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Mini Review

Self-Antigens Select B Cells: A New Perspective on B Cell Selection and Function

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ABSTRACT

The adaptive immune system is shaped by self-recognition, creating a paradox where autoreactivity is essential for immune regulation, yet implicated in autoimmune diseases. Traditionally, B cell selection in the bone marrow (BM) has been viewed through the lens of negative selection, eliminating potentially harmful clones. Emerging evidence challenges this perspective, revealing a subset of B suppressor cells (Bsup) that actively regulate immune homeostasis. Unlike conventional negative selection, C1-specific Bsup cells, which recognize collagen type II (Col2), engage Col2-specific regulatory T cells (Tregs) to suppress inflammation in healthy individuals. This suggests that Bsup play a role in both peripheral and central tolerance, akin to Tregs. However, the molecular mechanisms governing Bsup selection, differentiation, and function remain unknown. Understanding how Bsup distinguish homeostatic from pathogenic autoreactivity could transform autoimmune disease treatment, shifting the focus from eliminating autoreactive B cells to harnessing their regulatory potential for precision immunotherapy.

1 | The Paradox of Self-Recognition

The immune system developed to maintain tissue homeostasis in multicellular organisms. Over time, antigen specificity evolved alongside adaptive immune mechanisms, enabling the immune system to mount strong responses against foreign pathogens while maintaining tolerance to the body's tissues. Obviously, the immune system is fundamentally developed and shaped by self-recognition, leading to a paradox: autoreactivity is both essential for maintaining tissue homeostasis and potentially harmful in inducing autoimmune reactions. This duality is at the core of immunology, where the immune system must walk a fine line between beneficial self-recognition and detrimental autoimmunity. Two distinct sites in the body are responsible for educating the adaptive immune system to what is self and what is not: the bone marrow (BM) for B cells and the thymus for T cells. In these sites, T and B cells are selected based on the presented/available autoantigens.

For T cells, autoantigen presentation is mainly carried out by specialized cells known as medullary thymic epithelial cells (mTECs) that express a wide array of peripheral tissue antigens. Failure to express those autoantigens results in multiorgan autoimmunity. While this mechanism has been traditionally attributed to the expression of the autoimmune regulator (AIRE) [1] and Fezf2 [2], recent studies indicate that T cell selection also involves multiple transcription factor (TF)-lineage-defining mechanisms [3]. Both systems induce clonal deletion of conventional T cells and positive selection of autoreactive Tregs. These autoreactive Tregs are crucial for preventing autoimmunity [4] by recognizing and tolerizing the immune response against autoantigens such as pancreatic islet cells [5], insulin beta chains [6], myelin basic

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protein [7], proteolipid peptides [8], and recently prostate [9], highlighting their importance in maintaining tissue homeostasis.

Although clonal deletion of autoreactive conventional T cells exists, the presence of autoreactive T cells in the periphery of healthy individuals indicates the imperfection of this tolerance system [10]. One example is the autoantigen collagen type II (COL2), which has unique properties (BOX 1) being expressed by mTECs in the thymus and is a major component of the trabecula in the BM. COL2-specific T cells escape central negative selection due to the inability of mTECs to present posttranslationally modified autoantigens. In the thymus, COL2 is presented in its native nonglycosylated form, whereas COL2, expressed in the articular cartilage, is predominantly glycosylated [11]. This could explain the physiologic occurrence of autoreactive COL2-specific T cells in both mice and humans.

BOX 1

Properties of COL2: It is the most abundant protein in articular cartilage, and a T cell and B cell response against COL2 has been associated with RA [12] which is a prototypic autoimmune disease that develops in three distinct stages: priming, onset, and chronic [13]. One dominant linear T cell epitope ($COL2_{259\text{-}273}$) [14] and several conserved triple helical B cell epitopes (U1, J1, C1, D3, E10, and F4) have been mapped on COL2 [15]. In RA, autoantibodies against COL2 can recognize the defined epitopes in their triple helical and cyclic conformation. The identified C1-Bsup, however, recognize only the C1 triple-helical epitope [16].

Indeed, COL2 is predominantly produced by chondrocytes in cartilage and is not widely expressed in many tissues like collagen type I (COL1). Consequently, there is a strong negative selection of both B and T cells reactive with COL1, but not with COL2. A recent study neatly demonstrates that overt reactivity to widespread self-ligands found in the salivary glands and prostate does not lead to the deletion of autoreactive T conventional cells but rather their positive selection. Instead, these cells are enriched in non-lymphoid organs post-Treg depletion and adopt a T follicular helper (Tfh) cell signature [17]. These examples demonstrate that autoreactivity in the T cell compartment is physiologic and important for maintaining tissue homeostasis and may be adaptive immune cell regulatory functions.

2 | Autoreactivity in B Cell Selection: Beyond Negative Selection

Unlike the protective autoreactivity seen in T cell selection, much of the literature regarding B cell selection in the BM focuses on the exclusive negative selection of dangerous autoreactive B cell clones through clonal deletion [18], anergy [19], or receptor editing [20]. However, the concept of positive selection in the B cell compartment is well established in fetal liver-derived B1 cells [21], and for selection of early B cell receptors in the BM, whereas there is limited knowledge of self-antigen selection of adult BM-derived B2 cells.

Autoreactive B1 cells contribute significantly to tissue homeostasis by producing polyreactive natural antibodies, which could be regulatory, but could also serve as a first line of immune defense [22]. These natural antibodies have the ability to bind to a diverse range of pathogens, preventing excessive inflammation, clearing apoptotic cells, and maintaining immune balance [23–25]. The early selection of B1 cells in the yolk sac and fetal liver has been shown to be related to reduced levels of STAT5 signaling, facilitating the positive selection of an assembled autoreactive BCR. However, this process is blocked in the adult BM for the high STAT5 phosphorylation, leading to the pairing of a productive heavy chain and a surrogate light chain in B2 cells. This checkpoint is thought to disfavor autoreactivity, as the surrogate light chain poorly binds autoreactive heavy chains [26].

Experiments using cellular barcoding displayed a common progenitor cell capable of differentiating into both B1 and B2 B cells [27]. This phenomenon circumvents the known mechanisms for negative selection of autoreactive B2 B cells but cannot explain fully why approximately 20% of mature B cells in humans retain autoreactivity detectable with in vitro assays, with around 5% exhibiting polyreactivity [28]. Given that the human body contains approximately 3×10^{11} B2 B cells [29], the translated absolute number of persisting autoreactive B cells is likely to be positively selected to serve an essential purpose beyond their assumed pathogenic potential.

3 | Discovery of Autoreactive B2 Cells in Healthy Donors

The current understanding of antigen-specific autoreactive B cells has largely been derived from studies using artificial systems, such as transgenic mice engineered to express specific autoantigens and corresponding B cell receptors, which allow for easier experimental tracking and analysis [18, 19]. In contrast, we adopted a more physiologically relevant approach by focusing on a naturally occurring autoantigen present peripherally in the articular joint, such as COL2, and also expressed in central lymphoid organs (thymus and BM), which is recognized by positively selected T and B cells in both mice and humans. Using this model, we successfully cloned an autoreactive B2 B cell specific for the triple-helical C1 epitope of COL2 and expressed its recombined VDJ heavy chain region in vivo [16]. Remarkably, the secreted autoantibodies retained the ability to bind COL2 in vivo and contributed to the development of arthritis [30]. However, in contrast to traditional views that associate autoreactivity with pathogenicity, these C1-specific B cells were positively selected [31]. Notably, the measured affinity of the C1-specific BCR is relatively weak as compared with HEL/anti-HEL binding [19] or other somatically mutated autoantibodies [32], yet sufficient to permit in vivo recognition without triggering deletion. This is further supported by observations in a mutant mouse model expressing a single point mutation in the C1 epitope of COL2 ($COL2.^{R360Q}$), which abolishes C1 binding. In these mice, we observe a light chain receptor editing, but this time to rescue the selection of autoreactive C1-Bsup lineage [16]. These findings suggest that, unlike the strong BCR signaling that selects B1 cells

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[33], positive selection of B2 cells is more complex, involving the avidity, affinity, and the in vivo nature of the interaction between the BCR to its cognate autoantigen.

Remarkably, these C1-Bsup cells were able to suppress COL2-specific inflammation in vivo, as demonstrated by adoptive transfer experiments where administration of C1-Bsup prior to disease onset inhibited arthritis development. This effect was antigen-specific, as no suppression was observed in a model of MOG-induced EAE. Notably, transfer of C1-Bsup after disease onset, when T cell priming is complete, did not affect disease progression, suggesting that their regulatory role is confined to the priming phase and does not extend to the effector phase, which is dominated by neutrophils, autoantibodies, and other innate immune mediators. Mechanistically, this suppression was linked to enhanced activation and proliferation of COL2-specific Tregs, observed in vivo and in vitro when C1-Bsup were co-cultured with COL2-specific T cells. The requirement for direct antigen presentation was confirmed by the loss of this effect in transwell assays, indicating that cytokines alone are not responsible for Treg activation. Since the suppressive function of these B2 B cells was irrespective of IL-10, coining them here as B suppressor cells or "Bsup" is deemed necessary to distance them from the IL-10-producing regulatory B cells, denoted as "B10" [34] or "Bregs" [35]. While the exact molecules involved in this T-B interaction are not fully elucidated, co-stimulatory molecules (signal 2) and the cytokine milieu (signal 3) likely determine the activation status of Tregs [16]. It remains unclear how these Bsup cells, despite possessing a naïve phenotype (IgM and IgD double positive) and an antigen-processing and presentation transcriptional signature, could exceptionally differentiate into pathogenic plasma cells producing autoantibodies.

4 | Unanswered Questions and Knowledge Gaps

The mature B cell repertoire is enriched in autoreactive cells that, while often appearing anergic, remain responsive to autoantigens [36]. Despite their prevalence, the selection and transcriptional regulation of these cells remain poorly understood. Key outstanding questions include:

1. Which autoantigens select autoreactive B cells, and what characterizes such antigenic epitopes?
2. Is there a TF analogous to Foxp3 in Tregs that governs the selection of autoreactive B cells in the BM?
3. Do these cells employ unique regulatory networks to control their differentiation into autoantibody-producing plasma cells?

TF are critical in selecting and driving the differentiation of B cells. As B cells migrate to follicles, a complex of TF-driven processes (involving Pax5, Bcl6, IRF4, and Blimp1) dictate their entry, selection, and differentiation in GCs [37–39]. We propose that a unique set of TFs regulates Bsup at some point during their ontogeny and maintenance in the periphery. Identifying this TF will require complex genomic techniques but will serve as a biomarker for autoreactive Bsup analogous to Foxp3 in autoreactive Tregs [40]. Here comes the amplified relevance of C1-Bsup, for they can be harnessed to address these unanswered questions and will help abstract this knowledge to other autoimmune diseases, irrespective of the antigen specificity.

5 | Are All Autoantibodies Harmful?

COL2 provides a compelling example of how autoreactivity can be protective and pathogenic. The observed immune response against COL2 in individuals with rheumatoid arthritis (RA) underscores the importance of this autoantigen in shaping immune function. For instance, COL2-reactive T cells, which are positively selected in the thymus of healthy individuals, can also be pathogenic and drive disease progression [11, 41, 42].

The same applies to COL2 autoreactive B cells, where six dominant epitopes have been mapped and autoantibodies against all 6 epitopes (C1, J1, U1, E10, D3, and F4) have been implicated in models of autoimmunity in mice [43].

Notably, arginine residues are common within all mapped COL2 B cell epitopes, making them susceptible to citrullination by protein arginine deiminase enzymes. Autoantibodies against citrullinated COL2 B cell epitopes can cause arthritis in animal models [44] and have been associated strongly with RA [45], reinforcing the relevance of COL2 in the anticitrullinated protein antibody (ACPA) response, a defining characteristic of RA [46]. Understanding the factors that dictate the shift from homeostatic to pathogenic autoreactivity, whether environmental, genetic, or both, is crucial to explaining why some individuals develop autoimmunity while others do not.

That said, not all autoantibodies are inherently pathogenic. Since their discovery, ACPA have been widely considered disease-driving, but this assumption was based primarily on associations rather than definitive causation. Not until recently that this belief was shaken by three independent studies with one conclusion: ACPA are regulatory rather than pathogenic [47]. This was elegantly demonstrated in animal models, where the injection of cloned human ACPA inhibited rather than exacerbated arthritis, both before and after disease onset [48–50]. The mechanism of suppression was linked to the inhibitory FCGR2b-IL10 axis [48]. Furthermore, autoantibodies against the native (noncitrullinated) F4 epitope on COL2 have been negatively correlated with RA severity [51]. Recombinantly expressed F4-specific autoantibodies, generated using phage-display technology, showed a potent inhibitory effect on arthritis in mice. This suppression was mediated via FcGR3 signaling, which impaired IL-1β secretion and neutrophil recruitment [51].

6 | Do Autoreactive B Cells Orchestrate Peripheral and Central Tolerance?

It is tempting to hypothesize that Bsup not only control peripheral Tregs but also contribute to their selection in the thymus. A key but often overlooked role of autoreactive B cells is their role in central tolerance. Resident thymic autoreactive B cells specific for the autoantigen glucose-6-phosphate isomerase, present this autoantigen to T cells, ensuring the deletion of pathogenic autoreactive T cells [52, 53]. Although these resident thymic B cells were initially thought to develop de novo within the thymus,

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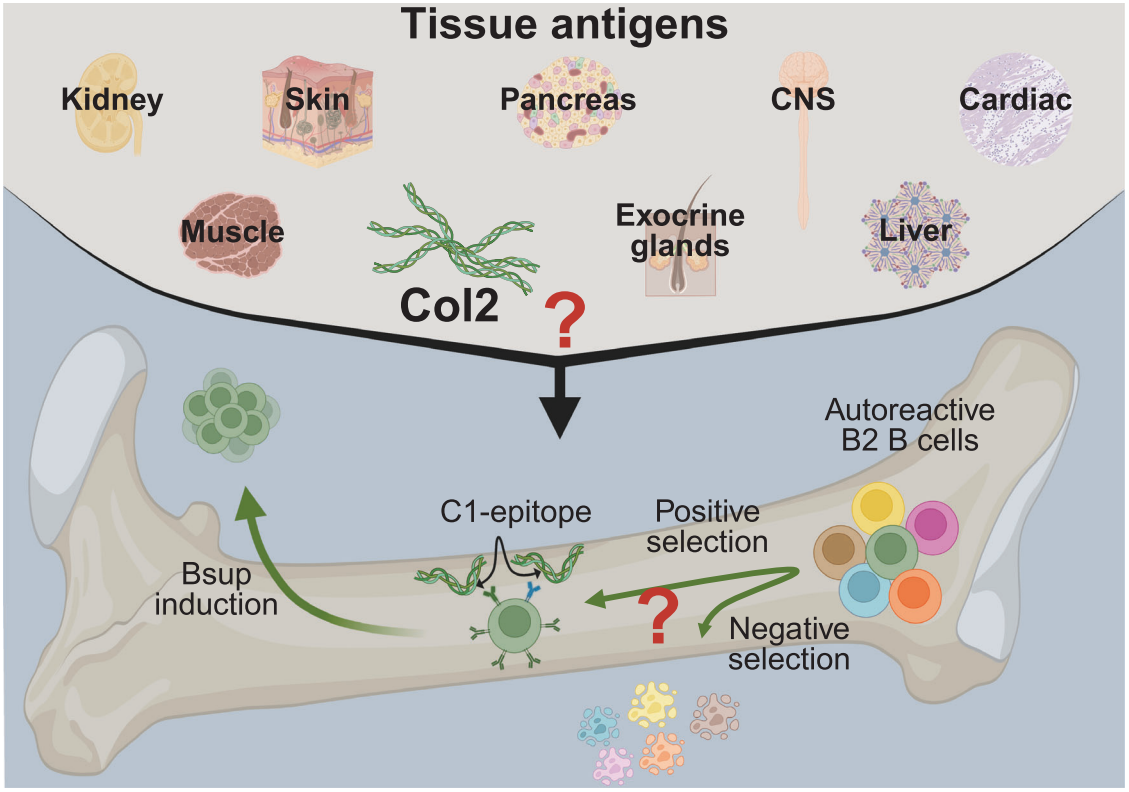

FIGURE 1 | Peripheral tissue antigens positively select autoreactive Bsup to maintain immune homeostasis.

GPI-specific B cells have also been detected in the periphery and BM [54]. It remains crucial to determine if these positively selected GPI-specific B cells only regulate thymic T cell selection or orchestrate as well peripheral tolerance as Bsup.

Alongside GPI-specific B cells, other examples of autoreactive B cells that exert regulatory effects through antigen presentation have emerged. Aquaporin 4-specific B cells promote Foxp3 expression in CD4+ T cells through direct co-culture, indicating their potential to facilitate Treg development. These examples underscore a broader role for autoreactive B cells not only in autoantibody production but also in orchestrating central [55] and peripheral tolerance [56] via direct interaction with developing or mature T cells. Similarly, insulin-binding B cells, found in both healthy individuals and type 1 diabetes patients, display an antigen presentation transcriptional profile and can produce cytokines, suggesting they retain functional capacity and are not truly anergic [57].

Together, these findings reinforce the view that autoreactive B cells contribute to immune regulation, both through antibody-mediated and antigen presentation-mediated mechanisms, expanding our understanding of their functional repertoire beyond pathogenicity.

7 | Concluding Remarks

Figure 1 presents a conceptual framework for the positive selection of autoreactive B cells, revisiting the traditional paradigm that solely focuses on their negative selection. It illustrates how autoreactive B cells encounter COL2, where the C1-epitope, which was shown to be exposed in the BM, plays a role in the selection of C1-Bsup. It is possible that this process is duplicated for a limited set of autoantigens derived from various tissues, such as the kidney, skin, pancreas, central nervous system (CNS), cardiac tissue, liver, exocrine glands, and muscle, but which are also accessible in both the thymus and bone marrow.

Alas, the mechanisms underlying this process remain unclear: Are these tissue antigens passively abundant in the bone marrow, actively trafficked, or presented by specialized cells? What determines whether certain autoreactive B cells are selected while others are deleted? Is there a transcriptional signature that drives Bsup survival? These open questions highlight the need for a reevaluation of B cell tolerance and the potential for autoreactive B cells to contribute to immune homeostasis rather than autoimmunity.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Data Availability Statement

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

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