Review article

Emerging insights into atypical B cells in pediatric chronic infectious diseases and immune system disorders: T(o)-bet on control of B-cell immune activation

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Repetitive or persistent cellular stimulation *in vivo* has been associated with the development of a heterogeneous B-cell population that exhibits a distinctive phenotype and, in addition to classical B-cell markers, often expresses the transcription factor T-bet and myeloid marker CD11c. Research suggests that this atypical population consists of B cells with distinct B-cell receptor specificities capable of binding the antigens responsible for their development. The expansion of this population occurs in the presence of chronic inflammatory conditions and autoimmune diseases where different nomenclatures have been used to describe them. However, as a result of the diverse contexts in which they have been investigated, these cells have remained largely enigmatic, with much ambiguity remaining regarding their phenotype and function in humoral immune response as well as their role in autoimmunity. Atypical B cells have garnered considerable interest because of their ability to produce specific antibodies and/or autoantibodies and because of their association with key disease manifestations. Although they have been widely described in the context of adults, little information is present for children. Therefore, the aim of this narrative review is to describe the characteristics of this population, suggest their function in pediatric immune-related diseases and chronic infections, and explore their potential therapeutic avenues. (J Allergy Clin Immunol 2024;153:12-27.)

Key words: *Atypical B cells, B cells, CD11c^{+}, T-bet^{+}, double-negative B cells, CD21^{low}, pediatric diseases*

Abbreviations used

ABC:	Age-associated B cell
ANA:	Antinuclear antibody
ASC:	Antibody-secreting cell
atBC:	Atypical B cell
BAFF:	B-cell activating factor
BCR:	B-cell receptor
CVID:	Common variable immunodeficiency
DN:	Double negative
EF:	Extrafollicular
GC:	Germinal center
HIV:	Human immunodeficiency virus
JIA:	Juvenile idiopathic arthritis
MBC:	Memory B cell
PB:	Plasma blast
PC:	Plasma cell
SARS-CoV-2:	Severe acute respiratory syndrome coronavirus 2
SHM:	Somatic hypermutation
SLE:	Systemic lupus erythematosus
Tfh:	T follicular helper
TLR:	Toll-like receptor
XCI:	X chromosome inactivation
XIST:	X-inactive specific transcript

B cells constitute a critical arm of the immune system and are responsible for short- and long-term generation of humoral antibody responses. B cells also perform antibody-independent functions including antigen presentation, modulation of T-cell differentiation and survival, and production of both regulatory and proinflammatory cytokines.[1-3] The B-cell lineage undergoes a maturation process resulting in considerable plasticity of the antibody response. The differentiation process results in the generation of 2 types of affinity-matured B cells: memory B cells (MBCs) and antibody-secreting plasma cells (PCs).[4-6] Although the steps that underlie the activation and differentiation of antigen-engaged B cells have been extensively characterized, studies have revealed additional complexities to these responses, especially in the context of chronic immune stimulation. Indeed, over the past decade, it has become increasingly evident that many chronic human infectious diseases as well as immune system disorders are associated with alterations in the composition of MBCs' compartment. A common feature of these diseases appears to be a large expansion of a unique B-cell subset, often denoted as age-associated B cells (ABCs), atypical B cells, or proinflammatory B cells.[7-10] Since their initial discovery, downregulation of both CD21 and CD27 and expression of the T_H1 master transcription factor T-bet and the integrin CD11c have become a well-known feature of this population, so these cells are also

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Received for publication August 4, 2023; revised October 13, 2023; accepted for publication October 13, 2023.

Available online October 25, 2023.

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0091-6749

https://doi.org/10.1016/j.jaci.2023.10.009

now known as T-bet$^+$CD11c$^+$ B cells.[7,11,12] This novel population was classified as a memory cell because of the negligible expression of *BCL6* and *BLIMP1,* which are hallmark transcription factors of germinal center (GC) B cells and PC, respectively.[13] Moreover, these cells were identified as MBCs on the basis of the presence of additional markers, such as CD95 and CD62L, similar to classical MBCs.[14]

Atypical B cells (atBCs) proliferate after exposure to innate and adaptive signals, in particular activation of the endosomal Toll-like receptor (TLR)-7 and TLR-9 and cytokines like IFN-γ and IL-21.[12] This cell population displays a wide variety of functional abilities.[8] They are potent antigen-presenting cells, can develop into plasma blasts (PBs), and generate antibodies in addition to having a greater propensity than other B-cell subsets to produce proinflammatory cytokines and chemokines.[7,15,16] It has been proven that this peculiar population plays a significant role in various pathologic conditions, including immune system disorders, transplant rejection, and inappropriate responses to chronic infections.[17-20] Additionally, a recent study utilizing single-cell RNA sequencing revealed that a distinct group of atBCs are part of an alternative B-cell lineage that participates in normal responses to vaccination and infections.[21] As a result, researchers are paying more attention to this population. In this narrative review, we further discuss these cells in the context of various pediatric diseases and emphasize what is known about their genesis, differentiation, and migration, as well as any potential role they could play in immune response.

THE MANY NAMES OF atBCs

Although this review focuses on the role of atBCs in pediatric conditions, it is necessary to specify that much information on their role, development, and function is drawn from studies conducted on adult patients with several diseases. Moreover, as a result of the broad range of pathologic conditions in which these cells have been studied, it is not surprising that a wide range of terminology has been used to define this population. Initially described as ABCs on the basis of their prominence in aging mice,[22] these cells were then identified in young lupus-prone mice and were demonstrated to be critical for virus clearance.[23,24] Similar populations have been reported in humans and are often lumped together as ABCs despite growing evidence for a high degree of heterogeneity within these populations. Indeed, in many studies, this population has often been defined on the basis of the expression of 1 or more ABC markers (preferably CD21$^{low/-}$, CD11c$^+$, or T-bet$^+$) in MBCs. However, ABC-like populations have also been reported according to the expression of additional markers in chronic infectious diseases such as FCRL4 and FCRL5.[25-27] Lack of CD27 and CD21 has been frequently used to identify human ABCs during chronic or repeated *Plasmodium* infection, in this scenario referred to as atypical B cells.[28-30] Human immunodeficiency virus (HIV)-associated atBCs were first identified in 2008 by Moir et al as tissue-like MBCs, which were abnormally expanded in the blood of HIV-viremic patients.[31] Tissue-like MBCs have a similar CD21$^-$CD27$^-$ phenotype as malaria atBCs, but they also express high levels of several inhibitory receptors, including FCRL4, CD22, and CD85j. Because of the evidence of a profile of trafficking receptors (CXCR3 and CCR6) similar to those described for antigen-specific T-cell exhaustion, they have also been defined as exhausted MBCs.[31,32]

In the contest of autoimmune diseases and immune system disorders, other names have been used. Early studies in common variable immunodeficiency (CVID) detected a population of CD19^{high}CD21^{low}CD11c$^+$ cells that was aberrantly expanded in a subgroup of patients who developed autoimmune complications, especially autoimmune cytopenia.[33,34] Reports in systemic lupus erythematosus (SLE) patients identified an atBC population within a specific subset of double-negative (DN) B cells, known as DN2 (CD27$^-$, IgD$^-$, CD21$^-$, T-bet$^+$, CD11c$^+$, and CXCR5$^-$). These cells have been shown to be correlated with disease activity, autoantibody production, and renal manifestations.[35] It is now generally considered that atBCs comprise a heterogeneous population, which might partly account for the lack of a uniform definition and the various phenotyping criteria applied among different groups, and because they represent different maturational stages differentiation according to B-cell receptor (BCR) isotype and expression of CD27.[36] Notably, despite their different maturation stages, a 2021 study demonstrated a similar global transcriptomic profile between circulating atBCs induced by infections (HIV and malaria) and autoimmune diseases (SLE and rheumatoid arthritis) and immune system disorders (CVID).[37] Common features characterizing atBCs generally encompass the downregulation of CD21, increased expression of CD11c, the presence of inhibitory receptors such as CD95, FCRL4, and FCRL5, the expression of the transcription factor T-bet, and downregulation of receptors involved in B-cell survival and homeostasis (BAFF-R, CXCR4, CXCR5, and CCR7).[36,38] Flow cytometric analysis of T-bet$^+$CD21^{low} B cells from individuals with autoimmune disorders and infections not only supported the notion of a shared phenotype but also revealed a notable impairment in their signaling cascade after BCR activation as an additional shared attribute.[39] Interestingly, a study utilizing an *in vitro* B-cell culture system highlighted a notable overlap in the regulation of CD11c and FcRL5 in response to BCR and TLR-9 activation. In contrast, T-bet expression demonstrated a strong dependency on IFN-γ signaling.[40]

These findings suggest that CD11c, FcRL5, and T-bet expression represent various stages of activation and underscore the importance of using multiple markers when assessing atBC differentiation. Because of the inconsistency of T-bet$^+$CD21^{low} B-cell nomenclature across studies (Table I) and the limited evaluation in the pediatric setting, we defined this population as atBCs according to the shared markers most frequently found in the scientific literature.

Therefore, on the basis of the current knowledge, we suggest considering that atBCs be identified by the following markers: CD19$^+$, CD27$^-$, IgD$^-$, CD21^{low}, CD11c$^+$, and T-bet$^+$.

B-CELL SUBSETS AND atBC MODIFICATION DURING CHILDHOOD

Changes in the composition of the peripheral B-cell pool occur in the first 5 years of life, when children encounter a multitude of different antigens.[70,71] A meta-analysis encompassing 28 studies reported significant fluctuations in B cells within the first year of life.[72] According to this report, the changes in B-cell levels can be summarized as follows. (1) Initially, B-cell levels decrease from cord blood to the first week of life. (2) Subsequently, there is a rapid increase over the next 2 months. (3) B-cell levels continue to expand until they peak at approximately 6 months of age. (4) After reaching their peak, B-cell levels gradually decline and (5) may

TABLE I. Designations for atBCs

Characteristic	Condition	Name	Location	Phenotype	Additional markers	T-bet	Proposed functional role	Disease association	Reference
Adult									
Healthy subjects		Tissue resident	Tonsil	$CD19^+IgD^-$ $CD27^-CD38^-$	$FcRL4^+$ $CD11c^+$	−			13
Immune system disorders	SLE	DN2	Peripheral blood/ kidney	$CD19^+IgD^-$ $CD27^-CD21^-$	$CXCR5^-$ $FcRL5^+$	+	Precursor of extrafollicular ASCs	Auto-Abs, disease activity, lupus nephritis	35,41, 42
	Rheumatoid arthritis		Peripheral blood/ SF	$CD19^+IgD^-$ $CD27^-$ $CD21^{low}$		NA		Joint destruction in $ACPA^+/RF^+$ patients	43
	Primary Sjögren syndrome		Peripheral blood	$CD19^+CD27^-$ $CD21^{low}CD38^{low}$	$CD11c^+$	+	Anergic autoreactive memory cells	Associated with lymphoproliferation	44
	Systemic sclerosis		Peripheral blood	$CD19^+CD27^-$ $CD21^{low}CD38^{low}$	$CD11c^+$	NA		Disease activity, vascular complication	45
	Multiple sclerosis	$CD21^{low}$	Peripheral blood/ CSF	$CD19^+IgD^-$ $CD27^-$ $CD21^{low}$	$CD11c^+$		Switched memory	Correlated with the presence of brain inflammatory lesions	46,47
	CVID	$CD21^{low}$	Peripheral blood/ broncho alveolar lavage	$CD19^+IgD^+$ $CD27^-CD38^{low}$ $CD11c^+$	$FcRL4^+$	+		Splenomegaly and autoimmune manifestations	33,48
Infectious diseases	Malaria	Atypical	Peripheral blood	$CD19^+CD27^-$ $CD21^-$	$CD11c^+$ $CXCR5^-$ $FcRL5^+$	+/−	Precursor of antigen-specific Ab, auto-Abs to red blood cells	Associated with anemia	49,50
	HIV	Exhausted, tissue-like	Peripheral blood	$CD27^-CD21^-$	$CD11c^+$	+	Exhausted memory cells	HIV-specific Ig	31,51
	COVID-19	Atypical	Peripheral blood	$CD27^-CD21^-$	$CD11c^+$	+		Morbidity	52
Other conditions	Obesity	Aged-adipose B cells	Adipose tissue	$CD19^+IgD^-$ $CD27^-CD21^-$	$CD11c^+$	+	Precursor of extrafollicular ASCs	Auto-Ab production; exacerbates metabolic disorder in obesity	53-55
	Vaccinations	Atypical	Peripheral blood	$CD19^+CD20^{low}$ IgD^-CD27^-	$CD11c^+$ $CXCR3^+$	NA	Primary response to antigen vaccine and respond to booster immunization	Induced after vaccination against different pathogens	21,56, 57
Children									
Healthy children			Peripheral blood	$CD19^+CD27^-$ $CD21^-$		NA			58
Immune system disorders	CVID	$CD21^{low}$	Peripheral blood	$CD19^+$ $CD27^-CD21^{low}$		NA		Enteropathy and autoimmune symptoms	59,60
	SLE		Peripheral blood	$CD19^+CD27^-$	$CD11c^+$	+			61,62
	JIA		Peripheral blood/ SF	$CD19^+IgD^-$ $CD27^-CD21^-$	$CD11c^+$	NA			63,64
Infectious diseases	Malaria	Atypical	Peripheral blood	$CD19^+$ $CD27^-$ $CD21^-$	$CXCR3^+$ $CD86^+$ $FcRL5^+$	+	Precursors of ASCs	May contribute to humoral immunity to malaria	15

(Continued)

TABLE I. *(Continued)*

Characteristic	Condition	Name	Location	Phenotype	Additional markers	T-bet	Proposed functional role	Disease association	Reference
	HIV	DN	Peripheral blood	$CD19^+$ IgD^- $CD27^-$		NA	Exhausted memory cells	Negative correlation with immune response after seasonal influenza vaccination; negative correlation with time under antiretroviral therapy	65-67
	RSV	Atypical	Peripheral blood/ adenoid	$CD19^+IgA^-$ IgG^-CD27^-		NA		Produce RSV-neutralizing Abs in adenoid tissue	68
Other conditions	Trisomy 21		Peripheral blood	$CD19^+$ $CD27^-CD21^-$	$CD11c^+$ $CXCR5^-$ $CXCR3^+$	+	More likely to have self-reactive features	Correlated with cytokine levels, plasma IgG, and PCs	69

Shown are selected examples of diverse terms used to characterize cells exhibiting atBC-like features in healthy and pathologic conditions. *Ab,* Antibody; *ACPA,* anti-citrullinated protein Ab; *COVID-19,* coronavirus disease 2019; *CSF*, cerebrospinal fluid; *NA,* not available; *RF,* rheumatoid factor; *RSV,* respiratory syncytial virus; *SF,* synovial fluid.

plateau at around 10 to 12 months of age. Evidence in the literature suggests that this plateau might extend to the second year of life, followed by a gradual decrease until adulthood, where levels remain relatively stable.[73-75] The initial decline in B-cell numbers from cord blood to the first week of life is believed to be linked to significant phenotypic changes in B cells during the initial days of life. This is marked by a temporary reduction in transitional and naive B cells without a corresponding expansion in other B-cell subsets (Fig 1).[73,76,77] Then B-cell levels rise until 6 months of life, when immature/transitional and naive B-cell subsets reach their highest levels. Thereafter, after exposure to foreign antigens, the size of MBC and PC increases while the proportion of naive B cells gradually decreases, starting around 18 months of age.[70,73,74,77] In the first weeks of life, $CD27^+IgD^+$-unswitched MBCs constitute the largest subgroup within the MBC compartment. However, continuous exposure to foreign antigens leads to a reduction in the size of this subgroup during childhood, which stabilizes in young adults. Conversely, as children age, the number of switched MBCs slowly increases, progressing from ~0.3% in early life to ~12% of total B cells at 3 years of age.[70,74,78,79]

For atBCs, it has been observed that during the first year of life, there is an increase of proportion of MBCs that lacked CD21 (C3d receptor).[77] Although $CD21^-$ B cells are considered by many to be part of the atBC scenario, it should be noted that CD21 down-regulation might be not associated with a chronic inflammatory process but rather is the result of a limited availability of C3d and C3d–antigen complexes.[80] Indeed, the reduced serum levels of C3 in infants younger than 1 year old may contribute to less signaling for the expression of the CD21 receptor during antigen recognition.[81] Blanco et al reported that the proportion of atBCs (identified here as $CD27^-CD21^-$) increases and peaks during the first 5 months of life, reaching ~10% of total MBCs.[77] Interestingly, the majority of this population was $IgG_3{}^+$, aligning with previous research indicating that the expression of the transcription factor T-bet regulates the immunoglobulin isotype switching to IgG_3 in humans.[82,83] After the first year of life, Jalali et al observed a gradually decrease of $CD11c^+$ atBCs to ~1.4% in children aged 3 to 4 years,[79] which then raises again at 5 to 9 years of life, reaching ~5% of B cells in the peripheral blood of healthy children. This proportion decreases in adults to ~1.0%. Considering DN B cells, this study revealed that they constituted ~3% of total B cells during the first 4 years of life, increasing to ~12% in the 5- to 9-year-old age group, and maintained elevated levels over time (>10%). This is in contrast to previous studies reporting that this percentage was ~5%.[7,48,55] An extensive analysis of a large pediatric cohort revealed that the percentage of atBCs in healthy children ranged between 0.1% and 5.2%. This analysis also highlighted that within the entire cohort, the most abundant subsets in atBCs were IgM^+IgD^+ and IgM^+.[58]

ATYPICAL B-CELL ONTOGENESIS AND ROUTE OF DIFFERENTIATION

Atypical B cells primarily represent antigen-experienced MBCs, characterized by isotype switching and expression of BCRs that have undergone somatic hypermutation (SHM), but the precise origin of this population in humans is still uncertain (Fig 2). Indeed, a significant number of $CD21^{low}$T-bet^+ or $CD11c^+$ B cells exhibit an unswitched BCR,[84] suggesting they may originate from naive B cells. This is further supported by BCR sequencing, which reveals some shared repertoire and gene characteristics between naive B cells and unswitched $CD21^{low}$ B cells.[85] Moreover, this idea is supported by the observation that atBCs in *Plasmodium*-exposed Malian children could be separated into IgD^-IgG^+, IgD^+IgM^+, and IgD^+IgM^{low} subsets with SHM rates equivalent, respectively, to classical MBCs (suggesting GC and classical MBC origin), naive B cells (suggesting naive B-cell origin), and intermediate between naive and classical MBC (suggesting T-B border origin).[37]

Most atBCs show signs of a GC reaction, namely in their immunoglobulin isotype–switched phenotype and somatically mutated immunoglobulin genes.[86,87] The presence of SHM in atBCs does not prove their origin in the GC, although it may suggest it. In the case of HIV, these cells were found to have a clonal

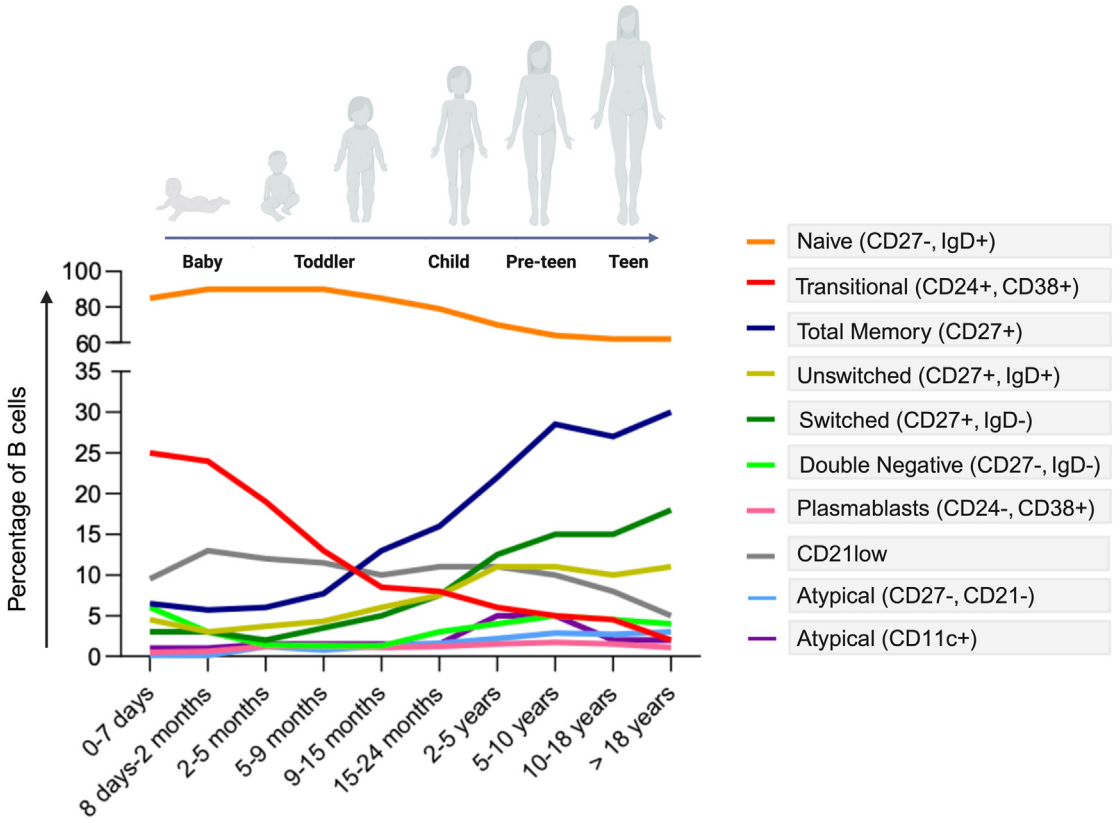

FIG 1. Variations in B-cell populations, encompassing atypical B-cell subsets, during childhood and adolescence. Adapted from references [58,71,75], and[77].

relationship with GC B cells, but with fewer SHMs and a reduced neutralization capacity.[36,51] This suggests that they may either originate from common progenitors that follow distinct differentiation pathways or that atBCs may exit the GC response at an earlier stage. After influenza or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination, SHM rates were similar to classical memory cells, and clonal relation was interpreted as post-GC B cells.[36,88,89] Although it could potentially develop within GCs, extrafollicular (EF) pathways have been suggested in some pathologic conditions, such as SLE.[35] Indeed, both EF and GC B cells can undergo class-switch recombination and SHM. Jenks et al identified various characteristics of atBCs observed in SLE patients, which are indicative of EF differentiation; features include the absence of CXCR5 and CD62L, which are, respectively, chemokine receptors responsible for migration to secondary lymphoid organs and crucial for lymph node trafficking.[35] Notably, the EF pathway has also been proposed for CVID, HIV, and toxoplasmosis, where atBCs were observed to accumulate outside GC.[51,90] Of note, atBCs could also be GC independent, but they carry high levels of SHM if they arose from GC-experienced classical MBCs. This idea was supported by the observation that secondary vaccination or infection can induce stronger CD11c$^+$ atBC production than the primary response.[21,84]

While it may be tempting to claim that CD11c$^+$T-bet$^+$ atBCs originate from a single source and follow a singular differentiation pathway, the EF pathways and GC development are not mutually exclusive. Moreover, it is plausible that the inflammatory conditions largely dictate the specific pathway chosen. Elsner and Shlomchik have further elaborated on this matter, proposing that elevated levels of IFN-γ hinder T follicular helper (Tfh) cell development and subsequent GC responses, leading to differentiation via the extrafollicular route.[41] Conversely, lower levels of IFN-γ may permit Tfh cell–mediated differentiation of T-bet$^+$ GC B cells.

The development and persistence of atBCs rely on T cells and IL-21R, with these 2 pathways likely not mutually exclusive and likely with varying impacts across different disorders. Although a stronger involvement of TLR-7/8 and -9 signals has been suggested in the context of SLE,[35,91] investigations on patients with monogenic inborn errors of immunity have revealed the critical importance of IFN-γR and nuclear factor kappa–light-chain enhancer of activated B cells (aka NF-κB) signaling for the differentiation of human atBCs, both *in vitro* and *in vivo*.[92] IFN-γ is a T_H1 cytokine, which, on binding to the IFN-γR on B cells, activates the JAK-STAT signaling pathway, resulting in upregulation of the transcription factor T-bet.[93] These findings strongly suggest a unique role of T-cell assistance, as evidenced by the reduced presence of atBCs in patients with deficiencies in IL-21R, CD40, or CD40L.[92] For these reasons, both T peripheral helper cells in inflamed tissues and Tfh cells with a T_H1 profile in secondary lymphoid tissues emerge as excellent candidates for delivering the necessary factors for their alternative

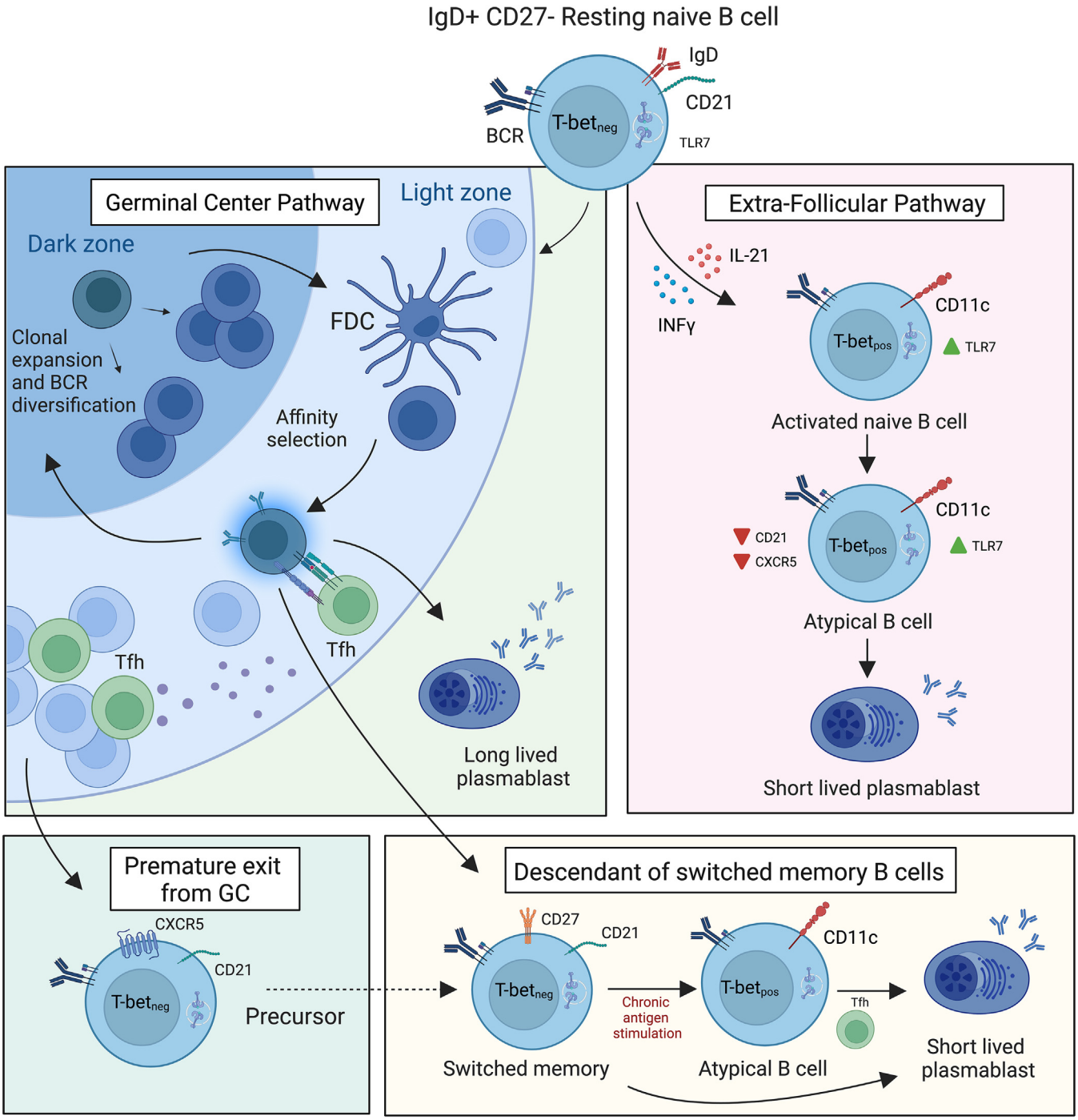

FIG 2. Possible origins of atBCs during persistent antigen stimulation. Multiple pathways by which atypical B cells arise have been proposed: (1) via extrafollicular differentiation pathway; (2) via premature exit from GC reaction; and (3) via altered lineage pathway compared to classical MBCs. *Dashed lines* indicate potential developmental pathways that need further investigation.

B-cell differentiation. Interestingly, it was observed that atBCs exhibited normal development in patients lacking MyD88 and IRAK4, which suggests that the classical TLR-7/8/9 signaling pathway is not essential for the formation of atBCs in humans.[92] In addition, the evaluation of the first reported T-bet–deficient patient highlighted a crucial role of T-bet for the differentiation of atBCs even if other transcription factors play a critical role in influencing the gene expression of additional characteristic markers.[94]

TRANSCRIPTIONAL PROFILE OF atBCs

T-bet, encoded by *TBX21* gene, is often considered a key transcription factor for atBC formation. Perhaps the best described role of T-bet in the humoral immune system is to regulate antibody class switching to IgG_2a/c in mice and IgG_1 or IgG_3 in humans.[9] But other roles have also been highlighted. In infection models, expression of B-cell T-bet had a greater impact on the control of chronic than acute viral infections and, while not necessary for the initial phase, was required for optimal protective

humoral responses.[95] Moreover, T-bet in B cells was linked to the expression of CXCR3 or S1pr5, which controls the migration and tissue residency of immune cells.[96,97] Thus, the expression of T-bet may be particularly important in regulating the trafficking and homing patterns of atBCs and ensuring their proper colocalization with other effector cells. In addition, compared to other B-cell subsets, atBCs usually upregulate the integrin CD11c (encoded by *ITGAX*) as well as other myeloid markers like FcγRs, CD14, CD68, and CD163, thus suggesting that these cells use unique trafficking patterns and can target distinct microenvironmental niches.[12,56,98] Notably, CD11c emerges as a valuable marker for identifying atBCs, as highlighted in a study using time-of-flight cytometry to examine 351 surface molecules on human circulating B cells.[99] These cells exhibited elevated expression of inhibitory markers (CD95, FCRL4, and FCRL5) and activation-related molecules (TACI, CD80, and CD86) as well as downregulation of receptors involved in B-cell survival and homeostasis (BAFF-R, CXCR4, CXCR5, and CCR7).[17,38]

As mentioned above, human T-bet governed atBCs differentiation by controlling chromatin accessibility of lineage-defining genes: *FAS, IL-21R, SEC61B, DUSP4, DAPP1, SOX5*, *CD79B*, and *CXCR4*.[94] *IRF5* and *ZEB2* had also been reported to be required for atBC formation in the SWAP-70 and *DEF6* double-knockout lupus model,[98,100] as excellently reported elsewhere.[12] The functional outcomes regulated by T-bet become more intricate as atBCs differentiate into various effector progeny, including GC B cells and PBs/PCs, as a result of the interplay between T-bet, *BCL6,* and *BLIMP1*.[101] Research by Pernis's group indicates that certain $CD11c^+$ effector progeny, like PBs, can exhibit a core atypical transcriptional profile even when T-bet expression is downregulated; this finding supports the notion that an "atypical signature" can persist in the absence of this transcription factor.[12,102] Indeed, using RNA sequencing, Wang et al noted that $CD11c^+$ B cells in SLE had upregulated genes associated with antibody-secreting cell (ASC) differentiation, such as *PRDM1, AICDA, XBP1,* and *BMP6*.[103] Similarly, Golinski et al discovered that a greater proportion of $CD11c^+$ B cells underwent differentiation into ASC after 7-day culture with BCR ligation, TLR-9 ligand, and IL-21.[104] Characterization of *in vitro* responses of human $CD11c^+$ B-cell subsets by Steuten et al revealed that different $CD11c^+$ B cells yielded ASCs as well as $CD138^+$ PCs in response to stimulation with CD40L/IL-21.[16] The capacity of distinct $CD11c^+$ B-cell subsets to produce ASCs *in vitro* aligns with previous observations indicating that $CD21^{low}$ B cells possess a transcriptional profile indicative of pre-PCs, characterized by elevated expressions of *BLIMP1, XBP1, IGJ, IL6R,* and *TNFRSF17 (BCMA),* along with diminished levels of *BACH2*.[56]

These findings contrast with initial studies conducted in patients with chronic diseases, which did not report a capacity of this cell population to differentiate PBs/PCs. This could be attributed to intrinsic differences between autoimmune and infectious diseases. Additionally, it is important to consider the influence of experimental conditions and the specific cell types (according to the phenotype) studied; these factors can contribute to the observed discrepancies.

Moreover, one study provides additional insights into a poorly investigated role of atBCs as antigen-presenting cells, a function previously observed in mice where these cells exhibited superior antigen presentation to T cells compared to follicular B cells.[105] Kleberg et al demonstrated that atBCs could enhance $CD4^+$ T-cell survival and proliferation through IL-6 production.[40] Surprisingly, this capacity was not clearly associated with T-bet levels but rather to the BCR. However, this connection was not clearly dependent on specific levels of other atBC markers, such as CD11c or FcRL5. Therefore, additional research is required to delve deeper into this topic.

ATYPICAL B CELLS IN INFECTIOUS DISEASES

Atypical B cells have been identified in the context of several infections, including HIV,[31,83] malaria,[15,37] hepatitis B virus,[106] hepatitis C virus,[107] tuberculosis,[108] SARS-CoV-2,[109] respiratory syncytial virus,[68] dengue,[110] and influenza,[111] but its role changes depending on whether the infection is acute or chronic. On the one hand, expansion of atBCs during natural acute infection and vaccination has been linked to various useful functionalities. Eccles et al demonstrated that the acute phase of human rhinovirus infection coincided with local rapid expansion of T-bet^+ B cells and with their secretion of cross-reactive IgG.[112] On the other hand, excessive expansion of atBCs during acute infections has been correlated with pathogenic responses. Indeed, in patients with severe coronavirus disease 2019 (COVID-19), atBCs have been associated with poor outcomes and high mortality rates as well as with the production of autoantibodies.[52,91,113,114] In contrast, in chronic infections like HIV, hepatitis C virus, and malaria, atBC expression of many inhibitory receptors (FcRL4, FcRL5, CD85j, and CD22) and their refractoriness to stimulation through their BCR, TLR, CD40, and cytokine receptors have been suggested to be critical aspects of the ineffective immune responses known to accompany these infections.[8,115] Alternatively, the anergic nature of these B cells may also be beneficial to protect against a potentially damaging immune response.

Malaria

Children generally mount short-lived antibody responses to *Plasmodium falciparum* infection, leaving them susceptible to repeated bouts of malaria.[116] As a result, most cases of malaria occur in children under the age of 10, while adults with lifelong exposure have asymptomatic infections. atBCs can represent up to 20% of the circulating B cells in children living in malaria-endemic areas and in children persistently exposed to malaria.[27,117] A longitudinal analysis of *P falciparum*–infected children has suggested a positive correlation between the incidence of febrile malaria and the expansion of T-bet B cells via T_H1 cytokines.[118] Malaria may also potentially affect the B-cell compartment by affecting the B-cell repertoire, although this area of research has not yet been thoroughly explored. One study examined the V gene repertoires of naive B cells, atBCs, and MBCs and found that the variable heavy chain and variable light chain repertoires of classical MBCs and atBCs had similar V gene usage, SHM rates, and variable heavy chain complementarity determining region 3 (aka CDR3) length and composition.[119] Using an accurate, high-coverage immunoglobulin sequencing method, the same research group found unexpectedly high levels of SHM in infants as young as 3 months.[120] Antibody lineage analysis showed that SHM also increased in both infants and young children with febrile malaria.

Atypical B cells have been hypothesized to be exhausted or dysfunctional according to their increased expression of

inhibitory receptors, such as CD22, CD85j, and FcγRIIB, and homing receptors, such as CD11c, CCR6, CXCR4, and CXCR3.[118] In addition, these cells have reduced responsiveness to restimulation of sorted human $CD21^{lo}FcRL5^{+}$ or $FcRL4^{+}$ B cells.[121] Works by Crompton's group highlighted FcRL5 as an inhibitory indicator on atBCs because $FcRL5^{high}$-expressing B cells were less responsive to BCR stimulation and revealed a key role of T-bet, which correlates inversely with BCR signaling and skews toward IgG_3 class switching.[28,118] Muellenbeck et al showed that these cells were enriched for self- or polyreactive BCR specificities, suggesting that they could be anergic in order to safeguard the host from autoimmune reactions.[49] Indeed, in some patients (including children) with acute malaria, the expansion of atBCs correlates with the production of autoantibodies against phosphatidylserine, contributing to the development of anemia.[100]

Although atBCs can appear dysfunctional, one report provided evidence of *P falciparum*–specific immunoglobulin transcripts produced by atBCs *in vivo* and showed that broadly neutralizing *P falciparum*–specific antibodies can be cloned from atBCs.[49] In addition, atBCs expand in response to *P falciparum* sporozoite vaccination.[21] According to Ambegaonkar et al, atBCs can still contribute to the production of protective antibodies.[122] The authors proposed that inhibitory receptors, particularly FcγRIIB, were responsible for restricting the responsiveness of $CD21^{low}CD27^{low}$ B cells to soluble antigen. However, when the BCR ligand or antigen was presented to the cells while fixed in a lipid bilayer, FcγRIIB was removed from the immunologic synapse, making it possible for CD19 to engage with the BCR (Fig 3).[122]

Recent research has indicated that atBCs may actively contribute to humoral immunity to infectious pathogens. Hopp et al found that in response to acute malaria, *P falciparum*–specific atBCs of Malian children are activated, with increased frequency and upregulation of molecules (CXCR3 and CD86) that mediate B- and T-cell interactions.[15] Consistent with this *ex vivo* finding, the authors found that atBCs upregulated *PRDM1* and the activation PC marker CD38 when cocultured with autologous Tfh cells from malaria-exposed individuals, suggesting that atBCs may actively contribute to humoral immunity to infectious pathogens. Reyes et al showed that CXCR3 and CD95 atBC expression was higher in adults than children, suggesting that this marker is acquired as a result of chronic antigen exposure and should probably be considered a marker of activation.[124] Moreover, the study unraveled through single-cell sequencing and BCR analysis that atBC, in the setting of malaria, contributes to a productive and antigen-specific immune response against infection.

HIV

HIV infection exerts a significant impact on the B-cell compartment, resulting in marked changes in cell phenotype and functionality.[32,125,126] B cells lacking CD21 and CD27, but expressing CD11c and FcRL4, appear in association with HIV viremia, are more frequent in viremic compared to nonviremic patients, and decreased with antiretroviral treatment.[31,32,125] A 2019 study analyzing lymph nodes showed that HIV-specific B cells in infected individuals were enriched among $CD19^{+}$T-bet^{high} B cells and that this population was not present in healthy individuals.[51] This subset exhibits a weak response to BCR stimulation and expresses inhibitory receptors, resulting in decreased capacity for proliferation, affinity maturation, and secretion of cytokines or antibodies.[51,127] However, Knox et al found that during HIV infection in adult patients, the specific HIV gp140 response is dominated by expanded atBCs.[25] Atypical B-cell dysfunction is deemed to be associated with the binding of soluble IgG_3 to IgM-expressing B cells, along with C1q and the inhibitory Fc receptor CD32b (also known as FcγRIIB), which leads to increased clustering of the IgM BCR and decreased response to stimulation.[123] In line with this "exhausted" status, our group showed a positive association between atBCs and plasma complement cascade proteins in children.[128] Additionally, our group's studies have indicated that atBCs expansion in HIV-infected children is associated with a decreased ability to respond to childhood influenza and measles–mumps–rubella vaccination.[65,128,129] We recently investigated the evolution and maturation of the B-cell compartment over the first 2 years of life in children with perinatal HIV infection; we observed an expansion of atBCs at 40 days of life, which may contribute to B-cell exhaustion.[66] Indeed, in our study, children with perinatal HIV infection and uncontrolled virus replication exhibited a diminished capacity to sustain protective tetanus antibody titers over time. Notably, in HIV-infected children, a longer duration of receipt of antiretroviral treatment is related to lower atBCs, while an earlier start is associated with lower frequencies of mature activated B cells ($CD19^{+}CD10^{-}CD21^{-}$).[67,130,131]

The poor response to BCR stimulation had led to the original designation that atBCs comprised anergic or exhausted cells. Recent discoveries, especially in field of malaria, suggest that current *in vitro* investigations may not have adequately replicated the *in vivo* functionality of this population. To better mimic their natural function, it is crucial to consider additional factors such as cytokines, B-cell activating factor (BAFF), TLR ligands, and various forms of costimulation.

ATYPICAL B CELLS IN VACCINE-INDUCED RESPONSES

Evidence suggests that atBCs play a significant role in the adaptive response triggered by vaccines in healthy adults.[21,132] Steuten et al undertook a dedicated endeavor to provide a more comprehensive understanding of these cells in the context of immunization using SARS-CoV-2 mRNA vaccines.[16] Their investigation unveiled a substantial increase of atBCs, exhibiting a remarkable 20- to 40-fold increase after SARS-CoV-2 vaccination. Interestingly, their study highlighted variations across distinct $CD11c^{+}$T-bet^{+} B-cell subsets. The expansion of spike-specific $CD11c^{+}$ B cells was primarily orchestrated by the DN2 ($CD11c^{+}$, IgD^{-}, and $CD27^{-}$) and ABC ($CD11c^{+}$) subsets, which exhibited robust expansion shortly after the second vaccination, followed by subsequent contraction.[16] These findings on SARS-CoV-2 immunization align with those documented in studies about seasonal influenza[56,57] and tetanus[132] vaccinations. In their study, Lau et al demonstrated that atBCs emerged as the predominant subset among hemagglutinin-specific B cells, maintaining their dominance for an extended 60-day period after vaccine boost.[56] Furthermore, Sutton et al established that B cells with an atypical transcriptional profile emerge during the primary immune response to vaccination and can be reactivated on subsequent exposure, as evidenced through influenza vaccine challenges and sporozoite immunizations.[21] However,

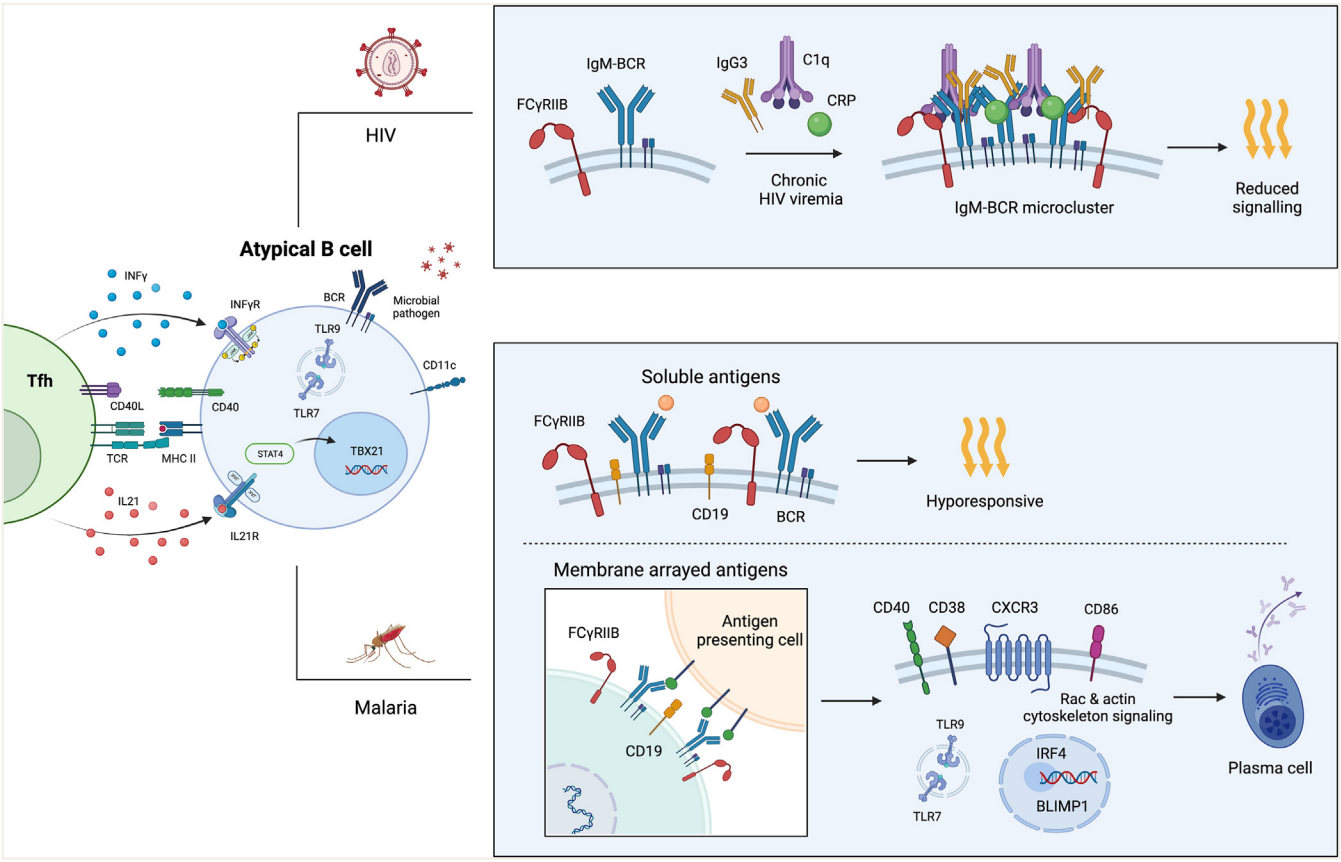

FIG 3. During chronic HIV-1 viremia, inhibitory Fc receptor FcγRIIB (CD32b) arises and becomes linked to microclusters of IgG_3-IgM-BCR, in addition to C1q and C-reactive protein (CRP). This clustering predominantly takes place in atBCs and involves direct engagements between IgG_3 and IgM-BCR, leading to reduced intracellular signaling.[123] In malaria, atBC responsiveness relies on the way antigen is presented. atBCs that express CD11c, T-bet, and FCRL5 also exhibit heightened expression of inhibitory receptors, such as FcγRIIB. When BCR is bound, FcγRIIB diminishes interaction between CD19 and BCR, thus impeding downstream signaling and resulting in reduced responsiveness. Conversely, atBCs that bind to antigens arrayed on cell membrane establish immunologic synapse that excludes FcγRIIB. This exclusion enables CD19 to effectively engage BCR and facilitate downstream signaling, which subsequently triggers transcription of *IRF4* and *BLIMP1*. This process promotes differentiation into ASCs. In addition, atBCs may capture membrane-bound antigen for presentation to Tfh cells. Acute malaria may also prime atBCs to respond to TLR-7/9, which, together with IFN-γ, may contribute to T-bet expression.[15]

investigation of atBCs' transcriptome has revealed that these cells do not exhibit spontaneous antibody secretion and are primed for PC differentiation while exhibiting resistance to further differentiation in the GC.[56]

Despite these results, which highlight that atBCs are part of a normal B-cell antigen response,[21,27,56,57,133] the relevance of antibody production by this population in infection control is less clear. A fundamental issue that remains unresolved is whether atBCs yield antibodies with distinct qualitative properties compared to those generated through the conventional GC pathway. Of note, in the first described T-bet–deficient patient, the vaccination response against the investigate bacterial antigens seemed normal, but respiratory virus (influenza and SARS-CoV-2) response was not investigated in this patient.[94] Additionally, the consequences of accumulated atBCs in vaccine-induced immunity in children with chronic inflammation remains unclear. This uncertainty primarily stems from the lack of dedicated research on healthy children and reports describing HIV-infected children. Indeed, HIV-infected children with an expansion of atBCs demonstrate a compromised vaccine response.[129] Thus, it is plausible that the inflammatory context makes the atBCs anergic or exhausted, as previously suggested.[32]

These disparate observations may also stem from the existence of various subsets of atBCs with different effector functions or stages of maturation; or they may be attributable to differences in context in what was being investigated. Further investigations into the role, breadth, and dynamics of atypical B cells in the context of vaccination among healthy children and adults are warranted.

ATYPICAL B CELLS IN SYSTEMIC IMMUNE DISORDERS

The connection between atBCs and autoimmunity has been firmly established and widely acknowledged. This population has been found elevated in adults patients with rheumatoid arthritis,[43] SLE,[35,103] primary Sjögren syndrome,[44] systemic sclerosis,[45] ANCA-associated vasculitis,[39] multiple sclerosis,[46,47,86] Crohn

disease,[134] Graves disease,[135] Hashimoto thyroiditis,[136] myasthenia gravis,[137] and Guillain-Barré syndrome.[137] Furthermore, research linking atBCs to autoimmune and inflammatory diseases indicates that TLR-7/9, IFN-γ, and IL-21 play crucial roles in enabling differentiation into PBs.[7,87] Moreover, atBCs have also been linked to several immunodeficiency disorders, especially CVID,[33,34] ataxia-telangiectasia,[138] Wiskott-Aldrich syndrome,[139] IgA deficiency,[140] chronic granulomatous disease,[141] and partial RAG deficiency,[142] but their role in these conditions remains controversial.

RHEUMATIC DISEASES

SLE

SLE is a chronic autoimmune disease characterized by the production of autoantibodies and a wide spectrum of clinical manifestations. In this scenario, atBCs can contribute more than 50% of all B cells in active SLE and may become the largest circulating population of isotype-switched IgD^- cells; this may also occur in young children with active disease.[35] In this scenario, atBCs have been identified as DN2 cells ($CD27^-$, IgD^-, $CD38^{low}$, $CD11c^+$, $CXCR5^-$, $FcRL5^+$, $FcRL4^-$, and T-bet^+) or as $CD27^-$, $CD38^{low}$, $CD11c^+$, $FRL5^+$, $FcRL4^+$, and T-bet^+ have been shown to be major producers of autoantibodies (anti-Sm, anti-RNP), and their accumulation has been demonstrated to correlate with disease activity and severe clinical manifestations, such as lupus nephritis.[35,103] Moreover, these cells have been identified not just in peripheral blood but also in areas of organ injury, such as the kidneys.[42,143,144] The transcriptional profile found higher expression of *IRF4* and lower expression of *IFR8* compared to other B-cell subsets, indicating the tendency toward differentiation into PBs/PCs.[145]

Although atBCs have been extensively studied in SLE mouse models and adult patients, there is very little information on pediatric populations. Corrente et al reported an increase of atBCs ($CD21^{low}CD11c^+$ B cells) in children with immune system disorders, including SLE.[58] A recent study revealed a notable increase in T-bet–expressing naive B cells and DN ($CD21^-$, $CD11c^+$) B cells in patients with childhood SLE as opposed to healthy children.[61] Approximately half of T-bet^+ B cells displayed an activated phenotype, characterized by CD21 negativity and CD11c positivity. The expression of T-bet is induced specifically by IFN-γ and not by IFN-α and defines a patient population with higher disease severity, higher frequency of extractable nuclear antigen and anti–double-stranded DNA positivity, and higher proportion of proliferative lupus nephritis.[61] In another study, a multiomics approach combined with unsupervised hierarchical clustering analysis was performed on children with SLE and resulted in the identification of clusters of patients with distinct biological phenotypes associated with disease activity states.[62] In this regard, atBCs were increased in the group of patients with high cytokine profile and high gene expression.

Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood, affecting not only joints but also extra-articular structures such as eyes, skin, and internal organs. Although the pathogenesis is still unexplained, the occurrence of autoantibodies (eg, antinuclear antibodies [ANA]) in a significant proportion of patients suggests the involvement of autoreactive B cells.[146,147] A 2021 study investigated the differences in B cells among ANA^+ JIA patients by analyzing the distribution of B-cell subpopulations in peripheral blood and synovial fluid. Increased frequencies of atBCs ($CD21^{low/-}CD27^-$ IgM DN2 B cells) were observed in the synovial fluid of ANA^+ JIA patients, suggesting that DN B cells might be involved in the development of disease and could be a characteristic subset in ANA^+ JIA patients.[148] A previous study showed that atBCs accumulated in the joints of JIA patients and displayed features of antigen-presenting cells, with expression of costimulatory molecules (CD80/CD86) and a polarized pattern of cytokine secretion capable of inducing T-cell activation and T_H1 differentiation.[149] Fischer et al reported that synovial $CD4^+$ T cells promote aberrant B-cell activation in ANA^+ JIA by promoting the differentiation of B cells toward the $CD21^{low}$/-$CD11c^+$ phenotype through the secretion of cytokines like IL-21 and IFN-γ.[64] These findings suggest that in the setting of inflammatory arthritis in children, expanded Tfh cells in the synovium might promote B-cell differentiation into atBCs via secretion of cytokines such as IL-21 and IFN-γ.

IMMUNODEFICIENCY DISORDERS

CVID

CVID is a heterogeneous disease characterized by hypogammaglobulinemia, defective antibody responses, and recurrent infections. atBCs have been extensively studied in adult CVID patients, where they have been linked to splenomegaly and autoimmune cytopenia,[33] and subsequently to granulomatous disease.[48] Results in the pediatric population have been mixed. On the one hand, in pediatric patients, a study revealed that the increase in atBCs (referred here as $CD21^{low}$) was linked to the development of enteropathy and autoimmune symptoms, but it was not found to be associated with developing splenomegaly.[59] On the other hand, granuloma formation was not confirmed in another single-center pediatric cohort study.[60] In CVID patients, atBCs were $CD21^{-/low}$, $CD27^-$, $CD38^{low}$, $CD11c^+$, $FcRL4^+$, and $FcRL5^+$ and expressed unmutated IgM and IgD, although this may reflect an inability to class switch or form functional GCs.[149] It was recently discovered that this population expresses T-bet. Interestingly, these cells have been observed not only in secondary lymphoid organs and spleen but also in bronchoalveolar lavage samples obtained from patients who had developed interstitial lung disease.[92]

Other immunodeficiency syndromes

A study involving 1180 pediatric patients demonstrated significant variability in the percentage of atBCs, depending on the underlying medical condition.[58] Among these patients, ~16% exhibited an elevated population of this cell population (>5% of total B cells). Notably, patients with primary immunodeficiency accounted for approximately half of those with a moderate (10-20%) or high (>20%) increase in atBCs. The authors reported a high increase of atBCs in children with combined immunodeficiencies and severe combined immunodeficiencies, as well as Wiskott-Aldrich syndrome and ataxia-telangiectasia, and a low increase (5-9%) in patients with DiGeorge syndrome and IgA deficiency. Further, it has been reported that children with impaired RAG function had impaired primary BCR repertoire formation with remarkable alterations in the composition of

B-cell subsets, along with widespread, promiscuous activation that favors extrafollicular pathway and expansion of T-bet$^+$ B cells and poly- or autoreactive B-cell clones in the periphery.[142] These alterations are likely caused by environmental triggers (eg, chronic infection and microbiota translocation) along with intrinsic factors (eg, elevated BAFF levels, reduced regulatory T/Tfh cell ratio, and inflammatory cytokine milieu). In addition, heightened levels of this population of atBCs have been observed in pediatric cases of Fisher-Evans syndrome, immune thrombocytopenia, and autoimmune hemolytic anemia. These findings align with previous observations of increased atBCs in children with these conditions.[150,151] Nevertheless, the function of these cells in these diseases is still unknown, although an association with the development of autoimmune cytopenia has been suggested.[151]

According to this finding, several studies suggest rituximab as an effective second- or third-line off-label treatment for autoimmune cytopenia in children with autoimmune cytopenia associated with an expansion of these subsets.[152] Further studies are needed to better characterize the function of these cells in patients with immunodeficiency syndromes.

OBESITY AND METABOLIC DISEASES

Obesity generated low-grade chronic inflammation that led multiple metabolic diseases such as insulin resistance, type 2 diabetes, and nonalcoholic fatty liver disease.[153] Atypical B cells have gained attention in recent years because of their potential involvement in obesity-related inflammation and metabolic dysfunction.

Research from Blomberg's group initially identified a connection between CD21$^-$T-bet$^+$ B cells and obesity. Their findings revealed an accumulation of this B-cell subset in white adipose tissue of obese patients and demonstrated a correlation with body mass index and weight.[53,154] Subsequently, Frasca et al reported that atBCs (CD21$^-$, CD27$^-$, IgD$^-$, T-bet$^+$, and CD11c$^+$) in obese patients was associated with increased secretion of IgG with autoimmune specificity.[54] Hägglöf et al in 2022 deepened this topic, showing that T-bet$^+$CD11c$^+$ B cells were causally related to onset and exacerbation of metabolic disease in obese patients.[55] The authors demonstrated that adipose tissue–resident atBCs were regulated by invariant natural killer T cells and that this atypical B-cell population could be expanded by stimulation of TLR-7, in an invariant natural killer T-cell–dependent manner.[55,155] These interactions result in the production of chemokines and antibody mediators (IgG_2c) that amplify the initiation and severity of metabolic disorders. Using a murine model with a B-cell–specific knockout of T-bet, the researchers demonstrated that the lack of atBCs diminishes the prevalence and onset of metabolic disease. Furthermore, they established that glucose intolerance can be restored by transferring either whole serum or purified IgG obtained from obese mice, a process that recruits proinflammatory macrophages. This approach unveils pathologic immunoglobulins as the central mechanism driving atBC inflammation in obesity, thereby highlighting the potential of targeting atBCs in future therapeutic strategies to limit metabolic disorders.

However, for this specific topic, there are no data available in the pediatric population. Therefore, additional studies are required to gain a better understanding of the role and functions of these cells in children with obesity and metabolic disorders.

FUTURE PERSPECTIVES

One of the most striking aspects of the atBC population is its potential to be controlled in a sex-specific manner, with a greater degree in female than male subjects. The expansion of this compartment in female subjects suggests their role in autoimmune disease development and potentially contributes to the documented sex-based differences in immune responses during viral infection and vaccination.[156] However, sex differences extend beyond mere accumulation of atBCs, encompassing various aspects within the atBC compartment. Research using murine lupus models revealed that atBCs from female animals, but not male, express an interferon signature and are more prone to differentiate in CD11c$^+$ effector populations.[102] Moreover, the duplication of TLR-7 in male mice lacking SWEF proteins overrode the sex-related bias and intensified the pathogenic effects of atBCs.[102] Recent work has provided interesting insights into the mechanisms that might contribute to incomplete X chromosome inactivation (XCI), particularly in atBCs. These investigations have unveiled that the long noncoding RNA X-inactive specific transcript (XIST), the responsible XCI in female cells during development, plays a crucial role in preserving XCI for a specific group of X-linked genes in B cells, including *TLR7* and *CXorf21/TASL* (an adaptor that regulates *IRF5* activity).[157] Interestingly, escape of XIST-dependent genes, coupled with TLR-7 activation, facilitates the development of CD11c$^+$ B cells in autoimmune settings (Fig 4).[12,157,158] Further exploration of the atBC population in male versus female subjects during infection and vaccination is necessary to ascertain whether the sex bias extends beyond frequency and leads to distinct functional capacities in atBC populations between the sexes.

Delving into the mechanisms underlying the differentiation of these cells offers promising therapeutic perspectives. Little is known about the effectiveness of drugs on this cell population. B-cell–depleting drugs have demonstrated the ability to reduce atBCs in SLE (Fig 4).[159,160] There is significant evidence indicating a connection between the process of reconstitution of B-cell subsets after B-cell depletion and the clinical progression of autoimmune diseases. Therefore, it is necessary to analyze the reconstitution pattern of atBCs, including both the percentage of reappearing atBCs and their distinct phenotypic and functional traits. Unraveling these mechanisms could prove important when developing drugs tailored for these cells.

CONCLUSION

In various pediatric chronic inflammatory conditions, there is consistent observation of an expanded population of atBCs with different physiologic and pathogenetic roles, although these different functions may be context dependent. According to the scientific literature, potential roles for atBCs have emerged.[161] They display exhaustion and functional deficits akin to CD8$^+$-exhausted memory T cells; they demonstrate a capacity for differentiation with reduced dependence on antigens compared to classical MBCs; and they potentially specialize in antigen presentation, primarily aimed at activating T cells.

In the field of autoimmunity, this cell population often correlates with disease-specific manifestations and autoantibody production, warranting consideration for its elimination. However, the exact function of atBCs during immunodeficiency and chronic infection remains unclear. Conflicting results on anergy versus hyperresponsiveness are likely context dependent, with a refractory phenotype in chronic exposure and hyperresponsiveness in acute

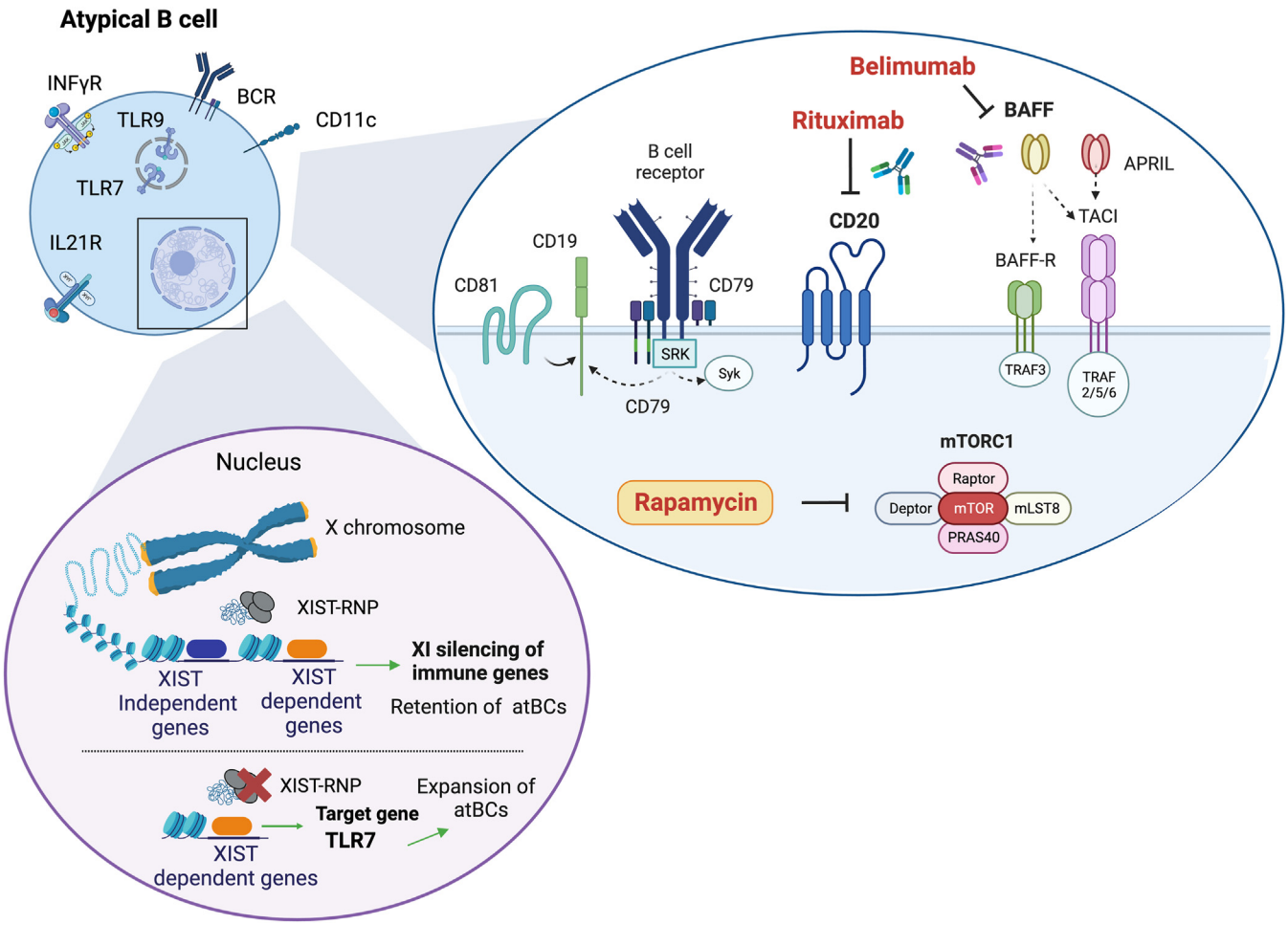

FIG 4. Rituximab (anti-CD20 monoclonal antibodies) and belimumab (anti–B-lymphocyte stimulator [BLyS] monoclonal antibodies) can reduce level of atBCs in patients with SLE.[159,160] Moreover, mechanistic target of rapamycin complex 1 (mTORC1) hyperactivation has been linked to atBC dysfunction in SLE.[144] Thus, this pathway's inhibition could reduce levels of this B-cell population. In cell nucleus is shown model proposed of XCI maintenance in human B cells.[157] XIST loss and TLR-7 stimulation promote $CD11c^{+}$ atypical B-cell formation.

antigenic exposure. In murine acute infection, atBCs have been postulated to participate directly in the antipathogen antibody response, while in humans, the relevance of antibody production by this population in infection control is less clear.

Notably, in the case of malaria, atBCs exhibit PC genes during the convalescent disease phase but not during the acute phase, implying different functions at different stages of the disease. While the expression of PC genes has not been reported in most other infectious conditions, it could be due to either the lack of testing or an undetectable expression. Hence, in other conditions, atBCs are unlikely to serve as precursors to PCs, indicating the presence of unknown functions.

In infectious scenarios, particularly those involving chronic infectious diseases, further research is therefore imperative to elucidate their precise function.

This review encompasses recent data derived from human samples across various research fields. Although the inconsistent use of names and markers to identify these cells often hinders direct comparisons, several studies indicate significant overlap in the phenotypic and transcriptional characteristics as well as homing patterns of atBCs. However, it should be noted that there is substantial heterogeneity in marker expression among these cells, both between different diseases and over time. Standardizing cell nomenclature and definition and providing clear cutoffs for abnormal expansion are crucial for driving immunomodulatory treatments and facilitating comparisons across various models and research findings offering insight into their role in immune responses and autoimmunity.

DISCLOSURE STATEMENT

Supported by US National Institutes of Health National Institute of Allergy and Infectious Diseases Immune Development in Early Life (IDEAL) award U19AI168643. This work was also supported by the Italian Ministry of Health with "Current Research fund".

Disclosure of potential conflict of interest: The authors declare that they have no relevant conflicts of interest.

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