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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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Abstract

Repetitive or persistent cellular stimulation in vivo has been associated with the development of a heterogeneous B cellular population which exhibit a distinctive phenotype and, in addition to classical B cell markers, often express the transcription factor T-bet and myeloid markers 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, due to the diverse contexts in which they have been investigated, these cells have remained largely enigmatic, with much ambiguity regarding their phenotype and function in humoral immune response, as well as their role in autoimmunity. Atypical B cells have garnered considerable interest due to their ability to produce specific antibodies/autoantibodies and with their association with key disease manifestations. Although they have been widely described in the adult context little is present for the pediatric side. 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.

Keywords

Atypical B cells; B cells; CD11c+; T-bet+; Double Negative B cells; CD21low; pediatric diseases

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Introduction

B cells constitute a critical arm of the immune system and are responsible for the short-term 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 pro-inflammatory cytokines[1,2,3.] The B cell lineage undergoes a maturation process resulting in considerable plasticity of the antibody response. The differentiation process results in the generation of two types of affinity-matured B-cells: memory B-cells (MBCs) and antibody- secreting plasma cells (PCs)[4,5,6]. 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, or pro-inflammatory [7,8,9,10]. Since their initial discovery, the downregulation of both CD21 and CD27 and the expression of the Th1 master transcription factor T-bet and the integrin CD11c have become a well-known feature of this population, and hence, these cells are also now known as T-bet+ CD11c+ B cells [7 ,11,12]. This novel population was classified as a memory cell due to their 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 based on the presence of additional markers, such as CD95 and CD62L, similar to classical MBC cells [14].

Atypical B cells (atBCs) proliferate following the 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 (APCs), 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 has a significant role in various pathological conditions, ranging from immune system disorders, transplant rejection and inappropriate responses to chronic infections [17,18,19,20.] Additionally, a recent study utilizing singlecell 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 giving 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, migration, and any potential roles they could play in the immune responses.

The many names of atypical B cells

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 functions is drawn from studies conducted on adult patients suffering from several diseases. Moreover, due to the

broad range of pathological 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 based on their prominence in aging mice [22], these cells were then identified in young lupus-prone mice and demonstrated to be critical for viral clearance [23,24]. Similar populations have been reported in humans and often lumped together as ABCs despite growing evidence for the presence of high degree of heterogeneity within these populations. Indeed, in many studies this population has often been defined based on the expression of one or more ABCs markers (preferably CD21low/−, CD11c+ or T-bet+) in MBCs. However, ABC-like populations have also been reported based on the expression of additional markers, in the contest of chronic infectious diseases such as FCRL4 and FCRL5 [25,26,27]. Lack of CD27 and CD21 has been frequently used to identify human ABCs during chronic or repeated Plasmodium infection, referred in this scenario as *atypical B cells* [28,29,30]. Human immunodeficiency virus (HIV)-associated atBCs were first identified in 2008 by Moir et al as *Tissue-like memory B cells* (TLM), which resulted abnormally expanded in the blood of HIV-viremic patients [31]. TLM have a similar CD21-CD27- phenotype as malaria atBCs, but also express high levels of several inhibitory receptors, including FCRL4, CD22 and CD85j. Due to the evidence of a profile of trafficking receptors (CXCR3, and CCR6) similar to those described for antigen-specific T cell exhaustion, they have also defined *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 CD19hiCD21low CD11c+ cells that was aberrantly expanded in the subgroup of patients who develop autoimmune complications, especially autoimmune cytopenia [33,34.] Reports in systemic lupus erythematosus (SLE) patients, identified atBCs population within a specific subset of *Double Negative* (DN) B cells, the so-called “DN2” (CD27−,IgD−,CD21−,T-bet+,CD11c+,CXCR5−). These cells have shown to be correlated with disease activity, autoantibodies production and renal manifestations [35]. It is now generally considered that atBCs are 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 the BCR isotype and the expression of CD27 [36]. Notably, despite their different maturation stages, a recent study demonstrated a similar global transcriptomic profile between circulating atBCs induced by infections (HIV and malaria) and autoimmune diseases (SLE, 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 as well as downregulation of receptors involved in B-cell survival and homeostasis (BAFF-R, CXCR4, CXCR5, and CCR7) [36, 38]. Flow cytometric analysis of T-bet+CD21low B cells from individuals with autoimmune disorders and infections, not only supported the shared phenotype but also revealed a notable impairment in their signaling cascade following B Cell Receptor (BCR) activation as an additional shared attribute [39]. Interestingly, a recent 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 employing multiple markers when assessing the atBCs differentiation. Due to the inconsistency of T-bet+CD21low B cells nomenclature across studies (Table 1) and the limited evaluation in the pediatric setting, we defined this population as atBCs based on the shared markers most frequently found in the scientific literature. Altogether, based upon current knowledge, we suggest considering atBCs as identified by the following markers: CD19+,CD27−, IgD−,CD21lo, CD11c+,T-bet+.

B cells subsets and atBCs 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 [41,42]. A recent meta-analysis encompassing 28 studies has reported significant fluctuations in B cells whitin the first year of life [43]. According to this report, the changes in B cell levels can be summarized as follow: 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 two months; 3) B cell levels continue to expand until they peak at approximately six months of age; 4) after reaching their peak, B cell levels gradually decline and 5) and may plateau at around 10-12 months of age. Literature evidence suggest that this plateau might extends to the second year of life, followed by a gradual decrease until adulthood, where levels remain relatively stable [44,45,46]. 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 [44,47,48] (Figure 1). Then, B cell levels rise until 6 months of life, when immature/transitional and naive B-cell subsets reach their highest levels ever. Thereafter, following exposure to foreign antigens, the size of MBCs and PCs increases, while the proportion of naïve B cells gradually decreases, starting around 18 months of age [41,44,45,48]. In the first weeks of life, CD27+IgD+ unswitched MBCs constitute the largest subgroup within the MBCs compartment. However, continuous exposure to foreign antigens leads to a reduction in the size of this subgroup during childhood, stabilizing in young adults. Conversely, as children age, the number of switched MBCs slowly increases, progressing from around 0.3% in early life to approximately 12% of total B cells at 3 years of age [41,45,49,50].

Moving to atBCs, it has been observed that during the first year of life there is an increase of proportion of MBCs which lacked CD21 (C3d receptor) [48]. Although CD21− B cells are considered by many authors as part of atBCs scenario, it should be noted that the CD21 downregulation by might be not associated to chronic inflammatory process but rather to a limited availability of C3d and C3d-antigen complexes [51]. Indeed, the reduced serum levels of C3 in infants less than one year may contribute to less signaling for the expression of the CD21 receptor during antigen recognition [52]. Blanco and colleagues reported that the proportion of atBCs (identified here as CD27−CD21−) increases and peaks during the first five months of life reaching about 10% of total MBCs. Interestingly, the majority of this population was IgG3+, aligning with previous research indicating that the expression of the transcription factor T-bet regulates the immunoglobulin isotype switching to IgG3 in humans [53,54]. After the first year of life, Jalali et al. observed a gradually decrease of CD11c+ atBCs to ~1.4% in children aged 3-4 years [50], which then raises again at 5-9 years of life

reaching approximately 5% of B cells in the peripheral blood of healthy children. This proportion decrease in adults to ~1.0%. Considering DN B cells, this study revealed that they constituted approximately 3% of total B cells during the first 4 years of life, increasing to around 12% in the 5–9-year age group, and maintaining elevated levels over time (>10%). This is in contrast with previous studies reporting that this percentage was around 5% [7,48,55]. An extensive analysis on a large pediatric cohort revealed that the percentage of atBCs in healthy children ranges 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+ [55].

Atypical B cells 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 (Figure 2). Indeed, a significant number of CD21lowT-bet+ or CD11c+ B cells exhibit an unswitched BCR [56], suggesting they may originate from naïve B cells. This is further supported by BCR sequencing, which reveals some shared repertoire and gene characteristics between naïve B cells and unswitched CD21low B cells [57]. 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+IgMlow subsets with SHM rates equivalent, respectively, to classical MBCs (suggesting GC and classical MBC origin), naïve B cells (suggesting a naïve B cell origin) and intermediate between naïve and classical MBC (suggesting T-B border origin) [37].

Most atBCs cells show signs of a GC reaction, namely in their Ig isotype-switched phenotype and somatically mutated Ig genes [58,59]. 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 relationship with GC B cells, but with fewer SHM and reduced neutralization capacity [36,60]. 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 as well as SARS-CoV-2 vaccination, SHM rates were similar to classical memory and clonal relation was interpreted as post GC B cells [36,61,62]. Although it could potentially develop within GCs, extrafollicular pathways (EF) have been suggested in some pathological conditions, such as SLE [35]. Indeed, both EF and GC B cells can undergo class-switch recombination and SHM. Jenks et al. identify various characteristics of atBCs, observed in SLE patients, which are indicative of EF differentiation. These features include the absence of CXCR5 and CD62L, a chemokine receptor responsible for migration to secondary lymphoid organs, and crucial for lymph node trafficking, respectively [35]. Notably, the EF pathway has been proposed also for CVID, HIV and toxoplasmosis, where atBCs were observed to accumulate outside GC [60,63]. Of note, atBCs could also be GC independent, but 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+ atBCs production than the primary response [21,56].

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 Schlomchik have further elaborated on this matter, proposing that elevated levels of IFN-γ hinder Tfh development and subsequent GC responses, leading to differentiation via the extrafollicular route [64]. Conversely, lower levels of IFN-γ may permit Tfh-mediated differentiation of T-bet+ GC B cells.

The development and persistence of atBCs rely on T cells and IL21R, where these two pathways are likely not mutually exclusive and may have varying impacts across different disorders. Although a stronger involvement of TLR 7/8 and 9 signals has been suggested in the context of SLE [35,65], investigations on patients with monogenic inborn errors of immunity have revealed the critical importance of IFNγR and NF-κB signaling for the differentiation of human atBCs cells, both in *vitro* and in *vivo* [66]. IFN-γ is a T helper type 1 (Th1) cytokine, which upon binding to the IFNγR on B cells activates the JAK-STAT signaling pathway, resulting in up- regulation of the transcription factor T-bet[67]. These findings strongly suggest a unique role of T cell assistance, as evidenced by the reduced presence of atBCs in patients with deficiencies in IL21R, CD40, or CD40L [66]. For these reasons both T peripheral helper cells in inflamed tissues and Tfh cells with a Th1 profile in secondary lymphoid tissues emerge as excellent candidates for delivering the necessary factors for their alternative 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 [66]. In addition, the evaluation of the first reported T-bet deficient patient highlighted the crucial role of the 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 [68].

Transcriptional profile of atBCs

T-bet, encoded by *TBX21* gene, is often considered a key transcription factor for atBCs formation. Perhaps the best described role of T-bet in the humoral immune system is to regulate antibody class switching to IgG2a/c in mice and IgG1 or IgG3 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 [69]. Moreover, T-bet in B cells was linked to the expression of CXCR3 or S1pr5, which control the migration and tissue residency of immune cells [70,71.] 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 upregulates the integrin CD11c (encoded by *ITGAX*) as well as other myeloid markers like FcγRs, CD14, CD68, CD163 hinting that these cells employ unique trafficking patterns and can target distinct microenvironmental niches [12,72,73]. Notably, CD11c emerges as a valuable marker for identifying atBCs, as highlighted in a recent cytometry study by CyToF examining 351 surface molecules on human circulating B cells [74]. Moreover, these cells exhibited elevated expression of inhibitory markers (CD95, FCRL4, and FCRL5), 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 in these cells: *FAS, IL21R, SEC61B, DUSP4, DAPP1, SOX5, CD79B* and *CXCR4* [68]. *IRF5* and *ZEB2* had also been reported to be required for atBCs formation in the SWAP-70 and DEF6 double knockout lupus model[72,75], as excellently reported in the ref[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, due to the interplay between T-bet, *BCL6*, and *BLIMP1* [76]. Research by Pernis' group indicates that certain CD11c+ effector progeny, like PBs, can exhibit a core atBCs 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 [12,77]. Indeed, using RNA sequencing, Wang et al. noted that CD11c+ B cells in SLE had upregulated genes associated with antibody-secreting cells (ASCs) differentiation, such as *PRDM1, AICDA, XBP1, BMP6* [78]. Similarly, Golinski and colleagues 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 [79]. 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 CD21low B cells possess a transcriptional profile indicative of pre-plasma cells, characterized by elevated expressions of *BLIMP1, XBP1, IGJ, IL6R*, and *TNFRSF17* (*BCMA*), along with diminished levels of *BACH2* [73].

These findings contrast to the initial reports conducted in patients with chronic diseases, which did not demonstrate the 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, as these factors can contribute to the observed discrepancies.

Moreover, a recent study provides additional insights into a poorly investigated role of atBCs as APC, a function previously observed in mice where these cells exhibited superior antigen presentation to T cells compared to FO B cells [80]. Kleberg et al. demonstrated that atBCs could enhance CD4+ T cell survival and proliferation through IL-6 production. 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 atBCs 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 has been identified in the contest of several infections such as: HIV [31,54], malaria [15,37], HBV[81], HCV [82], tuberculosis [83], SARS-CoV-2 [84], Respiratory Syncytial Virus [85], Dengue [86], Influenza [87], but its role changes depending on whether the infection is acute or chronic. For instance, an expansion of atBCs during natural acute infections and vaccinations, has been linked to various useful functionalities. Eccles et al. demonstrate

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 [88]. On the other hand, excessive expansion of atBCs during acute infections has been correlated with pathogenic responses. Indeed, in severe COVID-19 patients atBCs have been associated with poor outcomes, high mortality rates, and with the production of autoantibodies [89,90,91] [65]. In contrast, in chronic infections like HIV, HCV, and malaria, atBCs expression of many inhibitory receptors (FcRL4, FcRL5, CD85j and CD22) and the refractoriness to stimulation through their BCR, TLRs, CD40 and cytokine receptors have been suggested to be a critical aspect of the ineffective immune responses known to accompany these infections [8,92]. 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 (Pf)* infection, leaving them susceptible to repeated bouts of malaria [93]. As a result, most cases of malaria occur in children under the age of 10, while adults with life-long 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 [27,94]. A longitudinal analysis of *Pf* infected children has suggested a positive correlation between the incidence of febrile malaria and the expansion of T-bet B cells via Th1 cytokines [95]. Malaria may potentially impact the B cell compartment also 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 naïve B cells, atBCs, and MBCs and found that the VH and VL repertoires of classical MBCs and atBCs had similar V gene usage, SHM rates, VH CDR3 length and composition [96]. Using an accurate and high- coverage Ig sequencing method, the same researchers group found unexpected high levels of SHM in infants as young as 3 months [97]. Antibody lineage analysis showed that SHM also increased in both infants and young children upon febrile malaria.

Atypical B cells have been hypothesized to be exhausted or dysfunctional based on their increased expression of inhibitory receptors, such as CD22, CD85j, and FcgRIIB, and homing receptors, such as CD11c, CCR6, CXCR4, and CXCR3 [95]. In addition, these cells have reduced responsiveness to restimulation of sorted human CD21lo FcRL5+ or FcRL4+ B cells [98]. Works by Crompton's group highlighted FcRL5 as an inhibitory indicator on atBCs as FcRL5hi expressing B cells were less responsive to BCR stimulation and showed a key role of T-bet, which correlates inversely with BCR signaling and skews toward IgG3 class switching [28,95]. Muellenbeck et al. showed that these cells were enriched for self- or polyreactive BCR specificities, suggesting that they could be anergy in order to safeguard the host from autoimmune reactions [99]. Indeed, in some patients (including children) with acute malaria, the expansion of atBCs cells correlates with the production of autoantibodies against phosphatidylserine, contributing to the development of anemia [100].

Although atBCs cells can appear dysfunctional, one report provided evidence of *Pf*-specific Ig transcripts produced by atBCs in vivo and showed that broadly neutralizing *Pf*-specific antibodies can be cloned from atBCs [99]. In addition, atBCs expand in response to *Pf*

sporozoite vaccination [21] . According to Ambegaonkar et al., atBCs can still contribute to the production of protective antibodies [101]. The authors proposed that inhibitory receptors, particularly FcgRIIB, were responsible for restricting the responsiveness of CD21lowCD27lo B cells to soluble antigen. However, when the BCR ligand or antigen was presented to the cells while fixed in a lipid bilayer, FcgRIIB was removed from the immunological synapse, making it possible for CD19 to engage with the BCR [101] (Figure 3).

Recent research has indicated that atBCs may actively contribute to humoral immunity to infectious pathogens. Hopp and colleagues found that in response to acute malaria, *Pf*-specific atBCs of Malian children are activated, with increased frequency and up-regulation of molecules (CXCR3, CD86) that mediate B-T cell interactions [15]. Consistent with this ex vivo findings, the authors found that atBCs upregulated *PRDM1* and the activation PCs marker CD38 when co cultured with autologous Tfh cells from malaria-exposed individuals, suggesting that atBCs may actively contribute to humoral immunity to infectious pathogens. Recently, Reyes et al, showed that CXCR3 and CD95 atBCs 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[102]. Moreover, the study unraveled through a single cell sequencing and BCR analysis that atBCs cells, in malaria setting, contribute 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, 103,104]. B cells lacking CD21 and CD27, but expressing CD11c and FcRL4, appear in association with HIV viraemia, are more frequent in viremic compared with non-viremic patients, and decreased with antiretroviral treatment (ART) [31, 32, 103]. A recent study analyzing lymph nodes has shown that HIV-specific B cells in infected individuals were enriched among CD19+Tbet^{hi} B cells and that this population was not present in healthy individuals[60]. 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 [60 105]. However, Knox and colleagues revealed that during HIV infections in adult patients the specific HIV gp140 response is dominated by expanded atBCs [25]. Atypical B cells dysfunction is seemed to be associated with the binding of soluble IgG3 to IgM-expressing B cells, along with C1q and, the inhibitory Fc receptor CD32b (also known as FcRγIIB), which led to an increased clustering of the IgM BCR and decreased response to stimulation [106]. In line with this "*exhausted*" status, our group showed a positive association between atBCs, and plasma complement cascade proteins in children [107]. Additionally, our group's studies have indicated that the atBCs expansion in HIV infected pupils is associated with a decreased ability to respond to childhood influenza and MMR vaccinations [107],[108],[109]. Recently, we investigated the evolution and maturation of the B cell compartment over the first two years of life in children with perinatal HIV infection. We observed an expansion of atBCs at 40 days of life in these children, which may contribute to B-cell exhaustion [110]. Indeed, in our study, children with perinatal HIV infection and uncontrolled viral replication exhibited a diminished capacity to sustain protective tetanus antibody titers over time.

Notably, in pediatric HIV infected children, a longer time on ART is related to lower atBCs while an earlier start is associated with lower frequencies of mature activated B cells (CD19+CD10−CD21−)[111,112,111].

The poor response to BCR stimulation had led to the original designation that atBCs was anergic or exhausted cells. Recent discoveries, especially in the malaria field, 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

Recent evidence suggests that atBCs play a significant role in the adaptive response triggered by vaccines in healthy adult individuals [21, 114]. Steuten and colleagues 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 post SARS-CoV-2 vaccination. Interestingly, their study highlighted variations across distinct CD11c+Tbet+ B cell subsets. The expansion of spike-specific CD11c+ B cells was primarily orchestrated by the DN2 (CD11c+, IgD−,CD27−) and ABCs (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 [73,115] and tetanus vaccinations [116]. 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 days period following vaccine boost [73]. Furthermore, Sutton and colleagues established that B cells with an atypical transcriptional profile emerge during the primary immune response to vaccination and can be reactivated upon subsequent exposure, as evidenced through influenza vaccine challenges and sporozoite immunizations [21]. However, investigation of atBCs transcriptome have unveiled that these cells do not exhibit spontaneous antibody secretion and were primed for PC differentiation while exhibiting resistance to further differentiation in the GC [73].

Despite these results which highlight that atBCs are part of a normal B cell antigen-response [21,27,73,115, 116], the relevance of antibody production by this population in the infection control is less clear. A fundamental issue that remains unresolved is whether atBCs yields antibodies with distinct qualitative properties compared to those generated through the conventional GC- pathway.

Of note, in the first T-bet-deficient patient, the vaccination response against the investigate bacterial antigens seemed normal but respiratory viruses (Influenza, SARS-CoV-2) response was not investigated in this patient [68].

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 in HIV-infected children. Indeed, HIV infected children with an expansion of atBCs, demonstrate a compromised

vaccine response [108]. Thus, it is plausible that the inflammatory context makes them anergic or exhausted as previously suggested [32].

These disparate observations may also stem from the existence of various subsets of atBCs with differing effector functions, stages of maturation or attributable to differences in context in which have been 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 affected by Rheumatoid Arthritis [117], SLE [35,78], primary Sjogren Syndrome [118], Systemic Sclerosis [119], ANCA-associated vasculitis [39], Multiple Sclerosis [58,120,121], Crohn's disease [122], Graves' Disease [123], Hashimoto's thyroiditis [124], Myasthenia Gravis [125] and Guillain-Barrè syndrome [125]. 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 [7,59]. Moreover, atBCs have been linked also to several immunodeficiency disorders especially CVID[33,34], Ataxia-Telangiectasia[126], Wiskott-Aldrich syndrome [127], IgA deficiency [128], Chronic granulomatous disease [129] and partial RAG deficiency [130] but their role in this conditions, is still controversial.

Autoimmune diseases

Systemic Lupus Erythematosus—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, also in young children with active disease [35]. In this scenario, atBCs have been identified as DN2 cells (CD27−, IgD−,CD38low,CD11c+,CXCR5−,FcRL5+,FcRL4−,T-bet+) or as CD27−,CD38low, CD11c+, FRL5+;FcRL4+,T-bet + and 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 [35,78]. Moreover, these cells have been identified not just in the peripheral blood but also in areas of organ injury, such as the kidneys [131,132,133]. The transcriptional profile found higher expression of IRF4 and lower expression of IFR8 compared to other B cell subsets, indicating the tendency towards differentiation into PBs/PCs [134]. Although atBCs have been extensively studied in SLE mouse models and adult patients there is very few data on pediatric populations. Corrente and colleagues reported an increase of atBCs (CD21*low* CD11c+ B cells) in children with immune system disorders, including SLE [55]. A recent study revealed a notable increase in T-bet-expressing naïve B cells and DN B (CD21−,CD11c+) cells in patients with childhood SLE, as opposed to healthy children [135]. 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 define a patient population with higher disease severity, higher frequency of ENA and anti-dsDNA positivity and higher proportion of proliferative lupus

nephritis [135]. In another study, a multi omics approach combined with an 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 [136]. 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 (e.g., Antinuclear antibodies, ANA) in a significant proportion of patients suggests the involvement of autoreactive B cells [137],[138]. A recent 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 (SF). Increased frequencies of atBCs (CD21lo/−CD27− IgM DN2 B cells) were observed in the SF 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 [139]. A previous study showed that atBCs accumulated in the joints of JIA patients and displayed features of APCs, with expression of costimulatory molecules (CD80/CD86) and a polarized pattern of cytokine secretion capable of inducing T cell activation and Th1 differentiation [140]. Fischer and colleagues reported that synovial CD4+ T cells promote aberrant B cell activation in ANA+ JIA by promoting the differentiation of B cells toward the CD21low/− CD11c+ phenotype through the secretion of cytokines like IL-21 and IFN-γ [141]. These findings suggest that in children's inflammatory arthritis settings, expanded Tfh cells in the synovium might promote B cell differentiation into atBCs through the secretion of cytokines like IL-21 and IFN-γ.

Immunodeficiency disorders

Common Variable Immunodeficiency—CVID is a heterogeneous disease characterized by hypogammaglobulinemia, defective antibody responses and recurrent infections. atBCs have been extensively studied in CVID adult patients where they have been linked to splenomegaly and autoimmune cytopenia[33], and subsequently to granulomatous disease[142]. In pediatric patients, a study revealed that the increase in atBCs (referred here as CD21low), was linked to the development of enteropathy and autoimmune symptoms but, was not found to be associated with the development of splenomegaly [143]. On the other hand, granuloma formation was not confirmed in another single-center pediatric cohort study [144]. In CVID patients, atBCs were CD21−/low,CD27−,CD38low,CD11c+,FcRL4+,FcRL5+ and expressed unmutated IgM and IgD, although this may reflect an inability to class-switch or form functional GCs [145]. Recently, it has been discovered that this population expresses T-bet. Interestingly, these cells have been observed not only in secondary lymphoid organs and the spleen but also in bronchoalveolar lavage samples obtained from patients who have developed interstitial lung disease [66].

Other immunodeficiency syndromes—A recent study involving 1180 pediatric patients demonstrated significant variability in the percentage of atBCs depending on the underlying medical condition [55]. 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 Di George syndrome and IgA deficiency. Recently, 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/ autoreactive B cell clones in the periphery[130]. These alterations are likely to be caused by environmental triggers (such as chronic infections and microbiota translocation) along with intrinsic factors (such as elevated BAFF, reduced Treg/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 affected by these conditions [146,147]. Nevertheless, the function of these cells in these diseases is still unknown although an association with the development of autoimmune cytopenia has been suggested [147] .

According to this finding several authors 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 [148]. 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 non-alcoholic fatty liver disease [149]. Atypical B cells have gained attention in recent years due to their potential involvement in obesity-related inflammation and metabolic dysfunction.

Research from Blomberg' 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 [150,151]. Subsequently, Frasca et al. reported that atBCs (CD21−,CD27−,IgD−, T+bet+,CD11c+) in obese patients resulted associated with increased secretion of IgG with autoimmune specificity [152]. Recently, Hagglof and colleagues have deepened this topic, showing that T-bet+, CD11c+ B cells were causally related to the onset and exacerbation of metabolic disease in obese patients [153].

The authors demonstrated that adipose tissue-resident atBCs were regulated by invariant natural killer T (iNKT) cells and that this atypical B cell population could be expanded by stimulation of TLR-7, in an iNKT cell-dependent manner [153,154]. These interactions result in the production of chemokines and antibody mediators (IgG2c) that amplify the initiation and severity of metabolic disorders. By employing murine model with a B cell-specific knockout of T-bet the researchers demonstrate 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 pro-inflammatory macrophages. This approach unveils pathologic immunoglobulins as the central mechanism driving atBCs inflammation in obesity, thereby highlighting the potential of targeting atBCs in future therapeutic strategies to limit metabolic disorders. However, for this specific topic, there is 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 who suffer from obesity and metabolic disorders.

Future perspectives

Sex difference and potential therapeutic approaches for atBCs in autoimmune diseases

One of the most striking aspects of the atBCs population is its potential to be controlled in a sex-specific manner with a greater degree in females than males. The expansion of this compartment in females suggests their role in autoimmune disease development and potentially contributes to the documented sex-based differences in immune responses during viral infections and vaccinations [155]. However, sex differences extend beyond the mere accumulation of atBCs, encompassing various aspects within the atBCs compartment. Research on lupus murine models have revealed that atBCs from females but not male, express an “interferon signature” and were more prone to differentiate in CD11c+ effector population [77]. Moreover, the duplication of TLR-7 in male mice lacking SWEF proteins overrode the sex-related bias and intensified the pathogenic effects of atBCs [77]. 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 non-coding RNA XIST, 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 TLR-7 and CXorf21/TASL (an adaptor that regulates IRF5 activity) [156]. Interestingly, escape of XIST-dependent genes, coupled with TLR-7 activation, facilitate the development of CD11c+ B cells in autoimmune settings [12,156,157], (Figure 4). Further exploration of the atBCs population in males versus females during infections and vaccinations is necessary to ascertain whether the sex bias extends beyond frequency and leads in distinct functional capacities in the atBCs population between 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 depleting drugs have demonstrated the ability to reduce atBCs in SLE [158,159] (Figure 4). There is significant evidence indicating a connection between the process of reconstitution of B cell subsets following B cell depletion and the clinical progression in 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 in the development of tailored drugs for these cells.

Concluding remarks—In various pediatric chronic inflammatory conditions, there is a consistent observation of an expanded population of atBCs with different physiological and pathogenetic roles, although these different functions may be context dependent. According

to scientific literature[160], potential roles for atBCs emerge: they could 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 potentially specialize in antigen presentation, primarily aimed at activating T cells.

In the autoimmunity field, this cell populations often correlate with disease-specific manifestations and autoantibodies production, warranting consideration for elimination. However, the exact function of atBCs during immunodeficiencies and chronic infections remains unclear. Conflicting results on anergy versus hyperresponsiveness are likely context dependent, with refractory phenotype in chronic exposure and hyperresponsiveness in acute antigenic exposure. In murine acute infection, atBCs have been postulated to participate directly in the anti-pathogen antibody response while in human the relevance of antibody production by this population in the infection control is less clear.

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

Thus, in infectious scenarios, particularly those involving chronic infectious diseases, further research is 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, definition and clear cut-off of abnormal expansion is crucial for driving immunomodulatory treatments and facilitating comparisons across various models and research findings offering insight into their role in immune responses and autoimmunity.

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Abbreviations used.

ABCs	Age-associated B cells
ANA	Antinuclear antibodies
APCs	Antigen-presenting cells
ART	antiretroviral treatment
ASCs	Antibody-secreting cells

atBCs	Atypical B cells
BAFF	B-cell activating factor
BAL	Bronchoalveolar lavage
BCR	B Cell Receptor
CD	Cluster of Differentiation
CDR3	Complementarity determining region 3
CSF	Cerebrospinal fluid
CVID	common variable immunodeficiency
DN	Double Negative
EF	Extrafollicular
ENA	Extractable Nuclear Antigen
GC	Germinal Center
HIV	Human immunodeficiency virus
IFN	Interferon
iNKT	invariant natural killer T cells
JIA	Juvenile idiopathic arthritis
MBCs	Memory B-cells
PB	Peripheral blood
PBs	Plasma blasts
PCs	Plasma cells
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SF	Synovial fluid
SHM	Somatic hypermutation
SLE	Systemic Lupus Erythematosus
Tfh	T follicular helper cells
TLM	Tissue-like memory B cells
TLR	Toll Like Receptor
Treg	Regulatory T cells
VH	Variable heavy chain

VL	Variable light chain
XCI	X chromosome inactivation

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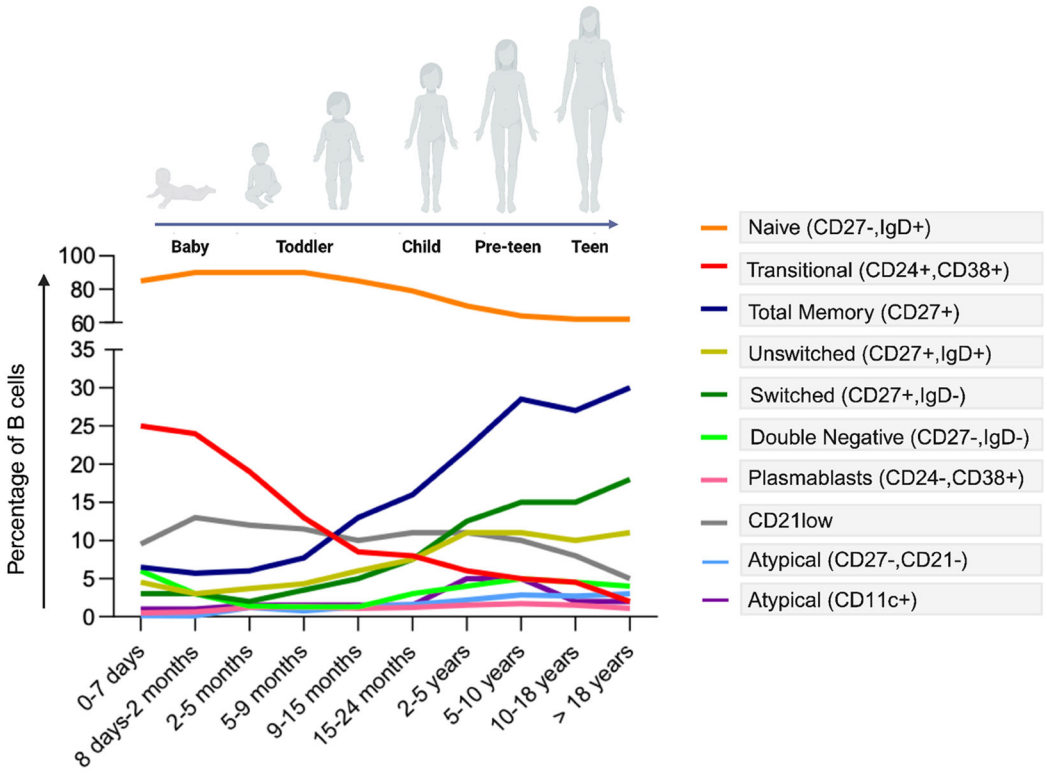

Figure 1.

Variations in B Cell Populations, encompassing atypical B cell subsets, during childhood and adolescence (adapted from references 42, 46, 48, 55)

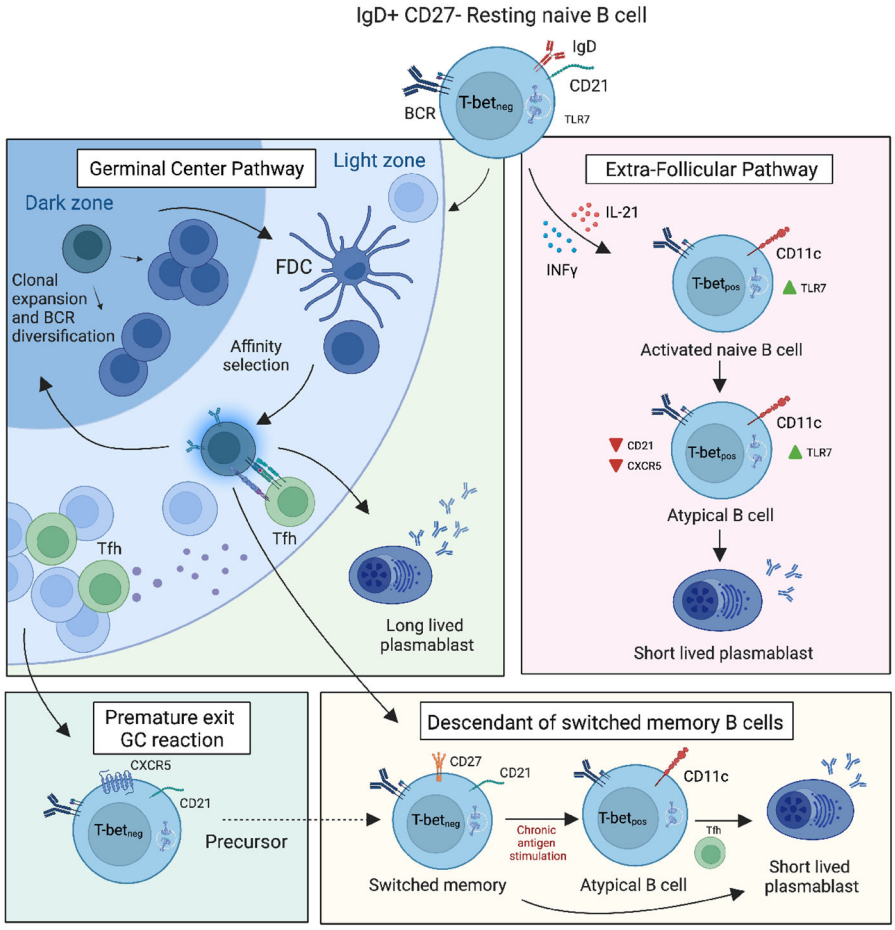

Figure 2.

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

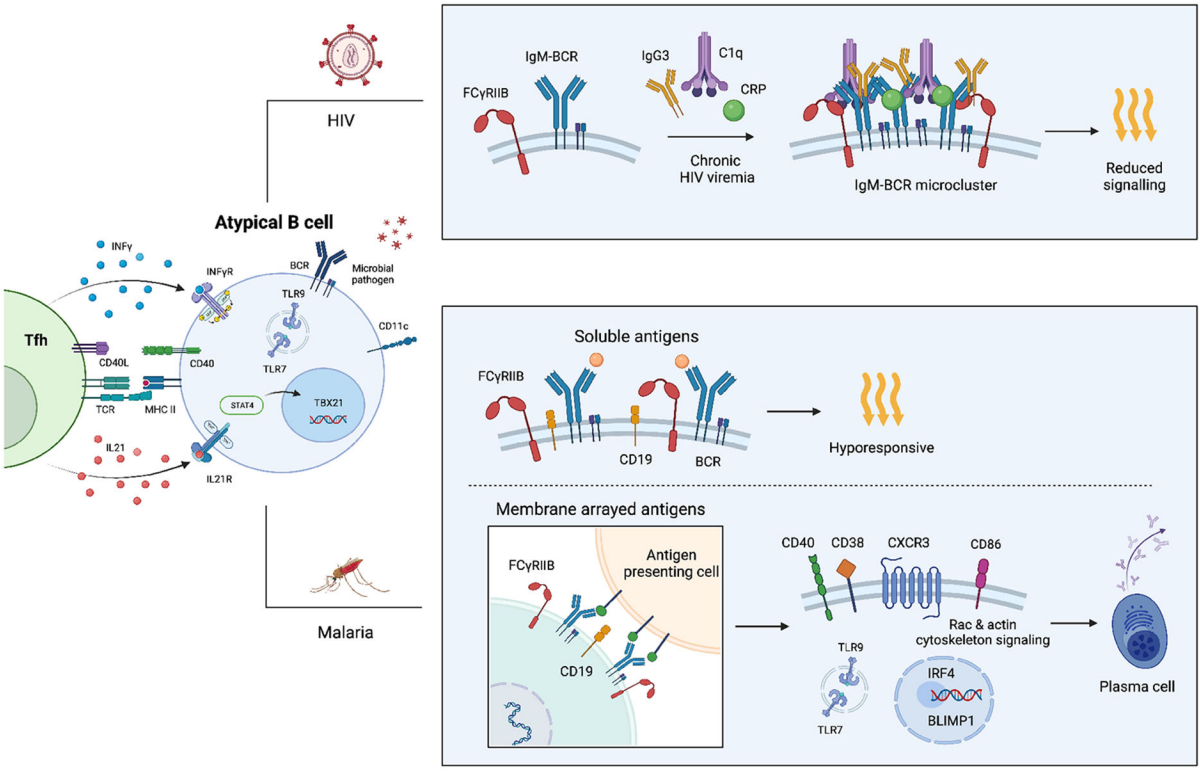

Figure 3.

During chronic HIV-1 viremia, the inhibitory Fc receptor FcgRIIB (CD32b) rises and becomes linked to micro clusters of IgG3−IgM−BCR, in addition to C1q and c-reactive protein (CRP). This clustering predominantly takes place in atBCs and involves direct engagements between IgG3 and the IgM− BCR, leading to a reduced intracellular signaling (106). In the context of malaria, the responsiveness of atBCs relies on the way the antigen is presented. atBCs that express CD11c, T-bet, and FCRL5 also exhibit heightened expression of inhibitory receptors, such as FcgRIIB. When the BCR is bound, FcgRIIB diminishes the interaction between CD19 and the BCR, thus impeding downstream signaling and resulting in reduced responsiveness. Conversely, atBCs cells that bind to antigens arrayed on the cell membrane establish an immunological synapse that excludes FcgRIIB. This exclusion enables CD19 to effectively engage the BCR and facilitate downstream signaling, which subsequently triggers the transcription of *IRF4* and *BLIMP1*. This process promotes differentiation into antibody-secreting cells. 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 IFNγ may contribute to T-bet expression (15).

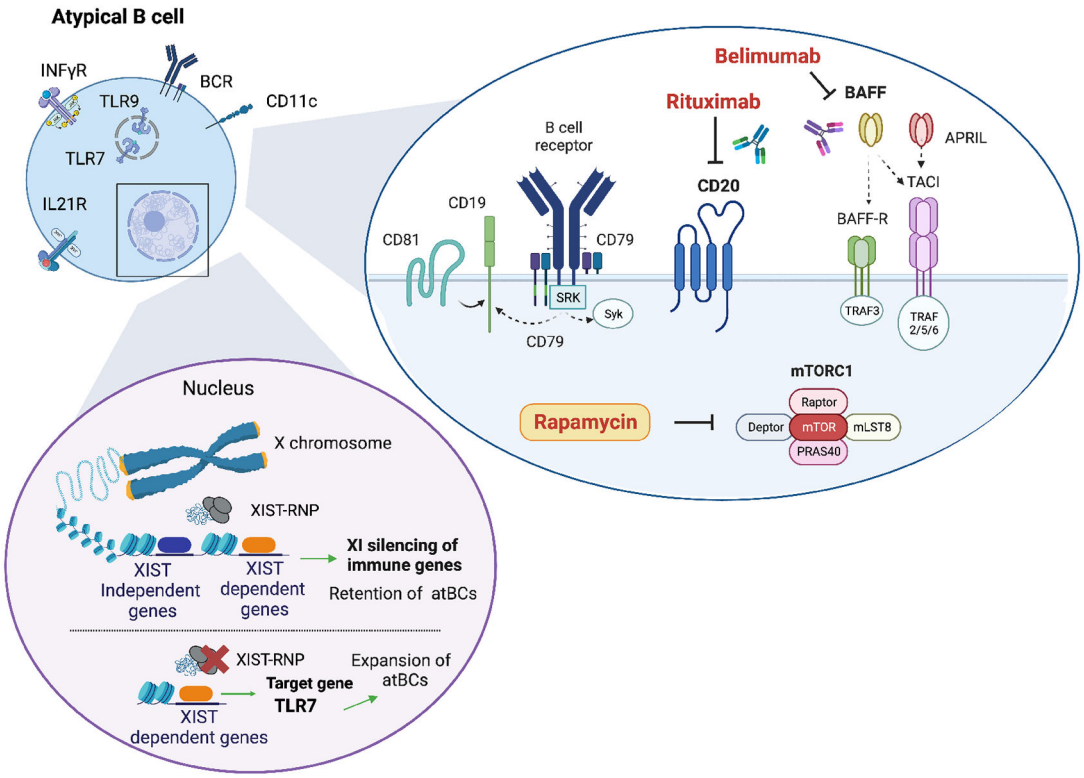

Figure 4.

Rituximab (anti-CD20 monoclonal antibodies) and Belimumab [anti-BLyS (B-Lymphocyte Stimulator) monoclonal antibodies] can reduce the level of atBCs cells in SLE patients (158, 159). Moreover, mTORC1 hyperactivation has been linked to the dysfunction of atBCs in SLE (133). Thus, the inhibition of this pathway could reduce the levels of this B cell population. In the cell nucleus is shown the model proposed of XCI maintenance in human B cells (156). In detail, XIST loss and TLR-7 stimulation promotes CD11c+ atypical B cell formation.

Table 1.

Numerous designations for atBCs. Selected examples of the diverse terms employed to characterize cells exhibiting atBCs-like features in healthy and pathological conditions.

	Condition	Name	Location	Phenotype	Additional markers	T bet	Proposed functional role	Disease association	Ref
Adult									
Healthy subjects		Tissue-resident	Tonsil	CD19+IgD− CD27−CD38−	FcRL4+ CD11c+	−			13
Immune system disorders	Systemic Lupus Erythematosus	DN2	PB/Kidney	CD19+IgD− CD27−CD21−	CXCR5−FcRL5+	+	Precursor of extrafollicular ASCs	Autoantibodies, disease activity, Lupus nephritis	35 64 131
	Rheumatoid Arthritis		PB/SF	CD19+IgD− CD27− CD21low		NA		Joint destruction in ACPA+/RF+ patients	117
	Primary Sjogren Syndrome		PB	CD19+CD27− CD21low CD38low	CD11c+	+	Anergic autoreactive memory cells	Associated with lymphoproliferation	118
	Systemic Sclerosis		PB	CD19+CD27− CD21lowCD38low	CD11c+	NA		Disease activity, vascular complication	119
	Multiple sclerosis	CD21low	PB/CSL	CD19+IgD−CD27− CD21low	CD11c+		Switched memory	Correlated with the presence of brain inflammatory lesions.	120 121
	CVID	CD21low	PB/BAL	CD19+IgD+CD27− CD38lowCD11c+	FcRL4+	+		Splenomegaly and autoimmune manifestations	33 142
Infectious diseases	Malaria	Atypical	PB	CD19+CD27−CD21−	CD11c+ CXCR5− FcRL5+	+/−	Precursor of antigen-specific ab, auto-abs to red blood cell	Associated with anaemia	99 100
	HIV	Exhausted, tissue-like	PB	CD27− CD21−	CD11c+	+	Exhausted memory cells	HIV-specific Ig	31 60
	COVID-19	Atypical	PB	CD27− CD21−	CD11c+	+		Morbidity	90
Other conditions	Obesity	Aged-Adipose B Cells	Adipose tissue	CD19+IgD−CD27− CD21−	CD11c+	+	Precursor of extrafollicular ASCs	Autoantibodies production Exacerbates metabolic disorder in obesity	151-153
	Vaccination	Atypical	PB	CD19+CD20lowIgD− CD27−	CD11c+ CXCR3+	NA	primary response to antigen vaccine and respond to booster immunization	Induced after vaccination against different pathogens	21 73, 115
Children									
Healthy children			PB	CD19+CD27−CD21−		NA			55
Immune system disorders	CVID	CD21low	PB	CD19+CD27− CD21low		NA		enteropathy and autoimmune symptoms	143,144

	Condition	Name	Location	Phenotype	Additional markers	T bet	Proposed functional role	Disease association	Ref
	Systemic Lupus Erythematosus		PB	CD19+CD27−	CD11c+	+			135 136
	Juvenile idiopathic Arthritis		PB/SF	CD19+IgD−CD27−CD21−	CD11c+	NA			140 141
Infectious diseases	Malaria	Atypical	PB	CD19+CD27−CD21−	CXCR3+ CD86+ FcRL5+	+	Precursors of ASCs	May contribute to humoral immunity to malaria	15
	HIV	DN	PB	CD19+IgD− CD27−		NA	Exhausted memory cells	Negative correlation with immune response after seasonal influenza vaccination. Negative correlation with time under antiretroviral therapy	109 110 112
	Respiratory Syncytial virus	Atypical	PB/Adenoid	CD19+IgA−IgG−CD27−		NA		Produce RSV neutralizing antibodies in adenoid tissue	85
Other conditions	Trisomy 21		PB	CD19+CD27−CD21−	CD11c+CXCR5−CXCR3+	+	More likely to have self-reactive features	Correlated with cytokine levels, plasma IgG and pCs	161

Abbreviations. ACPA: Anti-citrullinated protein antibodies; ASCs: Antibody-secreting cells; BAL: bronchoalveolar lavage; CSF: Cerebrospinal fluid; DN: Double Negative; SF: synovial fluid; ND: not available; PB: peripheral blood; RF: Rheumatoid Factor