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Atypical B cells in Malaria: Escape or Chase?

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Editorial

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Abbreviations: PF: Plasmodium falciparum; Ig: Immunoglobulin; HCV: Hepatitis C Virus; BCR: B Cell Receptor; aMBCs: Atypical Memory B Cells

Editorial

Malaria caused by Plasmodium falciparum (Pf), a protozoan parasite, is a deadly infectious disease in primarily young children, prevailing from sub-Saharan Africa [1]. A seminal study by Cohen, et al. [2] showed that the transfer of serum immunoglobulin (Ig) active against the malaria pathogen is effective in curing young children from febrile Malaria, indicating that humoral immunity plays a key role in the treatment of malaria [2]. Even though protective Ig is known to be important in preventive and therapeutic treatment for malaria, vaccine development has not yet been successful due to the complex characteristics and variations of the malaria pathogen in the host. By its very nature, effective humoral immunity is slowly acquired over time through repeated infections [3].

In malaria endemic areas, repeated infections drive an unusual B cell population, so called atypical memory B cells (aMBCs), among peripheral blood B cells that are one of the major arms in humoral immunity by differentiating into plasma cells producing protective secretory Ig [4]. For the last decade, studies of aMBCs, what they are and how they are induced, have emerged in the fields of chronic infectious diseases such as HIV, malaria, Hepatitis C virus (HCV), Tuberculosis (TB), as well as autoimmune diseases since CD21-CD27-memory B cells were first characterized in normal human tonsil named as tissue type memory B cells (tMBCs) in 2005 by Max Cooper's group [5]. tMBCs are distinct from CD21+CD27+ conventional resting memory B cells (cMBCs), in terms of a different pattern of surface marker expression such as increased multiple inhibitory receptors like FcRL4, CD32b, adhesion molecule CD11c in addition to the lack of CD21 and CD27. These tMBCs are also distinct from cMBCs in functionality, such as being refractory to the B cell receptor (BCR) signaling upon antigen engagement. Since then, for the first time in human infectious diseases, the expansion of CD21-CD27- B cells in circulation have been reported in patients with chronic HIV infection, which showed the refractoriness to BCR signaling, a shared characteristic with tMBCs, but severer dysfunction in B cell activation, in vitro B cell proliferation, induced Ig secretion, and as well evidence of less somatic hyper mutation as compared to cMBCs, named exhausted B cells [6]. A later study has shown that this exhaustion can be reversed by a knock down of inhibitory receptors, the most efficient being FcRL4 and Siglec-6 knock-down, suggesting that the increase of multiple inhibitory co-receptors for BCR can be a major cause of the exhausted phenotypes of these B cells [7]. After that, similar CD21-CD27-MBCs were first reported in Malian individuals in malaria high-endemic area by Pierce group and named as atypical memory B cells (aMBCs) that are also significantly increased in circulation with some shared but distinct phenotypes from HIV, for example, expression of FcRL5 instead of FcRL4 in Malaria and HIV, respectively [8]. With accumulating case reports about the expansion of aMBCs sharing common phenotype like expression of T-bet, CD11c, and FcRLs in chronic infectious diseases such as malaria, progress has been made in addressing, in both human and mouse, the cause of expansion of aMBCs in periphery and what their roles are in these diseases because of the importance of humoral immunity in these chronic diseases [9].

What then, are the current findings about the mechanism of aMBCs induction and the functions of aMBCs in the context of malaria?

aMBCs in malaria show the functionalities of reduced BCR signaling, proliferation, and in vitro Ig secretion similar to those in HIV patients. However, aMBCs in malaria are different from those in HIV, especially in the history of somatic hypermutation and Ig isotype class switching profile that are not dramatically different between aMBCs and cMBCs in malaria [8]. A recent study from Crompton and colleagues suggests that aMBCs might be induced by Th1-polarized PD-1+CXCR3+ T follicular helper cells (Tfh-1) secreting IFN-γ which appear more in peripheral blood in malaria pathogen infection than normal healthy individuals. These Tfh-1 cells were found to be poor inducers of Ig secretion when they were co-cultured with B cells in vitro, suggesting the possibility of poor helper function toward the GCB cells in vivo in malaria [10]. In their recent study, aMBC population in Malian young children, especially T-bet^{hi}-expressing aMBCs rather than T-bet^{lo} cells, were more closely correlated with episodes of febrile malaria and the level of serum IFN-γ, suggesting that inflammatory cytokines, primarily IFN-γ, and repeated pathogen antigen engagement might be the cause of induction of aMBCs, especially T-bet^{hi} aMBCs [11]. Our current study also supports the idea that aMBC can be induced in vivo from repeated BCR engagement with Toll-like receptor stimulation under inflammatory condition containing IFNγ. To study in detail the mechanism by which aMBCs can be induced in vivo, we developed an aMBC in vitro induction system using tonsillar B cells to determine the stimulant that is required for its induction. Using model Ag-bound membrane, refractory to Ag internalization when B cells are in contact with the Ag, T-bet^{hi} B cells with characteristic aMBC surface markers can be induced the most at the model membrane Ag refractory to the Ag internalization giving persistent Ag engagement in the presence of TLR9 ligand, CpG and IFN-γ, as compared to the soluble Ag with CpG plus IFNγ or any double stimulant combination of these three, especially in Naïve B cells (unpublished data). In summary, aMBCs in Malaria are possibly induced in vivo by repeated BCR engagement with Toll signal under inflammatory environment due to either repetitive pathogen infection with high frequency in young children or repeatedly infected adults over time in malaria high-endemic area. It is still uncertain whether the expansion of aMBCs is the mechanism of protection in the immune escape of the malaria pathogen or the host response against pathogen. Furthermore, 2-year longitudinal studies showed that young children experiencing febrile malaria episode greater than 5 times per year have significantly higher percentage of T-bet^{hi} aMBCs in memory B cell pool showing more severe inhibition of BCR signaling upon antigen engagement, supporting the possibility of B cell exhaustion by repetitive infection. Current emerging findings for the role of aMBCs in malaria in addition to the other chronic diseases favors the evidence of aMBCs as an immune escape mechanism for pathogens to stably maintain the pathogen in hosts by expanding functionally impaired MBCs incapable of adequate recall response and Pf clearance.

However, the role of aMBCs in malaria is still largely unknown and the protective role of aMBCs from clinical malaria is plausible. A recent study from Wardemann and colleagues shed a light on aMBCs in malaria as a host defense mechanism [12]. Using single cell sorting for Pf-specific B cells and gene sequencing techniques, cMBCs and aMBCs were isolated at single cell level and compared for the Ig sequences and suggested that natural Pf infection induces the development of both cMBCs and aMBCs that produce broadly neutralizing antibodies against blood stage Pf parasites. Furthermore, they showed that cMBCs and aMBCs contributed to anti-Pf serum IgG production, but only aMBCs showed signs of active antibody secretion. Based on this report, pathogen Ag-recognizing aMBCs as well as cMBCs play an important role in humoral immunity against malaria implicating aMBCs as a host defense mechanism against malaria. Even though aMBC in malaria showed reduced BCR signaling in response to the soluble Ag, it's still not known how they respond to the membrane-bound Ag which is dominant form of Ag presentation in vivo through cell-to-cell interaction by antigen presenting cells. Given that the way of BCR signaling is different between soluble and membrane antigen regarding to the usage of CD19 and aMBCs have higher CD19 expression, it is possible that aMBC might function well in BCR signaling in response to the membrane Ag. Surprisingly, in our experiment using artificial Ag-tethered membrane mimicking APC, planar lipid bilayer-Ag aMBCs are intact in BCR signaling in response to the membrane-Ag on the contrary to the response to the soluble Ag. Furthermore, aMBCs showed superior Ag internalization as compared to the cMBCs in response to the plasma membrane sheet-bound Ag which is membrane system letting B cells be able to capture Ag from membrane and internalize it (unpublished data). This finding with the fact that CD86 expression is higher in aMBCs than cMBCs and that CD86+CD21lo B cells in healthy individuals showed the better APC function [13], suggests that aMBCs derived in malaria might be better antigen presenting cells to the CD4+ Th cells. Interestingly

enough, during acute malaria, the levels of serum IFN-γ positively correlated with the amount of serum IgG3 which is the highest compliment activator among subclasses of IgG and have high affinity to the Fc receptors on phagocytes, and both T-bet^{hi} and T-bet^{int} aMBCs contained significantly higher IgG3 class-switched cells in population compared to the T-bet^{neg} B cells [11], suggesting the correlation between T-bet aMBCs and IgG3 class switching regardless of its expression level. All together, these evidences implicate the possible function of aMBCs for the host protection.

The story about "What is the role of aMBCs in malaria" is still controversial and left largely unknown although it is very important for the therapeutic and preventive malaria vaccine development because neutralizing antibody production is the major tool for the protection from malaria. To understand aMBC more in malaria would be great advantage for better design to improve efficacy of vaccine and protect individuals in high risk such as young children in malaria endemic area.

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