IgG4-related disease and its pathogenesis—cross-talk between innate and acquired immunity

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Abstract

IgG4-related disease (IgG4-RD) is a novel clinical entity proposed in Japan in the 21st century and is attracting strong attention over the world. The characteristic manifestations of IgG4-RD are increased serum IgG4 concentration and tumefaction by IgG4+ plasma cells. Although the clinical manifestations in various organs have been established, the pathogenesis of IgG4-RD is still unknown. Recently, many reports of aberrant acquired immunity such as T\(_h\)2-diminated immune responses have been published. However, many questions still remain, including questions about the pathogenesis of IgG4-RD and the roles of IgG4. In this review, we discuss the pathogenesis of IgG4-RD by focusing on the cross-talk between innate and acquired immunity.

Keywords: IgG4, regulatory T cell, T\(_h\)2, toll-like receptor

Introduction

IgG4-related disease (IgG4-RD) is a new emerging disease entity with multiorgan involvement characterized in most patients by increased serum IgG4 concentrations (1, 2). The concept of IgG4-RDs arose when increased serum IgG4 concentrations were observed in patients with sclerosing pancreatitis (3). Other manifestations of IgG-RD include a characteristic histopathological appearance and an increased number of IgG4+ plasma cells within tissue (1, 2, 4). IgG4-RD includes a wide variety of diseases, formerly diagnosed as Mikulicz’s disease (MD) (5, 6), autoimmune pancreatitis (AIP) (7), hypophysitis, Riedel thyroiditis (8), interstitial pneumonitis (9, 10), interstitial nephritis (11, 12), prostatitis, lymphadenopathy (13, 14), retroperitoneal fibrosis (RPF) (15, 16), inflammatory aortic aneurysm (17) and inflammatory pseudotumor (Table 1). Although IgG4-RD is now recognized worldwide, much remains unknown about the behavior of the IgG4 molecule in vivo, the pathways through which this immunoglobulin participates in disease and whether the role of IgG4 is primary or secondary.

General manifestations of IgG4-RD

The All Japan IgG4-RD Research Group, organized by the Ministry of Health, Labor and Welfare (MHLW) of Japan reached a consensus on the general concept of IgG4-RD (18): (i) IgG4-RD is characterized by organ enlargement or nodular/hyperplastic lesions in various organs concurrently
or metachronously, caused by marked infiltration of lymphocytes and IgG4+ plasma cells and fibrosis with unknown etiology; (ii) IgG4-RD can affect various organs, including the pancreas, bile duct, lacrimal gland, salivary gland, thyroid, lung, liver and kidney (Fig. 1); (iii) many patients with IgG4-RD may have lesions in several organs, either synchronously or metachronously; (iv) clinical symptoms vary depending on the affected organ(s), with some patients experiencing serious complications, such as obstruction or compression symptoms as a result of organomegaly or hypertrophy and organ dysfunction caused by cellular infiltration or fibrosis; (v) IgG4-RD mainly affects middle-aged to elderly men; (vi) many patients with IgG4-RD can be treated effectively by steroid therapy; (vii) although the infiltration of IgG4+ cells and increased serum concentrations of IgG4 are common features of IgG4-RD, the severity of fibrosis is dependent on the individual organs involved.

**Naming of IgG4-RD**

Many terms were previously used to describe IgG4-RD, including IgG4-related sclerosing disease (19), IgG4-related autoimmune disease (20), systemic IgG4 plasmacytic syndrome (21) and IgG4-related multigian lymphoproliferative syndrome (6). The All Japan IgG4-RD Research Group carefully examined reports using these different nomenclatures and concluded that they referred to the same condition. In addition, several reports have described patients with IgG4-associated conditions concomitant with malignant tumors, such as pancreatic and salivary carcinomas and ocular adnexal lymphoma. Therefore, using the term ‘systemic’ in the nomenclature may lead to an incorrect diagnosis of an IgG4-related condition in a patient with malignant tumors in other organs. On the basis of these findings, the All Japan IgG4 Team agreed to use a uniform nomenclature, ‘IgG4-related disease (IgG4-RD)’ (1). An international symposium on IgG4-RD was held in Boston in 2011; the organizing committee consisted of 35 experts on IgG4-RD, including clinicians in various fields, such as rheumatology, gastroenterology, allergy, immunology, nephrology, pulmonary medicine, oncology, ophthalmology, surgery, pathology and radiology, and basic scientists from all over the world. Nomenclature was a specific focus of a portion of the symposium. The term IgG4-RD was accepted by the members of the organizing committee, and recommendations related to terminology for individual organ system manifestations have been published (22).

**Diagnosis of IgG4-RD**

Because IgG4-RD may occur in many organs throughout the body including the pancreas, bile duct, lacrimal gland, salivary gland, thyroid, lung, liver, gastrointestinal tract, kidney and retroperitoneum, either synchronously or metachronously, detailed diagnostic criteria are needed for the involvement of each organ, including clinical symptoms, serological and histological findings and radiological images. Although organ-specific IgG4-RD criteria have been established, including the diagnostic criteria for IgG4-related MD (23), IgG4-related AIP type 1 (24), IgG4-related sclerosing cholangitis (25) and IgG4-related kidney disease (KD) (26), these organ-specific criteria are not suitable for the diagnosis of patients with involvement of other organs. In addition, organ-specific criteria may not be familiar to general clinicians and non-specialists in diseases of those organs. As all clinicians should become aware of this new disease entity, comprehensive diagnostic criteria (CD criteria) for IgG4-RD have been established for practical use and to differentiate among malignancies (27) (Table 2).
The CD criteria we have proposed for IgG4-RD consist of three parts: concept, diagnostic criteria and explanatory notes (27). The concept clarifies the features characteristic of IgG4-RD, such as location of lesions, symptoms and prognosis. Diagnostic criteria are based on the two major characteristics of IgG4-RD: increased serum IgG concentrations and infiltration of IgG4+ cells. Although tissue biopsies are difficult to obtain from some organs, including the pancreas, retroperitoneum and ocular cavity, histopathological examination is important. Because IgG4+ plasma cell infiltration has been reported in various diseases and clinical conditions, such as rheumatoid synovitis, inflammatory oral and skin lesions and carcinomas with a peritumoral inflammatory response, pathological criteria should be rigorous. Histopathological findings of marked IgG4+ cell infiltration (>10 cells per high-power field (HPF)) and an IgG4/IgG cell ratio >40% are diagnostic of IgG4-RD. A diagnostic algorithm for IgG4-RD, using comprehensive diagnostic criteria combined with organ-specific criteria, is shown in Fig. 2.

**Clinicopathological features of IgG4-RD**

IgG4-related dacryoadenitis, sialadenitis and parotitis, or IgG4-related submandibular gland disease (IgG4-related MD)

Some patients show typical symptoms of MD, such as swelling of the lachrymal, parotid and/or submandibular glands, similar to findings in Sjögren’s syndrome (SS). The most important difference between these two entities is that IgG4-RD is characterized by marked infiltration of IgG4+ plasma cells, with a ratio of IgG4+ to IgG+ cells >40%, a finding almost never seen in patients with SS (6, 23, 28, 29).

Type 1 AIP (IgG4-related pancreatitis)

Following the description of a patient with chronic pancreatitis due to an autoimmune mechanism (30), lymphoplasmacytic sclerosing pancreatitis was found to be a characteristic histopathological finding in patients with AIP (31). Recent studies have suggested that AIP manifests as two distinct subtypes (7). Type 1 AIP is defined by increased serum gammaglobulin, IgG and/or IgG4 concentrations and characteristic pathological features, including IgG4+ plasmacyte infiltration, fibrosis and obliterative phlebitis. In contrast, type 2 AIP is characterized by idiopathic duct-centric pancreatitis or AIP with granulocytic epithelial lesions with no increases in serum IgG4 or IgG, no autoantibodies and no involvement of other organs, except for inflammatory bowel disease. Therefore, type 1 AIP is considered the pancreatic manifestation of IgG4-RD (24, 32).

Table 2. Comprehensive diagnostic criteria for IgG4-RD, 2011 (27)

|   | Description                                                                 |
|---|-----------------------------------------------------------------------------|
| 1 | Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs. |
| 2 | Hematological examination shows increased serum IgG4 concentrations (≥135 mg dl⁻¹). |
| 3 | Histopathological examination shows |
|   | (i) Marked lymphocyte and plasmacyte infiltration and fibrosis. |
|   | (ii) Infiltration of IgG4+ plasma cells: ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells per HPF. |

Definite: 1 + 2 + 3
Probable: 1 + 3
Possible: 1 + 2

However, it is important to differentiate IgG4-RD from malignant tumors of each organ (e.g. cancer, lymphoma) and similar diseases (e.g. SS, primary sclerosing cholangitis, Castleman’s disease, secondary RPF, Wegener’s granulomatosis, sarcoidosis, Churg-Strauss syndrome) by additional histopathological examination.

Even when patients cannot be diagnosed using the CCD criteria, they may be diagnosed using organ-specific diagnostic criteria for IgG4-RD.
**Innate immunity in the pathogenesis of IgG4-RD**

**IgG4-related KD**

The kidney is a frequent target organ in IgG4-RD, with tubulointerstitial nephritis (TIN) and fibrosis and abundant IgG4+ plasma cell infiltration being diagnostically important (11, 33, 34). Compared with other types of interstitial nephritis, IgG4-related TIN is often associated with extrarenal lesions, such as pancreatitis, sialadenitis and lymphadenitis, and a high incidence of hypocomplementemia (35). Recently, a working group in the Japanese Society of Nephrology established diagnostic criteria for IgG4-related KD based on clinical features, including extrarenal organ involvement, urinalysis and serological features, including serum IgG4 levels, findings on computed tomography (CT) scanning, renal histology with IgG4 immunostaining and response to steroid therapy (26).

**Involvement of other organs in IgG4-RD**

**IgG4-related lung disease.** IgG4-related lung disease (LD) has been described as inflammatory pseudotumor, interstitial pneumonitis, organizing pneumonia and lymphomatoid granulomatosis (9). Some patients presented initially with respiratory symptoms, such as dry cough or dyspnea, whereas 75% of patients are asymptomatic and found incidentally by abnormal shadows on chest X-rays and CT scanning. Histopathologically, interstitial pneumonitis often shows a pattern previously classified as non-specific interstitial pneumonia (36). The diagnostic criteria for IgG4-related LD are currently being considered by a working group of the Japanese Respiratory Association.

**IgG4-related thyroid disease.** Recently, a unique subtype of Hashimoto’s thyroiditis (HT) was described, characterized by the presence of prominent fibrosis such as storiform fibrosis and swirling fibrosis, numerous IgG4+ plasma cells and increased serum IgG4 (37); this entity has been called IgG4-related HT (38). Positivity for antithyroglobulin antibody and antithyroid peroxidase antibody did not differ significantly between IgG4-related HT and non-IgG4 HT, but titters of both antibodies were significantly higher in IgG4-related HT than in non-IgG4 HT (39).

**IgG4-related RPF.** RPF is a chronic inflammatory condition with marked fibrosis in retroperitoneal tissue. In patients with advanced RPF, a retroperitoneal mass covers the abdominal aorta and compresses the ureters, leading to urinary obstruction. It has been reported that 58.8% of patients with RPF had both increased serum IgG4 and histopathological features typical of IgG4-RD (9).

**IgG4-related aortitis/periaortitis.** Several recent reports have described patients with inflammatory aeurysms in the abdominal or thoracic aorta (17, 40). For example, 40% of inflammatory abdominal aortic aneurysms were IgG4-RD, with increased IgG4 in serum and abundant infiltration of IgG4+ plasma cells and obliterative phlebitis (40).

**IgG4-related lymphadenopathy.** Patients with IgG4-RD and generalized lymphadenopathy should only be evaluated for lymphoma, sarcoidosis, multicentric Castleman’s disease and other malignancies. Patients with systemic IgG4-related lymphadenopathy were found to be significantly older and to have significantly lower C-reactive protein (CRP) and IL-6 concentrations than patients with multicentric Castleman’s disease (13).

**Pathogenesis of IgG4-RD**

Increased serum IgG4 concentration and tissue infiltration by IgG4+ cells are key events in IgG4-RD. Aberrant acquired immunological findings such as T,2-dominated cytokine production leading to IgG4 hyperproduction and increase in number of regulatory T cells (Treg cells) have been reported (41–43). Although some autoantibodies, including those to pancreatic trypsin inhibitor, lactoferrin and carbonic anhydrase have been reported in patients with IgG4-related AIP (44, 45), IgG4-type autoantibodies have not been detected.
in patients with other organ involvement of IgG4-RD. At present, it is not clear whether IgG4-RD is caused by abnormal acquired immunity like autoimmune diseases, and whether the enhanced production of IgG4 antibody is a true cause of IgG4-RD or an epiphenomenon associated with inflammatory reactions.

IgG4-RD occurs comparatively more in the older persons (median age, 58 years), slowly progresses and shows relatively weak inflammation signs such as low titer of CRP. Infections with various species of pathogens such as *Helicobacter pylori* (46, 47), Gram-negative bacteria (48) and *Mycobacterium tuberculosis* (49) have been reported in IgG4-RD. In addition, stimulation with toll-like receptor (TLR) ligands induces production of both IgG4 and IL-10 from PBMCs (50). It is likely that various species of pathogens induce productions of IgG4, which may prevent innate immunity, resulting in the persistence of infections. We therefore focused on the possibility that the innate immune system may be involved in the pathogenesis of IgG4-RD through cross-talk with acquired immunity.

**Characteristics of IgG4 and class switching of B-cell immunoglobulin**

Among the four subclasses of IgGs, the most abundant IgG is IgG1 ranging from 5 to 11 mg ml\(^{-1}\), whereas the least abundant subclass is IgG4 ranging from 0.35 to 0.51 mg ml\(^{-1}\) (51). The important differences between IgG1 and IgG4 are a few amino acid differences in the CH2 domain, CPSC and CPPC (P, proline; S, serine; C, cysteine) for IgG4 and IgG1 core hinge lesions, respectively. The S228 in IgG4 results in a more flexible hinge enabling the formation of an intrachain cyclized disulfide and leads to the appearance of half-antibodies, which contain non-covalently linked heavy chains as determined by analysis of IgG4 antibodies under denaturing conditions (51, 52). Thus, IgG4 antibodies can exchange Fab arms by swapping a heavy chain and attached light chain and form bispecific antibodies that function as monovalent molecules (Fig. 3) (51, 53).

Several lines of evidence suggest that IgG4 has an anti-inflammatory rather than a pro-inflammatory role. First, the interactions of IgG4 with the Fc\(\gamma\) receptor and C1q are weaker than those of other IgG subclasses (51, 54). Second, IgG4 antibodies can exchange Fab arms

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**Fig. 3.** Structural characteristics of IgG4 (51). Generally, each immunoglobulin monomer consists of two identical half-molecules; two such monomers recognizing different antigens are shown in pink or green at the top of the figure. Each half-molecule is a pair of a heavy chain (H strand) and a light chain (L chain). Two pairs are generally joined together by the non-covalent bond of the 3C domain and the covalent bond of the hinge segment. However, because IgG4 does not have a covalent bond between H strands and the covalent bond is carried out within the H strand, a characteristic space structure is taken. The important features of IgG4 are functional monovalency and half-molecule exchange. IgG4 antibodies may exist as pairs of different half-molecules (functional monovalency) by the intra-heavy-chain disulfide-bonded structure. Under certain conditions, IgG4-Fabs may join together, making a chimeric antibody by the inter-heavy-chain disulfide bonds. Therefore, IgG4 may decrease or neutralize the cellular immunity triggered by IgG1.
by swapping a heavy chain and an attached light chain (half-molecule) with a heavy–light chain pair from another molecule, resulting in bispecific antibodies (51, 53). Thus, IgG4 antibodies are unable to cross-link antigens to form immune complexes (ICs) for complement activation. These properties may protect against type I allergy by inhibiting IgE functions and may prevent type II and III allergies by blocking Fc-mediated effector functions of IgG1 and inhibiting the formation of large ICs (Fig. 4e) (51, 54, 55). Third, increased IgG4 levels during prolonged immunization are considered a marker of tolerance induction in IgE-related allergic disorders (56, 57). Fourth, IgG4 as well as IgG1 and IgG3 subclasses of PR3-ANCA are able to induce release of superoxide, degranulation and adhesion of neutrophils.

Fig. 4. Cross-talk between innate and acquired immunity in IgG4-RD. (a) T-cell differentiation (acquired immunity). Naive helper T cells (T<sub>0</sub>) can become either T<sub>1</sub> or T<sub>2</sub> under the instructive influence of IL-12 or IL-4, respectively. T<sub>2</sub> cells produce IL-4, IL-5 and IL-13, which are potent activators of B-cell IgE production and eosinophil recruitment. In addition, TGF-β induces Foxp3 and generates Treg cells. Whereas, T<sub>1</sub> cells, an important source of IL-10, are converted from T<sub>1</sub>, T<sub>2</sub> and Treg cells by IL-27. (b) Antigen-presenting cells (innate immunity). TLR4 recognizes LPS, which is unique to Gram-negative bacteria, whereas TLR2 is activated by lipoteichoic acid (LTA) or bacterial lipoproteins. Ligation of TLR2 by pathogenic micro-organisms such as fungi and mycobacteria induces a T<sub>2</sub> anti-inflammatory bias, either through release of IL-10 or through inhibition of IFN-γ signaling. IL-27 is produced primarily by antigen-presenting cells after stimulation by microbial products or inflammatory mediators and converts activated inflammatory CD4<sup>+</sup> T cells into IL-10-producing Tr1 cells. The activation of TLRs or NLRs (NOD-2) in APCs produces BAFF and APRIL, leading to IgG4 production. (c) Cross-talk between the complement system and TLRs (innate immunity). C3 activation generates effector molecules such as C3a and C5a anaphylatoxins, which activate specific G-protein-coupled receptors, CR3 and C5aR, respectively. Activation of C5aR in macrophages and dendritic cells inhibits TLR-4-induced production of IL-12, IL-23 and IL-27 proteins from these cells. This decreased cytokine response translates into a decreased T<sub>1</sub> response as an important mechanism for a shift of T<sub>1</sub> to T<sub>2</sub> polarization in response to innate and adaptive immune network activation. (d) B-cell immunoglobulin class switching to IgG4 (acquired immunity). Most antigens initiate class switching and SHM in the GC of lymphoid follicles through cognate interaction between B cells and Tfh cells that express CD40 ligand (CD40L). Tfh cells provide crucial signals to GC B cells undergoing SHM and selection that results in affinity maturation. BAFF and APRIL, in concert with IL-21, enhance IgG4 production via promoting the expansion of IgG4-committed B cells. The survival of B cells committed to IgG4 production is enhanced in the presence of IL-21. (e) Impairment of adaptive immunity (innate immunity). IgG4 antibodies can exchange Fab arms by swapping a heavy chain and attached light chain and form bispecific antibodies. The interactions of IgG4 with the Fcγ receptor and C1q are weaker than those of other IgG subclasses, resulting in blocking Fc-mediated effector functions of IgG1, inhibiting the formation of large immune complexes and decreasing IL-8 excretion from neutrophils. These properties of the IgG4 mediate impaired adaptive immunity.
However, the IgG4 subclass of PR3-ANCA was unable to stimulate neutrophil IL-8 release because of lack of binding with FcγRIIIb on neutrophils (58).

Although the essential role of IgG4 antibody remains to be made clear in the pathogenesis of IgG4-RD such as type I AIP, it has been reported that bispecific IgG4 antibodies can protect patients against the autoimmune myasthenia gravis by competing with pathogenic IgG1 antibodies against acetylcholine receptor (59, 60), and that an IgG4 antibody to desmoglein causes direct disruption of the epithelial layer and blister formation in pemphigus without antibody-dependent cellular cytotoxicity or complement activation (61).

Mature B cells diversify their immunoglobulin genes through class switching and somatic hypermutation (SHM), both of which require the DNA-editing enzyme activation-induced cytokine deaminase (AID) (62). Most antigens initiate class switching and SHM in the germinal center (GC) of lymphoid follicles through cognate interaction between B cells and CD4+ helper T cells that express CD40 ligand (CD40L), whereas dendritic cells recognize microbial products through TLRs and produce CD40L-related class switch-inducing factors. B cell-activating factor (BAFF), which is in the TNF family and a proliferation-inducing ligand (APRIL) (63), both of which cooperate with TLR ligands to induce AID expression in B cells (62). It has been reported that by analysis of immunoglobulin heavy chain gene rearrangement and SHM, rates of unmutated VH fragments, especially VH3 family, were significantly higher in IgG4-related sclerosing sialoadenitis as well as SS than in control sialolithiasis (64) (Fig. 4d).

Cross-talk in the cytokine network

Many reports have indicated that T,2-dominant immune responses and the production of T,2-type cytokines, including IL-4, IL-5 and IL-13 as well as the regulatory cytokines IL-10 and TGF-β are increased in IgG4-RD (Fig. 4a) (41, 42, 50, 66–67). Recently, the levels of expression of IL-10, TGF-β and AID were reported to be significantly higher in the labial salivary glands (LSGs) of patients with IgG4-RD than in the LSGs of patients with SS and controls (68). Because the T,2 cytokines and IL-10 can induce IgG4- and IgE-specific class-switch recombination (69), the over-expression of these factors may be involved in the pathogenesis of IgG4-RD through IgG4-specific class-switch recombination and fibrosis. IL-21 produced by macrophages has been reported to control the functional activity of effector follicular helper T (Tfh) cells and to promote their formation of ectopic GCs, which are often seen in lesions of IgG4-RD. Recently, IL-21 expression in LSGs was shown to correlate with the number of GCs and the IgG4/IgG4 ratio in patients with IgG4-RD (Fig. 4b) (70).

IL-27, a member of the IL-12 family, including IL-12, IL-23, IL-27 and IL-35, is produced primarily by antigen-presenting cells (APCs), macrophages and dendritic cells, after stimulation by microbial products or inflammatory mediators (71). IL-27 and IL-35 have anti-inflammatory properties, whereas IL-12 and IL-23 have pro-inflammatory properties (72). In addition, IL-27 converts activated inflammatory CD4+ T cells into IL-10-producing T,1 or type 1 Treg (Tr1) cells (73). Therefore, IL-21 and IL-27 may participate in the pathogenesis of IgG4-RD through hyperproduction of IL-10 and increase of GCs and Treg cells (Fig. 4a, b and d).

BAFF mediates the regulation of B-cell maturation, survival, CD40L-independent antibody production and induces IgG4 class-switch DNA recombination in the presence of IL-4 (63). Because serum concentrations of BAFF and its homolog, APRIL, were found to be significantly higher in patients with IgG4-RD than healthy individuals (74), BAFF and APRIL may also be involved in increasing IgG4 in patients with IgG4-RD (Fig. 4b and d).

Involvement of TLRs and nucleotide-binding oligomerization domain-like receptors in IgG4-RD

TLRs recognize pathogen-associated molecular patterns and activate immune responses as a frontline of host defense. On the basis of cellular distribution and/or ligand specificity, TLRs can be divided into two groups: TLR1, TLR2, TLR4, TLR5 and TLR6 are mainly present on the cell membrane and sense lipids or proteins unique to bacteria, whereas TLR3, TLR7, TLR8 and TLR9 reside in the endosomes or the endoplasmic reticulum and sense nucleic acids (75). Furthermore, the nucleotide-binding oligomerization domain (NOD) family of proteins (NOD-1 and NOD-2), i.e. NOD-like receptors (NLRs) plays an important role in the recognition of intracellular bacteria (Fig. 4b) (76).

TLRs were initially regarded as being expressed primarily by APCs, such as macrophages and dendritic cells. However, TLR expression was observed on various T-cell subsets, including conventional αβ T, regulatory and γδ T cells, as well as on NK T cells, and these T cells can sense pathogens directly through TLRs, modifying their behavior (77). For example, TLR4 is associated with the efficient release of pro-inflammatory T,1 cytokines, whereas TLR2 promotes T,2 responses by increasing the production of the anti-inflammatory cytokine IL-10 (78). Thus, the TLR and NLR systems may contribute to T,2-dominant immune responses in IgG4-RD.

The characteristic features of aberrant immunological findings in IgG4-RD are the T,2-dominant immune response and the increased production of T,2-type cytokines, such as IL-4, IL-5, IL-10 and IL-13 (42, 50, 66). In addition, the numbers of CD4+CD25+Foxp3+ Treg cells are significantly higher in the affected tissues and peripheral blood of patients with IgG4-RD than those with autoimmune diseases (41, 65).

In addition to T,1 and T,2 subsets, the repertoire of effector CD4+ T-cell subsets has recently expanded to include Treg cells, Tr1 cells, Thf cells and follicular Treg cells (Tfr cells) (79). In response to T-dependent antigens, a proportion of naive Treg cells can express Bcl-6, which allows them to adopt the Tfh cell differentiation program, express the follicular homing receptor CXCR5 and localize to GCs. Thf cells provide crucial signals to GC B cells undergoing SHM and selection that results in affinity maturation. Tight control of Tfh is maintained by CXCR5`, PD-1`, CD4+ Tfr cells. GC reactions can be controlled by limiting the numbers of Tfh cells and by inhibiting the selection of non-antigen-specific B cells, including those carrying self-reactive receptors (Fig. 4a and d). Tr1 cells (Foxp3–CD4+ Treg cells) have been found to be important sources of IL-10, an anti-inflammatory cytokine that limits inflammation (Fig. 4a).
TLR expression is higher on Treg cells than on conventional CD4+ T cells, suggesting that the expansion and function of Treg cells may be closely influenced by TLR ligands. Exposure of Treg cells to the TLR4 ligand LPS up-regulates the expression of several activation markers, enhancing cell survival and/or proliferation. In contrast, administration of TLR2 ligands, such as Pam3Cys-SK4 and heat shock protein 60, was found to significantly increase the number of Treg cells, while temporarily abrogating their immunosuppressive function (77, 80, 81).

Activation of TLRs and NLRs in APCs, including in dendritic cells, monocytes and macrophages, has been reported to lead to immunoglobulin class switching through the production of BAFF and its homolog, APRIL (63, 82). Watanabe et al. (83) reported that BAFF-dependent IgG4 production may enhance the activation or expansion of B cells already committed to IgG4 production. Activation of NOD-2 in monocytes from healthy individuals induced IgG4 production by B cells in a BAFF-dependent and T-cell-independent manner, whereas stimulation of PBMCs from patients with IgG4-RD with NLR and TLR ligands produced large amounts of IgG4, associated with the induction of BAFF by NLR and TLR ligands (Fig. 4b).

TLR activation in basophils has also been reported to contribute to the development of IgG4-RD (84). Although basophils have been considered T2 effector cells, TLR activation in basophils from healthy individuals induced IgG4 production by B cells, an effect associated with enhanced production of BAFF and IL-13 (85). Taken together, cells in innate immunity, such as monocytes and basophils, may be functionally involved in the immunopathogenesis of IgG4-RD, through the activation of TLRs and NLRs.

Cross-talk between the complement pathways and acquired immunity

IgG4 antibodies can exchange Fab arms and form bispecific antibodies, preventing complement activation in type II and III allergy by blocking Fc-mediated effector functions of IgG1 (51, 53) (Fig. 4e). However, more than half of all patients with IgG4-RD show hypocomplementemia (6), a discrepancy believed to be due to the ICs containing IgG1 or C1q detected in the affected organs, such as kidneys, of patients with IgG4-RD (86, 87). It has been also reported that the increased levels of ICs were associated with increased levels of IgG1 rather than those of IgG4 and decreased levels of C3 and C4 in cases of AIP (88). Thus, ICs containing IgG1, IgG2, IgG3 and IgM, except for IgG4 may cause complement activation via the classical pathway. Another possible mechanisms for hypocomplementemia may be mediated by anti-hinge antibodies (AHA), formerly called anti-F(ab’)2 antibody, which recognize epitopes in the hinge regions of immunoglobulins (89). It has been reported that AHA against the IgG4 F(ab’)2 fragment of anticitrullinated protein antibody are specific to rheumatoid arthritis and ICs of AHA with IgG4 F(ab’)2 were able to activate complement in some patients with rheumatoid arthritis (90). Because chronic inflammation activates proteases such as elastase or cathepsin-G, which cleave IgGs into Fab or F(ab’)2 fragments, it may be possible that IgG4 deposition in tissues causes ICs of IgG4 and AHA, leading to complement activation in IgG4-RD.

In addition, most pathogens activate complement directly as well as through TLRs (91), suggesting another mechanisms underlying hypocomplementemia in patients with IgG4-RD and the potential for cross-talk between the two systems.

The complement cascade can be triggered via three distinct pathways, the classical, lectin and alternative pathways, which converge at the third component of complement (C3). C3 activation by pathway-specific C3 convertases leads to the generation of effector molecules involved in (i) recruitment and activation of inflammatory cells (e.g. the C3a and C5a anaphylatoxins, which activate specific G-protein-coupled receptors, C3aR and C5aR, respectively), (ii) microbial opsonization and phagocytosis (e.g. the IC3b opsonin, which interacts with CR3) and (iii) direct lysis of targeted pathogens (via the C5b-9 membrane attack complex). Certain microbial molecules, including LPS (TLR4 agonist), zymosan (TLR2/6 agonist) and CpG DNA (TLR9 agonist), activate complement as well as initiating TLR signaling (Fig. 4c).

On inflammation, activation of C5aR in macrophages inhibits the production of IL-12, IL-23 and IL-27 proteins through the reduction of TLR-4-induced expression of mRNAs encoding IL-12p35, IL-12/IL-23p40, IL-23p19 and IL-27p28 (91). IL-12 drives the differentiation of the T1 subset from naive CD4+ T cells. IL-23 promotes the expansion of the T17 lineage, whereas IL-27 seems to regulate the balance between T1 and T17 by limiting T17 cell development in favor of T1. Therefore, the decrease of these cytokines results in a shift from T1 to T2 polarization through cross-talk of the innate and acquired immune networks (Fig. 4c) (92).

Cross-talk between innate and acquired immunity in fibrosis

Another hallmark of IgG4-RD is the characteristic fibrosis such as storiform or swirling fibrosis along with obliterative phlebitis, especially observed in IgG4-related pancreatitis, IgG4-related RPF and IgG4-related KD (4, 93). Because fibrosis is the final pathological outcome of chronic inflammation, dense fibrosis may be frequently observed in anatomically deep lesions that would be difficult to detect at an early stage.

At early inflammation, innate immune cells such as macrophages, neutrophils and dendritic cells are activated and produce profibrotic cytokines such as IL-4 and IL-13, along with platelet-derived growth factor, which promote the differentiation of CD14+ precursors to fibrocytes. Macrophages as well as other myeloid-lineage cells (such as mast cells, eosinophils and basophils) are also major producers of TGF-β, which drives fibrosis. In addition, macrophages activated with IL-4 (or IL-13) turned to the phenotype of so-called M2 macrophages distinct from classical macrophages (M1) activated by IFN-γ. M2 macrophages have been implicated in the development of T2-effector responses (i.e. production of IL-4, IL-5 and IL-13) that drive progression of fibrosis (94). Although the severity of fibrosis may differ in organs, hyper-production of T2-type cytokines, including IL-4, IL-5 and IL-13 as well as the regulatory cytokines IL-10 and TGF-β may be involved in fibrosis of IgG4-RD.
Future aspects

IgG4-RD is a disease that has transcended the old concept of individual disease categories, such as MD, AIP and so on. Although all of these diseases have characteristics in common, such as high serum IgG4 concentrations and IgG4+ plasma cell infiltration, there are many questions concerning the etiologic function of IgG4 and the mechanisms under class switching from other IgGs to IgG4. Several studies have addressed aberrant acquired immunity of the T2-dominant immune response and the hyperproduction of T2-type cytokines in IgG4-RD (42, 50, 66). More recent studies of innate immunity in patients with IgG4-RD have reported that macrophages and basophils function abnormally and that macrophages over-express BAFF, APRIL and other cytokines (74, 83, 84). Similarly, our microarray analysis showed that many of the genes showing a >3-fold difference in expression between IgG4-RD patients and healthy controls were genes related to innate immunity (A. Nakajima et al., submitted for publication). Conventionally, many underlying diseases, such as tuberculosis, other infections and lymphoma, have been reported to cause MD. Similarly, the underlying causes of IgG4-RD may differ. Further investigations of IgG4-RD are needed to clarify the mechanisms underlying IgG4 hyperproduction and the roles of IgG4 in IgG4-RD, including investigations of the cross-talk between innate and acquired immunity.

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Competing interests

The authors declare that they have no competing interests.

References

1. Umehara, H., Okazaki, K., Masaki, Y. et al. 2012. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod. Rheumatol. 22:1.
2. Stone, J. H., Zen, Y. and Deshpande, V. 2012. IgG4-related disease. N. Engl. J. Med. 366:539.
3. Hamano, H., Kawa, S., Horuchi, A. et al. 2001. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N. Engl. J. Med. 344:732.
4. Deshpande, V., Zen, Y., Chan, J. K. et al. 2012. Consensus statement on the pathology of IgG4-related disease. Mod. Pathol. 25:1181.
5. Yamamoto, M., Ohara, M., Suzuki, C. et al. 2004. Elevated IgG4 concentrations in serum of patients with Mikulicz’s disease. Scand. J. Rheumatol. 33:432.
6. Masaki, Y., Dong, L., Kurose, N. et al. 2009. Proposal for a new clinical entity, IgG4-positive multi-organ lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders. Ann. Rheum. Dis. 63:1310.
7. Okazaki, K., Uchida, K., Koyabu, M., Miyoshi, H. and Takacoka, M. 2011. Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. J. Gastroenterol. 46:277.
8. Dahlgren, M., Khosroshahi, A., Nielsen, G. P., Deshpande, V. and Stone, J. H. 2010. Riedel’s thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum. Arthritis Care Res. 62:1312.
9. Zen, Y., Inoue, D., Kitao, A. et al. 2009. IgG4-related lung and pleural disease: a clinicopathological study of 21 cases. Am. J. Surg. Pathol. 33:1886.
10. Inoue, D., Zen, Y., Abo, H. et al. 2009. Immunoglobulin G4-related lung disease: CT findings with pathologic correlations. Radiology 251:260.
11. Saeki, T., Saito, A., Yamazaki, H. et al. 2007. Tubulointerstitial nephritis associated with IgG4-related systemic disease. Clin. Exp. Nephrol. 11:168.
12. Saeki, T., Nishi, S., Imai, N. et al. 2010. Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis. Kidney Int. 78:1016.
13. Sato, Y., Kojima, M., Takata, K. et al. 2009. Systemic IgG4-related lymphadenopathy: a clinical and pathologic comparison to multicentric Castleman’s disease. Mod. Pathol. 22:589.
14. Sato, Y., Notohara, K., Kojima, M., Takata, K., Masaki, Y. and Yoshino, T. 2010. IgG4-related disease: historical overview and pathology of hematological disorders. Pathol. Int. 60:247.
15. Hamano, H., Kawa, S., Ochi, Y. et al. 2002. Hydrenephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. Lancet 359:1403.
16. Zen, Y., Onodera, M., Inoue, D. et al. 2009. Retroperitoneal fibrosis: a clinicopathologic study with respect to immunoglobulin G4. Am. J. Surg. Pathol. 33:1833.
17. Stone, J. H., Khosroshahi, A., Hilgenberg, A., Spooner, A., Isselbacher, E. M. and Stone, J. R. 2009. IgG4-related systemic disease and lymphoplasmacytic arthritis. Arthritis Rheum. 60:3139.
18. Umehara, H. 2010. The Reports of the Grant from the Intractable Disease, Health and Labor Science Research Grants from the Ministry of Health, Labor and Welfare[H21-Nanchi-Ippann-112, representative Umehara H] [in Japanese]. Ministry of Health, Labor and Welfare, Japan.
19. Kamisawa, T., Nakajima, H., Egawa, N., Funatan, N., Tsuruta, K. and Okamoto, A. 2006. IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy. Pancreatology 6:132.
20. Kamisawa, T., Funata, N. and Hayashi, Y. 2004. Lymphoplasmacytic sclerosing pancreatitis is a pancreatic lesion of IgG4-related systemic disease. Am. J. Surg. Pathol. 28:1114.
21. Yamamoto, M., Takahashi, H., Hasebe, K. et al. 2009. The analysis of interleukin-6 in patients with systemic IgG4-related plasmacytic syndrome-expansion of SIPS to the territory of Castleman’s disease. Rheumatoloiy 48:860.
22. Stone, J. H., Khosroshahi, A., Deshpande, V. et al. 2012. IgG4-related disease: recommendations for the nomenclature of this condition and its individual organ system manifestations. Arthritis Rheum. 64:3061.
23. Masaki, Y., Sugai, S. and Umehara, H. 2010. IgG4-related diseases including Mikulicz’s disease and sclerosing pancreatitis: diagnostic insights. J. Rheumatol. 37:1300.
24. Shimosegawa, T., Ohari, S. T., Frulloni, L. et al. 2011. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology Pancreas. 40:352.
25. Ohara, H., Okazaki, K., Tsuouchi, H. et al. 2012. Clinical diagnostic criteria of IgG4-related sclerosing cholangitis. 2012. J. Hepatobiliary Pancreat Sci. 19:536.
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26 Kawano, M., Saeki, T., Nakashima, H. et al. 2011. Proposal for diagnostic criteria for IgG4-related kidney disease. Clin. Exp. Nephrol. 15:616.

27 Umehara, H., Okazaki, K., Masaki, Y. et al. 2011. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD). 2011. Mod. Rheumatol. 22:21.

28 Yamamoto, M., Takahashi, H., Ohara, M. et al. 2006. A case of Mikulicz’s disease (IgG4-related plasmacytic disease) complicated by autoimmune hypophysitis. Scand. J. Rheumatol. 35:410.

29 Yamamoto, M., Takahashi, H., Sugai, S. and Imai, K. 2005. Clinical and pathological observations of Mikulicz’s disease (IgG4-related plasmacytic exocrinopathy). Autoimmun. Rev. 4:195.

30 Sarles, H., Sarles, J. C., Muratore, R. and Guien, C. 1961. Chronic inflammatory sclerosis of the pancreas—an autonomous pancreatic disease? Am. J. Dig. Dis. 6:688.

31 Kawaguchi, K., Koike, M., Tsuruta, K., Okamoto, A., Tabata, I. and Fujita, N. 1991. Lymphoplasmocytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. Hum. Pathol. 22:387.

32 Okazaki, K., Uchida, K., Miyoshi, H., Ikeura, T., Takaoka, M. and Nishio, A. 2011. Recent concepts of autoimmune pancreatitis and IgG4-related disease. Clin. Rev. Allergy Immunol. 41:126.

33 Uchiyama-Tanaka, Y., Mori, Y., Kimura, T. et al. 2004. Acute tubulointerstitial nephritis associated with autoimmune-related pancreatitis. Am. J. Kidney Dis. 43:e18.

34 Takeda, S., Haratake, J., Kasai, T., Takaeda, C. and Takazakura, E. 2004. IgG4-associated idiopathic tubulointerstitial nephritis complicating autoimmune pancreatitis. Nephrol. Dial. Transplant. 19:474.

35 Saeki, T., Imai, N., Ito, T., Yamazaki, H. and Hishi, S. 2009. Membranous nephropathy associated with IgG4-related systemic disease and without autoimmune pancreatitis. Clin. Nephrol. 2:173.

36 Takato, K., Yasui, M., Ichikawa, Y. et al. 2008. Nonspecific interstitial pneumonia with abundant IgG4-positive cells infiltration, which was thought as pulmonary involvement of IgG4-related autoimmune disease. Intern. Med. 47:291.

37 Li, Y., Bai, Y., Liu, Z. et al. 2009. Immunohistochemistry of IgG4 can help subclassify Hashimoto’s autoimmune thyroiditis. Pathol. Int. 59:636.

38 Kakudo, K., Li, Y., Hirokawa, M. and Ozaki, T. 2011. Diagnosis of Hashimoto’s thyroiditis and IgG4-related sclerosing disease. Pathol. Int. 61:175.

39 Kojima, M., Hinokawa, M., Kuma, H. et al. 2010. Distribution of IgG4- and IgG4-positive cells in Hashimoto’s thyroiditis: an immunohistochemical study. Pathobiology 77:267.

40 Kasashima, S. and Zen, Y. 2011. IgG4-related inflammatory abdominal aortic aneurysm. Curr. Opin. Rheumatol. 23:18.

41 Zen, Y., Fuji, T., Harada, K. et al. 2007. Th2 and regulatory immune reactions are increased in immunoglobulin G4-related sclerosing pancreatitis and cholangitis. Hepatology 45:1538.

42 Miyake, K., Moriyama, M., Aizawa, K. et al. 2008. Peripheral CD4+ T cells showing a Th2 phenotype in a patient with Mikulicz’s disease associated with lymphadenopathy and pleural effusion. Mod. Rheumatol. 18:86.

43 Tanaka, A., Moriyama, M., Nakashima, H. et al. 2012. Th2 and regulatory immune reactions contribute to IgG4 production and the initiation of Mikulicz’s disease. Arthritis Rheum. 64:254.

44 Aparisi, L., Farre, A., Gomez-Cambronero, L. et al. 2005. Antibodies to carbonic anhydrase and IgG4 levels in idiopathic chronic pancreatitis: relevance for diagnosis of autoimmune pancreatitis. Gut 54:703.

45 Okazaki, K., Uchida, K. and Fukui, T. 2008. Recent advances in autoimmune pancreatitis: concept, diagnosis, and pathogenesis. J. Gastroenterol. 43:409.

46 Guarneri, F., Guarneri, C. and Benvenga, S. 2005. Helicobacter pylori and autoimmune pancreatitis: role of carbonic anhydrase via molecular mimicry? J. Cell. Mol. Med. 9:741.

47 Frulloni, L., Lunardi, C., Simone, R. et al. 2009. Identification of a novel antibody associated with autoimmune pancreatitis. N. Engl. J. Med. 361:2135.

48 Siddiquee, Z., Zane, N. A., Smith, R. N. and Stone, J. R. 2012. Dense IgG4 plasma cell infiltrates associated with chronic infectious aortitis: implications for the diagnosis of IgG4-related disease. Cardiovasc. Pathol. 21:470.

49 Kawano, M., Yamada, K., Kakuchi, Y. et al. 2009. A case of immunoglobulin G4-related chronic sclerosing sialadenitis and dacryoadenitis associated with tuberculosis. Mod. Rheumatol. 19:87.

50 Akitake, R., Watanabe, T., Zaima, C. et al. 2010. Possible involvement of T helper type 2 responses to Toll-like receptor ligands in IgG4-related sclerosing disease. Gut 59:542.

51 Aalberse, R. C. and Schuurman, J. 2002. IgG4 breaking the rules. Immunology 105:9.

52 Schuurman, J., Perdok, G. J., Gorter, A. D. and Aalberse, R. C. 2001. The inter-heavy chain disulfide bonds of IgG4 are in equilibrium with intra-chain disulfide bonds. Mol. Immunol. 38:1.

53 van der Neut Kolfschoten, M., Schuurman, J., Losen, M. et al. 2007. Anti-inflammatory activity of human IgG4 antibodies by dynamic Fab arm exchange. Science 317:1554.

54 van der Zee, J. S., van Swieten, P. and Aalberse, R. C. 1986. Inhibition of complement activation by IgG4 antibodies. Clin. Exp. Immunol. 64:415.

55 van der Zee, J. S., van Swieten, P. and Aalberse, R. C. 1986. Serologic aspects of IgG4 antibodies. II. IgG4 antibodies form small, nonprecipitating immune complexes due to functional monovalency. J. Immunol. 137:3566.

56 Aalberse, R. C., van der Gaag, R. and van Leeuwen, J. 1983. Serologic aspects of IgG4 antibodies. I. Prolonged immunization results in an IgG4-restricted response. J. Immunol. 130:722.

57 Nanda, A., O’Connor, M., Anand, M. et al. 2004. Dose dependence and time course of the immunologic response to administration of standardized cat allergen extract. J. Allergy Clin. Immunol. 114:1339.

58 Hussain, A., Parkhurst, T., Goodall, M. et al. 2009. Chimeric IgG4 PR5-ANCA induces selective inflammatory responses from neutrophils through engagement of Fcg receptors. Immunology 128:236.

59 Plomp, J. J., Huijbers, M. G., van der Maarel, S. M. and Verschuuren, J. J. 2012. Pathogenic IgG4 subclass autoantibodies in MuSK myasthenia gravis. Ann. N. Y. Acad. Sci. 1275:114.

60 Huijbers, M. G., Zhang, W., Klooster, R. et al. 2013. MuSK IgG4 autoantibodies cause myasthenia gravis by inhibiting binding between MuSK and Lrp4. Proc. Natl Acad. Sci. USA 110:20783.

61 Gniadecki, R. 2006. Desmoglein autoimmunity in the pathogenesis of pemphigus. Autoimmunity 39:541.

62 Cerutti, A., Puga, I. andCols, M. 2011. Innate control of B cell responses. Trends Immunol. 32:202.

63 Lifitsky, M. B., Nardozza, R. and Pupilli, H. 2002. DCs induce CD40-independent immunoglobulin class switching through BLyS and APRIL. Nat. Immunol. 3:822.

64 Sakuma, H., Okumura, F., Miyabe, S. et al. 2010. Analysis of VH gene rearrangement and somatic hypermutation in Sjögren’s syndrome and IgG4-related sclerosing sialadenitis. Scand. J. Immunol. 72:44.

65 Miyoshi, H., Uchida, K., Taniguchi, T. et al. 2008. Circulating naive and CD4+CD25high regulatory T cells in patients with autoimmune pancreatitis. Pancreas. 36:133.

66 Suzuki, K., Tamaru, J., Okuyama, A. et al. 2010. IgG4-positive multi-organ lymphoproliferative syndrome manifesting as chronic symmetrical sclerosing dacryo-sialoadenitis with subsequent secondary portal hypertension and remarkable IgG4-linked IL-4 elevation. Rheumatol. 49:1789.

67 Nakashima, H., Miyake, K., Moriyama, M. et al. 2010. An amplification of IL-10 and TGF-beta in patients with IgG4-related tubulointerstitial nephritis. Clin. Nephrol. 73:385.

68 Tsuibo, H., Matsu, N., Izuka, M. et al. 2012. Analysis of IgG4 class switch-related molecules in IgG4-related disease. Arthritis Res. Ther. 14:R171.

69 Jeannin, P., Lecanet, S., Delneste, Y., Gauchat, J. F. and Bonnefoy, J. Y. 1998. IgE versus IgG4 production can be different. Science 317:1554.
sialoadenitis, so-called Mikulicz’s disease. *Ann. Rheum. Dis.* 71:2011.

71 Wojno, E. D. and Hunter, C. A. 2012. New directions in the basic and translational biology of interleukin-27. *Trends Immunol.* 33:91.

72 Banchereau, J., Pascual, V. and O’Garra, A. 2013. From IL-2 to IL-37: the expanding spectrum of anti-inflammatory cytokines. *Nat. Immunol.* 13:925.

73 Apetoh, L., Quintana, F. J., Pot, C. et al. 2010. The aryl hydrocarbon receptor interacts with c-Maf to promote the differentiation of type 1 regulatory T cells induced by IL-27. *Nat. Immunol.* 11:854.

74 Kiyama, K., Kawabata, D., Hosono, Y. et al. 2012. Serum BAFF and APRIL levels in patients with IgG4-related disease and their clinical significance. *Arthritis Res. Ther.* 14:R86.

75 Fukui, R. and Miyake, K. 2010. Controlling systems of nucleic acid sensing-TLRs restrict homeostatic inflammation. *Exp. Cell Res.* 318:1461.

76 Takeda, K. and Akira, S. 2005. Toll-like receptors in innate immunity. *Int. Immunol.* 17:1.

77 Sutmuller, R. P., Morgan, M. E., Netea, M. G., Grauer, O. and Adema, G. J. 2006. Toll-like receptors on regulatory T cells: expanding immune regulation. *Trends Immunol.* 27:387.

78 Pot, C., Apetoh, L., Awasthi, A. and Kuchroo, V. K. 2011. Induction of regulatory Tr1 cells and inhibition of T(H)17 cells by IL-27. *Semin. Immunol.* 23:438.

79 Liu, G. and Zhao, Y. 2007. Toll-like receptors and immune regulation: their direct and indirect modulation on regulatory CD4+ CD25+ T cells. *Immunology* 122:149.

80 Kulkarni, R., Behboudi, S. and Sharif, S. 2011. Insights into the role of Toll-like receptors in modulation of T cell responses. *Cell Tissue Res.* 343:141.

81 He, B., Qiao, X. and Cerutti, A. 2004. CpG DNA induces IgG class switch DNA recombination by activating human B cells through an innate pathway that requires TLR9 and cooperates with IL-10. *J. Immunol.* 173:4479.

82 Watanabe, T., Yamashita, K., Fujikawa, S. et al. 2012. Involvement of activation of toll-like receptors and nucleotide-binding oligomerization domain-like receptors in enhanced IgG4 responses in autoimmune pancreatitis. *Arthritis Rheum.* 64:914.

83 Watanabe, T., Yamashita, K., Sakurai, T. et al. 2013. Toll-like receptor activation in basophils contributes to the development of IgG4-related disease. *J. Gastroenterol.* 48:247.

84 Paul, W. E. and Zhu, J. 2010. How are T(H)2-type immune responses initiated and amplified? *Nat. Rev. Immunol.* 10:225.

85 Nagamachi, S., Ohsawa, I., Sato, N. et al. 2011. Immune complex-mediated complement activation in a patient with IgG4-related tubulointerstitial nephritis. *Case Rep. Nephrol. Urol.* 1:7.

86 Kawano, M., Mizushima, I., Yamaguchi, Y. et al. 2012. Immunohistochemical characteristics of IgG4-related tubulointerstitial nephritis: detailed analysis of 20 Japanese cases. *Int. J. Rheumatol.* 2012:609795.

87 Muráki, T., Hamano, H., Ochi, Y. et al. 2006. Autoimmune pancreatitis and complement activation system. *Panreas* 32:16.

88 Terness, P., Kohl, I., Hubener, G. et al. 1995. The natural human IgG anti-F(ab')2 antibody recognizes a conformational IgG1 hinge epitope. *J. Immunol.* 154:6446.

89 van de Stadt, L. A., Vrieze, H. D., Derksen, N. I. L. et al. 2014. Antibodies to IgG4 hinge can be found in rheumatoid arthritis patients during all stages of disease and may exacerbate chronic antibody-mediated inflammation. *Arthritis Rheumatol.* 66:1133.

90 Hajishengallis, G. and Lambris, J. D. 2010. Crosstalk pathways between toll-like receptors and the complement system. *Trends Immunol.* 31:154.

91 Havelich, H., Belkaid, Y., Baelder, R., Hildeman, D., Gerard, C. and Kohl, J. 2005. C5a negatively regulates toll-like receptor 4-induced immune responses. *Immunity* 22:415.

92 Zen, Y. and Nakanuma, Y. 2010. IgG4-related disease: a cross-sectional study of 114 cases. *Am. J. Surg. Pathol.* 34:1812.

93 Wynn, T. A. and Ramalingam, T. R. 2012. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. *Nat. Med.* 18:1028.