in GCs and MBC generation. Mutations in B-cell intrinsic genes – *CD19*, *CD81* [30,31] – also reduce MBCs, indicating the importance of signalling through the BCR complex (Figure 1). MBCs are also reduced in individuals with mutations in genes broadly expressed throughout the immune system and implicated in the normal function of B cells and $CD4^+$ T cells. This includes loss-of function mutations in *DOCK8* [32], *NEMO/IKBKG*, *STAT3* or *IL21/IL21R* [12••,33], or gain-of function mutations in *STAT1* [12••] or *PIK3CD* encoding the p110δ catalytic subunit of PI3 kinase [34]. In addition, B cell-intrinsic IL-21R/STAT3 signalling is required for MBC formation since patient-derived MBCs fail to reconstitute normally in X-linked or autosomal recessive SCID patients (with mutations in *IL2RG* or *JAK3*, respectively) following hematopoietic stem cell transplantation and successful reconstitution of the CD4 T cell compartment [35].

The identification of new PIDs has provided additional mechanisms underlying MBC formation. Thus, inactivating mutations in *CD27* [36] and *CD70* [37] result in hypogammaglobulinemia, and $CD27^+$ MBCs are reduced in CD70-deficient patients [37], demonstrating a functional requirement for CD27/CD70 signalling in establishing humoral memory, at least in humans. Mutations in *CARMIL2* (capping protein regulator and myosin 1 linker 2]; also known as *RLTPR* [RGD motif, leucine rich repeats, tropomodulin domain and proline-rich containing) cause a novel combined immunodeficiency, including recurrent bacterial infections and impaired Ab responses to infection or vaccination [38]. Correspondingly, RLTPR-deficient individuals have dramatic reductions in total MBCs, and impaired switching *in vivo* to IgG [38]. While RLTPR is required for CD28-induced activation of human $CD4^+$ T cells, it is expressed in most leukocyte populations [38]. Indeed, BCR-mediated signalling was compromised by *RLTPR* mutations [38]. Thus, the MBC deficit likely results from defects in $CD4^+$ T cell help combined with B-cell intrinsic defects downstream of BCR signalling. MBCs are also reduced in patients with *STK4* deficiency, although it remains to be seen if this is B cell-intrinsic or secondary to T cell defects [39,40] (Figure 1).

PIDs also inform us of the requirements for MBC function. Hypomorphic mutations in *STAT3* or *NEMO*, or

Figure 2



Anatomical and functional layering of memory. Systemic and site-specific humoral immunity is provided by multiple subsets of MBCs. Typical CD27$^+$ MBCs express *RUNX1* and recirculate between secondary lymphoid organs via the circulation. FcRL4$^+$ atypical MBCs express *RUNX2* and *SOX5* and localise to mucosal sites. In addition, Ig-class specific functions are performed by IgM$^+$ MBCs which preferentially seed secondary GCs and class-switched MBCs which preferentially differentiate into short-lived plasmablasts. IgA$^+$ MBCs express *RORα* and localise to mucosal epithelium and mucosa-draining lymph nodes via the integrin $\alpha_4\beta_7$ and CCR1/CCR5; IgG2a$^+$ MBCs express *Tbx21* and localise to inflamed tissue using CXCR3.

hypermorphic *STAT1* mutations, compromise differentiation *in vitro* of human naïve B cells into Ab-secreting plasmablasts [33,41]. Although these mutations reduce the proportions of MBCs [12••], the function of these MBCs *in vitro* is largely intact [33,41], indicating distinct requirements or differences in thresholds of activation between naïve and memory cells. These observations potentially explain the variability in defects in humoral immunity in these patients. In contrast, mutations in *WASP* do not impair MBC generation; however, WASP-deficient MBCs are functionally-impaired, shown by poor recruitment of CD19 into BCR signalling clusters [42].

Selection of GC B cells into the memory compartment

An unanswered question is how GC B cells are selected to differentiate into MBCs. Long-lived plasma cells accumulate more SHM [43] and are more stringently selected based on Ag affinity than MBCs [43,44]. Moreover, the affinity of MBCs emerging from GCs increases over time, in parallel with affinity maturation of the GC [43,45]. Consistent with this, the output from the GC 'switches' from producing MBCs early (when the overall affinity is low), to LLPCs late in the response (when the overall affinity is high) [46]. These data suggests that unlike LLPC differentiation, which follows an instructive model, MBC differentiation is a default stochastic process occurring in the absence of Ag-derived signals (BCR, T cell help).

However, evidence for a more instructive role for Ag affinity and T cell help in MBC differentiation has recently emerged [47••]. It was shown that low affinity GC B cells upregulated *Bach2*, a repressor of *Prdm1* and plasma cell differentiation, and were actively selected to become MBCs. Inducible combined deletion of both *Bach2* and *Prdm1* resulted in a reduction in MBCs. Importantly, *Bach2* expression is inversely correlated with the strength of T cell help. Thus, increased delivery of peptide antigens to GC B cells downregulated whereas CD40 blockade upregulated, *Bach2*. Taken together,

these data suggest that while high affinity GC B cells upregulate *Prdm1* and differentiate into LLPCs, low affinity GC B cells upregulate *Bach2* to become MBCs [47••].

MBC localisation and trafficking

MBCs are found in the circulation [2,5] and are widely distributed throughout lymphoid tissues in persistent GCs in follicles [48], bone marrow [49], tonsillar mucosal epithelium [50] and the splenic marginal zone [51,52] (Figure 2). MBCs also persist and accumulate in skin-draining lymph nodes following subcutaneous immunisation [53]. Interestingly, MBCs persist at the site of infection in murine lung and lung-draining lymph nodes following influenza virus infection [54,55], suggesting tissue-resident MBCs may also exist. The strategic localisation and recirculation of MBCs thus optimises the probability of Ag encounter.

'Atypical' human MBCs characterised by differential expression of CD21 and FcR-like molecues have been identified in tonsils, intestinal lymphoid tissues and mesenteric lymph nodes [56,57] (Figure 2). These mucosal-associated atypical MBCs lack CD27, express inhibitory receptors, and are hyporesponsive to BCR stimulation, but under some circumstances can differentiate into plasmablasts upon cytokine stimulation [56,58]. Atypical MBCs express *RUNX2* and *SOX5* whereas typical MBCs express *RUNX1* [59]. SOX5 impairs proliferation and promotes plasmablast differentiation by human B cells [60]. Importantly, atypical MBCs cells are found predominantly in subcapsular and cortical sinuses, with a few scattered in GCs, of inflamed lymph nodes from toxoplasmosis, HIV or EBV infected patients [61]. They are also increased in the circulation of patients with chronic HIV viremia [62] and endemic malaria [58,63] where they have an 'exhausted' phenotype, analogous to exhausted memory T cells, and are arrested in their ability to generate plasmablasts. Thus, in settings of chronic infection, classic MBCs give rise to atypical MBCs which, due to their impaired function, compromise host humoral immunity [58]. In keeping with the mucosal origin of atypical MBCs, FcRL4 is an inhibitory Fc receptor for IgA [64] and co-ligation of the BCR and FcRL4 by Ag bound to secreted IgA may feedback to regulate Ab secretion and commensal flora at mucosal surfaces.

While the dynamic changes in chemokine receptor expression during naïve B cell recirculation and activation have been well documented [65], much less is known as to how this varies as recirculating MBCs enter and leave the lymph node. Following generation in GCs, MBCs re-express the mucosal homing chemokine receptor CCR6 [66,67]. CCR6-deficient mice generate and maintain MBCs but have defective secondary Ab responses in the spleen [68]. Interestingly, CCR6 deficiency mislocalizes MBCs from the marginal zone and perifollicular region to the follicle and GC [68]. Splenic $CD4^+$ T cells are the major source of the CCR6 ligand CCL20, and it was suggested that the defective memory response was due to a failure of MBCs to co-localise with CCL20-expressing $CD4^+$ T cells. It will be interesting to determine whether CCR6-deficient MBCs are also mislocalised in lymph nodes where CCL20 is also produced by lymphatic endothelial cells lining the subcapsular sinus (SCS) [69]. Atypical MBCs are characterised by expression of CCR1 and CCR5, and a lack of CXCR5, and this may explain their preferential localisation in lymphoid tissue near epithelial surfaces [56]. $IgG2a^+$ MBCs express CXCR3 which promotes localisation to sites of inflammation [29].

MBC reactivation and the need for T cell help

Reactivation of MBCs in secondary Ab responses typically requires signals from Ag and Tfh cells [70], although in some anti-viral memory responses Ab production is T-independent [71]. Thus, MBCs need to first acquire Ag and then co-localise and interact with cognate $CD4^+$ T cells to produce a clonal burst of short-lived plasmablasts and secondary GCs. Naïve B cells may be activated early in the response by Ag captured from the lymph by $CD169^+$ SCS macrophages [72–74] or later in the response by Ag transported into the follicle and deposited on follicular dendritic cells [75]. It is likely that similar immune response pathways operate to activate MBCs. In this regard, a subpopulation of memory $CD4^+$ T cells resides in the periphery of the B cell follicle where they scan SCS macrophages for Ag [76••]. Tfh cells can also give rise to $CD4^+CXCR5^+$ memory T cells which home to the splenic T-B border following adoptive transfer [77•]. These memory Tfh cells rapidly re-express Bcl6 and differentiate into effector Tfh cells in response to peptide:MHCII presented by MBCs. In addition, $CXCR5^+PD\text{-}1^+$ circulating Tfh cells (cTfh) have been described as resting memory cells capable of providing help to B cells *in vitro* [12••,78–80]. While Tfh cells in the secondary Ab response can migrate outside the follicle and may enter the circulation [76••], it appears that some cTfh cells are GC-independent and may not be derived from GC Tfh cells [78].

IgE^+ and self-reactive MBCs

Chronic allergic diseases such as atopic asthma and immunity against helminth parasites are mediated by specific IgE Abs. However, IgE^+ MBCs and LLPCs are not readily detectable, suggesting they are very rare and difficult to detect, or do not exist. Indeed, it has been suggested that most IgE arises from sequential switching of $IgG1^+$ MBCs [81]. Three independent IgE reporter mice [81–83] showed that once generated, IgE^+ GC B cells promptly exited the GC as short-lived plasmablasts. These data lead to the notion that mIgE expression predisposed GC B cells to either undergo apoptosis [84] or express high levels of *Prdm1* and rapidly

differentiate into plasma cells [85]. This was confirmed by studies using 'class-swapping' to directly compare the function of mIgG1 and mIgE under the same *in vitro* culture conditions [86••]. This showed that the ectodomain of mIgE spontaneously aggregated to induce plasma cell differentiation via CD19-PI3K-Akt-IRF4 and apoptosis via BLNK-Jnk/p38 pathways. Thus, autonomous IgE signalling actively prevents IgE^+ MBC and LLPC formation.

Self-reactive MBCs represent another potentially dangerous MBC population that needs to be restrained. Indeed, low affinity polyreactive and self-reactive post-GC IgG^+ MBCs are enriched in peripheral blood of healthy donors [87]. Selective defects in MBCs have been described in SLE [88]. In particular, expansion of an activated population of $CD27^-IgD^-CD95^+$ MBCs correlated with serum biomarkers and disease activity [89]. The connection between CD95 (Fas) and SLE is intriguing as a recent study showed that Fas-deficiency results in escape of 'rogue' GC B cells that have lost reactivity against the immunising antigen and are predisposed to differentiate into IgE^+ plasmablasts [90]. It will be interesting to determine if polyreactive and self-reactive MBCs are also generated in this system, as has been described for patients with Fas mutations and ALPS [91]. Interestingly, IgE anti-dsDNA autoantibodies are prevalent in SLE [92,93,94•] and positively correlate with disease severity [92,93]. Autoreactive IgE in SLE patients also correlated with increased activation of granulocytes, [93], while in mouse models it triggered FcεRI-mediated activation and secretion of type I interferon by plasmacytoid dendritic cells [94•]. The enhanced pathogenicity from this double hit of self-reactive IgE further reinforces the need for restraining the emergence of self-reactive and IgE MBCs.

Conclusion

There has been tremendous progress in our understanding of MBC formation, function and fate from analyses of human primary immunodeficiencies and mouse models. These studies have revealed multiple anatomical and functional layers of memory that have evolved to provide systemic and site-specific immunity. However, many questions remain, such as how and where MBCs are reactivated and the role of MBCs in allergic and autoimmune diseases. Nevertheless, it is hoped that co-operative and complementary studies in mouse and humans will continue to provide future insights into these questions.

Cyster and colleagues recently identified a subpopulation of Ephrin-B1-positive GC B cells that downregulated S1pr2 and upregulated CD38 and EBI2; these cells likely represent GC memory precursor cells [ref 95]. Allen and colleagues reported that the IgE antigen receptor constrains responses of IgE+ B cells, predisposing them to differentiate into plasma cells [ref 96].

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