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An antigen to remember: regulation of B cell memory in health and disease
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Vaccine success relies on the formation of immunity. Humoral immunity is critical and is mediated by long-lived antibody-secreting cells and memory B cells (MBCs). Chronic infectious diseases cause a significant global burden of disease; pathogens that evade the immune system can cause phenotypical and functional changes to immune memory populations. Thus, recent studies have focused on MBC subset function. IgM+ MBCs have emerged as important early responders in malaria. Atypical MBCs have functional qualities associated with exhaustion in chronic infectious diseases, but the requirements for their formation and whether they localize remains unknown. Similarly, the T-bet-driven transcriptional regulation drives formation of MBCs phenotypically similar to atypical MBCs. Identifying protective or detrimental roles of MBC subsets, and their regulators, will be important for clinical intervention.

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Introduction
Infectious diseases are responsible for a significant global burden of disease [1–5]. These include human immunodeficiency virus (HIV) (which causes acquired immune deficiency syndrome (AIDS)), malaria, tuberculosis [3], neglected tropical diseases (caused by protozoan parasites, parasitic worms and animal-borne viruses) [4] and newly emerging infectious agents (including severe acute respiratory syndrome-coronavirus, Middle East respiratory syndrome-coronavirus, West Nile virus, Nipah virus, methicillin-resistant Staphylococcus aureus, novel influenza-A strains and the Ebola virus) [5]. Diseases such as HIV/AIDS, malaria and tuberculosis are particularly more pronounced in low socio-economic regions of developing countries [1,2] and high rates of co-infection cause additional obstacles to successful clinical intervention [1].

Protective immunity depends on the longevity and rapid responsiveness to antigen of immune memory populations [6]. In the humoral arm of the immune system, immune memory consists of long-lived antibody-secreting plasma cells and memory B cells (MBCs). These high-affinity populations are generated during the initial immune response to infection and are mainly generated within the germinal center (GC), although they can also be generated in GC-independent pathways. Vaccines replicate this process without the threat replicating pathogens pose to the body. While vaccines have been the most effective intervention for many infectious diseases, there are still pathogens that have evaded successful vaccine design [7]. This can be the result of the genetic diversity of the pathogen, immune subversion and immunosuppression, and inconsistencies between local and systemic responses, for example, where a vaccine is not targeted to generating a mucosal immune response that may be critical for successful protection. In particular, persisting or recurrent pathogens such as HIV and Plasmodium are linked to an inadequate humoral response, in which the production of high-affinity neutralizing antibodies is delayed and the immune memory repertoire appears to be ineffective.

MBC population heterogeneity provides the functional diversity needed for the immune system to fight infection and disease [6]. MBC subsets can be segregated based on B cell receptor (BCR) isotype, phenotype, and distinct functional responses in health or immune disorders. Disease can drive alterations to MBC phenotype and function, which in turn influence antibody responses to vaccination [6]. The characteristics and regulators that shape the role of MBC subsets in infection and disease remain to be elucidated, and delineating these will provide insight into whether MBCs are beneficial or detrimental in different disease states. This review will focus on dissecting the diversity and roles of MBCs currently trending in the literature, including immunoglobulin (Ig) M+ atypical and T box transcription factor (T-bet)+ MBCs, and their roles during infectious disease.

Function of IgM+ MBC in protective responses and in disease
The MBC population is heterogenous in both phenotype and function [8]. This diversity allows the population to
balance self-renewal with differentiation during a secondary response. Classically, MBCs have been distinguished by their Ig isotype: IgM+ or class switched (IgG+, IgA+ and IgE+) [6], but they can also be distinguished into subsets by surface markers such as CD73, CD80 and PD-L2 [9*]. MBC function had been defined by these subdivisions, for example, IgM+ MBCs proliferate and form secondary GCs for self-renewal and longevity of the MBC population, whilst IgG+ MBCs differentiate to become antibody-secreting cells [6] (Figure 1, top panel). This distinction, however, is not absolute. It appears that the maturity of an MBC is the main predictor of whether it will reenter GCs or differentiate into an antibody-secreting cell during a secondary response, which correlates but is not absolutely dependent on Ig isotype. It is now evident that IgM+ MBCs can be both GC-derived and GC-independent, have unique phenotypes and functional properties compared to switched MBC, and persist to provide long-term memory [9*,10,11].

While recent research has focused on defining subsets in vivo using immunization models, the role of IgM+ MBCs in chronic and recurrent disease remains ill defined. To this end, Pepper and colleagues produced B cell tetramers specific for blood stage Plasmodium chabaudi antigen, merozoite surface protein 1 (MSP1), to study antigen-specific MBCs in a model of malaria. MSP1-specific IgM+ MBCs were comparable to switched MBCs with respect to phenotypic expression of CD80 and CD73, their somatic hypermutation rates, affinity and function [12**]. Interestingly, MSP1-specific MBCs were early responders, persisted and were dominant producers of antibody-secreting cells during secondary responses [12**], suggesting that these cells play a protective role during reinfection (Figure 1, middle panel). Further, they

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**Figure 1**

Diversity of IgM+ MBCs in health and disease. (Top panel) Antigen-specific IgM+ MBCs can renew the MBC repertoire through GC formation and re-entry, form antibody-secreting cells and undergo isotype switching to form IgG+ MBCs that terminally differentiate into antibody-secreting cells. (Middle panel) MSP1-specific IgM+ MBCs encompass characteristics of switched MBC, including the phenotypic expression of CD80 and CD73, and the ability to differentiate into antibody-secreting cells in either a T-dependent or T-independent manner. (Bottom panel) IgM+ MBCs that constitutively express BCL2 and contain the t(14;18)(q32;q21) translocation, are able to re-enter the GC and undergo positive selection to drive the formation of follicular lymphoma.
were able to form antibody-secreting cells in the absence of T cell help. Genetic resistance to malaria has been correlated with enhanced IgM responses compared to IgG responses [8], also suggesting a possible role for IgM+ MBCs in long term protection from malaria. Given the propensity of IgM+ MBCs to generate new GCs [10,11], IgM+ MBCs may also be important for expanding the MBC repertoire to target diversifying antigens.

By providing the ability of GC re-entry, the option to renew the repertoire allows for flexibility to contain fast evolving antigens. However, if a mutation disrupts this process it may lead to development of disease. In this regard, in a chronic infection model where MBCs constitutively express B cell lymphoma 2 (BCL2) and contain the follicular lymphoma hallmark, IgH/BCL2 (t(14;18) (q32;q21)) translocation, IgM+ MBCs are able to re-enter GCs repeatedly upon chronic immunization, leading to and driving follicular lymphomagenesis [13*] (Figure 1, lower panel). This finding reveals a novel role for IgM MBCs in cancer development and progression. A number of B cell leukemias and lymphomas express IgM and resemble MBCs in terms of phenotype and genetics [14]. It is unknown why IgM is commonly expressed, but considering IgM+ MBCs are poised to proliferate upon activation in comparison to switched MBCs, IgM+ MBCs may be at an increased risk to transform into constantly proliferating lymphomas [14].

**Atypical MBCs are associated with exhaustion in chronic or recurrent infectious disease**

MBC phenotype and function appears to be correlated with the nature of the infectious agent. In particular, the emergence of atypical or unresponsive MBCs has been associated with the presence of persistent antigen [15,16]. Several studies have described the presence of an atypical MBC subset that is prominent in chronic infections including human immunodeficiency virus (HIV) [16,17], malaria [15,18*,19,20], HIV/malaria co-infected patients [21], hepatitis C [22] and cytomegalovirus infection [23]. These atypical MBCs are reportedly functionally impaired, often referred to as ‘exhausted’, due to the upregulation of inhibitory receptors, modulation of tissue trafficking receptors and poor proliferative abilities and antibody responses [15,16,18*,19]. HIV-specific responses are enriched in functionally impaired atypical MBCs, suggesting that these cells are unable to produce antibody to target HIV antigens, thus explaining the poor HIV-specific antibody response in individuals [16]. This study was confirmed at a single cell level, using a trimERIC HIV envelope probe, which directly showed that HIV-specific responses were enriched in an activated MBC subset prone to apoptosis [17]. Although a similar subset has been characterized in malaria patients, it is unclear whether atypical MBC are dysfunctional in malaria patients and thus whether they can be defined as the same subset as that found in HIV patients. A number of studies provide evidence of atypical dysfunctional MBCs in malaria [18*,19,20], although a conflicting study showed that atypical memory subsets could proliferate and secrete antibody [24**]. While the latter study suggested atypical MBCs might originate from different precursors due to differences in their somatic hypermutation loads and clonal relationship, others have shown a common developmental history [19,25]. This discrepancy may be related to the large diversity of antigens in this disease. The majority of studies to date did not profile antigen specificity of atypical MBCs, making it difficult to fully elucidate their biological roles in disease. B cell tetramers targeted for different antigens will be useful in future studies of phenotypes and functions of antigen-specific MBCs in responses to persisting or recurrent pathogens that can lead to chronic disease.

**MBC tissue localization and the importance of defining tissue-based memory**

The markers that are used to distinguish atypical MBCs from other MBC subsets include downregulation of CD27 and CD21 [15–17,18*,19–23,24*,25,26]. Atypical MBCs and other CD21neg B cell subsets [27–32] are enriched in the peripheral blood of patients with diseases involving chronic immune stimulation [33]. While CD21neg subsets tend to differ in the expression of CD27 and BCRs in different diseases, atypical and CD21neg subsets exhibit common expression of many inhibitory and cell activation receptors that are associated with exhaustion and anergy (Table 1) [33]. Commonalities across subsets includes the increased expression of CD11c and CXCR3, which are molecules involved in homing to sites of inflammation and reduced expression of CCR7, CD62L, CXCR4 and CXCR5 which are required for migration to spleen or lymph nodes (Table 1). This suggests that atypical MBCs and CD21neg B cells migrate to sites of inflammation. Fc-receptor like (FCRL) receptors, in particular FCRL4, was also commonly expressed on these subsets (Table 1). FCRL4 MBCs were first described as tissue-localized memory cells in healthy individuals [34], and are speculated to define atypical MBCs in malaria [15,24**] and HIV [16] (Figure 2). Other more recent studies suggest that functionally impaired atypical memory in malaria is delineated by the expression of FCRL5 rather than FCRL4 [18*,19,35], which may be due to cross reactivity of FCRL4 antibodies used in previous studies [18*], a factor that needs to be addressed in future studies.

The role of atypical MBCs in tissue localization is undefined in disease and warrants investigation, given that a recent study suggested tissue localization could provide broader protection from highly mutating viruses [36**]. MBCs residing at the site of influenza infection develop from persistent GCs in the lung, are highly mutated, and have cross-reactive antibody responses that neutralize flu escape variants [36**]. Defining the pathways that result
in cross-reactivity may have significant implications for the creation of broadly protective vaccines against highly mutating pathogens and may help to shed light on discrepancies between systemic versus localized responses to vaccines. Furthermore, characterizing migration to and out of tissues will shed light on intrinsic and extrinsic regulators of MBCs during chronic infection. For example, IFN-γ production in chronic lymphocytic choriomeningitis virus (LCMV) infection recruits T cells, monocytes and dendritic cells to directly act on antigen-specific B cells and thus inhibit LCMV-neutralizing antibody responses [37–39]. Currently there are no in vitro models of atypical memory, yet understanding migration and localization of both classical and atypical memory will be important in determining targets for clinical intervention.

**Formation and regulation of T-bet+ MBCs after infection and in autoimmune conditions**

Transcription factors are essential in regulating B cell differentiation [40]. B cell-specific T-bet expression is essential for IgG2a/c MBC survival [41], drives interferon γ (IFNγ)-mediated IgG2a/c class switching and upregulates CXCR3 expression on MBCs to allow migration to sites of inflammation [42]. In chronic LCMV infection, B cell-specific T-bet controls IgG2a/c production and is required to contain persistent infection [43] (Figure 3), as well as a transcriptional program that affects cell migration, localization, differentiation, proliferation and antibody development compared to T-bet− cells [43]. In particular, T-bet+ MBCs express high levels of CXCR3 (Figure 3), which is also expressed on atypical MBCs [15,16,23] and other CD21neg B cell subsets [33] (Table 1). Consistent with CXCR3 expression, T-bet MBCs have been found in small intestinal mucosa [43*], which is a site of inflammation induced by chronic LCMV infection [44]. This suggests that T-bet is involved in the control of multiple immune functions including tissue localization during chronic infection [43*]. In this regard, T-bet may be involved in the formation and function of MBCs that reside at the site of influenza infection and have cross-reactive antibody responses that neutralize flu escape variants [36**]. While there is a lack of studies examining the role of T-bet on atypical MBCs; one study has shown high expression of the T-bet gene, Thbx21 in FCR5+ cells in healthy individuals [35]. Furthermore, T-bet is reported to regulate CD8*T cell exhaustion in HIV infection [45]. Revealing a role for T-bet in formation and/or function of atypical MBCs may prove additional insight into dysfunctional humoral responses.

| Infection/disease | Receptor/gene expression | Reference |
|-------------------|--------------------------|-----------|
| Malaria           | CD11c ↑, CD22 ↓, CD72 ↓, CD85j ↑, CD200R1 ↑, CXCR3 ↓, FCGR2B ↓ | [20,23,24**.29] |
| Human immunodeficiency virus | CD11c ↑, CD22 ↓, CD72 ↓, CD85j ↑, CXCR3 ↓, CCR6 ↑, FCGR2B ↓, FCRL4 ↓, LILRB1 ↑, LILRB2 ↑, SIGLEC-6 ↓, CCR7 ↓, CD62L ↓, CXCR5 ↓ | [20,22] |
| Cytomegalovirus    | CD11c ↑, CD22 ↓, CD72 ↓, CD85j ↑, CXCR3 ↓, CCR7 ↓, CD62L ↓, CXCR4 ↓, CXCR5 ↓ | [23] |
| Primary Sjogren’s syndrome | CD11c ↑, CD22 ↓, CD72 ↓, FCRL2 ↓, FCRL3 ↓, SIGLEC ↓, CD1c ↓ | [31] |
| Rheumatoid arthritis and common variable immune deficiency | CD11c ↑, CD72 ↓, CRL2 ↓, CXCR3 ↓, CXCR6 ↓, FCGR2B ↑, FCRL5 ↓, FORML1 ↓, FORML2 ↓, LILRB1 ↑, SIGLEC ↓, SOX5 ↓, BCMA ↓, CCR7 ↓, CD40 ↓, CXCR5 ↓, IL4R ↓, IL13R ↓, OX40L ↓ | [32–34] |
| Hepatitis C associated-mixed cryoglobulinemia | CBLB ↓, CD22 ↓, CD72 ↓, CD200R1 ↓, EG2 ↓, FCRL4 ↓, LAX1 ↓, LGALS1 ↓, Strata ↓, ZEB2 ↓, FOXP1 ↓, IL-4R ↓, TCL1 ↓ | [35,36**.37] |
Diversity of FCRL4+ MBCs in health and disease. (1) FCRL4+ tissue-like MBCs derived from tonsils of healthy individuals are poised to secrete antibody but do not proliferate after BCR ligation or bacterial stimulation. Tissue-like MBCs express high levels of CXCR3, CD11c and CCR6 and low levels of CCR7, CXCR5 and CXCR4. These cells also express activation markers CD80 and CD86. (2) FCRL4+ tissue-like MBCs found in the blood of patients with HIV are associated with exhaustion. Like tonsil-derived MBCs, these have a similar expression profile of trafficking receptors, but express additional inhibitory receptors and proliferate poorly after BCR ligation or bacterial stimulation. (3) Whether FCRL4+ atypical MBCs found in malaria are exhausted remains controversial. While some studies have shown factors associated with exhaustion including a lack of antibody secretion, poor proliferation, inhibitory receptor expression and similar trafficking expression profile to FCRL4+ MBCs in HIV, others have shown these cells secrete neutralizing antibody, proliferate and express activation markers.

Figure 2

1. Tonsils from healthy individuals: tissue-like MBCs

2. Blood from HIV viremic individuals: tissue-like MBCs associated with exhaustion

3. Blood from malaria infected individuals: atypical MBCs- are they exhausted?

Diversity of FCRL4+ MBCs in health and disease. (1) FCRL4+ tissue-like MBCs derived from tonsils of healthy individuals are poised to secrete antibody but do not proliferate after BCR ligation or bacterial stimulation. Tissue-like MBCs express high levels of CXCR3, CD11c and CCR6 and low levels of CCR7, CXCR5 and CXCR4. These cells also express activation markers CD80 and CD86. (2) FCRL4+ tissue-like MBCs found in the blood of patients with HIV are associated with exhaustion. Like tonsil-derived MBCs, these have a similar expression profile of trafficking receptors, but express additional inhibitory receptors and proliferate poorly after BCR ligation or bacterial stimulation. (3) Whether FCRL4+ atypical MBCs found in malaria are exhausted remains controversial. While some studies have shown factors associated with exhaustion including a lack of antibody secretion, poor proliferation, inhibitory receptor expression and similar trafficking expression profile to FCRL4+ MBCs in HIV, others have shown these cells secrete neutralizing antibody, proliferate and express activation markers.

accumulates in aged female mice, forms early in female autoimmune prone mice and is present in patients with rheumatoid arthritis [28,47]. Furthermore, this subset directly contributes to the production of autoantibodies and therefore may contribute to autoimmunity [28] (Figure 3). CD11c is also highly expressed on atypical MBCs, other CD21neg subsets (Table 1) [15,16,19,20,24**,26,28,29], and in FCRL4+ MBCs that may play a role in mucosal defense [48]. Interestingly, many CD21neg subsets in disease also express IgM [33]. Determining the relationship between TLR engagement, T-bet activation, CD21, CXCR3, CD11c and IgM in MBCs may reveal mechanistic commonalities in dysfunctional humoral disorders that are characterized by aberrant immune stimulation.

Formation and regulation of MBC subsets

The common expression of inhibitory, migration and activation markers on atypical MBCs (Table 1) and in T-bet+ MBCs present in chronic infection, aging and autoimmunity suggests that a T-bet-driven transcriptional program may regulate the formation and/or function of atypical memory, in addition to age/autoimmune-associated subsets. Several questions arise: Is T-bet involved in tissue
localization of atypical MBCs and other MBC subsets, if so how does this contribute to disease? In IL-4 low disease environments, such as T helper cell 1 dominant conditions, do T-bet+ CD11c+ MBCs possess the phenotypical and functional qualities of exhausted atypical MBCs and CD21<sup>neg</sup> cells? It will be critical to determine both intrinsic and extrinsic regulators of these cells to understand their contribution to immune responses in both health and disease. Although this population has been described in many studies, there is currently no <i>in vivo</i> model of atypical MBCs. Developing such a model would allow mechanistic studies into the formation, function and cellular interactions between different memory subsets, as well as with T cells, in an environment of persistent antigen. These studies may reveal if atypical MBCs and related subsets are protective or detrimental in acute or chronic infections.

**Conclusions**

In diseases involving highly diversifying antigen, MBC heterogeneity may be central in containing chronic infection. IgM<sup>+</sup> MBCs have emerged as important early responders in malaria re-infection and therefore may be vital in early parasite clearance in humans. Whether IgM<sup>+</sup> MBCs function as early responders in other chronic infections remains to be determined. Atypical MBCs and other CD21<sup>neg</sup> subsets are exhausted in several different chronic infectious diseases, but how these different diseases affect this subset and how they are formed and function within these diseases remains unknown. Targeting commonly expressed inhibitory and activation markers may provide a therapeutic avenue to ameliorate putative detrimental effects of atypical MBCs. Short inhibitory RNA knockdown of inhibitory receptors on atypical MBCs in HIV enhanced BCR-mediated proliferation, in particular the largest effect was observed when targeting FCRL4 and sialic acid-binding immunoglobulin-type lectin 6 (Siglec-6) [49]. These and other commonly expressed receptors may be potential targets for receptor antagonists to reivate MBCs and induce protective antibody responses. Lastly, T-bet-driven transcriptional regulation may be involved in the formation and function of atypical MBCs and age/autoimmune-associated subsets. Identifying the characteristics and regulators of MBC heterogeneity in the context of chronic infection, and the impact on the generation of classical memory, will be important for innovative solutions to eradicate these diseases.

**Conflict of interest**

The authors declare no conflict of interest.

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