



The Immunologic Paradoxes of IgG4-Related Disease

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Abstract

IgG4-related disease (IgG4-RD), which usually occurs in middle-aged and elderly men, is a newly recognized fibroinflammatory condition characterized by swelling and sclerosis of involved organs, increased IgG4-positive plasma cell infiltration in lesions, and elevated IgG4 concentration in serum. Despite growing interest in the research, the pathophysiological mechanism remains elusive. Most IgG4-RD patients respond well to steroid therapy initially, but recurrent and refractory cases are common, especially in advanced fibrotic stage. Recent studies have documented the heterogeneity of the B cell lineages, which suggests their multiple functions in IgG4-RD beyond IgG4 production, such as cytokine secretion, antigen presentation, autoantibody production, and modulation of T and B cell interactions. Thus, a critical balance exists between pathogenic and regulatory B subsets to prevent immunopathology. A prompt response to B cell depletion therapy reported in recent cases strongly suggests the imbalance within B cell lineages in IgG4-RD. A more precise understanding of the pathogenesis of IgG4-RD will open up new perspectives for therapeutic strategy. With a particular emphasis on the novel B cell-targeted therapeutic strategies, this review highlights the immunologic features of IgG4-RD and the possible roles of B cell lineages in the pathogenesis of IgG4-RD.

Keywords IgG4 · IgG4-related disease · B cells · Plasmablasts · Rituximab

Introduction

Immunoglobulin (Ig) G4-related disease (IgG4-RD), which usually occurs in middle-aged and elderly men, is a systemic condition characterized by elevated serum IgG4 level and increased infiltration of lymphocytes and IgG4-positive plasma cells in lesions, leading to swelling and sclerosis of involved organs [1]. Nearly any organ can be affected in IgG4-RD, but the most frequently involved are lymph nodes, submandibular and lacrimal glands, pancreas, and retroperitoneum [2]. Although a great attention has been paid, the pathophysiology

of IgG4-RD remains unclear. In particular, most IgG4-RD patients respond well to steroid therapy initially, but recurrent and refractory cases are common, especially in advanced fibrotic stage [3]. To improve the clinical prognosis of IgG4-RD, further exploration for the potential mechanisms is urgently needed to develop better and more effective treatments for IgG4-RD.

B cells are widely involved in the pathogenesis of various autoimmune disorders, including systemic lupus erythematosus (SLE), multiple sclerosis (MS), type 1 diabetes, and rheumatoid arthritis (RA) [4, 5]. In the etiology of autoimmune

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disorders, B cells are engaged in a variety of functions, including autoantigen presentation, pathogenic T cell activation, autoantibodies production, and modulation of autoimmune process through regulatory mechanisms [4, 6–8]. The presence of high serum IgG4 level and abundant IgG4-expressing plasma cell infiltration in lesions, together with a prompt response to B cell-depletion therapy, suggests the hyperactivation of B cell lineages in IgG4-RD [9]. Given the fact that several IgG1 rather than IgG4 autoantibodies was detected in autoimmune pancreatitis (AIP) patients [10], it is still controversial whether IgG4 is a pathogenic antibody in IgG4-RD or only a side-product of inflammatory reaction. In addition, studies demonstrated that IgG4-RD patients have substantially expanded population of plasmablasts (CD19 + CD20-CD27 + CD38hi), as well as perturbed regulatory B cells [11–15]. In this article, we will focus on the most recent advances in the functions of B cell lineages and B cell-targeted therapies in IgG4-RD.

B Cell Development and Activation

B cells go through multiple stages of development in their lifecycle. The initial phase occurs in bone marrow. In this phase, progenitor B cells, developed from hematopoietic stem cells, undergo V(D)-J gene rearrangement and selection process to generate mature B cells. Mature B cells express B cell receptor (BCR)-enabling naïve B cells to bind specific antigens. Mature B cells leave the bone marrow and migrate to secondary lymphoid organs (SLOs), such as the spleen and lymph nodes. At SLOs, naïve mature B cells complete further, antigen-dependent activation into either memory B cells or antibody-secreting cells. B cell activation begins when their BCRs bind to particular antigens through circulating lymph. Classically, antigen responses are divided into those that are T cell-independent and those that are T cell-dependent. Except for the stimulation from antigens, B cells need additional stimuli to complete activation progress, which are either Toll-like receptor ligands (such as lipopolysaccharide) that are associated with T cell-independent responses or cognate helper T cell-derived signals that are associated with T cell-dependent responses [16]. Activated B cells go on proliferation, immunoglobulin class-switch recombination, and differentiation into short-lived plasmablasts that produce early but weak antibodies mostly belonging to IgM class [17]. B cells activated by T cell-dependent antigens can also accumulate in a lymphoid follicle to form a germinal center (GC). In GC, T cell-derived factors, including CD40 ligand, interleukin-21 (IL-21), and IL-4 and IL-10, promote the rapid proliferation and facilitate the affinity maturation. B cells with high-affinity antigen receptors exit the GC and differentiate into either memory B cells or long-lived plasma cells which produce large quantities of antibodies. [16]

IgG4 Production

Although infiltration of IgG4-bearing cells in tissues and elevated IgG4 serum level are observed in IgG4-RDs with different organ involvements, the precise role of IgG4 in the pathogenesis of IgG4-RD remains unclear. There are four IgG subclasses (IgG1, 2, 3, and 4) in humans. Under physiological conditions, the amount of IgG4 is limited in the peripheral blood, compared with other IgGs, representing the smallest fraction at only 4–6% of total IgG. But its unique structural features correspond to the special immunological properties of IgG4, namely Fab-arm exchange and rheumatoid factor (RF)-like activity [18–20]. IgG4 differs from IgG1 by only a few amino acid residues resulting in a more flexible hinge region. This structure variation causes the exchange of Fab segments between different IgG4 molecules. Such a bi-specific antibody containing two different antigen-binding sites have only limited ability to cross-link antigen to form immune complexes; hence, they are unable to activate the complement cascade to cause cell lysis [21]. IgG4 also possesses an RF-like activity, that is, binding to the Fc portion of IgG via Fc-Fc interactions [20]. Although it is implicated in the process of IgG4 Fab-arm exchange, it remains unclear whether and how this RF-like activity contributes to IgG4-RD [21]. Given this particular characteristic, IgG4 is considered traditionally as a non-inflammatory immunoglobulin.

The primary roles of IgG4 appear to be binding circulating allergic substances which contributes to the attenuation of the inflammatory action of Th2 cells [22]. However, IgG4 is also proved to participate in the pathogenesis of certain diseases with antigen-specific IgG4 autoantibodies, such as pemphigus vulgaris, idiopathic membranous glomerulonephritis, acquired thrombocytopenic purpura, and muscle-specific kinase myasthenia gravis [18]. Although the specificity has not been clearly defined, autoreactive IgG4 antibody has been documented in AIP [23]. Aoki et al. reported that IgG4 antibody from the AIP patients' sera showed binding activity to the normal epithelia of the pancreatic ducts, bile ducts, gallbladder and salivary gland ducts, indicating IgG4 might be pathogenic in IgG4-RD [23].

Autoantibodies Production

In AIP, several pancreas-specific self-antigens have been reported, including lactoferrin (LF), carbonic anhydrase (CA), amylase- α , pancreas secretory trypsin inhibitor (PSTI), and plasminogen-binding protein [24–31]. Interestingly, autoantibodies to all of these self-antigens are IgG1, not IgG4. In a study reported by Asada et al. [24], antibodies against PSTI were detected in 42.3% of AIP patients by immunoblotting and 30.8% by ELISA, compared to none of the controls. Antibodies against LF and CA-II are the most frequently

detected autoantibodies in AIP, with a positive rate of 73 and 54%, respectively [32]. Of note, despite the exclusive presence of IgG4 in humans, animal models of AIP were established by immunizing neonatally thymectomized mice with CA-II or LF [10]. In these pancreatitis models, inflammation was detected in pancreas, as well as in salivary gland and around the bile duct [10]. In addition, Endo et al. reported that antibodies against amylase- α -2A were detected in all 15 AIP patients and 88% of patients with fulminant type 1 diabetes (T1DM), indicating amylase- α might be a specific marker for AIP and T1DM [26]. Very little is known about the autoantibodies in IgG4-RD with involvement of other organs.

Molecular mimicry hypothesis was developed to explain the production of autoantibodies in autoimmune disorders [33]. Exogenous pathogens, such as bacteria or virus, may trigger the production of antibodies and activate immune response. A link between *Helicobacter pylori* (*H. pylori*) infection and AIP has been implicated in several studies [25, 30, 31]. Frulloni et al. [25] screened a random peptide library with IgG from 20 patients with confirmed AIP and found that 95% of patients produced antibodies against plasminogen-binding protein (PBP) of *H. pylori*. The PBP peptide has significant homology with ubiquitin-protein ligase E3 component n-recogin 2 (UBR2), an enzyme highly expressed in the pancreatic acinar cells. The result suggested that molecular mimicry between *H. pylori* and pancreatic self-proteins might be a stimulating factor for the pathogenesis of AIP.

Plasmablasts Expansion

Plasmablasts, characterized as CD19 + CD20-CD27 + CD38hi, are immediate precursors of antibody-secreting plasma cells, developed from activated naïve/memory B cells. Circulating plasmablasts, largely IgG4+ plasmablasts, are found to be expanded in a majority of untreated IgG4-RD patients compared with healthy controls and other inflammatory diseases [14, 15, 34]. Circulating IgG4+ plasmablast counts strongly correlate with serum IgG4 levels, the number of involved organs, and the IgG4-related Disease Responder Index refined by members of the International IgG4-RD Symposium Organizing Committee [35], suggesting it might be a surrogate marker for diagnosis and assessment with greater sensitivity and specificity than serum IgG4 level [14, 15]. In patient relapse after rituximab therapy, the re-emerged plasmablasts in IgG4-RD are oligoclonal, largely IgG4 positive, and exhibit increased somatic hypermutation, indicating a T cell-dependent immune response involving repeated rounds of mutation and selection driven by a specific antigen [12].

Alteration of Regulatory B Cells

The initial discovery of regulatory B cells (Bregs) in mouse implies that antigen-specific B cells may have a regulatory function to suppress autoreactive lymphocytes [36]. IL-10 is considered as the major effector released by Bregs to exert the immunoregulatory effects. Despite the findings in mouse models, Bregs remain poorly characterized in humans. IL-10 production has been detected in both CD19 + CD24hiCD27+ (B10) and CD19 + CD24hiCD38hi (immature) B cell populations in human peripheral blood [37, 38]. Either decreased number or impaired function of IL-10-producing B cells was detected in relapsing-remitting multiple sclerosis (RRMS), SLE, and RA [38–40]. Regarding IgG4-RD, Sumimoto et al. analyzed the Breg subtypes, CD19 + CD24hiCD38hi and CD19 + CD24hiCD27+ from the peripheral blood of patients with type 1 AIP [13]. CD19 + CD24hiCD38hi cells were significantly increased in the type 1 AIP patients compared with patients of chronic pancreatitis and pancreatic cancer and healthy controls, while CD19 + CD24hiCD27+ cells were decreased in type 1 AIP compared to those of the control groups. The data suggested that CD19 + CD24hiCD38hi Bregs seemed to increase reactively to suppress the disease activity, and CD19 + CD24hiCD27+ Bregs might be involved in the development of type 1 AIP, although the exact mechanism remains to be explored. In contrast, Lin et al. reported a lower frequency of CD19 + CD24hiCD38hi regulatory B cells in IgG4-RD patients compared to primary Sjögren's syndrome (pSS) as well as in healthy controls [11]. Considering these inconsistent findings, further researches are needed to evaluate the abnormalities of B cell subpopulations in IgG4-RD with different organ involvement.

B and T Cell Interaction

Recent studies demonstrated that T cell subsets, including Th1, Th2, regulatory T cells (Treg), T follicular helper cells (Tfh), and CD4+ cytotoxic T cells (CD4+ CTLs), have critical roles in the pathogenesis of IgG4-RD [41]. In IgG4-RD, Treg cells (CD4 + CD25 + Foxp3+) infiltrated into the affected organs and produced IL-10 and TGF- β [42]. Moreover, mRNA expression of IL-4, IL-10, and Foxp3 in salivary glands from patients with IgG4-related dacryoadenitis and sialadenitis were positively correlated with the IgG4/IgG ratio [43]. The results suggested that Th2 and regulatory immune reactions might promote B cells to produce IgG4, since the class switching to IgG4 could be caused by co-stimulation with IL-4 and IL-10 [44]. Tfh cells were identified as a unique CD4+ helper T subset, contributing to isotype switching, somatic hypermutation, and GC formation. Akiyama M et al. reported circulating Tfh2 cells positively correlated with IgG4 levels and plasmablast numbers, suggesting an interaction

between the Tfh cells and plasmablasts [45]. Recently, Mattoo et al. reported that a clonally expanded population of CD4+ CTLs were the dominant T cells in both peripheral blood and inflamed IgG4-RD tissues [46–48]. These CD4+ CTLs expressed SLAMF7, perforin, granzyme A and B, IL-1 β , TGF- β 1, and IFN- γ , which could be the reasons for chronic inflammation and storiform fibrosis that characterizes IgG4-RD [46, 48]. Furthermore, a reduction in numbers of CD4+ CTLs was observed following rituximab-mediated B cell depletion. Since there was no CD20 expressing on CTLs, a speculative explanation of this phenomenon was that CD4+ CTLs were sustained by B cells through interaction between MHC class II molecules and T cell receptors. Given the understanding of frequent interactions between T and B cells in pathogenesis of IgG4-RD (Fig. 1), it is not surprising that T or B cells targeting drugs such as abatacept and rituximab could lead to prompt clinical improvement in IgG4-RD [9, 49].

B Cell-Targeted Therapies

Glucocorticoids are the first-line, standard treatment for most IgG4-RD patients. Although most patients respond to glucocorticoids initially, recurrent and refractory cases are common. In particular, combination therapy of immunomodulators and steroids cannot significantly decrease the relapse rates [50]. Thus, new therapies have emerged to improve the clinical

prognosis of IgG4-RD, of which B cell-targeted treatment bears a powerful therapeutic potential.

B Cell Depletion Therapy

Rituximab (RTX) is a chimeric monoclonal antibody binding to CD20, a common surface marker of precursor B cells, mature B cells, and memory B cells. Following antibody binding, B cells are depleted via apoptosis led by antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [51]. RTX was initially used to treat B cell non-Hodgkin lymphomas in 1997 and subsequently proved effective in CD20+ chronic lymphocytic leukemia and several autoimmune diseases, including RA, granulomatosis with polyangiitis, and other antineutrophil cytoplasmic antibody-associated vasculitides [52–55]. Though controversial, studies reported RTX had promising outcomes in other autoimmune conditions, including SLE, type 1 diabetes, MS, pemphigus vulgaris, antiphospholipid syndrome, immune thrombocytopenia, and myasthenia gravis [56–59]. Recently, increasing data suggested an efficacy of B cell depletion on treating both steroid resistant and intolerant IgG4-RD patients [9, 50, 60–65]. Prompt clinical improvement accompanied by rapid declines in serum IgG4 levels were observed after infusion of RTX, even without concomitant glucocorticoid therapy. However, the mechanism underlying beneficial effects of RTX for IgG4-RD is poorly understood. Wallace et al. found the number of plasmablasts was sharply

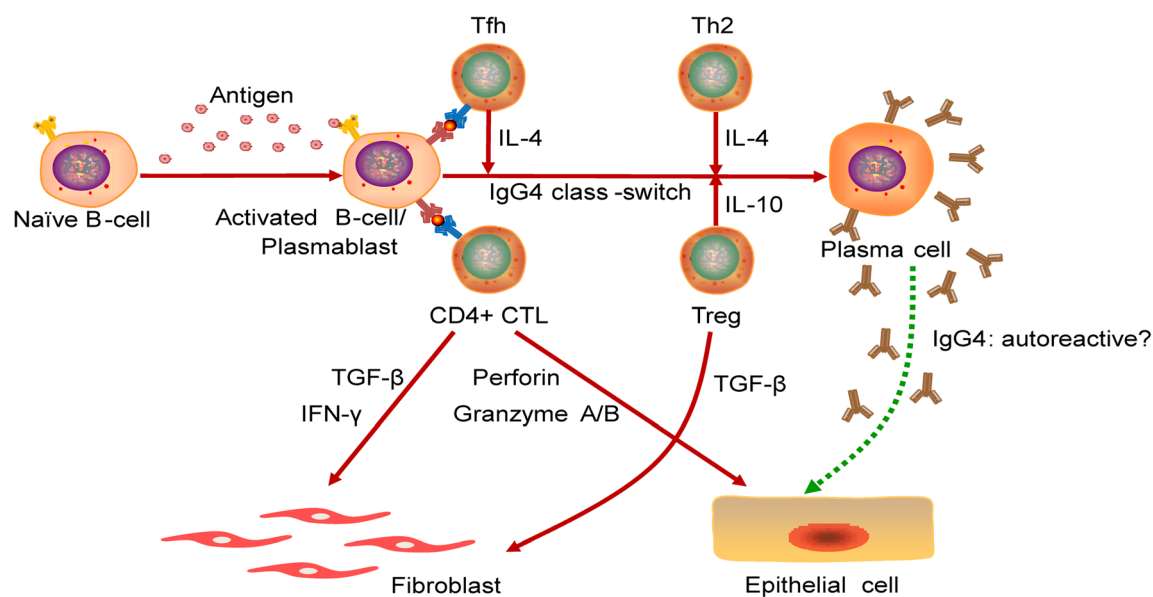


Fig. 1 The possible interactive model between B cells and T cells in IgG4-RD pathogenesis. B cells are activated after binding unknown antigens and differentiated into IgG4+ plasma cells. CD4+ cytotoxic T cells are dominant T cells in affected tissues, causing fibrosis and inflammation by cytokine and chemokine secretion. Activated B cells or plasmablasts are probably required for the sustenance of CD4+ CTL and Tfh cells, presumably through interaction between MHC class

II molecules and T cell receptors. The class switching to IgG4 could be caused by co-stimulation with IL-4 and IL-10, which are secreted by Tfh, Treg, Th2, and other cells. IgG4 antibodies might be autoreactive and lead to tissue damage directly. Abbreviations: CTL cytotoxic T cell, Tfh T follicular helper, Th T helper cell, Treg regulatory T cell, TGF transforming growth factor, IL interleukin, IFN interferon

decreased after RTX treatment, which was a result of the depletion of CD20+ precursors, since plasmablasts do not express CD20 [14]. Furthermore, the frequency of lately identified CD4+ SLAMF7+ CTL also declined following B cell depletion in patients with IgG4-RD, which might be a result of the loss of the maintenance from B cell lineage [46, 47]. Further studies are needed to reveal the accurate mechanism and identify the optimal dosage and frequency of administration.

BAFF-Targeted Therapy

B cell-activating factor (BAFF), also known as B lymphocyte stimulator, is a member of the TNF-like cytokine family and secreted from activated monocytes, macrophages, dendritic cells, and T cells. BAFF is the natural ligand of three TNF receptors (TNF-Rs), BAFF-R (BR3), TACI (trans-membrane activator and calcium modulator and cyclophilin ligand interactor), and BCMA (B cell maturation antigen). Downstream signals of BAFF-R and BCMA stimulate proliferation and inhibit apoptosis of B lymphocytes [66]. In addition, it has been demonstrated that BAFF enhances the production of plasmablasts and antibody class switching to produce IgG4 and IgE in the presence of IL-4 [66–68]. BAFF-neutralizing monoclonal antibody (Belimumab) was developed with the goal of inhibiting the binding of soluble BAFF to its target receptors on B cells. Belimumab was approved by the FDA in 2010 for SLE [69–72]. Belimumab therapy reduced the number of circulating naive B cells, activated B cells, and plasma cells in SLE patients but did not reduce the number of circulating memory B cells or T cells [72]. Recently, an open-labeled phase II study was conducted to evaluate the efficacy and safety of Belimumab in pSS [73]. The result suggested that long-term treatment with Belimumab might be beneficial in pSS, but randomized, double-blind, controlled studies in larger populations were needed [73]. Over-expression of BAFF in IgG4-RD patients has been observed in several studies [74, 75]. Serum BAFF levels decreased significantly after glucocorticoid therapy indicating a crucial role of BAFF in the pathogenesis of IgG4-RD [74, 75]. Given the successful application in SLE and encouraging data from trials conducted in pSS patients, neutralization of BAFF by Belimumab may be a promising therapy for IgG4-RD patients [2, 76–80].

Conclusions

The successful application of rituximab for IgG4-RD is a major advance in the treatment of this disease, which confirms a role for B cell lineages in the pathogenesis of IgG4-RD. Accumulating data indicates that B cells likely contribute to IgG4-RD through multiple mechanisms that include

production of IgG4 and autoreactive antibodies, T cell activation and polarization, and immune regulation by secreting cytokines. Belimumab, which neutralizes BAFF and has effects on the activation and proliferation of B cells, might be a potential therapy for IgG4-RD. But, more researches and clinical trials are required to evaluate the safety and efficacy. Further investigation of the precise role of B cells in the pathogenesis of IgG4-RD will provide new insights into potential strategies and improve treatments for IgG4-RD.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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