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Memory B cells and tuberculosis

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ABSTRACT

Immunological memory is a central feature of adaptive immunity. Memory B cells are generated upon stimulation with antigen presented by follicular dendritic cells in the peripheral lymphoid tissues. This process typically involves class-switch recombination and somatic hypermutation and it can be dependent or independent on germinal centers or T cell help. The mature B cell memory pool is generally characterized by remarkable heterogeneity of functionally and phenotypically distinct sub-populations supporting multi-layer immune plasticity. Memory B cells found in human patients infected with *Mycobacterium tuberculosis* include IgD+ CD27+ and IgM+ CD27+ subsets. In addition, expansion of atypical memory B cells characterized by the lack of CD27 expression and by inability to respond to antigen-induced re-activation is documented in human tuberculosis. These functionally impaired memory B cells are believed to have adverse effects on host immunity. Human and animal studies demonstrate recruitment of antigen-activated B cells to the infection sites and their presence in lung granulomas where proliferating B cells are organized into discrete clusters resembling germinal centers of secondary lymphoid organs. Cattle studies show development of IgM+, IgG+, and IgA+ memory B cells in *M. bovis* infection with the ability to rapidly differentiate into antibody-producing plasma cells upon antigen re-exposure. This review discusses recent advances in research on generation, re-activation, heterogeneity, and immunobiological functions of memory B cells in tuberculosis. The role of memory B cells in post-skin test recall antibody responses in bovine tuberculosis and implications for development of improved immunodiagnostics are also reviewed.

1. Introduction

Acquired immunity in infectious diseases relies on the sustainable ability of the immune system to rapidly and efficiently respond to pathogens. Memory lymphocyte populations, including T cells and B cells, generated upon initial antigen encounter significantly contribute to this critical function for host survival. Immunological memory is a hallmark of adaptive immunity and a key prerequisite for development of effective vaccines (Kirman et al., 2016; Pupovac, Good-Jacobson, 2017; Zhu et al., 2018). Central to development of protective antibody responses is the differentiation of antigen-induced B cells into short-lived plasmablasts, long-lived antibody-secreting cells, or rapidly reactive memory B cells that are responsible for containing early infection, prevention of relapse, and more effective recall response to re-infection, respectively (Harms Prichard and Pepper, 2018; Inoue et al., 2018).

Memory B cells derive from naïve B cells stimulated by antigen in the peripheral lymphoid organs during primary immune responses. This process involves close interactions between B cells, antigen-presenting dendritic cells, and activated CD4+ T cells and depends on synchronized expression of certain cell receptors and required co-stimulatory signals (Bergmann et al., 2013; Pupovac, Good-Jacobson, 2017). Once generated, memory B cells enter the peripheral blood circulation and repopulate other lymphoid tissues, mainly bone marrow, to establish a long-term memory pool. Upon antigen re-stimulation, activated memory B cells differentiate into plasma cells to produce an accelerated and robust anamnestic response mediated predominantly by class-switched antibodies of higher affinity that can clear the antigen more efficiently (Eisen, 2014; Inoue et al., 2018).

Tuberculosis is a zoonotic disease caused by organisms of the *Mycobacterium tuberculosis* complex in a wide range of host species including humans primarily susceptible to *M. tuberculosis* as well as cattle and other domestic and wildlife species predominantly susceptible to *Mycobacterium bovis* (Waters et al., 2014; Gormley, Corner, 2018). Protective immunity in tuberculosis is believed to rely primarily on

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CD4+ and CD8+ T cells involved in central and effector memory responses (Cooper, Flynn, 1995; Jasenosky et al., 2015; Arrigucci et al., 2018; Orme, Henao-Tamayo, 2018; Zhu et al., 2018). Therefore, research on the immunology of tuberculosis has focused mainly on cell-mediated immunity, especially Th1 responses, with much less attention paid to B cell biology. Emerging evidence indicates, however, that B cells are multifunctional and their various roles are not limited to antibody production, but also include antigen presentation, cytokine production, and modulation of T cell-mediated immunity (Lund, 2008; Maglione, Chan, 2009; Chan et al., 2014; Rao et al., 2015; Steigler et al., 2019; Tanner et al., 2019). The significance of memory B cells in tuberculosis remains poorly understood, although various memory populations have been described (Feng et al., 2011; Sebina et al., 2012; du Plessis et al., 2016a,b). In bovine tuberculosis, it is well established that antibody levels in cattle infected with *M. bovis* are sharply increased shortly after administration of the intradermal tuberculin test (Harboe et al., 1990; Lyashchenko et al., 2004; Palmer et al., 2006; Waters et al., 2014), strongly suggesting a key role for memory B cells in the antibody-boosting effect. However, this phenomenon has not been systematically analyzed in the context of immunological memory.

The present review highlights recent advances in the understanding of generation and activation of memory B cells, their phenotypic and functional characteristics in human and animal tuberculosis, and role in post-skin test recall antibody responses in infected cattle and other host species. We also discuss possible implications of favorable and detrimental effects of memory B cells for anti-tuberculosis immunity and for development of improved vaccines and diagnostics.

2. Generation of memory B cells

Antigen-induced B cell differentiation has been extensively studied in mouse models (Bergmann et al., 2013; Chong and Ansari, 2018). Upon initial infection or primary immunization, naïve B cells in secondary lymphoid organs, such as spleen or draining lymph node, recognize T-cell dependent antigens by IgM receptors, followed by proliferation of the activated clones and migration to the T cell-B cell interface in the follicle. Further events take place in germinal centers (GCs), dynamic and highly specialized microstructures in lymphoid tissues providing the cellular microenvironment and activation signals required for B cell differentiation into plasma cells or memory cells (Kurosaki et al., 2015; Harms Pritchard, Pepper, 2018; Inoue et al., 2018). Initiation and maintenance of GCs requires the stromal network, highly coordinated interactions of different cell types, and chemotactic support for orchestrated cell trafficking and antigen delivery (Stebegg et al., 2018). Antigen-presenting follicular dendritic cells (FDCs) and T follicular helper (Tfh) cells are critical players in the GC response and B cell differentiation (Heesters et al., 2014; Chong and Ansari, 2018; Shah et al., 2019). It should be noted, however, that under certain conditions memory B cells can also be generated via GC-independent pathways and in the absence of T cell assistance (Taylor et al., 2012; Kurosaki et al., 2015; Pupovac, Good-Jacobson, 2017), as summarized in Table 1.

Differentiation fate decisions for primed B cells are determined by multiple factors including the nature of antigen, expression and affinity of cell receptors, access to FDCs, and productive engagement with Tfh cells (Chong and Ansari, 2018; Inoue et al., 2018; Stebegg et al., 2018). Antigen in the form of immune complexes can be captured by FDCs via Fc receptors and retained on the cell surface for an extended time; thus, providing B cells with the prolonged opportunity to sense the antigen when migrating through such “interrogation points” within the stromal network of the GC (Suzuki et al., 2009). Subsequently, cognate interactions between the primed B cells, FDCs, and Tfh cells lead to proliferation and differentiation into extrafollicular memory B cells, short-lived plasmablasts, or B cells migrating to the center of the follicle to initiate clonal expansion and GC response (Heesters et al., 2014; Stebegg et al., 2018), thus fueling strategic compartments of long-term humoral immunity.

The affinity of the B cell receptor for its cognate antigen plays a key role in B cell differentiation. Selection for plasma cells is mainly associated with higher affinity, whereas lower affinity is a feature of memory B cells, and intermediate affinity is generally found with activated B cells returning to the GC (Pupovac, Good-Jacobson, 2017). It has been proposed that B cell receptors of higher affinity can provide improved antigen recognition and endocytosis, leading to more efficient interactions with Tfh cells (Victora, Nussenzweig, 2012). However, recent studies have revealed that a single naïve B cell can differentiate into any of the three types, including plasma, memory, or GC cells (Inoue et al., 2018). Thus, the differentiation pathway is determined not only by the affinity of B cell receptors but it also depends on the signals received from Tfh cells.

B cell differentiation is characterized by affinity maturation and isotype switching of receptors on activated B cells starting at the pre-GC phase when most of them still express low-affinity un-mutated IgM receptors with some switching to IgG+ or IgA+ memory B cells (Taylor et al., 2012; Kaji et al., 2012). Histologically, the GC is divided into two compartments that include the light zone, which is enriched with FDCs where positive selection with Tfh cells takes place, and the dark zone, where B cells known as centroblasts rapidly proliferate and undergo IgH class-switch recombination (CSR) and somatic hypermutation (SHM) ultimately leading to antibody response diversification and affinity maturation. In the light zone, antigen displayed on FDCs is presented to B cells and Tfh cells (Heesters et al., 2014). The efficiency of these interactions is determined by the affinity of B cell receptors and by the surface density of peptide-MHC II complexes, respectively. Subsequently, light zone B cells can determine their fate between recycling to the dark zone and exiting the GC as plasma cells or memory B cells (Stebegg et al., 2018). During the affinity-based selection in the GC, B cells receiving strong cognate help from Tfh cells are most likely to differentiate into antibody-secreting plasma cells, while those receiving low or even no cognate help from Tfh cells are more likely to differentiate into memory B cells (Inoue et al., 2018). Consistent with these observations are results of adoptive transfer experiments using athymic (nude) mice to reveal that, in contrast to the induction of primary antibody response to T-cell dependent antigen that requires cooperation between naïve B and T cells, concurrent generation of memory B cells specific to the same antigen can take place in the absence of functional T cells *in vivo* (Liashchenko and Bobrovnik, 1990).

3. Reactivation of memory B cells

Mature memory B cells exit the GC and migrate to preferred anatomic niches indicated below when guided by distinct humoral signals received via chemokine receptors. Effective humoral immunity benefits from distribution of long-lived memory B cells throughout the body where they can be strategically positioned at likely pathogen entry sites to achieve timely and efficient interception of the re-infecting agent. Based on the location, receptor isotype, and specific function, as summarized in Table 1, the tissue-resident memory B cell compartment includes three lines of defense: 1) IgM+ memory B cells residing mainly in the bone marrow and spleen, 2) IgG+ memory B cells located predominantly in draining lymph nodes, and 3) IgA+ memory B cells associated with mucosal and cutaneous surfaces (Pupovac and Good-Jacobson, 2017). These subsets can also be found in peripheral blood (Krishnamurty et al., 2016; Inoue et al., 2018). Lung-resident memory B cells, phenotypically and functionally different from the systemic memory pool, have recently been described in the context of pulmonary influenza infection (Allie et al., 2019).

While the generation of B cell memory has been studied extensively, less is known about its reactivation sites, interactions with other cell types, and immunoregulation. Mouse model experiments have shown that memory B cells can migrate to the bone marrow within several days following intravenous injection with staphylococcal particulate antigen (Bobrovnik and Liashchenko, 1989). The study revealed a

Table 1
Generation and heterogeneity of memory B cells.

Defining feature	Sub-populations	Key characteristics	References
Differentiation pathway	GC-dependent or GC-independent	Long-lasting memory B cells develop mainly in GCs at early stages of primary immune response; their differentiation is induced by antigen, characterized by SHM and CSR, and aided by antigen-presenting FDCs and Tfh cells within the B cell follicles. In contrast, GC-independent memory B cells are induced in the presence of antigen and T cell-produced activation signals including CD40 outside the B cell follicles, express mainly IgD and/or IgM, and are less mutated than GC-derived B cell memory pool.	Bergmann et al. (2013) Eisen (2014) Kurosaki et al. (2015) Pupovac, Good-Jacobson (2017) Harms Pritchard and Pepper (2018) Hendricks et al. (2018) Inoue et al. (2018) Stebegg et al. (2018) Shah et al. (2019)
	T cell-dependent or T cell-independent	Differentiation into mature memory B cells requires T cell assistance and relies on selection of high-affinity B cell receptors capable of making longer contact with FDCs and Tfh cells within GCs. T cell-independent mechanism involve B1 cells persisting predominantly in peritoneal cavity and/or T cell-independent antigens.	Bergmann et al. (2013) Kurosaki et al. (2015) Hendricks et al. (2018) Shah et al. (2019)
Cell surface phenotype	CD27+, CD73+, CD80+, PD-L2+	Costimulatory receptor CD27 is the main biomarker of human memory B cells; antigen-primed B cells expressing CD73, CD80, PD-L2 can promptly differentiate into antibody-producing plasmablasts, while CD80- PD-L2- cells are more likely to re-enter GC reaction; > 60 % of DC80+ memory B cells undergo SHM.	Bergmann et al. (2013) Kurosaki et al. (2015) Pupovac, Good-Jacobson (2017) Shah et al. (2019) Tomayko and Allman (2019)
Cell receptor isotype	IgM+	Upon antigen re-stimulation, IgM+ memory B cells proliferate and re-enter GCs, thus contributing to B cell memory self-renewal and repertoire diversification or rapidly differentiate into plasmablasts producing IgM, IgG, IgA, or IgE; all express CD27, reside mainly in the bone marrow and spleen.	Bergmann et al. (2013) Kurosaki et al. (2015) Krishnamurty et al. (2016) Pupovac, Good-Jacobson (2017) Harms Pritchard, Pepper (2018) Shah et al. (2019)
	IgG+	IgG+ memory B cells derive from IgM + B cells through CSR process; ~80 % express CD27, are mainly located in the draining lymph nodes, and constitute ~20 % of peripheral blood B cells; upon antigen re-stimulation, predominantly differentiate into IgG-producing cells.	Bergmann et al. (2013) Kurosaki et al. (2015) Asrir et al. (2017) Pupovac and Good-Jacobson (2017) Shah et al. (2019)
	IgA+	IgA+ memory B cells derive from IgM+ (switched) or IgG+ (sequentially switched) memory B cells; they express CD27, constitute ~10 % of peripheral blood B cells, and are predominantly associated with cutaneous and mucosal antibody responses.	Bergmann et al. (2013) Kurosaki et al. (2015) Harms Pritchard and Pepper (2018) Inoue et al. (2018) Shah et al. (2019)
Functions and immunobiological roles	Conventional	Classical memory B cells are progenies of antigen-experienced, GC-derived, and T-cell-promoted B cells characterized by isotype switching, affinity maturation, broader immune repertoire, expression of CD27, CD80, PD-L2, long life span, multi-layer immune cell plasticity, and the ability to develop a rapid and robust antibody response to antigen re-exposure; they repopulate the bone marrow, spleen, and draining lymph nodes, but can be also found in peripheral blood; besides the effector functions, memory B cells may play regulatory roles in T cell immunity.	Bergmann et al. (2013) Eisen (2014) Kurosaki et al. (2015) Rao et al. (2015) Chong and Ansari (2018) Laurent et al. (2017) Stebegg et al. (2018) Steigler et al. (2019) Tomayko and Allman (2019)
	Atypical	Distinguished by lacking CD27 and CXCR5 expression and ability to produce recall antibody responses, presumably due to long-term antigen persistence and immunoinflammation, these functionally “impaired” or “exhausted” memory B cells are found in tonsils, intestinal lymphoid tissues, and peripheral blood of patients diagnosed with hepatitis C, HIV infection, malaria, or tuberculosis; atypical memory B cells are believed to be implicated in insufficient immunity in the chronic infections, thus contributing to disease progression.	Kurosaki et al. (2015) Portugal et al. (2017) Pupovac, Good-Jacobson (2017) Inoue et al. (2018) Shah et al. (2019)

GC, germinal center; SHM, somatic hypermutation; CSR, class switch recombination; FDC, follicular dendritic cells; Tfh, T follicular helper; PD-L2, programmed death-ligand 2.

significant expansion of IgG-producing plasma cells in the bone marrow following secondary immunization, in sharp contrast to very few antibody-secreting cells found in the bone marrow during the primary response. Migration of memory B cells to bone marrow was also demonstrated in humans (Paramithiotis and Cooper, 1997). Subsequent studies have shown that memory B cells can differentiate into short-lived plasma cells in the bone marrow in the absence of the secondary lymphoid tissue microenvironment including Tfh cells (Ochsenbein et al., 2000; Rao et al., 2015) that are normally required for differentiation of memory B cells into plasmablasts in the secondary lymphoid organs (Asrir et al., 2017). Earlier experiments on nude mice suggested that the recall antibody response to T cell-dependent antigen is relatively independent of the presence of functional T cells, as compared to the primary response (Liashchenko and Bobrovnik, 1990). Recent studies have shown, however, that memory B cell reactivation in human tonsils is promoted by extrafollicular CD4+ T cells expressing CXCR5 and residing in close proximity to the B cell follicle (Kim et al., 2018).

Similar to naïve B cells facing fate decision options, reactivated memory B cells can either differentiate into antibody-secreting plasma cells or re-enter the GC. The latter path provides opportunities for class-switching and affinity maturation, thus facilitating diversity and sustainability of the memory B cell compartment (Inoue et al., 2018; Stebegg et al., 2018). Once reactivated with antigen, most circulating IgM+ memory B cells re-enter the GCs, whereas local tissue-resident IgG+ and IgA+ memory B cells predominantly differentiate into

plasma cells (Asrir et al., 2017). Malaria re-challenge experiments in mice have demonstrated the prominent role of IgM+ memory B cells in generating rapid (three days after secondary antigen encounter) and IgM-dominant anamnestic responses (Krishnamurty et al., 2016). Thus, the most effective recall response requires multiple subsets of memory B cells.

4. Heterogeneity of memory B cells

Classically, memory B cells are defined as non-dividing, antigen-primed, mainly GC-derived, long-lived, class-switched, and somatically hyper-mutated B cells with potential for a rapid reactivation and differentiation into antibody-secreting plasma cells (Kurosaki et al., 2015; Rao et al., 2015). However, recent human and mouse studies have demonstrated significant heterogeneity of phenotypic and functional characteristics of memory B cells (Harms Pritchard and Pepper, 2018; Chong and Ansari, 2018). As summarized in Table 1, memory B cell subsets can be distinguished by receptor isotype, other surface biomarkers, preferred anatomic location, CSR potential, SHM rate, multilayer immune cell plasticity, and other features (Bergmann et al., 2013; Kurosaki et al., 2015; Pupovac and Good-Jacobson, 2017). In infectious diseases, the host can benefit from the heterogeneity of memory populations by diversifying immune repertoire, maintaining GC-dependent and GC-independent self-renewal of long-term memory, and promoting the most efficient antibody responses to T cell-dependent and T cell-independent antigens.

Based on the receptor expression, three types of memory B cells were originally described in rodents, namely IgD+ IgM-, IgM+ IgD-, and IgG+ IgD- (Dell et al., 1989). Generation of IgM+ and IgG+ memory B cells is mostly GC-dependent, whereas development of IgD+ memory B cells is GC-independent (Pupovac and Good-Jacobson, 2017). Circulating IgM+ memory B cells reportedly survive longer than IgG+ memory B cells (Pape et al., 2011), although other investigators have found no significant difference between lifespans of IgM+ and IgG+ memory B cells (Jones et al., 2015). Upon secondary antigen encounter, IgM+ memory B cells can rapidly switch to IgM+, IgG+, IgA+, or IgE+ plasmablasts, while IgG+ memory B cells form IgG+ plasmablasts (Kurosaki et al., 2015; Harms Pritchard and Pepper, 2018).

In cattle, the percentages of IgD+ B cells present in the blood circulation and certain lymphoid tissues are significantly lower than those found in mice and humans (Xu et al., 2012). In contrast to IgM+ and IgG+ memory B cells, IgD+ memory B cells show much lower SHM rates (Rakhmanov et al., 2009) and they survive longer than IgM+ and IgG+ memory B cells (Harms Pritchard and Pepper, 2018). The specific effector function of IgD+ memory B cells remains unknown, although this subset is believed to form secondary GCs, along with IgM+ memory B cells (Kurosaki et al., 2015), thus contributing to regeneration and longevity of the mature memory pool. CD27+ memory B cells from human tonsils can differentiate into IgM or IgG antibody-producing plasma cells (Maurer et al., 1992). Other surface biomarkers used to distinguish memory B cell subsets include CD73, CD80, and PD-L2 (Bergmann et al., 2013; Pupovac, Good-Jacobson, 2017; Shah et al., 2019).

Phenotype and function of memory B cells may be affected by pathogens displaying high antigenic diversity for immune evasion. For example, atypical memory B cells characterized as functionally impaired, unresponsive to antigen, and lacking expression of CD27 and CXCR5 have been recently described in human patients diagnosed with chronic or recurrent infections associated with immune inflammation, such as HIV, hepatitis C, malaria, and tuberculosis (Portugal et al., 2017). In these infections, the numbers of atypical memory B cells in the peripheral blood are significantly elevated, but their immunobiological role is unclear. It has been proposed that atypical memory B cells, probably generated in abnormal GCs, represent an exhausted memory subset, presumably due to the immunomodulation of inhibitory and trafficking receptors in the presence of persisting antigen (Kurosaki et al., 2015; Pupovac and Good-Jacobson, 2017). As a result, the ability of atypical memory B cells to differentiate into functional plasma cell precursors for adequate antibody responses is impaired. Thus, protective immunity in these chronic infectious diseases may be compromised due to fundamental alterations in the memory B cell compartment. Potential detrimental effects of atypical memory B cells in tuberculosis are discussed below.

5. Memory B cells in tuberculosis

Improved understanding of memory responses in tuberculosis is required to make evidence-based rational decisions for developing new strategies towards better vaccines and immunodiagnostics. B cell biology of tuberculosis has received relatively little attention as mycobacterial infections are believed to be controlled primarily by cellular immunity imparted by T cells (Waters et al., 2014; Jasenosky et al., 2015; Behar et al., 2014). The role of T cell memory in anti-tuberculosis defense has been extensively reviewed (Vordermeier et al., 2009; Behar et al., 2014; Blunt et al., 2015; Kirman et al., 2016). In the past decade, however, interest in B cell research in tuberculosis has increased due to the growing body of evidence for regulatory effects of B cells shaping T-cell responses and hence significantly modulating the course and outcomes of infection (Maglione and Chan, 2009; Chan et al., 2014; Achkar et al., 2015; Steigler et al., 2019; Tanner et al., 2019).

Consistent with this view are numerous findings of activated B cells in tuberculous lesions or peripheral blood from infected mice (Gonzalez-Juarrero et al., 2001), humans (Ulrichs et al., 2004; du Plessis et al., 2016a), cattle (Aranday-Cortes et al., 2013), and other host species (García-Jiménez et al., 2012; Phuah et al., 2012; Vallejo et al., 2018). Formation of B cell follicles in the lung tissues of *M. tuberculosis*-infected mice is dependent on IL-23 and CXCL13, with the latter chemokine being in turn dependent upon IL-17A and IL-22 (Khader et al., 2011). In human tuberculosis, recently described innate B cells produce IL-12, IFN-γ, and TNF-α (Lund, 2008; Bao et al., 2014), thus promoting a Th1-type response. Memory B cells (IgM+ CD27+) are found in the peripheral blood of patients diagnosed with latent tuberculosis or active disease (du Plessis et al., 2016a, 2016b). These cells are strongly involved in cytokine secretion (IL-10, IL-17, IL-21, TNF-α) and their numbers decline following anti-tuberculosis treatment. Decreased frequencies of circulating un-switched memory B cells (IgD+ CD27+) have also been detected in patients infected with multidrug-resistant *M. tuberculosis* (Abreu et al., 2014). Human monoclonal antibodies of IgM and IgG isotypes against *M. tuberculosis* lipoarabinomannan (LAM) have been recently generated from memory B cells isolated from infected patients (Choudhary et al., 2018).

Development of the granuloma is the hallmark of tuberculous infection (Orme and Basaraba, 2014). Human lung granulomas contain aggregates of B cells (naïve and memory) and plasma cells intermixed with eosinophils, neutrophils, FDCs, $CD4^+$ and $CD8^+$ T cells (Lasco et al., 2004; Ulrichs et al., 2004; Achkar et al., 2015). B cells appear to stay in close proximity to CXCR5+ T cells and *M. tuberculosis*-infected macrophages (Chan et al., 2014). Similar findings in non-human primates show numerous activated B cells organized into discrete clusters in lung granulomas, reminiscent of GCs normally found in secondary lymphoid organs (Phuah et al., 2012). These B cells express CD20 and CXCR5 and have elevated HLA-DR expression. Although antigen-specific IgG-secreting plasma cells are present in the draining lymph node and lung granulomas, the antibody response develops much faster in the draining lymph node (Phauh et al., 2012). This difference suggests that the plasma cells found in the secondary lymphoid tissue stem from memory B cells, whereas the antibody-secreting cells detected in the infected lungs derive from activated B cells probably recruited to the granulomas.

Cattle studies on *M. bovis* infection also demonstrate recruitment of B cells (CD79a+) during granuloma development (Aranday-Cortes

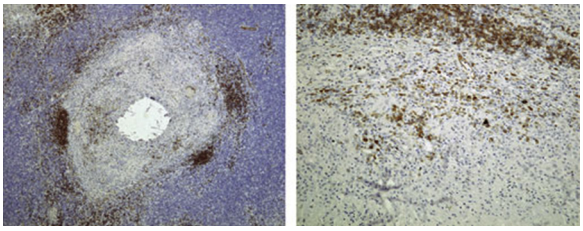

Fig. 1. Nests of CD79+ B cells surrounding granuloma in the lymph node from a calf experimentally infected with *M. bovis* (Aranday-Cortes et al., 2013). Left image, 40x; right image, 200x.

et al., 2013; Salguero et al., 2017): while early granulomas (stages I and II) display scattered B cells, more advanced granulomas (stages III and IV) show satellite nests of CD79a+ cells (Fig. 1). Similar to other host species (e.g., mice and humans), a role for IL17A- and IL22-producing T cells has been postulated to be involved in both protective and detrimental inflammatory responses, including the formation of granulomas, in *M. bovis*-infected cattle (Aranday-Cortes et al., 2013; Waters et al., 2015a,b). These findings suggest a similar role for TH17 cells in the development of B cell follicles in cattle, as shown in murine studies. Likewise, in *M. bovis*-infected fallow deer or sheep, granuloma B cell numbers increase considerably as the granuloma develops (García-Jiménez et al., 2012; Vallejo et al., 2018). Thus, B cell populations including memory B cells constitute a significant cell compartment of granuloma formation in tuberculosis.

The findings of activated B cells in the development of GC-like structures at the infection site suggest their role in the host response. The presence of memory B cells in ectopic GCs in tuberculosis appears particularly intriguing in the context of the classical B cell memory generation discussed in the previous sections. It raises the question whether there may be alternative mechanisms for conventional memory B cell development in tuberculosis and other diseases, which would not require the GC reactions in the secondary lymphoid organs. It has been proposed that the follicles in granulomas provide at least a partial framework for coordinated immune control of mycobacterial growth in the affected tissues (Ulrichs et al., 2004). Furthermore, granulomas may function as tertiary GCs providing the microenvironment for the T cells to be continuously stimulated via B cell-mediated antigen presentation (Phuah et al., 2012). The latter function of B cells is believed to be critical to enable the recall response by CD4+ memory T cells (Chan et al., 2014). In support of the B cell involvement in the local control of infection are recent human studies demonstrating that 1) proportions of activated memory B cells in patients with active tuberculosis or latent infection negatively correlate with mycobacterial growth (O'Shea et al., 2018), 2) classical memory B cells (CD19+ CD27+) provide a major contribution in the secretion of pro- and anti-inflammatory cytokines implicated in communication with effector T cells involved in the protective immunity (du Plessis et al., 2016a), and 3) calcified (healed) lung granulomas of patients recovered from past active tuberculosis contain functional memory B cells (Rao et al., 2015). Interestingly, ectopic GCs in non-lymphoid tissues have been described in other infectious diseases and cancer (Pitzalis et al., 2014), but their immunobiologic role is unclear.

Vaccination with *M. bovis* Bacillus Calmette Guerin (BCG) results in generation of long-lived memory B cells that are responsive to mycobacterial antigens (Sebina et al., 2012). Mouse experiments have shown a significantly higher anamnestic IgG response to BCG re-immunization in animals primed with live vaccine, as compared to those initially receiving heat-killed BCG (Liashchenko, 1993). To achieve the level of memory B cell response provided by priming with live BCG, a 50-fold higher dose of the killed vaccine was required, in contrast to the primary antibody response being independent on the BCG viability. Intriguingly, similar differences have been demonstrated in animal model experiments showing that the BCG vaccine must be alive and capable of replicating *in vivo* to generate protective immunity (Orme, 1988). The strong immunogenicity of live anti-tuberculosis vaccines is believed to be due to their ability to release secreted proteins by actively dividing mycobacteria (Wiker, 2009; Majlessi et al., 2015). Indeed, secreted proteins of *M. tuberculosis* or *M. bovis* elicit strong T cell and B cell responses and can induce immune protection when used as sub-unit vaccine formulations in animal models (Andersen and Heron, 1993; Hewinson et al., 1996; Zhu et al., 2018).

Prior cattle studies have demonstrated that an increase in serum antibodies against MPB83 is inversely associated with BCG-induced protection (Lyashchenko et al., 2004) and that B cell numbers in advanced granulomas of BCG-vaccinated calves are higher than those in the same stage granulomas found in unvaccinated *M. bovis*-infected animals (Salguero et al., 2017), suggesting an association between B cells and immune protection. Collectively, the animal studies suggest that memory B cells may be involved in protective immunity to mycobacterial diseases. This view is supported by recent findings in humans demonstrating the ability of memory B cells isolated from patients with active tuberculosis to control the growth of mycobacteria *in vitro* (O'Shea et al., 2018).

6. Detrimental effects of memory B cells in tuberculosis

In infectious diseases, certain B cell subsets may be involved in unfavorable effects to the host, thus facilitating pathogen survival. One example is the atypical memory B cells implicated in chronic inflammatory infections including tuberculosis, (Portugal et al., 2017), as discussed above (Table 1). Besides generation of a conventional memory pool, human tuberculosis is characterized by significant expansion of "exhausted" memory B cells that lack expression of CD27 and CXCR5, are non-responsive to antigen or to stimulation by cross-linking with CD40, and have diminished ability to proliferate and produce cytokines or chemokines (O'Shea et al., 2018). The dysfunctional features of these cells are resolved after successful anti-tuberculosis treatment. It is suggested that the atypical memory B cells may contribute to the failure of immune responses, thus facilitating progression from latent tuberculosis infection to active disease. Similar factors may contribute to the impaired anti-malaria immunity after repeated *Plasmodium falciparum* infections shown to be associated with significant expansion of atypical memory B cells (Muellenbeck et al., 2013). Emerging data indicates that excessive antigen persistence promotes development of an impaired memory compartment in tuberculosis, as it has been also suggested for the atypical memory B cells found in other chronic infections including HIV, hepatitis C, and malaria (Portugal et al., 2017).

Another example of B cell memory manifestation that may compromise the host response is the phenomenon known as original antigenic sin (OAS) described in human viral infections, such as influenza, HIV, Zika, and dengue fever (Linderman and Hensley, 2016; Vatti et al., 2017). The OAS is typically observed after re-infection with a different but antigenically related strain of the pathogen when the recall response to the new strain is characterized by dominant antibody specificity against the previous strain without sufficient recognition of new epitopes from the re-infecting strain. Paradoxically, this OAS memory response leads to antibody binding to the priming antigen with higher affinity than the newly acquired pathogen that is actually eliciting the secondary response. As a result, the protection against the new strain becomes less efficient, often giving rise to development of virus-entry enhancing antibodies, rather than neutralizing antibodies. The memory B cells involved in the OAS are believed to be products of clonal selection and affinity maturation from primed lymphocytes specific to most conservative epitopes recognized at primary antigen encounter, thus eventually leading to the predominance of cross-reactive antibody responses upon secondary exposure (Park et al., 2016; Vatti et al., 2017).

Similar to the viral infections with diverse but inter-related strains,

mycobacterioses in humans or animals caused by various strains that are characterized by close genetic similarity and largely shared antigens represent one of the most suitable niches for OAS expression among bacterial diseases. Indeed, this phenomenon has been recently reviewed in detail by Jenkins et al. (2017) as "Original Mycobacterial Sin" resulting from highly homologous antigens eliciting immune responses after repeated exposures. If infection with pathogenic mycobacteria, such as tuberculosis, is preceded by environmental sensitization to a non-virulent strain expressing similar antigens, the memory response will be biased toward mainly shared epitopes, thus allowing the pathogen to benefit from immune evasion by escaping sub-optimal host responses. Vatti et al. (2017) have recently reviewed studies describing typical signs of OAS in other non-viral infections, including leptospirosis and malaria.

In addition to memory B cells, the OAS phenomenon may involve T cell responses (Jenkins et al., 2017). Guinea pigs pre-sensitized with heat-killed *M. avium* several months prior to BCG vaccination develop reduced delayed-type hypersensitivity (DTH) reactions to bovine tuberculin and enlarged reactions to avian tuberculin, as compared to the skin test responses in BCG only vaccinates (Liashchenko et al., 1991). Such paradoxical recall responses can potentially compromise the diagnostic specificity of the comparative tuberculin tests and IFN-γ release assays used in cattle and other animal species. Past exposure to non-tuberculous mycobacteria has shown variable effects on the BCG-induced protective immunity to *M. bovis* infection in cattle (Buddle et al., 2002; Hope et al., 2005; Thom et al., 2008). T cell populations involved in the OAS responses are believed to be implicated in development of antigen-specific skin test unresponsiveness, i.e., anergy (Jenkins et al., 2017), frequently observed at advanced stages of bovine tuberculosis.

Cellular mechanisms underlying generation and functions of atypical memory B cells and OAS responses are not fully understood. Although relationship between these memory-driven phenomena are unclear, recent studies suggest that each of them may have adverse effects on adaptive immunity, vaccine efficacy, and immunodiagnostic accuracy in tuberculosis and other mycobacterial diseases. A dynamic balance between classical and atypical memory B-cell populations evolving over the course of infection is likely to affect both humoral and cell-mediated responses in different ways. Therefore, this previously unrecognized factor might have contributed to the controversy in current understanding of the role of antibody responses in tuberculosis. It is generally accepted that clinical progression of tuberculosis is associated with the presence of elevated titers of anti-mycobacterial IgG (Maglione and Chan, 2009; Waters et al., 2014); however, the growing body of evidence indicates that multifunctional B-cell populations involved in antigen presentation and production of cytokines can shape T cell responses and hence may contribute to the protective immunity in tuberculosis (Chan et al., 2014; Achkar et al., 2015; Rao et al., 2015; Tanner et al., 2019; Counoupas et al., 2019).

7. Memory B cells and tuberculin-induced antibody boost

In cattle, the principal ante-mortem test for detection of *M. bovis* infection is the tuberculin skin test (TST). This test was first developed in the late 1800's and has been a mainstay of bovine tuberculosis eradication/control programs around the world (Palmer and Waters, 2011). Likewise, the intradermal tuberculin test is widely used for the diagnosis of *M. tuberculosis* infection in humans.

In animal tuberculosis, the use of serologic assays in conjunction with TST has revealed a striking effect of injected tuberculin purified protein derivative (PPD) on humoral responses. Numerous studies have shown that TST administration leads to a sharp increase of antibody levels to mycobacterial antigens in cattle or cervids infected with *M. bovis* but not in non-infected animals (Harboe et al., 1990; Harrington et al., 2008; Casal et al., 2014; Busch et al., 2017), suggesting implication of memory B cells (Waters et al., 2014). The antibody levels

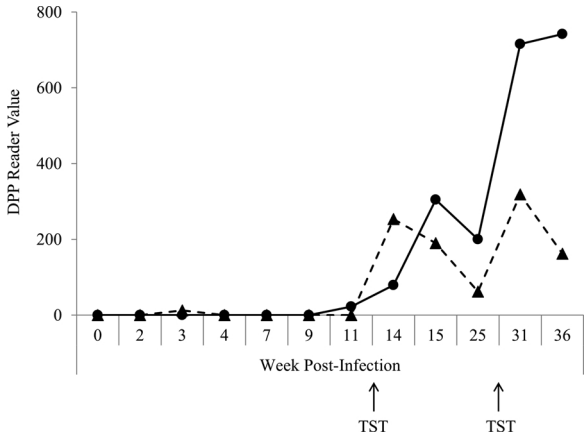

Fig. 2. IgM (triangles, dotted line) and IgG (circles, solid line) antibody responses to MPB70/MPB83 fusion protein detected by Dual-Path Platform (DPP) assay in serum samples serially collected from a calf aerosol-inoculated with *M. bovis* following TST administration at weeks 13 and 30 post-infection (Lyashchenko et al., 2017).

are usually boosted from 1 to 2 weeks following PPD injection (Fig. 2) and can persist for several weeks to many months depending on the TST type (e.g., comparative versus single tuberculin test), PPD dose, stage of disease, and antigens used in the serologic assay (Lyashchenko et al., 2004, 2017; Palmer et al., 2006; Chambers, 2013). Importantly, PPD administration not only enhances pre-TST antibody levels, but it also elicits humoral responses in seronegative cattle during the pre-seroconversion phase of early *M. bovis* infection, thus substantially increasing the sensitivity of serological assays for bovine tuberculosis (Casal et al., 2014; Waters et al., 2015a,b). Besides cattle and cervids, the antibody-boosting effects have been also reported in other domestic and wildlife species including bison, goats, camelids, rhinoceros, and non-human primates infected with tuberculous or non-tuberculous mycobacteria (Lyashchenko et al., 2007; Dean et al., 2009; Himsworth et al., 2010; Waters et al., 2010; Miller et al., 2015; Bezos et al., 2018).

In cattle experimentally inoculated with *M. bovis*, the TST-boosted antibody responses involve IgM, IgG, and IgA isotypes to a variety of protein and non-protein antigens, such as ESAT-6, CFP10, Acr1, MPB59, MPB64, MPB70, MPB83, and LAM (Lyashchenko et al., 2004; our unpublished data). To elicit secondary antibody responses, bovine PPD would have to contain these antigens or their derivatives capable of re-activating memory B cells in the infected animals. Indeed, antibody-reactive epitopes of the above *M. bovis* proteins are present in bovine PPD (Harboe et al., 1990; Lyashchenko et al., 2004; our unpublished data). The TST-induced anamnestic response in cattle involves both IgG1 and IgG2 subclasses, with a predominant IgG1 response to a linear epitope within residues 51–70 of MPB70 protein (Lightbody et al., 2000). The TST-induced antibody reactivity pattern, however, is unlikely to reflect the entire specificity spectrum of memory B cells generated in bovine tuberculosis. Recent studies demonstrate that memory B cell repertoire can be broader than the plasma cell repertoire (Chong and Ansari, 2018; Shah et al., 2019), implying that serological recognition profiles may not necessarily be equivalent to that of reactivated memory B cells.

Hadi et al. (2018) have proposed an alternative approach to identify antigens eliciting IgM+ memory B cells in bovine tuberculosis. Using high-resolution liquid chromatography followed by dual mass-spectrometry, the investigators have analyzed IgM-associated immune complexes isolated from post-TST serum samples of *M. bovis*-infected cattle. The study has revealed a series of *M. bovis*-derived peptides eluted from the TST-boosted IgM antibodies. Such a multi-epitope biosignature is likely to reflect the specificities within the IgM+ memory B cell pool, in addition to its conventional characterization by seroreactivity patterns. Shah and co-workers (2019) have reviewed other advanced

technologies to explore immune repertoires, including next generation sequencing of paired IgH/IgL chains and production of monoclonal antibodies from individual memory B cells. A recent study has used the latter approach to generate human IgM and IgG monoclonal antibodies to *M. tuberculosis* LAM from memory B cells isolated from infected patients (Choudhary et al., 2018).

Following TST, anamnestic IgM responses in *M. bovis*-infected cattle typically peak one week following TST, while achieving the highest IgG antibody levels requires at least two weeks (Lyashchenko et al., 2017). Repeated PPD injections result in gradually increasing recall IgG responses over time, whereas the magnitude of boosted IgM responses tends to remain unchanged following serial TST administrations (Waters et al., 2015a,b; Lyashchenko et al., 2017). This distinct feature may stem from a down-regulating effect of Fc receptors for IgM and IgA (Fcα/μR) expressed by FDCs on the retention of soluble IgM-containing immune complexes, leading to suppressed formation of GCs and generation of memory B cells (Shibuya and Honda, 2015). Our recent experiments in *M. bovis*-infected cattle have demonstrated a rapid IgM antibody response and simultaneous accumulation of circulating immune complexes, mainly including IgM, one week after first TST administration with no further elevated secondary IgM response following repeated PPD injection, in contrast to the IgG recall responses which tend to strengthen over time (Lyashchenko et al., 2017), as illustrated on Fig. 2. The avidity of IgG antibodies to MPB70 and MPB83 in *M. bovis*-infected cattle also increases following serial TST administrations (Waters et al., 2015a,b). Collectively, the studies strongly support the role of PPD-reactivated memory B cells in post-TST recall antibody responses in *M. bovis*-infected animals.

Whether memory B cells become antigen-activated to differentiate into plasma cells at the site of PPD injection, remains unknown. Cattle studies demonstrating predominant accumulation of macrophages, CD4+ and CD8+ T cells, few γδ T cells and neutrophils, have found no B cells in the skin infiltrates between 24 and 72 h after the intradermal PPD administration (Doherty et al., 1996). A more recent study has revealed very few sparse IgM+ B cells at the site of intradermal injection of recombinant CFP10/ESAT-6 fusion protein (Waters et al., 2009). These reports would not support the possibility of recruiting memory B cells by the antigen-enriched skin area. Alternatively, the recall response may be initiated by migratory dendritic cells present in the skin that can sense antigen and transport it to the draining lymph nodes for presentation to Tfh cells and memory B cells (Waters et al., 2009; Segura, Amigorena, 2013), thereby prompting expansion of plasma cells. Consistent with this assumption are the results of guinea pig experiments demonstrating that 95 % of radio-labeled PPD disappears from the skin test site within 18−24 hours of intradermal injection (Landi et al., 1974), suggesting active (probably, cell-assisted), rather than passive, clearance of antigen. Human studies have found that several types of professional antigen-presenting cells in the skin, including CD14+ dermal dendritic cells, are able to promote antibody production (Romani et al., 2012). In mouse experiments, BCG skin infection triggers co-migration of CD11b+ dermal dendritic cells and mycobacteria from the inoculation site to the draining lymph node (Bollampalli et al., 2015). The study has also shown that blocking the skin dendritic cells by pre-treatment with Pertussis toxin dramatically reduces both mycobacterial entry into the draining lymph node and priming of CD4+ T cells. Cattle studies have also shown that migratory dendritic cells can take up BCG following intradermal vaccination and present mycobacterial antigens to T cells (Hope et al., 2012).

The DTH response following intradermal injection of recombinant CFP10/ESAT-6 fusion protein in cattle experimentally infected with *M. bovis* involves mainly CD4+ T cells, CD8+ T cells, and CD172a+ dendritic cells, as well as a few IgM+ B cells found in the skin infiltrates (Waters et al., 2009). The stimulated CD172a+ cells can bind the antigen and proliferate *in vitro*. As CD47-CD172a interaction is essential for migration of the respective dendritic cells to the skin and secondary lymphoid organs, it has been suggested that the antigen-induced expansion of CD172a+ cells in *M. bovis*-infected cattle results in increased trafficking to the infection foci (Waters et al., 2009). This effect is likely to promote the granuloma formation and the TST-boosted antibody responses in *M. bovis*-infected cattle and other host species.

Cell-mediated immunity in tuberculosis may also be affected by TST administration (Schiller et al., 2010). Repeated PPD injections lead to gradual desensitization over time in *M. tuberculosis*-infected non-human primates (Lyashchenko et al., 2007). A similar effect observed in bovine tuberculosis is associated with increased IL-10 and decreased IL-1β production in cattle (Thom et al., 2006; Coad et al., 2010). In contrast, IFN-γ responses to specific peptide cocktail (ESAT-6, CFP10, Rv3615c) in *M. bovis*-infected cattle are elevated for up to two weeks after PPD injection (Jones et al., 2017). Schiller and co-workers (2010) have extensively reviewed the effects of TST administration on *in vitro* IFN-γ responses.

Unlike the cell-mediated immunity, pre- and particularly post-TST antibody responses in *M. bovis*-infected cattle are typically associated with the presence of gross lesions and high mycobacterial load in the affected tissues (Lightbody et al., 2000; Lyashchenko et al., 2004). Memory B cells are generated regardless of mycobacterial disease manifestation or etiology (e.g., with *M. bovis, M. tuberculosis, M. kansasii* or *M. avium* subsp. *paratuberculosis* inoculation in cattle or deer experiments), as anamnestic antibody responses can be elicited by re-exposure to mycobacterial antigens, such as PPD or live mycobacteria (Buddle et al., 2010; Waters et al., 2010). Close association between recall antibody responses and presence of visible lesions has also been reported for non-bovine hosts of *M. bovis* infection (Lyashchenko et al., 2008; Boadella et al., 2012).

The expression of B-cell memory following TST administration in bovine tuberculosis offers strategic benefits to the serodiagnostic applications. The sensitivity of antibody assays is evidently improved when using post-TST samples from infected domestic or wildlife host species (Harboe et al., 1990; Lyashchenko et al., 2004, 2007; Casal et al., 2014; Miller et al., 2015; Bezos et al., 2018). Importantly, the specificity of serologic assays is not compromised, as the intradermal PPD injection cannot elicit antibodies in the absence of memory B cells in non-infected animals. Since DTH responses develop in early *M. bovis* infection and the antibody responses can be detected in most TST non-reactors in advanced tuberculosis (e.g., anergic cattle) (Coad et al., 2008; Whelan et al., 2011; Waters et al., 2011, 2017), the combined use of serology and TST can maximize the sensitivity of parallel testing algorithm to identify more infected animals over the spectrum of disease (Jaroso et al., 2010; Boadella et al., 2012; Bezos et al., 2018).

8. Conclusions

Recent advances in B cell immunobiology have generated novel insights for improved understanding of humoral immune responses maintained by long-term B cell memory in tuberculosis. While the protective role of T cell immunity to infections caused by intracellular pathogens including the organisms of the *M. tuberculosis* complex is well recognized, an emerging body of evidence indicates that antigen-stimulated B cells including memory sub-populations play a role in anti-tuberculosis immunity. In addition to the rapid differentiation into high-affinity antibody-secreting plasmablasts, reactivated memory B cells produce Th1 cytokines, such as IL-12 and IFN-gamma, and contribute to antigen presentation to CD4+ and CD8+ T cells, thus promoting disease-specific cell-mediated immune responses.

When B cells stimulated by mycobacterial antigens are recruited to the infection foci in the lungs, they proliferate to form ectopic GCs, where memory B cells are probably re-generated, and participate in development of granulomas. Functional heterogeneity of memory B cell subsets may have both positive and negative impact on the host immunity in tuberculosis. In contrast to conventional B cell memory responses, expansion of functionally impaired atypical memory B cells in human tuberculosis may have adverse effects potentially contributing

to disease pathogenesis.

One important practical application that benefits from memory B cell responses in bovine tuberculosis is based on the phenomenon of TST-induced boost of antibody responses in infected cattle and other animal species. This well-known effect translates into a substantially increased sensitivity of serodiagnostic tests. Moreover, since antibody detection assays and TST can identify complementary sub-populations of infected animals across the spectrum of disease, a combined test algorithm including these two ante-mortem diagnostic methods might significantly enhance the efficiency of bovine tuberculosis eradication programs. Future research aimed at dissecting molecular and cellular mechanisms of immunological memory in mycobacterial diseases of humans and animals will open new directions to provide advanced approaches and tools for development of improved vaccines and immunodiagnostics.

Declaration of Competing Interest

The authors declare no conflict of interest.

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