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Humoral immune responses to infection: Common mechanisms and unique strategies to combat pathogen immune evasion tactics

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Abstract

Humoral immune responses are crucial for protection against invading pathogens and are the underlying mechanism of protection for most successful vaccines. Our understanding of how humoral immunity develops is largely based upon animal models utilizing experimental immunization systems. While these studies have made enormous progress for the field and have defined many of the fundamental principles of B cell differentiation and function, we are only now beginning to appreciate the complexities of humoral immune responses induced by infection. Co-evolution of the adaptive immune system and the pathogenic world has created a diverse array of B cell responses to infections, with both shared and unique strategies. In this review, we consider the common mechanisms that regulate the development of humoral immune responses during infection and highlight recent findings demonstrating the evolution of unique strategies used by either host or pathogen for survival.

Introduction

Successful vaccination strategies against a number of pathogens including viruses and pathogenic bacteria depend upon the humoral immune response [1]. In addition, neutralising antibodies induced during infection with highly mutating viruses such as HIV, HCV and influenza have shaped current strategies for vaccine design [2-4]. B cell activation through binding of the B cell receptor (BCR) to a cognate antigen in the context of various additional signals drives both proliferative and differentiation programs. These processes result in expanded populations of both early effector cells that can secrete copious amounts of antibody as well as long-lived populations of B cells that can protect against secondary infections (Figure 1). In recent years, we have made considerable advances in our knowledge of the molecular regulation of the generation, function and maintenance of humoral immune responses induced by immunization. We have a better understanding of the

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Conflict of interest

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critical interactions between $CD4^+$ T cells and B cells and the key transcriptional regulators that are important for germinal center (GC) responses, and the heterogeneous populations of memory cells that emerge from the GC (both long-lived plasma cells (LLPCs) and memory B cells (MBCs)) [5,6]. In an effort to generate better vaccines however, we now need to understand how specific B cell populations can be optimally protective against specific microbial infections, taking into account unique inflammatory signatures, antigen loads, tropisms or immune evasion mechanisms. We propose that the evolution of host-pathogen interactions over time has led to a greater heterogeneity in the development and function of humoral immune responses than perhaps revealed by protein immunization models. Recent studies in this review illuminate both the common mechanisms shared by infection-specific humoral responses as well as highlighting unique characteristics of pathogen-specific responses to counteract immune evasion strategies. Since innate-like $CD5^+$ B1 B-cells are not thought to form memory and their role in infection has recently been extensively reviewed [7], this review will only focus on B2 B cells.

Kinetics of the B2 B cell response to infection

B2 B cells can be divided into distinct sub-populations based on their activation requirements, phenotype and localization [8-10]. The first B2 B cells to respond to infection are the innate-like $CD21^+$ marginal zone (MZ) B-cells, located primarily in the splenic MZ. The MZ separates the follicle from the red pulp and provides a unique environment in which resident lymphocytes can sample antigens in the blood. Marginal zone B cells have been shown to be critical early responders to bacterial [11,12], viral [13,14] and parasitic infections [15,16]. Furthermore, MZ B cells can respond to antigen in a T cell-independent manner to rapidly express antibodies and also present captured antigens to $CD4^+$ T cells [17-20], (Figure 1). Upon activation MZ B cells have also been shown to traffic into the B cell follicle where they can deliver antigen to follicular dendritic cells, and facilitate follicular B cell activation [21]. Follicular B cells localized to follicles within the spleen and lymph nodes, require additional time and signals for differentiation [22]. Follicular B-cells respond in a largely T-dependent manner to form either plasmablasts or GC B cells (Figure 1). Plasmablasts are short-lived effector cells that readily secrete antibodies that are critical for controlling a primary infection [23•,24]. Cells that enter the GC undergo mutations within their BCRs that are tested on antigen presented on follicular dendritic cells, resulting in both diversified and higher affinity BCRs. Germinal center-derived memory cells can persist either as long-lived, quiescent, circulating MBCs that remain responsive to reinvading pathogens or sessile long-lived plasma cells (LLPCs) in the bone marrow and spleen [21,25-28]. LLPCs secrete antibodies without requiring further antigenic stimulation [5], but are not thought to respond to a subsequent infection due to their low levels of BCR [25].

The early primary B cell response:

MZ B cells are rapid, T-independent responders to infections of the blood including encapsulated bacteria, parasites such as *Plasmodium* and some viruses (Figure 1). MZ B cells are able to recognize capsular polysaccharides on bacterial pathogens, microbial CPG DNA and highly repetitive viral motifs, which stimulate TLR and BCR signalling. This

enables MZ B cells to rapidly differentiate into plasmablasts, important for early protection against some bacterial and viral pathogens. Indeed, splenectomised individuals and those with disrupted splenic MZ B cells are highly susceptible to encapsulated bacterial pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitis* [29,30]. These individuals have reduced levels of serum IgM and IgG. Moreover, serum antibodies detected in these individuals exhibit limited capacity to opsonise encapsulated bacterial antigens. In a more recent study, stroke-induced loss of splenic MZ B cells in mice associated with significant reduction in IgM levels and a spontaneous increase in bacterial infection in the lungs of these mice, suggesting a potential role for MZ B cells in limiting infections throughout the body following a stroke episode [12]. Together, these data support a role for MZ B cell-derived antibodies in early protection against invading pathogens. However, despite their positive roles in immunity to blood-borne pathogens antigens, MZ B cells have also been associated with detrimental effects during some infections. For instance it has been suggested that MZ B cells may obstruct protective T cell responses during early *Leishmania donovani* infection [31]. In this report, MZ B cell deficiency was associated with improved T cell responses and reduced parasite burden *in vivo*. Therefore, these data suggest that MZ B cells may also drive pathology during some infections. Understanding how MZ B cells support critical early antibody responses during a specific infection will be important for understanding optimal control of acute infection.

Next phase: activation of the follicular B cell response

Follicular B cell responses are initiated when naïve B-cells encounter antigen situated within primary lymphoid follicles. Activated B-cells migrate via chemokine-sensing towards the T cell zone where they are able to interact with $CD4^+$ T cells, previously activated by dendritic cells [22,32], (Figure 1). Activated B cells present cognate peptides on MHC Class II to $CD4^+$ T cells in the context of co-stimulatory signals and cytokines [33,34]. As $CD4^+$ T follicular helper (Tfh) cells and B cells exchange signals, an extended program of differentiation and expansion begins. $CD4^+$ Tfh cells express co-stimulatory molecules including CD40 ligand and ICOS as well as cytokines essential for initiation of the GC response and the formation of MBC populations [35-39]. Multiple factors including antigen availability, the strength of BCR-signaling and the types of cytokines secreted by the $CD4^+$ T cells influence B cell fate and the decision to become either extrafollicular plasmablasts or GC B cells [5,40-42]. T-dependent plasmablasts can class-switch and can undergo somatic hypermutation and affinity maturation [43••]. In addition, while extra-follicular plasma cells are generally believed to be short-lived, there is some evidence that this is not always the case [44-46]. By immunizing T cell deficient mice with haptenated LPS, a model T-independent antigen, a recent study demonstrated that long-lived GC-independent plasma cells are readily formed and maintained both in the spleen and bone marrow, suggesting that some plasmablast populations may be longer lived than previously appreciated [45]. B cells that receive the appropriate differentiation signals can alternatively be recruited into the GC and undergo somatic hypermutation, class-switch recombination and affinity maturation, giving rise to MBCs and LLPCs [47]. The resulting MBCs and LLPCs, express a diverse array of high affinity BCRs and recent evidence has even demonstrated that non-templated mutations contribute to this process [23•,48]. Interestingly, the post-GC decision to become a

LLPC or MBC also appears to be binary and is tightly regulated by a network of transcription factors [5,49,50]. The development and function of LLPCs was recently attributed to three key transcription factors, IRF4, Blimp-1 and XBP-1 [51•]. By using a tamoxifen-driven Cre-recombinase depletion system to IRF4 in established plasma cells, this study demonstrated an essential role for IRF4 in the survival of LLPCs, as measured by upregulation of CD138 and Blimp1 on $B220^{lo}$ cells in the spleen and bone marrow [51•]. Using a similar approach, it was further demonstrated that Blimp-1 and XBP-1 were required for LLPC maturation and production of antibodies, but were not essential for LLPC survival, both in the steady state and after protein immunization. Unlike LLPC fate, transcription factors critical for MBC fate are still being elucidated. Nonetheless, it has been suggested that MBC formation and maintenance is dependent on transcription factors such as PAX5, Bach2 and BCL-6, which are believed to insulate mature B cells against plasma cell differentiation [5,52-54]. For example, in a recent study employing a protein immunization system, genetic ablation of Bach2 in pre-existing MBCs associated with their increased differentiation into CD138-expressing plasma cells [54]. These findings were further corroborated by a more recent report in mice, which established a requirement for Bach2 in the generation of MBCs within the light-zone of the GC following protein immunization [53]. However, in driving the selection of light-zone GC B-cells into MBCs, Bach2 acted in a Blimp1-independent manner, suggesting a more complex interplay among transcription factors in controlling MBC and LLPC fate. Identification of the signals important for the formation, function and maintenance of MBCs and LLPCs during infection is an ongoing area of investigation that will have important implications for vaccine development.

Memory B cells respond to a secondary infection

While it is clear that the presence of continuous antibody production from LLPCs is critical for protection against many subsequent infections (reviewed by Amanna and Slifka) [55], we are now just beginning to understand the contributions that MBCs provide during a homologous secondary infection [56•]. Interestingly, heterogeneous populations of $CD27^{+}$-expressing MBCs that express either class-switched or unswitched BCRs have been described in humans for many years [57-59]. Yet due to a lack of phenotypic markers to identify small populations of antigen-experienced MBCs in mice, relatively few mechanistic comparative studies have been performed on these cells [23•,60,61]. The advent of both antigen-specific B cell enrichment strategies as well as single cell RNA-seq have been pivotal to renewed efforts to understand the nature and function of endogenous MBCs after infection or immunization [23•,56••,60]. For example, studies from our lab have demonstrated that fluorescently-labeled B cell tetramers containing various *Plasmodium*-specific proteins can be used to study the development of the B cell response to malaria in both mice and humans and the panoply of different B cell subsets that can form at different times throughout the infection [56,62•]. These studies have revealed both interesting biology of MBCs (reviewed in [63]) and the unique immune evasion strategies that the parasite uses (discussed below). For example, we found that in mice, three different *Plasmodium*-specific MBC subsets persist in the spleen after a primary infection, exhibiting different phenotypic and functional qualities. The largest population was comprised of cells expressing high-

levels of the IgD isotype that resembled naïve follicular B cells. The next prominent population resembled classically defined, somatically hypermutated IgG-expressing MBCs while the smallest population consisted of somatically hypermutated, IgM^+ MBC population. Remarkably, despite this difference in number, the IgM^+ MBCs responded fastest to a secondary infection and could generate both IgM- and IgG-antibody secreting plasmablasts. These findings suggest that heterogeneity in MBC function may have evolved to control different types of infections that can occur in different regions of the body or require the unique functional attributes of distinct isotypes. Interestingly, IgM-like antibodies exist even in the earliest immune systems including the lamprey [64], suggesting a critical role for these cells throughout evolution. These often over-looked IgM^+ MBCs may be important targets for improved vaccine-induced immunity to certain infections and we are currently investigating the cues that lead to their differentiation.

Unique challenges of and responses to specific infections

We believe that heterogeneous populations of MBCs have evolved to control various types of infections as they provide an arsenal to prevent immune evasion. In the following section, we provide examples of some of the unique challenges to humoral immunity that can be ascribed to various infections.

a) Bacterial infection:

Many of the common mechanisms of B cell activation and function described above have been targeted by pathogen immune evasion mechanisms (Figure 1). For instance, antibodies acting via opsonic and complement fixation killing mechanisms have been associated with protection to *Salmonella* infection, while it exists in the extracellular environment [43••, 65-67]. Yet studies have also demonstrated that the bacteria have developed immune evasion strategies to modify the quality of *Salmonella*-specific B cell responses through the production of inefficient antibodies [66,68•]. One strategy that *Salmonella* uses is evasion of the GC response as demonstrated in a recent report employing transgenic ovalbumin-expressing *Salmonella* strains to study B cell responses during *Salmonella* infection [68•]. In this report, primary *Salmonella* infection significantly impaired the expansion of endogenous *Salmonella*-specific B cells and the formation of GCs [68•]. These defects were mediated by factors within the *Salmonella* Pathogenicity Island 2 (SPI2) since normal B-cell expansion and GC formation was restored in mice infected with SPI2-deficient mutant bacteria. Therefore, targeting bacterial-associated virulence factors such as SPI2 in attenuated bacteria may be a useful vaccine strategy for boosting humoral immunity to *Salmonella*.

Perhaps as a counter-strategy, the host mounts a robust extrafollicular plasmablast response against *Salmonella* that can control infection [69,70]. A previous study in mice infected with attenuated enteric *Salmonella typhimurium* suggested a role for a robust extrafollicular B cell response in limiting bacterial burdens within the extracellular environment in the absence of a GC response [69]. This supports the idea that potent extrafollicular B cell responses may compensate for loss of optimal GC B cell responses during infection. Although it was previously thought that these extrafollicular responses were largely

polyclonal and non-specific, a more recent study in mice infected with *Salmonella typhimurium* demonstrated that they were indeed specific for the bacteria [43••]. Importantly, this study demonstrated that B-cells activated by *Salmonella* infection are capable of undergoing somatic hypermutation within the extra-follicular environment, boosting affinity maturation and production of isotype-switched antibodies, which was previously thought to primarily occur within the GC. These data highlight the complexity of the humoral response during infection and highlight our need to understand B cell responses to specific pathogens.

b) Viral infection:

Vaccine-mediated humoral immunity has led to the eradication of several devastating infections including Small pox, Measles and Polio. One potential evolutionary mechanism that some viruses may have adapted in subverting humoral immune-mediated killing is the induction of strong inflammatory responses, which suppress B cell differentiation and antibody production [71,72]. Recent evidence in human studies using RNA-seq-based technologies showed a negative correlation between highly upregulated inflammatory transcripts and responses to hepatitis B vaccination (HBV) [71]. However, upregulation of genes associated with B cell signalling positively correlated with heightened responses to HBV, suggesting a potential interplay between inflammation and B cell signalling in regulating B cell responses to infection and vaccination. Indeed, reports in mice demonstrate roles for inflammation-induced disruption of the lymphoid organ architecture, which can also suppress GC formation [72, 73]. For example, a recent study, using influenza and vaccinia viral models demonstrated that infection-induced inflammation disrupts the organisation of sub-capsular macrophages within sub-capsular spaces and inter-follicular regions, impairing GC B-cell and plasma cell formation during secondary viral challenge [72]. As a counter-measure to this evasion mechanism, host regulatory mechanisms that limit excessive inflammation to viral infection have evolved. For instance, a recent report demonstrated a T cell-intrinsic requirement for TGFβ-signalling in the formation of influenza-specific GC B cells and the production of class-switched antibodies [74•]. TGFβ-signalling in T-cells acted by limiting IL-2-induced signals and the formation of virus-specific inflammatory-like Th1 precursor cells, which enhanced Tfh and B cell responses. Similarly, Laidlaw and colleagues more recently demonstrated a role for follicular regulatory T cell (Tfr)-derived IL-10 in promoting GC B cell responses in mice with acute LCMV infection [75•]. Genetic depletion of IL-10 in Tfr cells was associated with reduced frequencies of GC B cells, in particular, those within the dark zone, suggesting that Tfr-derived IL-10 may support dark zone GC responses. Taken together, these data suggest that regulatory mechanisms within the host may not only serve to limit infection-induced immunopathology but also boost immunity against invading pathogens. Therefore, targeting infection-induced inflammatory pathways may be an important avenue for improving humoral immunity to infection.

c) Parasitic infection:

Antibodies have also been shown to play important roles in several parasitic infections including *Trypanosomes* [15, 76], *Helminths* (reviewed in [77]) and *Plasmodium* [78•-82]. *Trypanosomes* have long been studied as an example of humoral immune evasion as they

have developed a robust antigenic variation system that enables them to evade antibody-mediated killing [83]. However, recent data further suggests that *Trypanosomes* can also directly modulate B cell differentiation and function during infection [15]. Using a mouse model of *Trypanosoma brucei*, Radwanska and colleagues illustrated that *Trypanosome*-infection induces apoptosis in MZ B cells, reducing antibody production and parasite control [15]. However, it remained unclear from this report whether cell-death was restricted to MZ B cells alone or affected other B cell subsets, since the latter were not directly examined in this study.

B cells are also critical for control of *Plasmodium* infections in both mice and humans. B cell deficient mice are unable to clear non-lethal blood-stage *Plasmodium* infections [84], while passively transferred antibodies are protective in both mice and humans [78•,85]. *Plasmodium* parasites have also developed strategies to evade these humoral immune responses, including antigenic variation [86], and repression of optimal B cell differentiation and antibody production during infection [62•,73,87]. Our work and that of others has shown that the blood-stage of *Plasmodium* infection can impinge upon the humoral immune response to the proceeding liver-stage parasites. An examination of the circumsporozoite protein (CSP)-specific B cell response in genetically attenuated parasites (*Pyfabb/f*) that are unable to establish blood-stage infection compared to wild type parasites, which establish a blood-stage infection [88] showed a direct effect of the blood stage on liver stage GC development [62•]. Moreover, this diminished GC response in the presence of a blood-stage infection alters the quality of CSP-specific MBCs and their ability to respond to a secondary challenge. These data highlight how immunization with attenuated parasites may drive optimal immunity to malaria and suggest further studies on how ongoing blood stage infections may alter immune memory. In addition, *Plasmodium* parasites may also modify optimal MBC formation and function during infection. Recent studies in humans have identified a unique subset of MBCs, ‘atypical’ MBCs, which develop during chronic *Plasmodium* infection [89-91]. When compared to classical MBCs, atypical MBCs display increased expression of inhibitory receptors, exhibit reduced BCR-signalling and are unable to differentiate into antibody secreting cells [89,90]. This suggests that these MBCs may be dysfunctional. Although their sources remain unclear, immunoglobulin gene sequencing techniques have predicted a shared developmental history between these atypical and classical MBCs [89].

d) Fungal infection:

Humoral immune responses are necessary for resistance against various fungal infections largely via antibody-mediated activation of the complement system (reviewed in [92,93]). For instance, complement-deficiency in mice has been associated with increased susceptibility to *Candida* [94], *Aspergillus* [95] and *Cryptococcal* [96] infections. This was associated with reduced opsonization and complement-mediated lysis of pathogenic fungi and decreased recruitment of phagocytic cells during infection. In order to subvert complement-mediated killing and establish infection, pathogenic fungi have adapted multiple survival strategies [92,93,97-99]. For example, *Candida albicans* may evade the complement system by expressing decoy inhibitory ligands such as phosphoglycerate mutase (Gmp1) and the pH-regulated antigen 1 (Pra1) that bind Factor H and Factor H-like

protein 1, which are key regulatory proteins in the alternative pathway [97-99]. These ligands have also been implicated in inhibiting the classical and lectin pathways during *Candida* and *Aspergillus* infections by binding the regulatory C4BP and thus restricting C3b and CD4b deposition on the fungal surface [97-100]. Pathogenic fungi may also secrete proteolytic enzymes that degrade effector components of the complement pathway hence inhibiting opsonization and phagocytosis [101,102]. For instance, *Aspergillus fumigatus* (*A. fumigatus*) secretion of the proteolytic enzyme, alkaline protease *Alp1* has been associated with increased degradation of C3, C4, C5 and C1q complement proteins purified from human sera [101] and reduced expression of complement receptor 3 on phagocytic cells in cultured cerebral spinal fluids from *A. fumigatus*-infected individuals [102]. Together, these evasive strategies may contribute to enhanced fungal infection. Therefore, these data suggest that infection-induced complement inhibitory pathways may be targeted for improved immunity to pathogenic fungal infections.

Conclusions

The ongoing co-evolution of pathogens and host immune responses has introduced critical diversity associated with survival of both. Whereas some responses may be protective to specific infections, they may alternatively be detrimental to others. Therefore, a more comprehensive understanding of the function and generation of heterogeneous humoral immune responses to specific microbial infections is required to lead to more efficacious vaccine strategies. This more comprehensive approach to humoral immunity may reveal B cell strategies that are not induced by current protein immunization strategies. The introduction of new analytical methods including tools to analyze small populations of polyclonal, antigen-specific B cells, improved DNA-sequencing and single cell RNAseq platforms have ushered in a new era of understanding for B cell immunology. It will next be important to develop vaccine platforms that can induce heterogeneous responses or even direct a specific MBC population. It will soon be possible to develop the types of truly rationale-based vaccine design strategies that will be necessary for generating immunity against some of our oldest foes.

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Highlights

- Humoral immune responses are crucial for protection against infections
- Current paradigms of humoral responses are based on protein immunization models
- Pathogens have evolved an array of strategies to evade humoral immunity
- Diverse B cell responses have evolved to ensure host survival

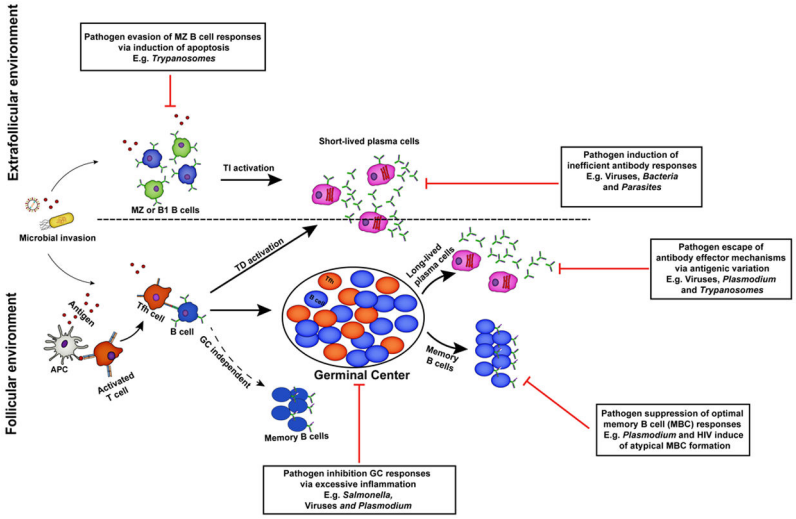

Figure 1. A schematic view of humoral immune responses to infection.

Extrafollicular and follicular antibody responses contribute to protection against invading microbial pathogens. B cells activated within the extrafollicular environment in the presence or absence of T cell help differentiate into short-lived antibody secreting cells that mediate early protection against infection. However, the formation of germinal center dependent or independent memory B cells and long-lived plasma cells in the B cell follicles facilitates complete resolution of primary infections and long-term protection against reinfection. For their survival, pathogens have evolved strategies that enable them to evade specific antibody-dependent killing mechanisms.