Immunological mechanism of IgG4-related disease

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ABSTRACT

IgG4-related disease (IgG4-RD) is an immune-mediated inflammatory disorder in multiple organs, characterized by abundant infiltration of IgG4-positive plasmacytes and fibrosis in the involved organs. The precise pathogenic mechanism of IgG4-RD still remains unclear. Aberrant innate and adaptive immunity are considered as the main pathogenesis of IgG4-RD. Recent studies have shown that abnormal adaptive immune responses mediated by T helper type 2 cells, regulatory T lymphocytes, CD4+ cytotoxic T lymphocytes, T follicular helper cells, T follicular regulatory cells, PD-1hiCXCR5-peripheral T helper cells and B cell subsets are involved in IgG4-RD. In addition to adaptive immune responses, innate immune responses play pathogenic roles in IgG4-RD. Macrophages, mast cells, basophils, complement, and plasmacytoid dendritic cells are activated to produce various kinds of cytokines in IgG4-RD. This review aims to summarize the most recent knowledge in the pathogenesis of IgG4-RD.

IgG4-related disease (IgG4-RD) is a chronic inflammatory and fibrosing disease characterized by tumefactive lesions, dense lymphoplasmacytic infiltrates, and abundant IgG4+ plasma cells in the affected tissues. Common histological features are now known to characterize IgG4-RD in essentially every organ in the body, including the pancreas, hepatobiliary duct, lacrimal and salivary glands, lung, kidney, retroperitoneum, aorta, and lymph nodes. However, the pathogenic and immunological mechanisms of IgG4-RD remain largely unclear. According to the literatures, innate and adaptive immunity are both involved, cross-talk between innate and acquired immunity is involved in the pathogenesis of IgG4-RD. In this review, we focus on a description of the current status of immune cells and related molecules in the pathogenesis of IgG4-RD.

1. Innate immunity

1.1. Macrophages

Macrophages are classified into M1 type (classically activated macrophages) and M2 type (alternatively activated macrophages) according to the respective activating pathway. IgG4-RD patients showed a predominant infiltration of M2 macrophages in multiple lesions including those of the pancreas, pleura, prostate glands, lacrimal glands, and salivary glands [1]. In IgG4-RD, infiltrating M2 macrophages are thought to play an important role in the generation of the characteristic pathophysiology such as Type 2 helper T lymphocytes (Th2) immune responses and fibrosis through the production of pro-fibrotic cytokines (IL-10, IL-33) and chemokines (The cc-chemokine ligand 18,CCL18) [2].

M2 macrophages (typically CD163+ M2 macrophages) recognize certain exogenous or endogenous molecules in affected organs through binding to pattern-recognition receptors, including Toll-like receptor-2+(TLR-2+), TLR-4+ or TLR-7+, which causes activated M2 macrophages to produce IL-33 and promote production of Th2 cytokines by various immune cells that lead to IgG4 class-switching and severe fibrosis [2,3].

The macrophage receptor with collagenous structure (MARCO), one of the scavenger receptors, was identified as a pattern-recognition receptor expressed by macrophages, and is considered to play an important role in the innate immune response by mediating ligand binding and phagocytosis [4]. Miho Ohta et al. found that MARCO was overexpressed around ectopic germinal center (GC) only in IgG4-RD patients and was coloclocalized with CD163+ cells (M2 macrophages). M2 macrophages may contribute to the initiation or maintenance of IgG4-RD via MARCO. M2 macrophages recognize certain exogenous or endogenous molecules through binding to MARCO which promotes the production of IL-10 and CCL18 et al., precipitating an exaggerated fibrosis and the pathology noted in IgG4-RD [5].

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1.2. Mast cells

Nishida K reported that mast cells exhibiting strong cytoplasmic staining for IgE, were increased in IgG4-RD [6]. Mast cells are involved in a variety of immune responses including chronic inflammation and autoimmune disease. IgE is a key stimulator of mast cells via binding to the high-affinity IgE receptor (FceRI). Mast cells activated by various biological substances (e.g. exogenous stimuli, endogenous peptides, chemokines, components of the complement system, and Fc receptors for IgE), secrete mediators including Th2 and regulatory cytokines [7]. Mast cells might also contribute to fibrosis, supported by the observation of IgE-positive mast cell infiltration in an IgG4-related fibrosclerotic mesenteric mass [8].

1.3. Basophils

Basophils comprise less than 1% of human peripheral blood leukocytes and can live only for a few days in the non-activated condition [9]. However, it has been shown that 10-times higher levels of Th2 cytokines such as IL-4 and IL-13 are immediately produced compared with those of lymphocytes, even when a small percentage of basophils are activated [10]. They are generally not present in normal tissue and become recruited to affected tissue sites only under certain conditions, for example, during allergic reactions [11]. It has been shown that basophils act as initiators of inflammatory cell recruitment during the progression of IgE-mediated chronic allergic inflammation. Watanabe et al. [12] also reported that TLRs and nucleotide-binding oligomerization domain-like receptors activation in the basophils in patients with IgG4-RD, enhanced IgG4 production by B-cells from healthy control individuals via production of B-cell-activating factor (BAFF). Activated basophils may lead to the differentiation of inflammatory monocytes into M2 macrophages, and influence the Th2 immune environment and may also affect the production of IgG4 via TLR signaling.

1.4. Complement

Complement 3 (C3) and C4 have been reported to be decreased (hypocomplementemia) in 36% of patients with IgG4-related autoimmune pancreatitis, suggesting that complement system may be involved in the pathogenesis of IgG4-RD. In addition, hypocomplementemia appears to correlate with the presence of IgG4-related tubulointerstitial nephritis, but low complement levels may also be observed in patients without overt renal disease.

The role of the complement system in IgG4-RD disease is controversial. Unlike other IgG subclasses, IgG4 does not bind to C1q compared with FcyRI, HII, and HIII [13]. But Sugimoto et al. showed that patients with hypocomplementemia in IgG4-RD have a high serum level of C1q-binding IgG4, thus implying that IgG4 participates in the activation of complement in these patients by an unknown mechanism [14]. Besides, serum C5a level was high in active disease and low in remission in IgG4-RD. Whether C5a could be a biological marker or therapeutic target need more study. Recent studies also showed that the agalactosylated IgG acts as an epitope for complement-activating mannose-binding lectins resulting in activation of the lectin complement pathway [15]. Furthermore, in addition to activation of the lectin complement pathway, IgGs with G0 glycans also activate the classical and alternative complement pathways [16]. Therefore, they expected that hypogalactosylated IgG4 may contribute to hypocomplementemia in patients with IgG4-RD.

1.5. Plasmacytoid dendritic cells

Plasmacytoid dendritic cells (pDCs) participate in IgG4-related pancreatitis, likely contributing to IFN-γ production [17,18]. Demonstration of a role for peripheral pDCs to enhance IgG4 antibody production in this disease comes from studies conducted on experimental autoimmune pancreatitis (AIP) models in which regression of the inflammation was seen to occur with depletion of IFN-γ production or signaling. Co-cultures of pDCs and neutrophils showed increased production of IFN-γ and the B lymphocyte activating factor known as B cell activating factor (BAFF). Moreover, when these cells were co-cultured together with B cells, they led to increases in IgG4 production.

Galectin-3 secreted by dendritic cells might play a role in cell-cell interactions [19,20]. Galectin-3 is also essential for effective phagocytosis by macrophages to remove apoptotic cells and therefore preventing autoimmune reactions [21]. In addition, endogenous galectin-3 has been found to drive a Th2 response in both dendritic cells and T cells, while galectin-3 deficiency resulted in the development of a Th1 response [22]. Extracellular galectin-3 directly induces T cell apoptosis in a carbohydrate-dependent manner by binding to its cell surface receptors, CD7 and CD29 [23]. Inhibition of galectin-3 in vivo skewed the balance toward plasma cell differentiation and increased immunoglobulin production through the up-regulation of Blimp-1, a transcription factor responsible for B cell apoptosis and essential for plasma cell commitment, in Trypanosoma cruzi infection model [24]. Additionally, galectin-3 acts as a negative regulator of the differentiation of B-1 lymphocytes into plasma cells [25]. Likewise, IgG4-activated B cells activation, resulting in their differentiation into memory cells, is accompanied by a significant increase in galectin-3 expression [24]. Therefore, galectin-3 may act as a protective factor against the progression of IgG4-RD since galectin-3 blocks plasma cell differentiation in B cells and apoptosis of T cells [24,25], although this protein has other biological roles [26].

2. Adaptive immunity

2.1. T cells and subsets

T cell responses have long been considered to be central to the pathophysiology of IgG4-RD. Th2 cells, CD4+ T cytotoxic T lymphocytes (CTLs), T follicular helper cells (Thf) and regulatory T lymphocytes (Treg) play important roles in the pathogenesis of IgG4-RD.

2.1.1. T helper type 2 cells and regulatory T lymphocytes

In vitro studies showed that human B cells production of IgG4 was promoted by Th2 cells producing IL-10 and IL-13 as well as by Tregs that produce IL-10. Both Th2 cells and Tregs were reported to be increased in IgG4-RD patients. In the affected tissues or organs of patients with IgG4-RD, Th2 secreted cytokines such as IL-4, IL-5, IL-13 and T regulatory cytokines such as IL-10 and TGF-β increased significantly. IL-10 is mainly produced by Th2 and Treg, which can promote the production of IgG4 antibodies by B lymphocytes and participate in the infiltration of IgG4-positive plasma cells in the affected tissues [27,28]. TGF-β mainly stimulates the differentiation of myofibroblasts to promote the formation of collagen I, heat shock protein 17 and peristeme proteins, thus promoting fibrosis. IL-4 and IL-13 can induce Periostin, regulate the proliferation and formation of fibroblasts, and participate in the formation of tissue fibrosis by promoting the synthesis and secretion of collagen. These data suggest that Th2 cell and/or Treg responses can contribute to IgG4 production in IgG4-RD, but recently, more and more evidences showed that T follicular helper cells and CD4 + cytotoxic T lymphocytes are of the important immune cells participated in the pathogenesis of IgG4-RD.

2.1.2. CD4 + cytotoxic T lymphocytes

CD4 + cytotoxic T lymphocytes (CD4 + CTLs), expressing granzyme A, perforin, and a cell surface protein of the SLAM family called SLAMF7 [29], were found to play an important role in IgG4-RD. Mattoo H. et al. [30] and Maehara T. et al. [31] in their study found a new phenotype of CD4 + CTLs involved in the pathogenesis of IgG4-RD, which were increased in the peripheral blood and accumulated in the affected tissues and could secret cytokines as IFN-γ, IL-1β and TGF-β1. Mattoo H. et al. [30] reported that Th2 cells can only be seen in IgG4-RD patients with apotic disease, while the CD4+SLAMF7+ CTLs were significantly
increased not only in patients with apotic disease but also in the patients without apotic disease (both in peripherical blood and affected tissues), and after B cell depletion therapy, the CD4⁺ CTLs decreased as the decline of IgG4-RD RI scores. Della-Torre E. et al. [31] found that CD8α-CD4⁺-SLAMF7⁺ CTLs had a stronger association with IgG4-RD, and after the glucocorticoids (GCs)-induced remission, circulating CD4⁺ CTLs decreased with their symptoms improved. In addition, examination of affected tissues by multi-color immunofluorescence revealed that tissues contained very few Th2 cells, but the dominant infiltrating T cells in the tissue were CD4⁺ CTLs [31]. In addition, CD4⁺ CTLs in the tissue sites actively secrete IL-17, IFN-γ, and TGF-β [29,31]. These data therefore suggest to us that in IgG4-RD, specific CD4⁺ CTLs clonally expand, infiltrate in lesion sites and are re-activated locally presumably by activated cognate B cells that capture the driving antigen through the BCR, internalize it and present to the CD4⁺ CTLs causing them to drive the inflammatory and fibrotic processes. Above evidences indicated that CD4⁺ CTLs were strongly associated with IgG4-RD pathogenesis, and can be the biomarker for diagnosis and disease activity of IgG4-RD.

SLAMF7 is a highly appealing target for the treatment of IgG4-RD. A proof of concept trial with elotuzumab, funded by the National Institutes of Health, is under development [32].

2.1.3. T follicular helper cells

T follicular helper (Thf) cells are a subset of CD4⁺+T cells that are known to be involved in the differentiation and class switch of B cells during their development, and to participate in the control of GC formation [33]. Thf2 cells secrete IL-4 after in vitro stimulation and can mediate class switching to IgA, IgE and essentially all IgG isotypes including IgG4. Thf cells are also a predominant source of IL-21 [34]. IgG4 production was positively correlated with the IL-21. IL-21 can promote CD40L-mediated GC B cell proliferation and drive human B cell differentiation into Ig-secreting cells in vitro [35]. Additionally, IL-21 controls the maintenance and optimal affinity maturation of the GC reaction by maintaining the B-cell lymphoma-6 (Bcl-6) expression in B cells in vivo [36]. Bcl-6 binding is associated with the control of Thf cell migration and repression of alternative cell fates [37]. The up regulation of inducible T-cell co-stimulator (ICOS) is essential for the initiation and maintenance of Thf differentiation [38]. Increased expression of both Bcl-6 and ICOS in involved tissues of patients with IgG4-RD indicated the presence of Thf cells.

Satoshi Kubo et al. [39] and Chen Y et al. [40] reported that Thf cells, especially the Thf2 cells were significantly increased in the IgG4-RD patients, Thf and Thf2 subset correlated positively with serum IgG4, IgG4/IgG ratio and plasmablasts. Akiyama M. et al. [41] then demonstrated that Thf2 cells correlated with serum IL-4 levels, meanwhile, activated Thf2 and Thf 1 cells were increased in IgG4-RD patients, positively correlated to sIL-2R levels, IgG4-RD Responder Index (IgG4-RD RI) and the number of affected organs, they both decreased after the GCs treatment, and activated Thf2 cells re-elevated in the relapsed patients. Furthermore, Akiyama et al. [41,42] revealed that among Thf cells subsets, Thf2 cells could induce the differentiation of naïve B cells into plasmablasts, subsequently promoting the production of IgG4 in active. Therefore, Thf cells, especially Thf2 cells might be a biomarker for diagnosis and disease monitor.

2.1.4. T follicular regulatory cells

T follicular regulatory (Tfr) cells, a specialized CD4⁺ T cell subset, participate in the control of GC formation and class-switch recombination of B cells [43-45]. Tfr cells present CXCR5, which is also shared by B cells and Thf cells. Moreover, they are regulated by Bcl-6, programmed cell death 1 (PD-1), and ICOS as well as forkhead box P3 (Foxp3), which is shared by Treg cells [44,46]. To exert GC responses, Tfr cells produce IL-10 and TGF-β for the direct regulation of B cells and Thf cells. Of note, IL-10 acts as a critical cytokine not only for a suppressive effect against immune cells but also for the class-switch recombination of IgG4 and for the promotion of GC responses [45,47,48]. Fumie Ito et al. [49] found that the numbers of Tfr cells in blood and submandibular glands (SMGs) from patients with IgG4-RD were significantly increased compared with those in peripheral blood and tonsils from healthy volunteers. The percentage of Tfr cells was positively correlated with clinical parameters including serum level of IgG4 and number of involved organs in IgG4-RD patients. In addition, the absolute number of IL-10-producing Tfr cells in IgG4-RD patients was significantly increased compared with that in age-matched healthy volunteers. An increased number of Tfr cells might lead to the activation of Thf cells and B cells, and an increased number of IL-10-producing Tfr cells is potentially involved in IgG4-specific class-switch recombination in a lesion of IgG4-RD. These findings suggested that an abnormal aging process of Tfr cells may be related to the pathogenesis of IgG4-RD.

2.1.5. PD-1hiCXCR5-peripheral T helper cells

In the recent studies, Ryuta Kamekura found that Circulating PD-1hiCXCR5-peripheral T helper (Tph)-like cells were increased in patients with IgG4-RD. As Tph-like cells express high levels of chemokine receptors and granzyme A, they have the capacity to infiltrate affected tissues and exert a cytotoxic function. Tph-like cells can also produce CXCL13, and CXCR5⁺ T follicular helper (Thf) cells and B cells are therefore preferentially recruited to form ectopic lymphoid structures in the sites. Tph cells may have a role to ignite inflammation and maintain persistent fibroinflammation in collaboration with Thf cells in lesions of IgG4-RD [50].

2.2. B cell subsets

Increasing evidences show that B cells play significant roles in the pathogenesis of IgG4-RD. In IgG4-RD patients, the fact that striking elevation of serum IgG4 and the abundance infiltration of IgG4⁺ plasma cells at involved lesions drives extensive researches on B cells. Actually, B cell depletion therapy with rituximab has successfully been employed in IgG4-RD for an effective glucocorticoid-sparing medication, in addition, anti-CD19 monoclonal antibody therapy is ready for clinical trial. The study of B cell subsets in IgG4-RD demonstrated disturbed B cell subpopulations, abnormal expression of key signaling molecules, co-stimulatory molecules, and inflammatory cytokines in B cells from IgG4-RD patients [51]. Compared with healthy controls, in peripheral blood of IgG4-RD patients, memory B cells were increased while regulatory B cells were decreased; the expression of CD80 and CD86 on peripheral CD19⁺ B cells was elevated. Prominently, a B cell subset (plasmablasts/plasma cells) expressing CD19⁺CD24⁻CD38hi surface markers was significantly increased in peripheral B cells, showing a positive correlation with the serum levels of IgG4, number of organs with disease involvement, and levels of disease activity [52]. After treatment with GCs and immunosuppressants, these levels of plasmablasts/plasma cells were significantly reduced. Mattoo et al. reported that the number of CD19⁺ CD20⁺ CD27⁺ CD38⁻ plasmablasts, which exhibit oligoclonal and extensive somatic hyper-frequency mutations, were increased in patients with active IgG4-RD [53]. The numbers of these expanded plasmablasts decreased after rituximab (RTX)-mediated B-cell depletion therapy, while in the relapsed patients, circulating plasmablasts re-emerged in these who were clonally distinct and exhibited enhanced somatic hypermutation. Clonally expanded CD19⁺ CD20⁺ CD27⁻ CD38⁺ plasmablasts are a hallmark of active IgG4-RD better than serum IgG4, since serum IgG4 levels are not always elevated in the disease. Enhanced somatic mutation in activated B cells and plasmablasts and emergence of distinct plasmablast clones on relapse indicate that the disease pathogenesis is linked to de novo recruitment of naïve B cells into T cell-dependent responses by CD4⁺ T cells, likely driving a self-reactive disease process. IgG4 plasmablasts in tissue sites may play a role in IgG4-RD pathogenesis and may be a potential therapeutic target.

Plasmablasts arise in GC following affinity maturation from naïve CD20⁺ precursors. Once in the bloodstream, plasmablasts differentiate
into antibody-secreting short- or long-lived plasma cells, accounting for the excess IgG4 production in this disease [54]. Plasmablast concentrations in the blood correlate well with disease activity.

The IgG4-switched B cells may be selectively triggered to expand and differentiate into plasma cells. This may involve IL-21 driving proliferation and expansion of IgG4-switched cells and the upregulation of activation-induced cytidine deaminase (AID), B-lymphocyte-induced maturation protein 1 (Blimp-1) and X box protein 1 (XBP-1), all of which have been shown to be upregulated in patients with various organ manifestations of IgG4-RD [48,55]. Alternatively, signals from the inflamed/fibrotic tissue, including cytokines such as IL-4, IL-13 or IL-10 could selectively stimulate B cells to proliferate into IgG4 plasma cells, either directly or via Th2 and Treg cells [47]. Such an environment may be actively sustained via signals from IgG4 secreting B cells themselves, possibly involving IL-10 [56]. Mechanisms responsible for driving IgG4-RD (e.g. Th2 cytokines) may also increase IgE secreting B cell expansion in certain individuals. In this instance, one may expect an increased predisposition to allergies in later years of life.

The fact that B-cell depletion has been shown to correlate with rapid improvement of tissue fibrosis in affected organs of patients with IgG4-RD raises the hypothesis that B lymphocytes might be involved in fibrogenesis through mechanisms unrelated to either production of autoantibodies or activation of fibrogenic T cells. Emanuel Della-Torre et al. demonstrated that B cells from patients with IgG4-RD (1) stimulated collagen production by activated fibroblasts through soluble profibrotic signals, such as PDGF-B; (2) organized the extracellular matrix through specialized enzymes, such as lysyl oxidases; and (3) directly produced collagenous proteins [57]. In addition, they revealed that B cells secreted chemotactic factors CCL4, CCL5, and CCL11 and induced the production of these chemokines by activated fibroblasts. Finally, they demonstrated that, among different B-cell subsets, plasmablasts displayed intrinsic fibrogenic properties since they expressed sets of genes implicated in fibroblast activation and proliferation. Taken together, these novel findings add important pieces to the complex pathogenesis of IgG4-RD and suggest a possible central role for B cells in the orchestration of fibrotic processes. Therefore depletion of B cells through target CD20 might rapidly halt fibroblast activation and collagen deposition [58].

2.3. B cell-activating factor (BAFF) and a proliferation-inducing ligand (APRIL)

B cell-activating factor of the tumor necrosis factor family (BAFF) can be produced by monocytes, macrophages in bone marrow and activated T cells and mast cells in peripheral blood. BAFF regulates the survival and maturation of B cells, promotes the transformation of B cells into plasma cells, and induces the classification transformation of IgG4 under the action of IL-4. A proliferation-inducing ligand (APRIL), a member of the tumor necrosis factor (TNF) superfamily, is produced mostly by cells from the myeloid lineage, including monocytes, macrophages, neutrophils and eosinophils [59]. APRIL has two signaling receptors, the transmembrane activator and calcium-modulating ligand interactor (TACI) and B-cell maturation antigen (BCMA) [60], expressed by cells from the B lineage, once B cells have encountered their antigen [61]. APRIL forms heterotrimers with BAFF and enhances BAFF mediated B cell activation in humoral immunity at the level of immunoglobulin class-switch and plasma cell generation/survival [62-64].

It has been reported that serum levels of BAFF and APRIL in IgG4-RD patients were significantly higher than those in healthy controls [53,65], and BAFF levels of patients with IgG4-RD were comparable to those of patients with primary Sjogren’s syndrome (pSS) [65]. For the correlation analysis, clinical parameters, such as serum IgG4 and the number of affected organs, were not correlated with the levels of BAFF, however, serum APRIL levels were inversely correlated with serum IgG4 levels. While serum BAFF levels decreased following GC therapy, serum APRIL levels increased during follow-up. Therefore, BAFF may promote the production of IgG4 in IgG4-RD patients. Another study found activation of TLRs in basophils and monocytes from healthy controls induced IgG4 production by B cells, which effect was associated with enhanced production of BAFF and IL-13. In addition, activation of TLRs in basophils from patients with IgG4-RD induced a large amount of IgG4 secretion by B cells, which again was associated with increased BAFF and IL-13 [66,67]. These data suggest that innate immune responses mediated through TLRs may play a role in the development of IgG4-RD, in part by production of BAFF from basophils. As we know that both BAFF and APRIL are important biomarkers in many autoimmune diseases, their roles are not unique or specific for IgG4-RD.

Anti-BAFF therapy (belimumab) has been proved in diseases such as systemic lupus erythematosus, recently, a case report also confirmed a patient with lupus nephritis and IgG4-RD was effectively treated using belimumab [68]. Therefore, BAFF inhibitor might be one of a promising option for IgG4-RD patients.

2.4. IgG4 antibody

Serum IgG4 is one of the most important biomarkers for IgG4-RD at present, both for diagnosis and monitoring treatment response. Elevated serum IgG4 presents in most patients, it is one of the diagnostic criteria for IgG4-RD. Evidence showed that serum IgG4 levels reflect the disease severity and activity, which positively correlate with the number of involved organs and IgG4-RD RI scores. It has been largely reported that serum IgG4 correlates with treatment response, which decreases after treatment with GCs or RTX. In addition, re-elevation of serum IgG4 level could predict flare of the disease.

IgG4 is one of the four subtypes of IgG. In normal blood, IgG4 only accounts for 1%-7% of IgG, however, the serum IgG4 level is significantly increased in the majority of IgG4-RD patients. Therefore, it is speculated that IgG4 plays an important role in the pathogenesis of IgG4-RD. Due to the characteristic structure of IgG4 monovalent molecules and the formation of bispecific antibodies by Fab exchange [69], IgG4 has anti-inflammatory rather than proinflammatory activity [70]. By binding to circulating allergens, IgG4 inhibits IgE binding to them, thereby reducing mast cell activation and inhibiting Th2 cell-related immune responses. Shiokawa M. et al. examined the pathogenic activity of circulating IgGs by subcutaneously injecting serum IgGs from IgG4-RD patients into neonatal male Balb/c mice. They found that both IgG1 and IgG4 injection resulted in pancreatic and salivary gland injuries, with more destructive changes induced by IgG1 than by IgG4. While the potent pathogenic activity of patient IgG1 was significantly inhibited by simultaneous injection of patient IgG4 [71]. The role of IgG4 in the pathogenesis of IgG4-RD needs to be further investigated.

3. Conclusions

In this article, we have reviewed the most recent advances pertaining to the immunopathology of IgG4-RD, and describe how the innate and the adaptive immune system might synergize to result in IgG4-RD. Despite the increased efforts, the exact pathophysiology standing behind this fibroinflammatory condition still remains enigmatic. Indeed, a number of unsolved questions need to be addressed in order to fully understand the pathogenesis of IgG4-RD. The mechanisms responsible for the increases in Tregs and Th2 cytokines remain unclear. Specific antigens that drive the IgG4-RD disease process have yet to be identified. The precise immunological mechanism leading to fibrosis is incompletely understood. Therefore, it is necessary to further investigate the pathogenesis of IgG4-RD.

**Declaration of competing interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.
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