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Review Article

The Integral Role of B Cells in Sarcoidosis Progression

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Received: July 27, 2021; **Published:** August 28, 2021

Abstract

Sarcoidosis is an inflammatory disease that affects multiple organs and tissues. While the etiology of sarcoidosis remains largely unknown, T cells have widely been implicated in the pathogenesis and progression of sarcoidosis. However, recent data has shown that B cells may have a more important role in the pathogenesis of sarcoidosis than previously thought. This paper aims to discuss the role that B cells play in the pathogenesis of sarcoidosis.

Keywords: *B Cell; Sarcoidosis; T Cell*

Abbreviations

Breg: Regulatory B Cells; IgA: Immunoglobulin A; Tfh cells: T Follicular Helper Cells; Ig: Immunoglobulin; IC: Immune Complex; BAFF: B-Cell Activating Factor; CD: Crohn's Disease; CVID: Common Variable Immunodeficiency; SAA: Serum Amyloid A; RA: Rheumatoid Arthritis; TB: Tuberculosis; IL: Interleukin

Introduction

Sarcoidosis is a multisystem disease of unknown etiology, characterized by the formation of noncaseating granulomas. These granulomas are most commonly found in the lungs, lymph nodes, skin, and eyes, but may appear in any organ of the body [1]. The disease has higher prevalence in Nordic countries and African Americans, and although sarcoidosis was originally thought to be quite rare, recent studies have shown that the prevalence of sarcoidosis is greater than 0.05% [2]. The rates of mortality in sarcoidosis range to up to 8%, with the highest rates of mortality in women, those older than 55 years old, and non-Hispanic black people [3]. A hallmark of sarcoidosis is a peripheral T cell anergy with locally hyperactive T lymphocytes in the lungs and other disease sites, which has often been the main mechanism described in the pathogenesis of sarcoidosis [4]. However, it has become clearer that B cells may have an important role in sarcoidosis through their various roles in immunity. Specifically, hypergammaglobulinemia and the presence of B cells and plasma cells in sarcoid granulomas are strong indicators for B cells' role in sarcoidosis. This paper aims to further examine the role that B cells may have in the pathogenesis of sarcoidosis.

There are multiple subtypes of B cells, including plasma cells, memory B cells, B-1 cells, B-2 cells, and regulatory B (Breg) cells. Each B cell type has a different function, releasing various cytokines to fulfill that function. B-1 cells recognize ubiquitous antigens and produce antibodies as part of the innate immune system, while B-2 cells produce specific antibodies against foreign antigens in secondary lymphoid organs. Meanwhile, Breg cells suppress T lymphocyte function and proliferation, functioning in a regulatory capacity [5]. B cells

can serve multiple roles, acting as antigen presenting cells, producing antibodies, and producing cytokines that regulate the response of T cells, as shown in Figure 1. Each B-cell subset and the cytokines produced by each respective subset are also depicted.

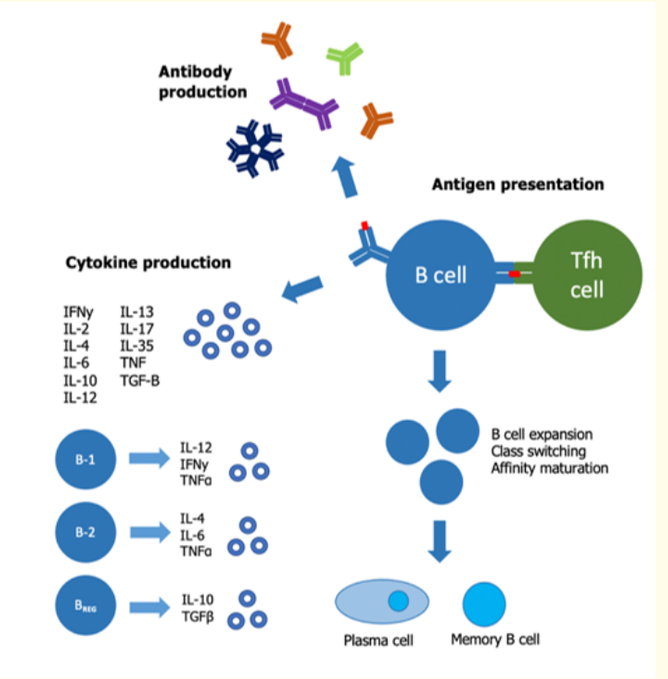

Figure 1: *B cells have multiple roles in normal immune function, including antigen presentation, cytokine production, and antibody production.*

The case for B cell involvement in sarcoidosis

Sarcoid granulomas are the main pathological feature of sarcoidosis. These granulomas are mainly formed by macrophages, epithelioid cells, giant cells, and CD4+ T cells in the central area, with CD8+ T cells and fibroblasts in the peripheral area, as shown in Figure 2 [6]. Importantly, B cells and plasma cells, have also been found in the periphery of sarcoid granulomas, indicating a potential role for these cells regulating granuloma development [7]. It has been shown that CCL20, a chemokine secreted by activated macrophages, signals B cells to join granuloma formation [7].

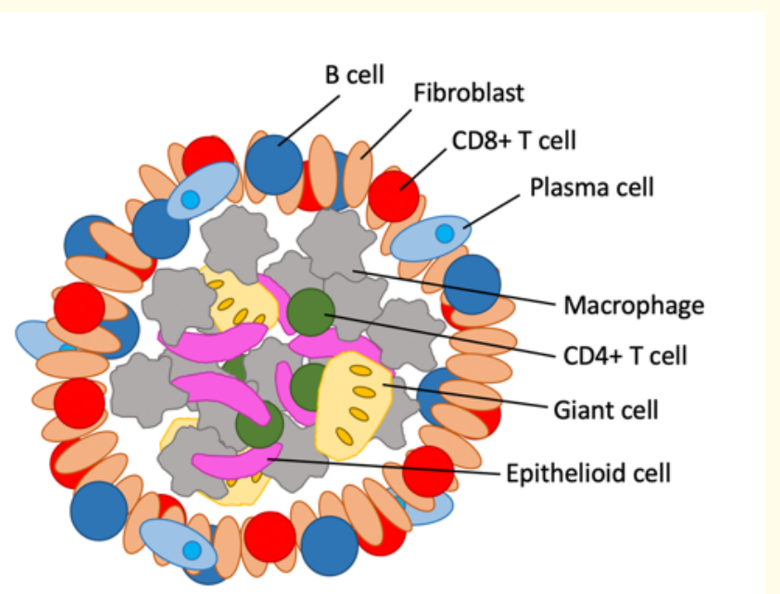

Figure 2: *Granulomas in sarcoidosis consist of giant cells, epithelioid cells, macrophages, and CD4+ T cells in the central area and CD8+ T cells, fibroblasts, B cells, and plasma cells in the peripheral area.*

CD27 is a differentiation marker found in memory B cells, and CD19+ cells which lack CD27 and express immunoglobulin A (IgA) (e.g., CD27-IgA+ B cells) have been found to be significantly increased in sarcoidosis, with large B cell infiltrates present in granulomatous tissue [8]. Additionally, perigranuloma localization of IgA-producing plasma cells and large numbers of B cells have been found in tissues affected in sarcoidosis, most commonly the lungs, along with increased levels of peripheral blood B cell subsets with regulatory capacities [9]. Furthermore, there is a circulating imbalance of T follicular helper cells (Tfh cells) in patients with sarcoidosis, such that Tfh2 and Tfh17 cell populations dominate over Tfh1. Tfh cells are important in the function in germinal center formation, affinity maturation, and assisting B cells in the development of antibodies and memory B cells [9]. Tfh1 cells usually respond to intracellular pathogens, while Tfh2 cells respond to extracellular parasites and Tfh17 cells are associated with extracellular bacteria and fungi, chronic inflammatory disease, and autoimmunity [10]. In the context of sarcoidosis, the specific Tfh cell imbalance found in sarcoidosis is important to consider, as unlike Th1 cells, the Tfh2 and Tfh17 cell populations are able to induce naïve B cells to produce antibodies [11,12]. This corresponds with the pathological features of sarcoidosis, which include increased levels of naïve B-cells, along with increased production of autoantibodies and hypergammaglobulinemia.

Hypergammaglobulinemia can occur when there is increased differentiation of B cells into plasma cells or plasmablasts that produce immunoglobulin. In sarcoidosis, Tfh cells in the lungs induced increased differentiation of B lymphocytes into immunoglobulin-secreting cells, resulting in polyclonal hypergammaglobulinemia [13]. With increased disease severity, there are higher levels of antibody titers, along with a strong presence of increased molecular signs of antibody maturation, such as somatic hypermutations and immunoglobulin (Ig) class switching [8].

These points tie in with the presence of B cells and plasma cells in the granulomas and further supports the idea that B cells have an important role and could be driving the altered humoral immune response seen in sarcoidosis. It has also been found that peripheral B cells are anergic in patients with severe chronic sarcoidosis. This anergic state was correlated with multiple intrinsic B-cell signaling defects and resulted in poor differentiation into plasma cells [14]. This supports the idea that the enhanced immunoglobulin synthesis found in sarcoidosis occurs at sites of disease activity.

To further support this idea of granuloma formation, a decreased expression of CD154 is found in sarcoid CD4 T cells. CD154, also known as CD40 ligand, is located on T cells and used to deliver an activation signal to B cells. Additionally, continuous interaction with CD154 provide signals that inhibit B-cell differentiation into plasma cells. Decreased expression of CD154 in sarcoidosis T cells suggests a potential induction of antibody response that is defective and unable to eliminate antigens that induce granuloma formation. Furthermore, decreased CD154 expression can result in interruption of the above-mentioned inhibitory signals, thus permitting plasma cell differentiation, explaining a contributor to the hypergammaglobulinemia found in sarcoidosis. This would explain how sarcoidosis can progress quickly [14,15].

Additionally, the role of immune complexes (ICs) in the pathogenesis of sarcoidosis should be considered. ICs fix complement and circulate in the blood, depositing in various tissues. It has been found that ICs derived from *Propionibacterium acnes* were abundantly found in lymph nodes in patients with sarcoidosis [16]. Furthermore, cutaneous sarcoidosis can present as vasculitis, an IC-mediated process [17]. This supports the idea that ICs are involved in sarcoidosis pathogenesis. The development of ICs is predisposed to by hypergammaglobulinemia, a hallmark of sarcoidosis, explaining that this could be an aspect of sarcoidosis pathogenesis.

Generally, the ratios between different B cell populations in disease-free individuals is constant for a given age group. In certain autoimmune diseases like systemic lupus erythematosus (SLE) where B cells and autoantibodies play an important pathogenic role, cell homeostatic disturbances have been found that are similar across these autoimmune diseases, suggesting that in sarcoidosis those same disturbances may play a pathogenic role [18]. An important distinction to be made is that naïve B cells and activated B cells are increased in sarcoidosis, while memory B cell populations are decreased [9]. Naïve B cells mainly produce chemokines that activate CD4+ T cells, which further drives the immune response [19]. Because naïve B cells and activated B cells often drive immune responses, while memory B cells are used for immune response to previously exposed antigens, this supports a strong role of B cells in the immune response in sarcoidosis. Specifically, in sarcoidosis, there are increased transitional B cells, decreased memory B cells, increased IL-10-producing regulatory B cells (Breg cells), and increased serum B-cell activating factor (BAFF) levels in patients with active chronic sarcoidosis [9]. To explain further, transitional B cells are immature B cells that mature in the spleen to become responsive to signaling; an increase in this cell population can suggest increased activity of B cells and corresponds with the increase in naïve B cells [20]. Memory B cells aid

in generating a strong antibody-mediated immune response, such as in the case of re-infection; a decrease in this cell population can be a result of memory B cells localizing more in the granulomas of affected organs in sarcoidosis rather than in the blood, which would result in further progression of the disease [9,21]. Further supporting this, B cells are often found in discrete clusters in the peripheral area of the granuloma in Tuberculosis (TB), which has a similar granuloma formation progression, and thus regulate the level of granulomatous reaction; TB has also been shown to have a reduced number of peripheral blood B cells as compared to healthy patients [22,23]. This is likely due to the aggregation of B cells to granulomas in TB. Another disease process to consider is Crohn's disease (CD), a form of inflammatory bowel disease with non-caseating granulomas as a hallmark of disease; this is very similar to sarcoidosis, which is also defined by the presence of non-caseating granulomas. B cells accumulate around granulomas in affected colon tissue in CD, similar to TB and sarcoidosis, further supporting the concept of B cells driving granuloma formation. B cells in patients with CD also showed localization to granulomas with resultant increased levels of immunoglobulin. Additionally, CD has been shown to have chronic, aberrant B-cell response, not unlike the imbalance described above in sarcoidosis. Infliximab is a commonly used treatment for CD that targets TNF, and this therapy has been shown to improve the abnormal response of B cells in patients with CD by normalizing spleen function and levels of circulating B cells, with recovery of systemic abnormalities of B cell compartments [24]. This is all evidence to support the role of B cells in granuloma formation and disease progression in CD, which would correspond to a similar role in sarcoidosis disease progression. All of this evidence, including in similar diseases of pathogenesis such as in TB and CD, reinforces the role of B cells in granuloma formation.

Breg cells serve to suppress pro-inflammatory cells and act in immunological homeostasis; an increase in this cell population can be explained as a homeostatic response to increased levels of inflammation found in sarcoidosis [25]. Common variable immunodeficiency (CVID) is a disease state resulting from decreased immunoglobulin levels despite adequate levels of B cells. Granulomas have been detected in the disease process, often coinciding with the CVID diagnosis. In the absence of regulatory B cells, as in this disease state, granulomas can develop [26]. This further reinforces our theory that B cells drive granuloma formation. This is important to consider, as granulomas are a hallmark of sarcoidosis progression and B cell involvement in granuloma formation would implicate B cells in the progression of sarcoidosis.

Furthermore, BAFF is a potent B cell survival and activating factor; an increase in serum BAFF levels can indicate systemic activation of the humoral immune system, and is often found increased in autoimmune diseases such as SLE and systemic sclerosis [27]. Finally, Bruton's Agammaglobulinemia, also known as X-linked agammaglobulinemia, is a disease state of significant B lymphocyte deficiency. Interestingly, patients with Bruton's do not develop granulomatous disease as seen in CVID [28]. Since Bruton's patients lack B cells, this important finding suggests that B cells are needed for granuloma formation. While there is not much similarity between Bruton's gammaglobulinemia and sarcoidosis, this further supports an essential role of B cells in granuloma formation, which is a critical aspect of sarcoidosis pathogenesis. This, along with the above explanation of imbalances in B cells, supports our theory that B cells are involved in the pathogenesis of sarcoidosis.

While one explanation for these imbalances in B cell populations is the earlier-explained Tfh cell activity, there are multiple antigens that are able to change the balance of these B cell populations in favor of naïve B cells rather than memory B cells. For example, chronic antigenic stimulation of B cells by "unknown" sarcoid antigens, such as serum amyloid A (SAA), can result in a shift towards naïve B cells. SAA aids in the expansion of Tfh17 cells which, as described above, help activate naïve B cells [29,30]. Persisting bacterial antigens, such as mKatG, can also potentially cause a shift in B cell populations. mKatG is a catalase-peroxidase protein found in *Mycobacterium tuberculosis* that triggers lymphocytes such as Tfh cells to get activated, resulting in an increase in activation of naïve B cells [31]. Both of these types of antigens play a role in the initial pathogenesis of sarcoidosis, tilting the balance of naïve B cell/memory B cells towards naïve B cells with associated results of somatic hypermutation and Ig-class switching.

Along with markedly reduced numbers of memory B cells, absolute B-cell lymphopenia and anergy in peripheral blood B-cell compartments have been found in patients with severe chronic sarcoidosis. While this may appear to invalidate the argument that B cells are involved in the pathogenesis of sarcoidosis, it has been shown that chronic and persistent stimulation of B cells by unknown sarcoid antigens can lead to anergy and exhaustion in the B cell compartment, explaining these findings [14]. These lower levels of memory B cells can indicate less of a response in eliminating antigens that can cause granuloma formation, exacerbating the progression of sarcoidosis. This can also potentially explain the increase in transitional B cell population as a method of compensating for lower levels of memory B cells.

The role of rituximab and B cell depletion

Rituximab is an anti-CD20 monoclonal antibody, classically used as treatment in non-Hodgkin's lymphoma and rheumatoid arthritis (RA). This therapy targets CD20 expressed on the surface of B lymphocytes, thus serving as a B-cell depleting therapy. By eliminating B cells, halting antigen-presenting events, and modulating the cytokine environment, rituximab results in immunosuppression. Rituximab has shown use in improving the clinical course of refractory sarcoidosis with lung, eye, lymph nodes, and skin involvement. Specifically, it has been effective in controlling most cases of granulomatous ocular disease, secondary to sarcoidosis [32]. There has also been clinical improvement in cases of refractory disease [33]. The use of rituximab in treating cardiac sarcoidosis was also successful in a patient, showing significant improvement in symptoms and severity [34]. Additionally, there are reports of patients with granulomatous lung disease who clinically improved with rituximab. The thought behind the clinical improvement in patients with granulomatous disease, often secondary to sarcoidosis, is that rituximab targets the B cells surrounding the granulomatous formations, thus preventing further damage [35].

Importantly, rituximab has not found to be effective in every case. For example, its use in patients with pulmonary sarcoidosis resulted in some patients having improvement, while others later had progression of sarcoidosis [33]. While it is not known why, a theory to explain this difference is a variable involvement of B cells in certain patients relative to others. Something to consider is that rituximab targets CD20, which is present on all B cells. While regulatory B cells would normally suppress granuloma formation, perhaps in some patients, rituximab depletes Breg cells, thus favoring inflammation and granuloma development in sarcoidosis.

Further support for the role of B cells in the pathogenesis of granulomas is shown in the disease process of *Mycobacterium tuberculosis*. A hallmark of the immune response to *M. tuberculosis* is the formation of germinal centers, similar to that found in patients with sarcoidosis [36]. Mice with *M. tuberculosis* infection that have an absence of B cells exhibit anti-tuberculous immunity. It has also been shown that B cell deficiency results in a delayed progression of inflammation during TB infection. B cell deficient animals have demonstrated defects in inflammation control, with a decrease in pro-inflammatory cytokines produced [37]. In terms of granulomas, mice with B cell deficiency have been shown to have markedly less severe pulmonary granuloma formation along with a delay in bacterial dissemination. When naïve B cells were transferred into B cell depleted mice, inflammation, dissemination, and granuloma development occurred readily [38]. This all suggests that B cells or their antibody products have an important role in regulating the granuloma formation and progression of TB.

B cells are also found in sarcoid granulomas. Although little is known regarding the cytokine profiles produced by B cells found in sarcoid granulomas, studies have shown that B cells found in lung granulomas in murine models of TB belong to the B-1 B cell subtype that produces inflammatory cytokines, suggesting a role for B cells in granuloma formation in sarcoidosis [39]. B cells could also have a possible role in the fibrotic lung disease found in some patients with sarcoidosis. B-2 cells are B cells that produce IL-4, and these cells could collaborate with Tfh2 cells, inducing type 2 macrophage polarization and Tfh2-driven granulomas in sarcoidosis [40]. Additionally, in SLE, which shares characteristics with sarcoidosis including antinuclear antibodies, disturbance in T and B lymphocyte ratio, and an elevation of immunoglobulin concentration, it has been shown that B cell depletion, an example being rituximab, resulted in complete or partial remission in 60-89% of lupus nephritis cases [41,42]. Both diseases have also been found to have antilymphocyte antibodies, as well as a reduction in antibody dependent cell-mediated cytotoxicity [43]. A common or similar pathogenesis for both sarcoidosis and SLE is supported. This information, along with the clear involvement of B cells in TB granuloma formation and role of rituximab in alleviating sarcoidosis, further supports the concept of B cells driving disease progression in sarcoidosis.

BAFF and IL-21 involvement sarcoidosis

B-cell activating factor (BAFF) and Interleukin (IL)-21 are both involved in B cell pathways and further analyzing their role in sarcoidosis allows a better understanding of the potential role B cells have in the pathogenesis of sarcoidosis. BAFF works as an important B cell survival factor, promoting the survival of plasma cells and other cells in the B cell lineage. IL-21 plays a key role in B cell differentiation to plasma cells, as well as in the development of Tfh cells. Both BAFF and IL-21 work together to activate and maintain humoral immunity [44].

BAFF is one of most important survival factors for B cells, produced mainly by myeloid cells, and functions to maintain plasma cell and B cell survival. As B cell maturation and function depends on BAFF, elevated BAFF can cause defective selection of autoreactive B

cells. Interestingly, following B cell depletion, BAFF levels are significantly increased, while once B cells reemerge in the periphery, BAFF levels are decreased, suggesting that BAFF levels are involved in B cell repopulation [45]. As mentioned earlier in this paper, serum BAFF levels have been found to be elevated in sarcoidosis, as well as in other autoimmune diseases such as SLE, RA, and Sjogren's syndrome-all with autoantibody function, similar to sarcoidosis [9,44,45]. Moreover, BAFF inhibitors, such as atacicept, have been used as treatment in patients with SLE, RA, and multiple sclerosis, resulting in a decrease in circulating autoantibodies [44]. These reduced antibody titers were also supported by a study in which BAFF knockout mice had decreased antibody levels, corresponding with the BAFF inhibitor study results [46]. Additionally, clinical trials have demonstrated that use of BAFF inhibitor particularly affects naïve B cells and transitional B cells more than memory B cells [44]. This illustrates not only that BAFF has an important role in regulating B cell populations and B cell function, but also, since naïve B cells and transitional B cells are dominant in sarcoidosis progression, using BAFF inhibition should slow progression of sarcoidosis, due to its targeting of these particular B cell groups.

SLE in particular, is similar to sarcoidosis in that both have been found to have antinuclear antibodies, a change in T and B lymphocyte ratio, and elevation of Ig concentration, and thus it is likely that they have similar mechanisms of disease progression. As mentioned, BAFF levels are elevated in SLE, and medications that target BAFF have been used in treatment of SLE, suggesting that BAFF has a role in perpetuating the disease [44,47]. Due to the similarity in mechanisms of disease progression between SLE and sarcoidosis, it would follow that BAFF likely has a role in sarcoidosis progression just as it does in SLE. To further support the idea that BAFF plays an important role in the pathogenesis and progression of sarcoidosis, serum BAFF levels have been successfully used as a surrogate marker of disease activity in sarcoidosis [45]. This is due to BAFF levels being positive correlated with disease severity and disease activity markers [48]. Therefore, it follows that it is very likely BAFF has an important role in the pathogenesis of sarcoidosis, thus implicating B cells in sarcoidosis.

IL-21 is also involved in regulating B cells and has been implicated in the humoral response involving B cells. The IL-21 receptor (IL-21R) is expressed by naïve B cells, plasma cells, germinal center B cells, and memory B cells. IL-21 mediates Ig production and B cell proliferation by acting at this receptor site [49]. IL-21 is produced by Tfh cells, which assist B cells in affinity-maturation of antibodies-thus IL-21 has a role in reinforcing humoral immunity [50]. The population of Tfh2 and Tfh17 cells, known as the "pro-inflammatory" Tfh cells, was significantly higher in patients with active SLE, which were then correlated with increased levels of autoantibodies in SLE. These increased levels of Tfh cells were also found in systemic sclerosis and myasthenia gravis, two other autoimmune diseases with autoantibody production at the center of disease progression [11]. This increased population of Tfh2 and Tfh17 cells was also found in patients with sarcoidosis, as mentioned earlier in this paper, and due to a shared autoantibody-mediated mechanism of disease progression, it follows that, as in SLE, sarcoidosis has disease progression mediated by B cells [11]. This is further supported by the production of IL-21 by these Tfh cells, which would allow the Tfh cells to produce autoantibodies in SLE and sarcoidosis, furthering disease progression [50].

The argument for IL-21 involvement in sarcoidosis is supported by multiple studies. One study showed that IL-21R knockout mice have abnormal B cell function with diminished levels of IgG antibodies when compared to wildtype IL-21R mice [51]. This supports the theory that IL-21 is important in B cell function and in antibody production, and thus would correspond to a role in both sarcoidosis and SLE autoantibody formation. Furthermore, IL-21R knockout mice have been demonstrated to have decreased SLE-like clinical features compared to wildtype IL-21R-competent mice, further supporting the idea that B cell involvement and autoantibody levels are important in SLE progression, and that IL-21 is a likely factor in pushing this progression via B cell regulation [52]. B cells are believed to contribute to the SLE disease state primarily by autoantibody production that targets nuclear components, such as histones and DNA [24]. Similar features to these could be found in sarcoidosis, as both SLE and sarcoidosis share similarities in pathogenesis and progression, and thus further supports B cell involvement in disease pathogenesis. Due to the similar autoantibody-mediated mechanism of disease in SLE and sarcoidosis, this would follow that IL-21 likely not only has a role in sarcoidosis, but also supports the idea that B cells have a role in disease progression, as IL-21 mediates humoral immunity and B cell function. To further support this idea, IL-21R signaling has been demonstrated as critical in enhancing the development of alternatively activated macrophages, which have been implicated in the mechanism of fibrosis and granuloma formation in sarcoidosis, further tying B cell activation and function to sarcoidosis progression [49]. B cells have also been shown to be involved in the response against TB infection-it has been shown that B cells can be induced by IL-21 to secrete immunoglobulins to participate in immune responses against TB infection [39]. The role of IL-21 in SLE, a similar autoimmune disease, and TB, a disease with similar granuloma formation, along with the importance of IL-21R signaling in macrophages and fibrosis in sarcoidosis

suggests IL-21 having an important role in the pathogenesis of sarcoidosis.

Conclusion

Sarcoidosis has often been thought to be primarily driven by T cell activity-however, it has become clearer with new data that B cells may be driving the disease progression. Imbalances in B cell populations in sarcoidosis result in autoantibody production and further the development of granulomas in the disease. Evidence for B cell involvement in autoimmune disease progression and granuloma formation can be found through looking at cytokines regulating B cells, such as BAFF and IL-21, other related autoimmune diseases such as SLE, CD Bruton's agammaglobulinemia, and CVID, and infectious diseases with granuloma formation such as TB. With this information, it is clear that B cells are a critical driving force in the disease progression for sarcoidosis and should be considered closely as a target for future therapies.

Conflicts of Interest

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Volume 10 Issue 9 September 2021
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