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Review

Atypical B cells in chronic infectious diseases and systemic autoimmunity: puzzles with many missing pieces

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The world's struggle to contain the SARS-CoV-2 epidemic, primarily through vaccination, has highlighted the importance of better understanding the biology of B cells that participate in defense against infectious diseases, both acute and chronic. Here, we focus on a population of human B cells, termed atypical B cells (ABCs), that comprise a distinct B-cell lineage that differentiates from naive B cells in an interferon-γ-driven process, and are infrequent in healthy individuals but significantly expanded in chronic infectious diseases, including malaria, as well as in systemic autoimmune diseases such as systemic lupus erythematosus (SLE). Recent comparisons of ABCs by single-cell RNAseq provided evidence that ABCs in diverse chronic infectious diseases and in systemic autoimmune diseases are highly related and share common drivers of differentiation and expansion. However, ABCs in different diseases are not identical and also show discrete disease-specific features. Here, we compare and contrast key features of two ABC populations, namely those that are expanded in individuals living in malaria-endemic areas of the world versus those in SLE patients. This comparison is of interest as it appears that unique features of these two diseases result in participation of autoreactive ABCs in parasite-specific responses in malaria but in pathogenic autoimmune responses in SLE. A better understanding of the commonality and differences in the ABC responses in these two diseases may provide critical insights into the development of vaccines that drive pathogen-specific antibody responses and avoid autoimmunity.

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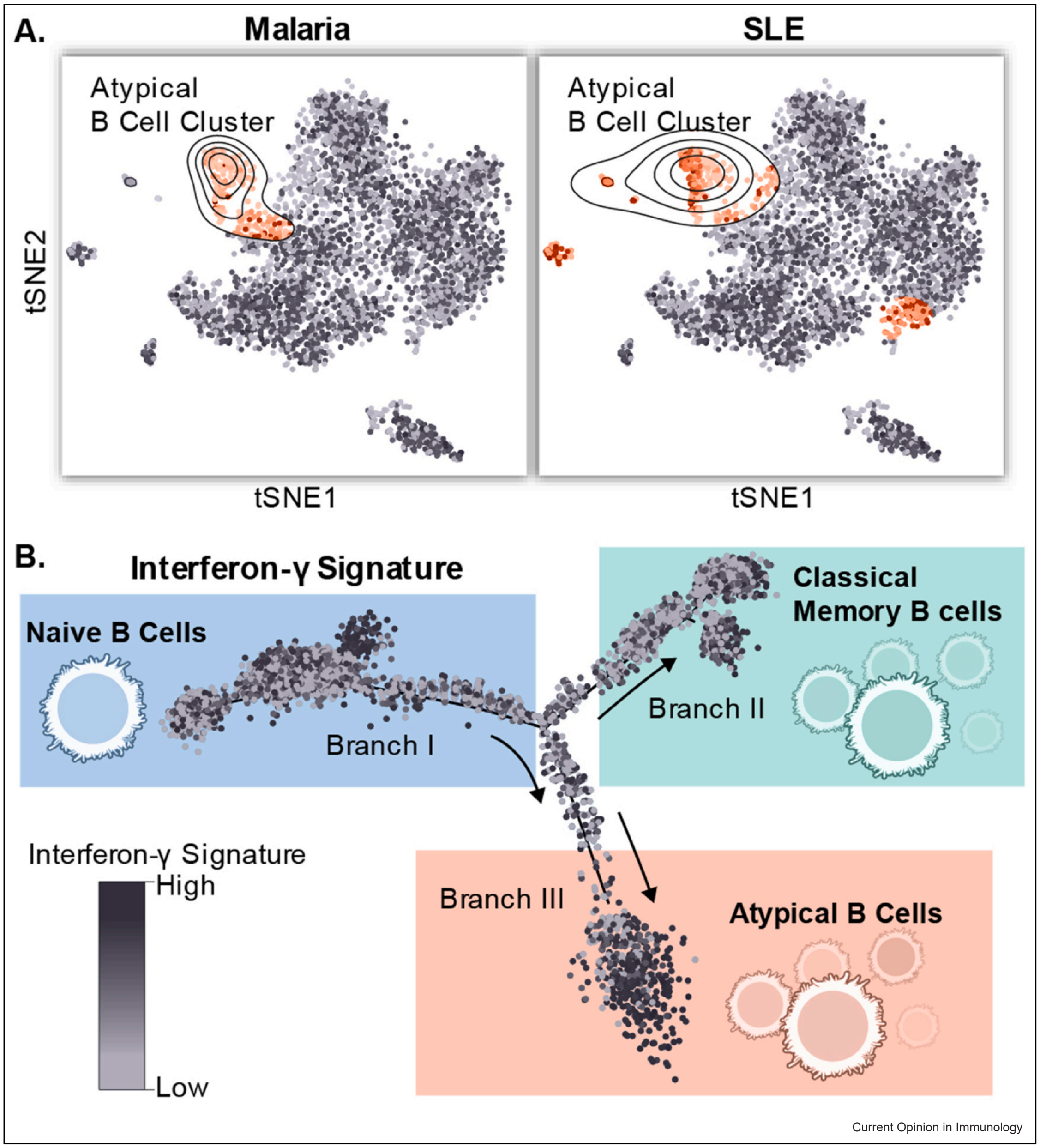
Introduction

Both malaria in endemic Africa and systemic lupus erythematosus (SLE) are chronic inflammatory conditions associated with high levels of autoantibodies. However, whether such autoantibodies are pathogenic or not is influenced by genetic determinants enriched in the African genome, thought to be selected by *P. falciparum* (Pf) malaria over thousands of years of coevolution with the human immune system [1,2]. In Africans living in malaria-endemic areas, chronic episodes of febrile malaria induce high titers of autoantibodies in the absence of evidence of clinical systemic autoimmune diseases, including SLE [3–5]. In fact, malaria is associated with protection from SLE in humans and SLE-like disease in genetically susceptible mice [6•]. However, individuals of African ancestry who live in malaria-free parts of the world, such as African Americans, are at significantly higher risk for SLE [7–9]. Both malaria and SLE are characterized by large expansions of B cells that express the transcription factor T-bet that may act as a master regulator of gene expression, and have a $CD21^{-}CD27^{-}CD11c^{+}$ surface phenotype.

Figure 1



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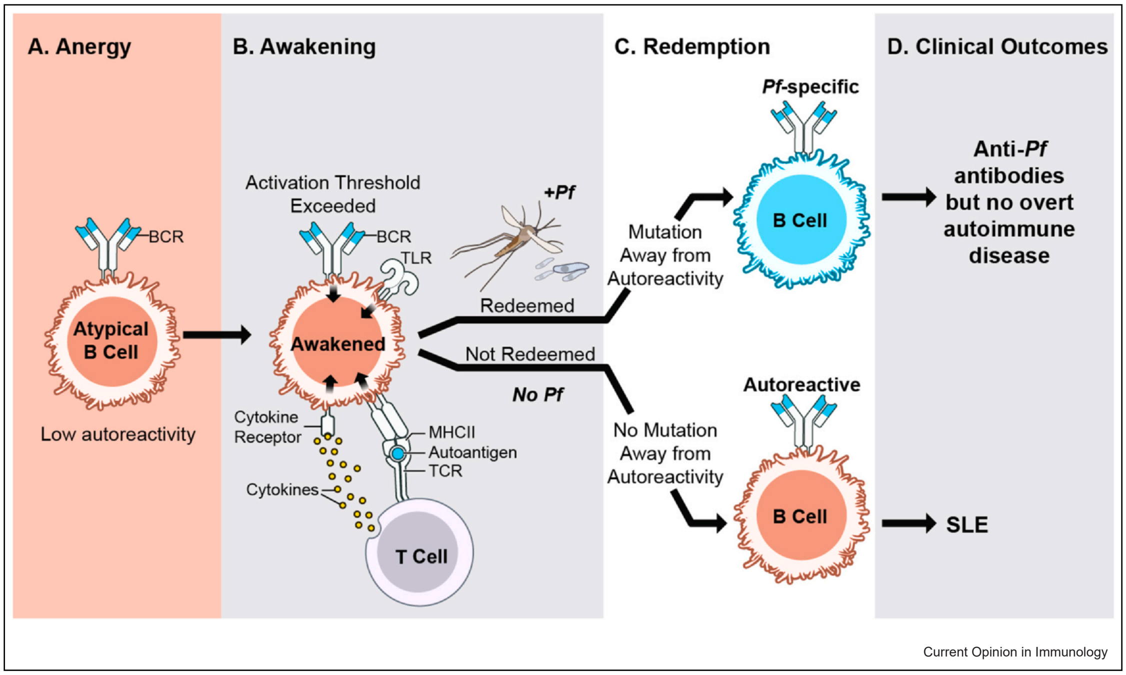
ABCs are transcriptionally similar in malaria and SLE and differentiate along and IFN-γ-driven pathway. **(a)** Gene signatures of ABCs from malaria exposure (left) or SLE (right) map to the same cluster of B cells, indicating a high degree of transcriptional overlap. **(b)** Pseudotime analysis of B cells from a malaria-exposed patient shows that naive B cells differentiate into either classical memory B cells or ABCs along a branched trajectory. Differentiation to ABCs occurs along an interferon-γ-driven path, with ABCs representing the highest expression of the IFN-γ signature (as denoted by increasing dark-gray color).
Figure adapted from [10].

We termed these atypical B cells (ABCs) in malaria [10•], and the corresponding cells in SLE are referred to as activated naive and double-negative B cells [11]. For simplicity in this review, we will refer to both as ABCs.

By single-cell (sc) RNAseq, we discovered that the transcriptomic profiles of malaria- and SLE-derived ABCs are highly similar, although not identical, and mapped to the same transcriptionally unique clusters of B cells present in the total B-cell scRNAseq data (Figure 1a) [10•]. Pseudotime trajectory analysis of the differentiation path of B cells from naive to memory B cells (MBCs) and ABCs using scRNAseq data provided evidence that ABCs in malaria arise as a consequence of

Figure 2



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A diagram illustrating a potential relationship between the high-activation thresholds of ABCs and their capacities for clonal redemption in individuals of African ancestry. The relative autoreactivity of B cells is indicated by color: red = autoreactive, blue = less autoreactive. In the periphery, ABCs exist as anergic B cells with BCRs with low affinity for autoantigen (autoreactive, indicated in red) **(a)**. A variety of triggers present in inflammation associated with malaria or SLE, which may include BCR engagement with antigen, TLR stimulation, cytokines, and/or T-cell help, may exceed the activation thresholds of ABCs, leading to their awakening **(b)**. In malaria, ABCs with BCRs with low affinity for foreign antigens expressed by Pf and infected RBCs undergo SHM away from autoreactivity to produce BCRs with higher affinity to foreign antigens than to autoantigens (less autoreactive, indicated in blue), and are redeemed. However, in the absence of Pf, clonal redemption does not occur; thus, autoreactivity is not reduced (indicated in red) **(c)**. In malaria, the outcome of clonal redemption is the production of Pf-specific antibodies and the risk of overt clinical autoimmunity is low. In the absence of malaria, the risk of clinical autoimmunity from SLE remains high.

differentiation of naive B cells along an IFN-γ-driven pathway that appears to represent a distinct B-cell lineage (Figure 1b).

The similarity of ABCs in malaria and SLE begs the question: how is it that autoantibodies that are prevalent in both diseases are only pathogenic in SLE and not in malaria? The human immature and mature naive B-cell repertoires contain significant autoreactivity (55–75% of new immature human B cells and 20% of mature naive human B cells are autoreactive) [12]. These are in general low-affinity, autoreactive B cells that escaped elimination by central tolerance mechanisms and entered the periphery where they were induced into a state of hyporesponsiveness to antigen challenge, termed anergy (Figure 2) [13,14]. ABCs have a key feature of anergic B cells, namely that they are hyporesponsive to B-cell receptor (BCR) cross-linking by soluble anti-Ig [15]. However, anergic B cells have been recently demonstrated to participate in antigen-specific immune responses through a process termed clonal redemption in which low-affinity, self-reactive anergic B cells are activated by infection or immunization to undergo somatic hypermutation (SHM) away from autoreactivity and toward specificities for the pathogen or vaccine antigens [16]. In malaria, we propose that various parasite and host factors present during febrile malaria may awaken autoreactive, anergic ABCs by exceeding their activation thresholds and initiating clonal redemption (reviewed in Ref. [17•]), which contributes to the generation of Pf-specific antibodies (Figure 2). Parasite factors that contribute to B-cell activation via Toll-like receptors (TLRs) include hemozoin and parasite DNA [18,19]. Malaria-induced cytokines such as IFN-γ and IL-21 also play a role in B-cell activation and ABC differentiation [10•,20], and may contribute to clonal redemption of ABCs. In contrast, we speculate that the mechanisms underlying clonal redemption may be dysregulated in SLE-derived autoreactive ABCs (reviewed in Ref. [17•]), thus expanding pathogenic autoreactive B cells that contribute to SLE disease (Figure 2). In this review, we compare a variety of features of malaria-derived and SLE-derived ABCs with a view toward contributing to the development of effective vaccines that induce protective pathogen-specific antibodies and avoid autoreactivity.

Redemption in the atypical B cell repertoire

ABCs are a mixture of both unswitched B cells, expressing IgD and IgM, and class-switched B cells, predominately expressing IgG or IgA. Unswitched ABCs in malaria are associated with an unusual expansion of IgD$^+$IgM^{lo} cells in which IgM is downregulated transcriptionally [10•]. IgD$^+$IgM^{lo} cells appear antigen-experienced, having accumulated SHM to a greater degree than naive B cells, but have fewer SHM as compared with class-switched MBCs [11,21]. Of interest, IgD$^+$IgM^{lo} ABCs show a 100-fold increase in the antigen-affinity threshold for activation as compared with IgD$^+$IgM$^+$ ABCs [10•], suggesting that redemption of these ABCs would require high-affinity antigen challenge. We previously found that cells expressing the inherently autoreactive VH4–34 BCR were highly expanded in classical MBCs and ABCs in malaria-infected Malian children [22]. These cells were detected using the anti-idiotypic antibody 9G4, which recognized the framework region 1 of the VH4–34 antibody [23]. In more recent studies, we observed that the VH4–34 genomic DNA sequences of the IgD$^+$IgM^{lo} ABCs had undergone mutations that are predicted to reduce autoreactivity of the expressed BCRs, suggesting that these ABCs were the product of redemption (unpublished results) (Figure 2).

An expansion of IgD$^+$IgM^{lo} cells was also observed in the ABC compartment in SLE [21], but have not been well-characterized in the context of SLE pathology. The Ig repertoires of ABCs in SLE patients were shown to be highly enriched in VH4–34$^+$-expressing cells, especially during high disease activity [11,24]. Unswitched ABCs were shown to be clonally related to autoreactive plasma cells (PCs) in SLE [25], and when cultured *in vitro*, switched ABCs from SLE patients produced predominantly autoantibodies [21]. Together, these findings suggest the possibility that SLE-derived ABCs are selected by engagement with self-antigens rather than redeemed by foreign antigens [11] (Figure 2).

Chronic antigen exposure and inflammation are drivers of atypical B cell differentiation

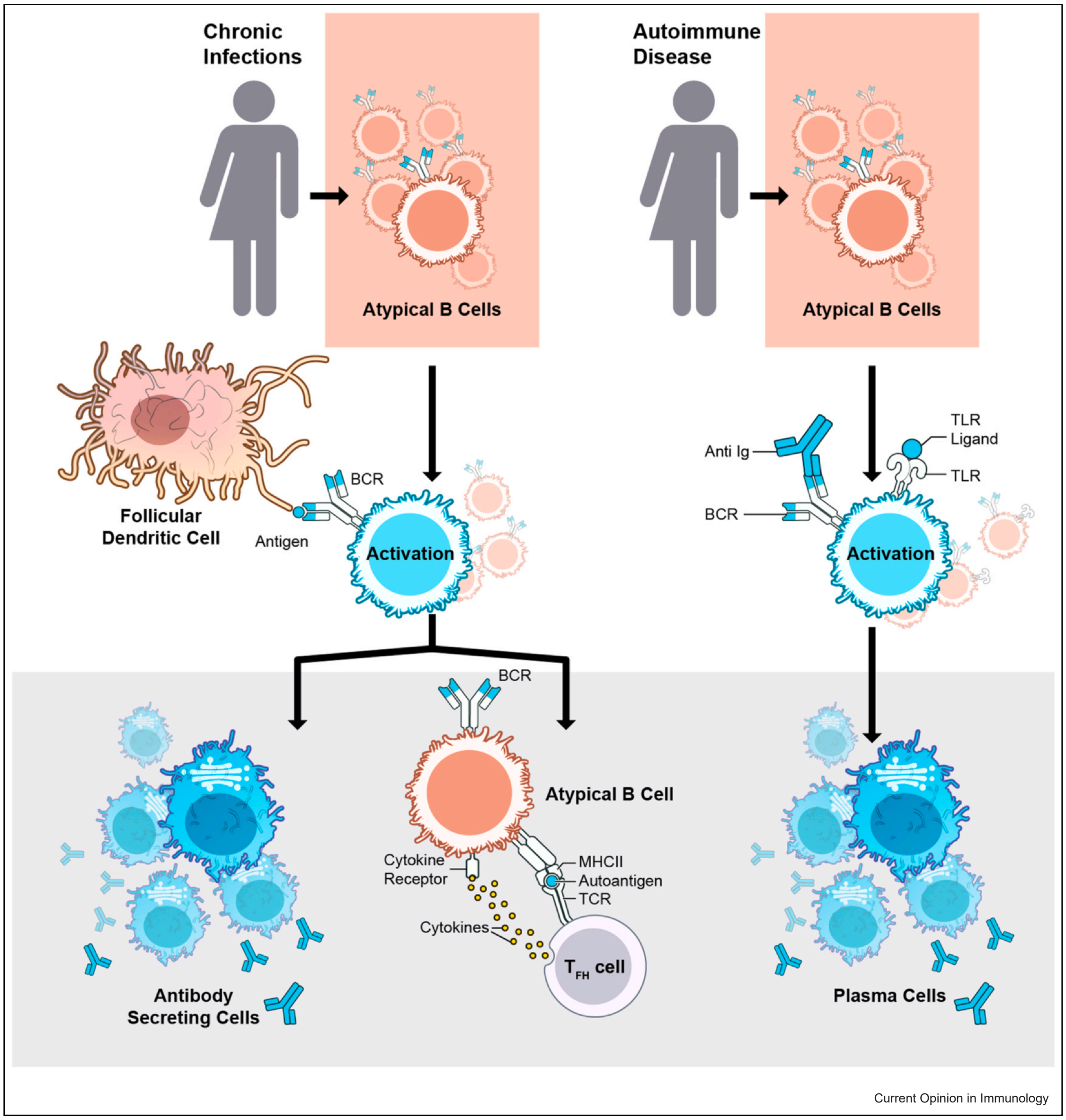
Chronic immune activation due to persistent antigen exposure and inflammation appears to be the major driver of ABC differentiation in malaria [20]. During malaria, IFN-γ secreted by Th1-polarized Tfh cells has been implicated in driving B-cell expression of T-bet and expansion of ABCs *in vivo* [26]. In addition, experiments *in vitro* provided evidence that for naive human B cells, prolonged antigen exposure in the presence of the TLR9 agonist, CpG, and IFN-γ induced maximal expression of T-bet and other phenotypic markers of malaria-associated ABCs [20]. A pseudotime trajectory analyses of scRNAseq data showed that in malaria-naive B cells, they differentiate to a decision fork at which point they either differentiate into MBCs or ABCs [27•]. Indeed, the highest expression of the IFN-γ signature was found in terminally differentiated ABCs (Figure 1b). Taken together, these data suggest that exposure to IFN-γ, chronic antigenic stimulation, and likely a direct effect of IFN-γ on T-bet expression may be responsible for skewing of naive B-cell differentiation toward ABCs in malaria. Similarly, B cells with the phenotype of ABCs in SLE were generated *in vitro* by exposure of naive human B cells to IFN-γ but not IL-4, in combination with R848, IL-2, BAFF, anti-Ig, and IL-21 [11].

Unique mechanisms of activation of atypical B cells

Earlier, we reported that malaria-associated ABCs exhibited markedly reduced BCR signaling and effector function when stimulated with soluble antigens *in vitro* [15]. Moreover, the ABCs did not secrete cytokines, proliferate, or differentiate into antibody-secreting cells in response to soluble antigens under conditions that induced robust responses in MBCs. However, we recently reported that ABCs in malaria provided with membrane-associated antigens, mimicking antigen presentation *in vivo* on the surfaces of follicular dendritic cells (DCs), robustly initiate BCR signaling, forming immune synapses and segregating inhibitory receptors to the periphery of immune synapse [28••]. In response to membrane antigens, ABCs also initiated differentiation toward PCs by upregulating IRF4 expression. The potential for PC differentiation is also supported by the observation that mRNA for secreted Ig transcripts was observed in ABCs specific for malarial antigens in malaria-exposed individuals [29]. ABCs in malaria were also able to extract and internalize antigens bound to the BCR and traffic these to acidic compartments. The ABCs also showed a unique polarization in which the internalized antigens were concentrated on the opposite pole to the immune synapse, that may facilitate presentation of antigens to T cells, while the ABC interacted with antigen-presenting cells. The potential function of ABCs in malaria to present antigens and modulate T-cell fates is also supported by the observation that ABCs upregulate B-cell–T-cell interaction markers, including HLA-DR, ICOS-L, and CD86 [20,26,30]. Taken together, these findings suggest the possibility that anergic ABCs can be activated and redeemed by membrane-associated antigens (Figure 2).

Similarly, SLE-derived ABCs appear to undergo little phosphorylation upon BCR cross-linking [31]. However, it is not yet known if ABCs in SLE are responsive to membrane-associated antigens. Functional analyses *in vitro* of purified SLE-derived switched ABCs cultured

Figure 3



Activation and fate of ABCs in chronic infections and autoimmunity. Malaria-associated ABCs are activated exclusively by antigens associated with membranes, such as antigens presented by DCs or follicular DCs. Upon activation, ABCs have the potential for presenting antigens to helper T cells and/or differentiation to antibody-secreting cells. ABCs in SLE are hyperresponsive to TLR7 stimulation, and rapidly differentiate to PCs upon activation with TLR7 ligands and BCR engagement by soluble anti-Ig.

with R848, IL-2, IL-21, BAFF, soluble anti-Ig, and IFN-γ revealed that ABCs could differentiate into PCs by a TLR7-dependent mechanism [11]. However, in the absence of TLR7, stimulation of switched SLE-derived ABCs led to apoptosis and lower frequencies of PCs [11]. This observation suggests that in SLE, ABCs respond to innate signals independently of BCR-induced signals to drive differentiation. Coculture of ABCs in SLE with anti-CD3-activated T cells led to PC development, again suggesting that differentiation of ABCs to PCs is BCR-independent [21], and may be linked to a subset of peripheral helper T cells in SLE [32]. These data suggest that in SLE, the inflammatory milieu of cytokines and TLR ligands may allow for activation of anergic ABCs (Figure 3).

Tissue localization of atypical B cells

In malaria, ABCs are present in peripheral blood and display a cell-surface phenotype indicative of egress from lymph nodes and homing to inflamed tissue, including upregulated expression of CXCR3 and CD11c, and downregulated expression of CD62L and CD73 [15,33•]. However, the exact tissue localization of ABCs in malaria is not known.

In SLE, ABCs have been shown to be present in peripheral blood and to expand with active SLE, especially disease flare. In addition, CD11c$^+$ and CD20$^+$ T-bet$^+$ B cells were found in high numbers in kidneys affected by SLE-associated nephritis, and their numbers were directly related to ABC frequencies in blood and to disease activity [21,31]. Transcriptomic analysis of nephritic kidneys demonstrated that these B cells may be generated in the kidney and comprise a spectrum of differentiation states from naive B cells to activated B cells, ABCs, and PCs, suggesting that the inflammatory milieu of the kidney promotes B-cell differentiation *in situ* [34]. Pseudotime trajectory analysis revealed that differentiation of B cells in inflamed kidney in SLE was correlated with increases in an ABC transcriptomic profile [34]. It is unclear whether SLE-derived ABCs are present in other tissues targeted in SLE, and if so, how they might function in such tissues.

Opinion

Here we compared a number of characteristic features of ABCs in malaria and SLE and suggested that ABCs in malaria may contribute to malaria-specific responses in contrast to ABCs in SLE that may contribute to autoimmune pathology. However, at present, these suggestions are highly speculative as many key features of ABCs in malaria and SLE remain only poorly understood. Thus, at present, we are left with fundamental unanswered questions, namely why are B cells of the ABC lineage a common feature of chronic infections and autoimmune disorders, and what roles do they play in such diseases? Clearly, efforts to better understand the biology of ABCs will contribute to the design of effective vaccines and insights for targets for therapies for systemic autoimmune diseases.

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Conflict of interest statement

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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- •• of outstanding interest.

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