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Clinical features and mechanistic insights regarding IgG4-related dacryoadenitis and sialoadenitis: a review

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Abstract. Immunoglobulin G4-related disease (IgG4-RD), recognized only recently as a single diagnostic entity, is a chronic inflammatory condition of unknown etiology. The diagnosis of IgG4-RD relies heavily on histopathological analysis and the correlation of histology findings with clinical, serological, and radiological data. $CD4^+$ T and B cells, including IgG4-expressing plasmablasts, constitute the major inflammatory cell populations in IgG4-RD and are believed to cause organ damage and tissue fibrosis. Patients with IgG4-RD, who have active, untreated disease, exhibit marked expansion of IgG4-secreting plasmablasts in the blood. Important mechanistic insights correlated with the pathogenesis of IgG4-RD have been disclosed in recent years through the application of novel molecular biology approaches, including next-generation and single-cell RNA sequencing. Exploration of the interactions between these $CD4^+$ T cells and cells of the B lymphocyte lineage is critical to understanding the pathophysiology of IgG4-RD. The establishment of pathogenic T cell clones and the identification of antigens specific to these clones constitute the first steps in determining the pathogenesis of this disease. This review focuses on clinical features and mechanistic insights regarding IgG4-related dacryoadenitis and sialoadenitis, from a perspective suitable for oral and maxillofacial surgeons.

Key words: IgG4-related disease; IgG4-related dacryoadenitis and sialoadenitis; T cell; B cell; $CD4^+$ cytotoxic T cell; submandibular gland biopsy.

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Immunoglobulin G4-related disease (IgG4-RD), recognized only recently as a single diagnostic entity, is an immune-mediated condition that can affect multiple organs simultaneously[1]. The disease mimics many malignant, infectious, and inflammatory disorders with histological features that are observed consistently across the organs involved. This disease is characterized by elevated serum IgG4 concentrations and tissue infiltration by $IgG4^+$ plasmacytes, as well as storiform fibrosis and obliterative phlebitis in various organs[1,2]. The most frequently involved organs are the pancreas, kidney, lung, lymph nodes, bile duct, liver, aorta, prostate, retroperitoneum, and lacrimal and major salivary glands[1]. International

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consensus statements have been published regarding the nomenclature, pathological findings, and clinical management of IgG4-RD[3,4]. The IgG4-RD responder index, designed to serve as an outcome measure for clinical trials, is now undergoing a worldwide validation study[5].

IgG4-RD is commonly encountered by oral surgeons in the context of Mikulicz's disease, which involves simultaneous bilateral and symmetrical enlargement of both the lacrimal and salivary glands. Some patients, however, solely exhibit lacrimal gland disease, or may present with unilateral submandibular gland involvement. For many decades, Mikulicz's disease was believed to represent a subtype of Sjögren's syndrome. Similarly, for more than a century, IgG4-related submandibular gland disease was known in the medical literature as 'Küttner's tumor'. Both major and minor salivary glands can be affected by IgG4-RD[1,6].

Comprehensive diagnostic criteria have been proposed for IgG4-RD; furthermore, organ-specific criteria have been proposed for IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS), IgG4-related kidney disease, and IgG4-related autoimmune pancreatitis (Fig. 1)[7,8]. In addition, international classification criteria supported by the American College of Rheumatology and the European League Against Rheumatism have been formulated and validated[4]. In all of these criteria, biopsies of affected lesions are recommended to exclude diseases that often mimic IgG4-RD, among which are malignant tumors, Sjögren's syndrome, granu-

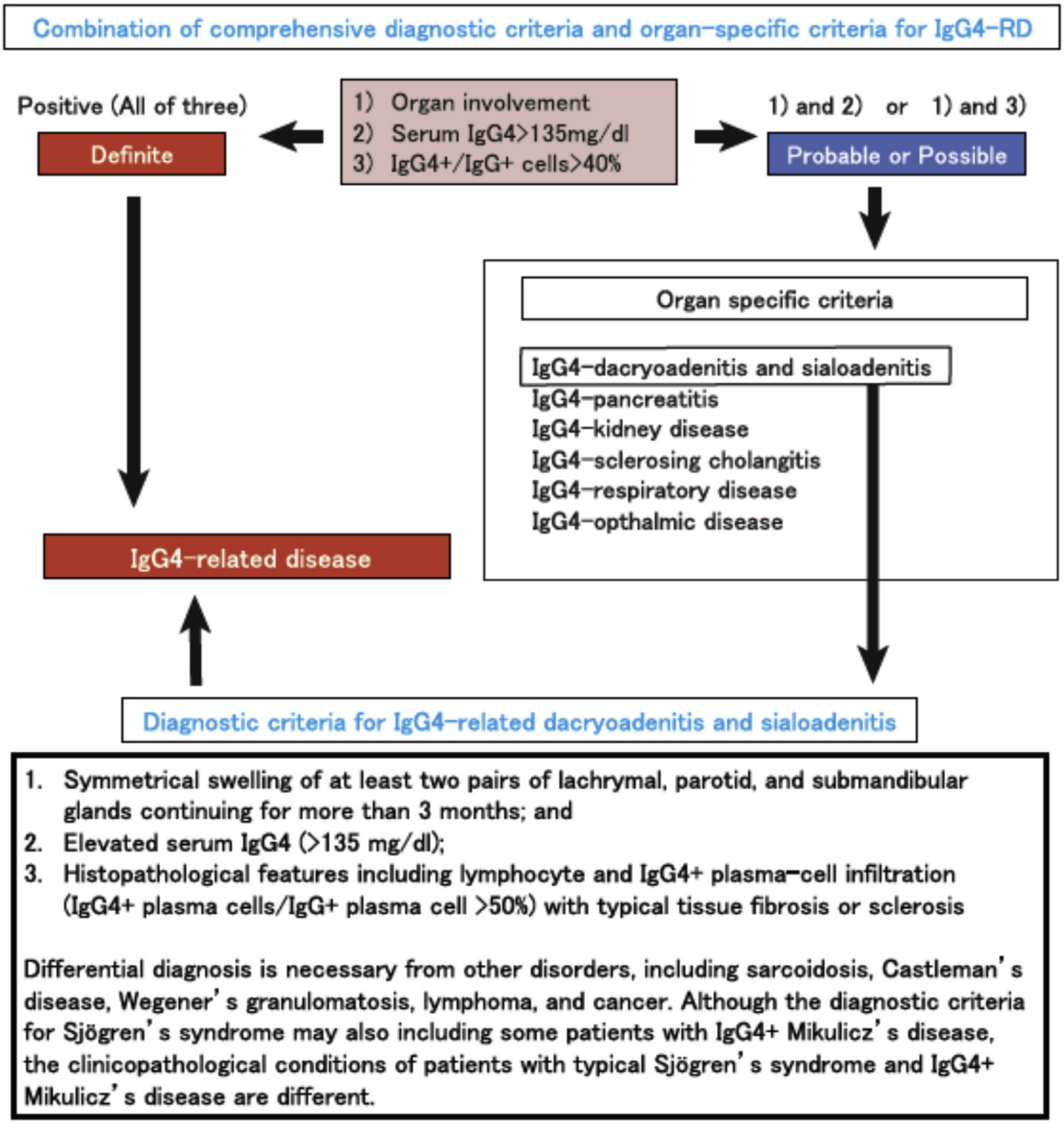

Fig. 1. Diagnostic algorithm for the comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD). The figure shows the diagnostic algorithm for IgG4-related dacryoadenitis and sialoadenitis (IgG4-DS), with organ-specific criteria. A diagnosis of IgG4-RD is definitive in patients who exhibit all three of the items (1) organ enlargement, mass or nodular lesions, or organ dysfunction; (2) serum IgG4 concentration >135 mg/dl; and (3) histopathological findings of >10 IgG4 cells/HPF and an $IgG4^+/IgG^+$ cell ratio >40%[8]. Patients with possible or probable IgG4-RD could be re-diagnosed using organ-specific IgG4-DS criteria[7].

lomatosis with polyangiitis, and multicentric Castleman disease[8,9]. An incisional or excisional biopsy of the affected submandibular glands is often the best means of establishing a definitive diagnosis of IgG4-DS[10] (Fig. 2).

CD4+ T cells in Sjögren's syndrome

Sjögren's syndrome is a chronic, systemic, autoimmune disease that is characterized by lymphocytic infiltration into the salivary and lacrimal glands, with concomitant autoantibody production and destruction of the glandular tissue. Typically, affected patients experience symptoms of dry mouth (xerostomia) and dry eyes (keratoconjunctivitis sicca). Clinical symptoms range from local exocrinopathy to a systemic disorder that affects parenchymal organs, lung, kidneys, and liver. In approximately 5% of patients, the disease may progress to the development of B cell lymphoma[11], and may be accompanied by hypergammaglobulinemia and immunodeficiency, in close association with the accumulation of B cells[12]. The major autoantibodies involved target intracellular antigens; these antibodies include anti-SSA/Ro and anti-SSB/La antibodies, rheumatoid factor, cryoglobulins, and antinuclear antibodies[13]. Certain autoantibodies are disease-specific, and the majority of autoantibodies detected thus far are of the immunoglobulin G (IgG) class; this observation is suggestive of a role for antigen-dependent $CD4^+$ T cells.

Sjögren's syndrome is an organ-specific autoimmune disease, which may be mediated by autoreactive T cells that infiltrate target salivary glands[14]. Some previous reports have shown that activated Th1 and Th2 $CD4^+$ helper T cell phenotypes arise; furthermore, Th17 and T follicular helper (Tfh) phenotypes predominate and likely provide a stimulus for B cells[15]. However, the clonality of disease-specific effector $CD4^+$ T cells in Sjögren's syndrome patients is unclear. Additional research is required to identify clonally expanded subsets of $CD4^+$ T cells in Sjögren's syndrome patients (these constitute putative disease-causing subsets of T cells) through the application of new technologies in molecular biology, including next-generation and single-cell RNA sequencing. Use of these unbiased approaches may aid the characterization of disease-specific $CD4^+$ effector T cells in Sjögren's syndrome. The establishment of pathogenic T cell clones and the identification of antigens specific to these clones constitute the first steps necessary for acquiring immunological mechanistic insights regarding the pathogenesis of Sjögren's syndrome.

IgG4-DS exhibits a number of differences when compared with typical Sjögren's syndrome: (1) persistent enlargement of the lacrimal and salivary glands; (2) normal or moderate salivary secretion dysfunction; (3) good responsiveness to corticosteroid treatment, and improvement of salivary function after steroid therapy; and (4) low frequencies of anti-SSA/Ro and anti-SSB/La autoantibodies, as determined by serological analyses[16–18]. Additionally, IgG4-DS can be differentiated from Sjögren's syndrome and other tumors through the use of computed tomography and ultrasonography[19].

Histopathology

Histopathology is key to the diagnosis of IgG4-RD, including IgG4-DS. Major central pathology features include lymphocytic infiltration, obliterative phlebitis and storiform fibrosis in the affected lesions. The lymphocytes and plasma cells are polyclonal. $IgG4^+$ plasma cells and $CD4^+$ T cells are generally present in the affected organs, but serum IgG4 concentrations are normal in a significant minority of cases[1,2]. The finding of abundant $IgG4^+$ plasma cells is helpful in differentiating IgG4-RD from other mimic disorders with similar presentation. However, IgG4-RD cannot be diagnosed solely on the basis of infiltration by $IgG4^+$ cells alone, because these plasma cells can be present in a large number of other inflammatory disorders[20].

IgG4 itself is generally considered a non-inflammatory immunoglobulin due to its limited ability to fix complement and bind activating Fc receptors[21]. There is no evidence that this type of immunoglobulin has a primary role in the pathophysiology of IgG4-RD. Moreover, the activity of IgG4-RD does not always correlate well with serum IgG4 concentrations[22].

Pathophysiology

It is important to determine which cells are crucial to the pathogenesis of IgG4-RD. Many important mechanistic insights re-

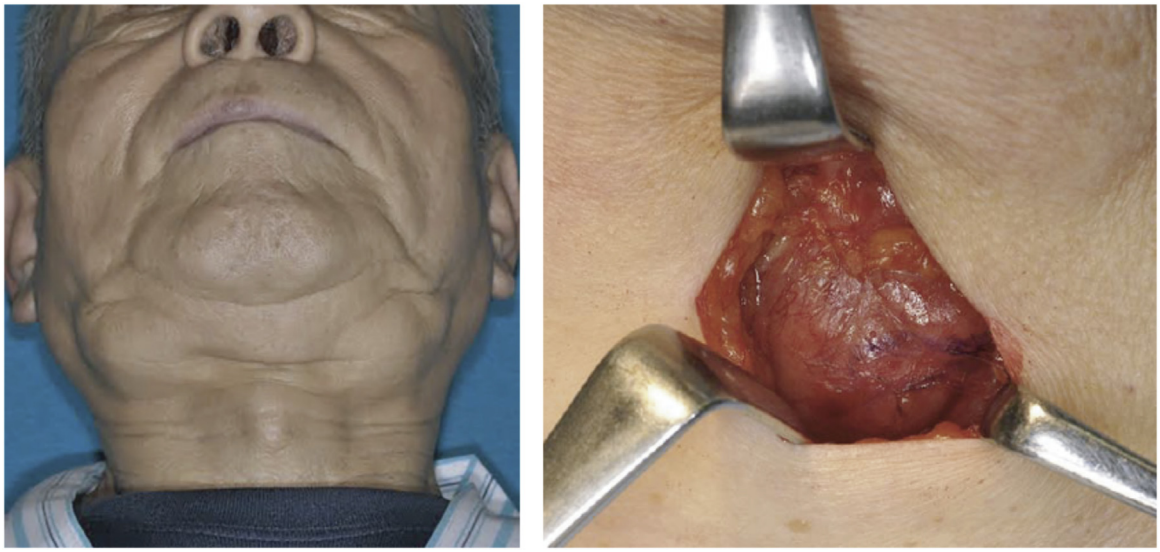

Fig. 2. Swollen submandibular glands and corresponding incisional biopsy.

lated to the pathogenesis of IgG4-RD have been unveiled through studies of patients treated by B cell depletion[23–25]. IgG4-RD patients have a restricted oligoclonal immunoglobulin repertoire[26]. Plasmablasts, which are defined by the cell surface markers of CD19, CD27, and CD38 but not CD20, are elevated in blood from activated IgG4-RD patients. The tightly restricted repertoire of these plasmablasts strongly suggests that IgG4-RD is an antigen-driven disease[27]. Clonally expanded $CD19^{+}CD27^{+}CD20^{-}CD38^{high}$ plasmablasts from IgG4-RD blood are a hallmark of active IgG4-RD. At tissue sites, IgG4 expressing $SLAMF7^{+}CD19^{+}$ B cells are expanded in lymph nodes from IgG4-RD patients (Fig. 3).

A genome-wide association study of IgG4-RD was performed in a Japanese population (Terao et al., International Symposium on IgG4-Related Diseases and Fibrosis, February 2017). This investigation revealed three susceptibility loci, consistent with antigen-driven disease: HLA-DRB1, HLA-A, and FCGR2B, the latter encoding a low affinity receptor for IgG[27]. These findings are consistent with the concept that activated B cells present antigens to a subset of disease-causing T cells at disease sites[24].

In affected tissues, $CD4^{+}$ T cells constitute the most abundant cell type[3]. Analyses of Th1, Th2, and Th17 $CD4^{+}$ helper T cells, as well as regulatory helper T cells (Tregs), from patients with IgG4-RD have led to conflicting results[28]. Of note, however, all previous reports have relied on indirect evidence in order to implicate subsets of $CD4^{+}$ T cells in this disease[29–31]; more direct analyses of T cells have only recently been undertaken. In addition, an analysis of these cells by next-generation sequencing revealed prominent clonal expansion of the $CD4^{+}$ cytotoxic T cells ($CD4^{+}$ CTLs) phenotype[25,32]. $CD4^{+}$ CTLs retain the ability to kill target cells in an MHC class II-restricted manner[33]. Notably, a significant reduction of circulating $CD4^{+}$ CTLs in IgG4-RD was observed following rituximab treatment (anti-CD20 B cell depletion)[25,34] and following glucocorticoid therapy[35]. In contrast, circulating naïve

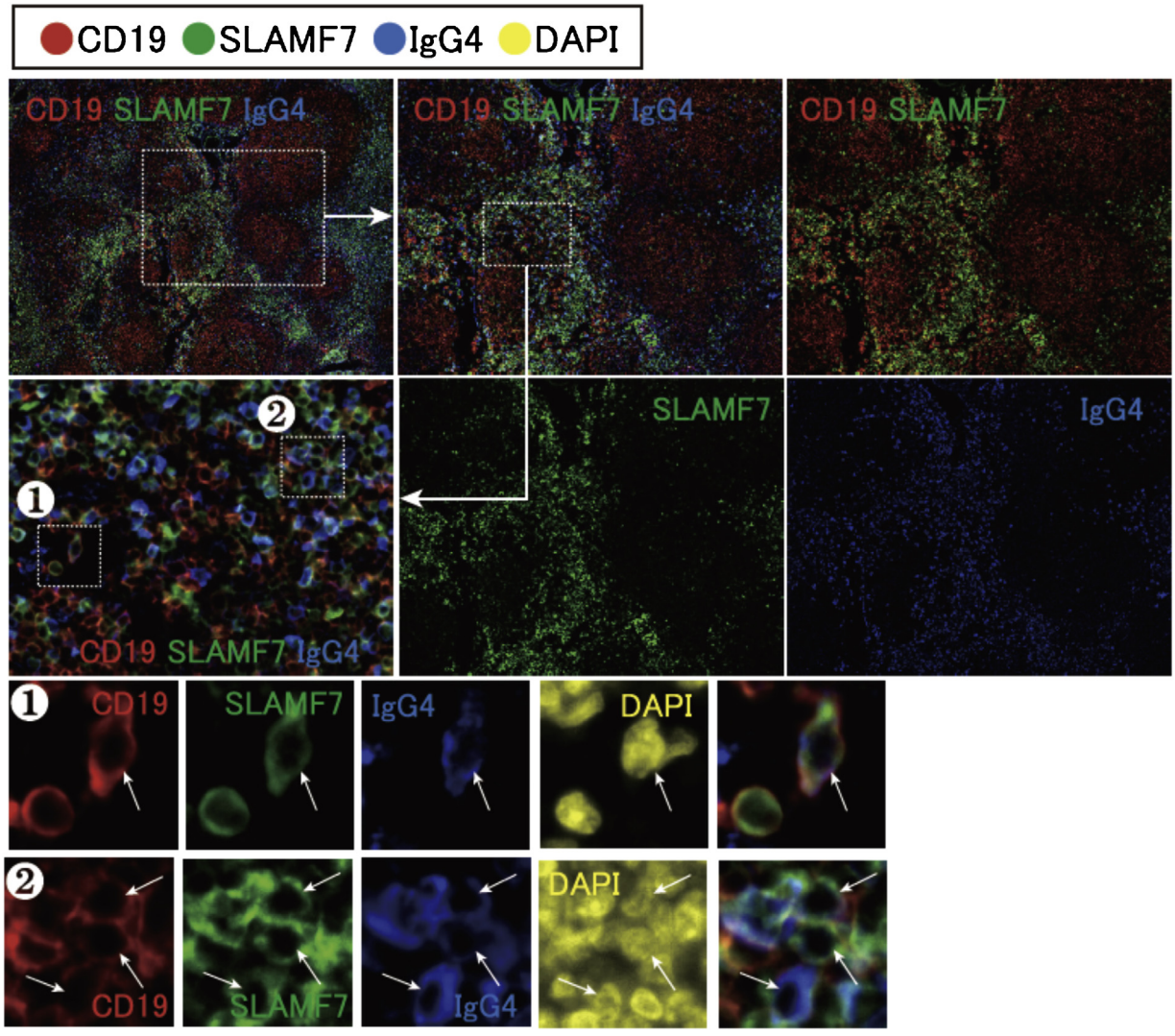

Fig. 3. IgG4-expressing $SLAMF7^{+}CD19^{+}$ B cells are abundant in secondary lymphoid organs in IgG4-related disease (IgG4-RD). A lymph node from an IgG4-RD patient was fixed in formalin, embedded in paraffin, and sectioned. Multi-color immunofluorescence staining of CD19 (red), SLAMF7 (green), IgG4 (blue), and DAPI (yellow) in IgG4-RD lymph nodes. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

$CD4^+$ T cells remain stable following these treatment interventions[25,34].

Pillai et al. showed that B cell depletion therapy is effective in autoimmune disease with somatically hypermutated B cells or plasmablasts at disease sites, which are likely to serve as crucial antigen-presenting cells for a subset of disease-causing T cells[36]. Taken together, these findings strongly suggest an antigen-driven process that requires a critical interaction between $CD4^+$ CTLs and activated B cells[28]. With regard to the pathophysiology, it is possible that dominantly expanded B cells maintain or present some antigens to a subset of the expanded $CD4^+$ CTLs in affected tissues of IgG4-RD patients[28].

A clonally expanded activated B cell population and multiple subsets of T cells is a hallmark of this disease. New molecular biological technologies have increased our understanding of the pathogenesis of this disease between activation-causing B cells and $CD4^+$ CTLs; the focus is now shifting to Tfh cells. Generally, Tfh cells aid B cells during T-dependent immune responses; Tfh cells are essential for germinal center formation and affinity maturation, as well as the development of most high-affinity antibodies and memory B cells[37]. Recently, an increase in blood memory type 2 Tfh cells has been noted in patients with IgG4-RD[38–40]. Furthermore, it has been reported that these circulating Tfh2 cells (cTfh2), but not cTfh1 or cTfh17 cells, induce the differentiation of naïve B cells into $CD19^+CD20^-CD27^+CD38^+$ plasmablasts and enhance the production of IgG4 in patients with IgG4-RD[39]. However, there is no evidence thus far connecting subsets of Tfh cells in the blood with functional

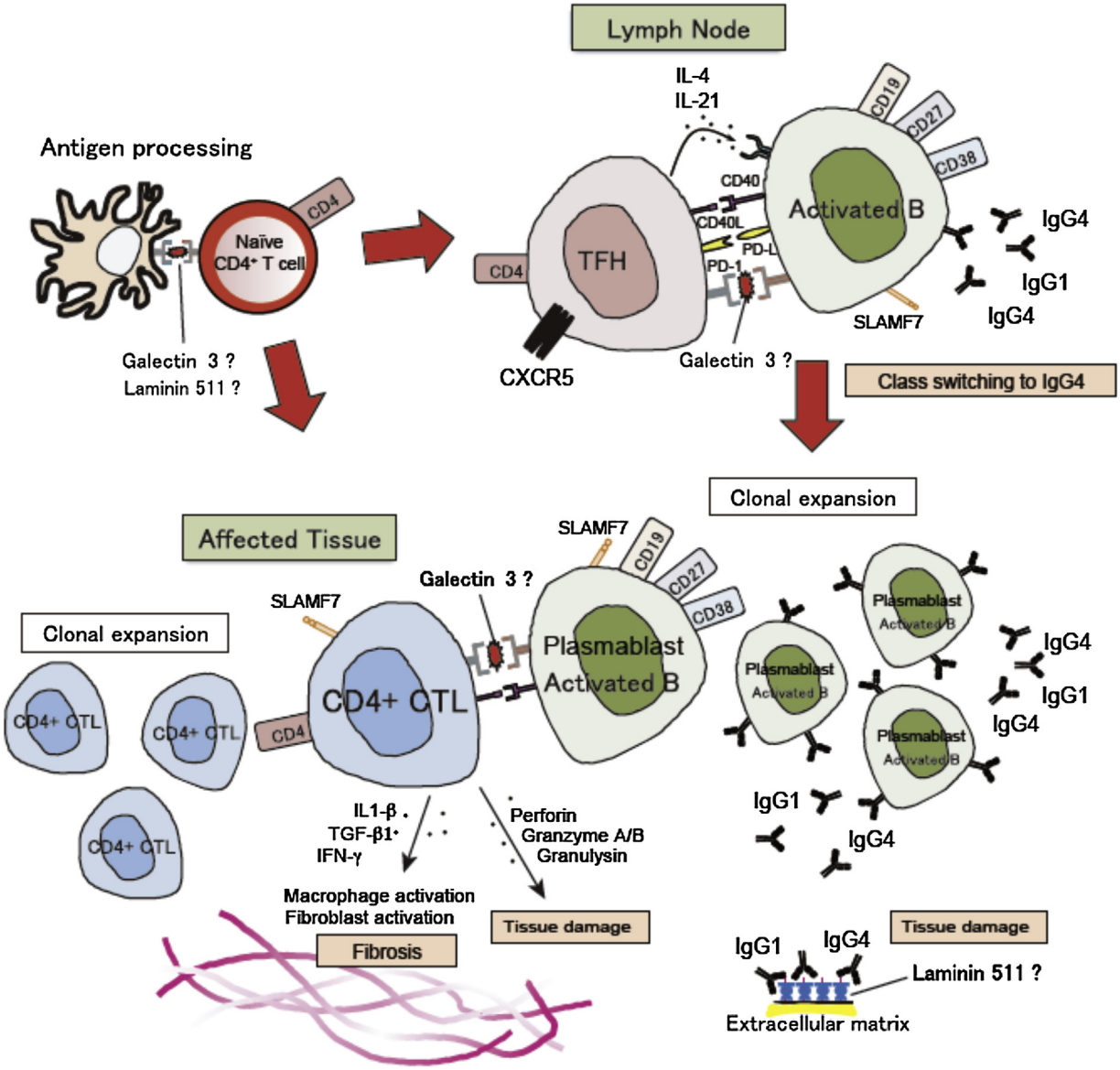

Fig. 4. Immunological responses in IgG4-related disease (IgG4-RD). Chronic stimulation via activated antigen-presenting cells induces the differentiation of naïve T cells into $CD4^+$ cytotoxic T cells (CTLs) and follicular helper T cells (Tfh). In secondary lymphoid organs, Tfh cells collaborate with B cells to drive IgG4 class switching, somatic hypermutation, and plasmablast differentiation of antigen-detecting B cells. Clonal expansion of $CD4^+$ CTLs and activated B cells, including IgG4 secreting plasmablasts, might cause this disease state. Reactivation of these $CD4^+$ CTLs may require antigen presentation, including galectin-3, by plasmablasts or other activated B cells at affected tissue sites. Activated $CD4^+$ CTLs may mediate fibrosis and inflammation as a result of cytokine secretion or the induction of cell death.

counterparts in secondary lymphoid organs or tertiary lymphoid organs.

These activated B cells can also present antigens to relevant Tfh cells, particularly IL-4 expressing Tfh cells, in patients with IgG4-RD. This latter interaction may be crucial to the development of germinal centers within lymph nodes and at extranodal sites in IgG4-RD, and to the IgG4 class switch[41] (Fig. 4).

What are the antigenic triggers of this disease?

Another important aspect to consider involves the specific antigens that drive the clonal expansion of T and B cells. To date, compelling cases can be made for two antigens (although there are, no doubt, more). Perugino et al. used next-generation sequencing to characterize monoclonal antibodies from the perspective of single-cell clones of dominantly expanded plasmablasts and then identified disease-relevant autoantigens from a patient with active IgG4-RD[42]. The method identified autoantibodies against galectin-3, predominantly of the IgG4 isotype[42]. An unbiased quantitative proteomic approach showed that galectin-3 was one of the highest expressed proteins in affected tissue lesions from IgG4-RD patients[43]. Galectin-3 plays an important role in cell proliferation, adhesion, differentiation, apoptosis, and migration, in inflammation, and in fibrosis[44]. Macrophages are the primary cellular source of secreted galectin-3. This protein contributes to numerous fibro-proliferative diseases, suggesting that it may contribute to tissue fibrosis[44].

In another study, Shiokawa et al. reported that the injection of serum IgG from an IgG4-related autoimmune pancreatitis patient into neonatal mice induced pancreatic injury, and this IgG bound to the extracellular matrix protein of the pancreatic acini[45]. Furthermore, Shiokawa et al. revealed autoantibodies against laminin-511, one of extracellular matrix proteins, in IgG4-related autoimmune pancreatitis[46]. Clinically, anti-laminin-511 IgG was present in 26 of 51 IgG4-related autoimmune pancreas patients, but not in controls. These discoveries pertaining to both galectin-3 and laminin-511 represent substantial advances in our understanding of IgG4-RD and offer additional avenues for investigation.

What targeted treatment has revealed

Most clinical manifestations of IgG4-RD respond to glucocorticoids. These agents comprise the first-line, standard care approach for most patients[1,47]. Masaki et al. reported a multicenter phase II prospective clinical trial of glucocorticoid therapy in Japanese patients with IgG4-RD[48]. Hong et al. reported that glucocorticoid therapy was beneficial for induction, as well as for maintenance therapy, in Chinese patients with IgG4-DS[49]. Masamune et al. also reported that maintenance glucocorticoid therapy was effective in reducing relapse in Japanese patients with IgG4-related pancreatitis, in a randomized controlled trial of long-term maintenance corticosteroid therapy[50]. One conventional treatment approach uses a starting prednisolone dose of 0.6–1.0 mg/kg daily. After 2–4 weeks, the dose is tapered by 5 mg every 1–2 weeks, on the basis of clinical responses[51]. Clinical improvement after the initiation of glucocorticoid therapy is rapid, and a follow-up serological evaluation should be performed approximately 2 weeks after the therapy. Positron emission tomography has some utility in the assessment of the treatment response; however, for the major salivary glands, excellent therapeutic responses can be appreciated readily on the basis of physical examination alone. A poor response to glucocorticoid therapy might be indicative of other diagnoses,

Table 1. Principal findings regarding the pathogenesis of IgG4-related disease.

Principal findings related to T and B cell phenotypes in IgG4-RD	**Reference**
Th2 responses may result from concomitant atopic manifestations	53
IL-33 might contribute to the pathogenesis via aberrant activation of Th2 immune responses	54
Th2 and Tregs play a key role in IgG4 production in IgG4-DS	30
Overexpression of IL-21 promotes tertiary lymphoid organ formation and IgG4 production in salivary glands from IgG4-DS	31
$CD4^+$ T cells in Sjögren's syndrome and IgG4-DS (Review)	29
$CD4^+$ CTLs are expanded in affected tissues from IgG4-DS	32
$CD4^+$ CTLs express granzymes and perforin and secrete cytokines, such as IL-1β, IFN-γ, and TGF-β, which are linked to fibrosis	32
$CD4^+$ CTLs are clonally expanded in IgG4-RD and decrease following rituximab treatment	24
$CD4^+$ CTLs are expanded in IgG4-RD and decrease following glucocorticoid treatment	35
Clonally expanded $CD4^+$ CTLs in the pathogenesis of IgG4-RD (Review)	24
Circulating $IgG4^+$ plasmablasts are oligoclonally expanded in active and relapsing IgG4-RD	26
Plasmablasts as a biomarker for IgG4-RD, independent of serum IgG4 levels	34
The expansion of IL-4 secreting Tfh cells is linked to IgG4 class switching in vivo	41
Increased circulating Tfh2 cells and their capacity to help naïve B cells to differentiate into plasmablasts and IgG4 production in vitro	38,39
Increased circulating Tfh1 cells in IgG4-RD	39
Tfh cells in the pathogenesis of IgG4-RD (Review)	55
Increased circulating Tregs	56–58
Tregs were higher in affected tissue in IgG4-RD	59
Increased circulating ICOS and IL-10 secreting Tregs	57
Principal findings related to auto-antigens in IgG4-RD	***Reference***
Identification of galectin-3 as an auto-antigen in IgG4-RD	42
Pathogenicity of IgG1 and IgG4 in IgG4-related pancreatitis	45
Laminin-511 is a target antigen in IgG4-related pancreatitis	45
Specific antigen in IgG4-RD (Review)	27
Annexin A11 is targeted by IgG4 and IgG1 autoantibodies in IgG4-RD	60

CTLs, cytotoxic T cells; ICOS, inducible T cell co-stimulator; IgG4-DS, IgG4-related dacryoadenitis and sialoadenitis; IFN-γ, interferon gamma; IgG4-RD, IgG4-related disease; IL, interleukin; Tfh, follicular helper T cells; TGF-β, transforming growth factor beta; Th2, type 2 helper T cells; Tregs, regulatory helper T cells.

particularly cancer. Furthermore, the response to glucocorticoids varies with respect to the affected organs and the degree of fibrosis. After the therapy, salivary secretion in patients with IgG4-DS is more likely to be improved, in contrast to glandular function in Sjögren's syndrome[52].

Rituximab therapy is typically employed in patients who do not respond to glucocorticoids or who experience disease flares during or after glucocorticoid tapers. Important mechanistic insights correlated with the pathogenesis of IgG4-RD have been revealed with B cell depletion[23–26,28]. As shown in Fig. 4, (1) IgG4-RD patients exhibit extensive clonal expansion of activated B cells and $CD4^+$ CTLs, consistent with an antigen-driven disease process[25,26]; (2) $CD4^+$ CTLs are the dominant population in affected tissues, whereas other $CD4^+$ T cell subsets are sparse[25,32]; (3) $CD4^+$ CTLs in affected lesions secrete cytotoxic, inflammatory, and pro-fibrotic cytokines, indicating antigen reactivation at tissue sites[32]; and (4) a reduction in number of $CD4^+$ CTLs by B cell depletion is associated with clinical remission in IgG4-RD patients[24,25].

The principal findings regarding the pathogenesis of IgG4-related disease are presented in Table 1[24,26,27,29–32,34,35,38,39,41,42,45,53–60].

In conclusion, in IgG4-RD subjects, plasmablasts or other activated B cells are specific for a subset of auto-antigens, including galectin-3; further, they exhibit oligoclonal restriction resulting in clonal expansion of $CD4^+$ CTLs at tissue sites. These B lineage cells might also present antigens to relevant Tfh cells[41]. Furthermore, in IgG4-RD, IL-4-secreting Tfh cells are expanded in blood and at tissue sites. These cells might enable a subset of B cells to undergo differentiation and somatic mutation. Recent studies have shown that interactions among clonally expanded $CD4^+$ CTLs, Tfh cells, and B cells are critical in the pathogenesis of IgG4-RD. Furthermore, the discovery of some autoantibodies in these patients should help our understanding of IgG4-RD pathophysiology.

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Competing interests

No conflict of interest exists.

Ethical approval

The study design and methods were approved by the Institutional Review Board of the Center for Clinical and Translational Research of Kyushu University Hospital (IRB serial numbers 25-287 and 26-86) and followed the tenets of the Declaration of Helsinki.

Patient consent

Informed consent was obtained from all patients.

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References

1. Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. *Lancet* 2015;**385**:1460–71.
2. Mahajan VS, Mattoo H, Deshpande V, Pillai SS, Stone JH. IgG4-related disease. *Annu Rev Pathol* 2014;**9**:315–47.
3. Deshpande V, Zen Y, Chan JK, Yi EEEE, Sato Y, Yoshino T, Kloppel G, Heathcote JG, Khosroshahi A, Ferry JA, Aalverse RC, Bloch DB, Brugge WR, Bateman AC, Carruthers MN, Chari ST, Cheuk W, Cornell LD, Fernandez-Del CC, Forcinone DG, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Lauwers GY, Masaki Y, Nakanuma Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani DV, Smyrk TC, Stone JR, Takahira M, Webster GJ, Yamamoto M, Zamboni G, Umehara H, Stone JH. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol* 2012;**25**:1181–92.
4. Khosroshahi A, Wallace ZS, Crowe JL, Akamizu T, Azumi A, Carruthers MN, Chari ST, Della-Torre E, Frulloni L, Goto H, Hart PA, Kamisawa T, Kawa S, Kawano M, Kim MH, Kodama Y, Kubota K, Lerch MM, Löhr M, Masaki Y, Matsui S, Mimori T, Nakamura S, Nakazawa T, Ohara H, Okazaki K, Ryu JH, Saeki T, Schleinitz N, Shimatsu A, Shimosegawa T, Takahashi H, Takahira M, Tanaka A, Topazian M, Umehara H, Webster GJ, Witzig TE, Yamamoto M, Zhang W, Chiba T, Stone JH, Second International Symposium on IgG-Related Disease. International consensus guidance statement on the management and treatment of IgG4-related disease. *Arthritis Rheumatol* 2015;**67**:1688–99.
5. Carruthers MN, Stone JH, Deshpande V, Khosroshahi A. Development of an IgG4-RD responder index. *Int J Rheumatol* 2012;**2012**:259408.
6. Harrison JD, Rodriguez-Justo M. Commentary on IgG4-related sialadenitis: Mikulicz's disease, Kuttner's tumour, and eponymy. *Histopathology* 2011;**58**:1164–6.
7. Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, Hamano H, Kamisawa T, Shimosegawa T, Shimatsu A, Nakamura S, Ito T, Notohara K, Sumida T, Tanaka Y, Mimori T, Chiba T, Mishima M, Hibi T, Tsubouchi H, Inui K, Ohara H. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012;**22**:21–30.
8. Umehara H, Okazaki K, Nakamura T, Satoh-Nakamura T, Nakajima A, Kawano M, Mimori T, Chiba T. Current approach to the diagnosis of IgG4-related disease - Combination of comprehensive diagnostic and organ-specific criteria. *Modern rheumatology/the Japan Rheumatism Association* 2017;**27**:381–91.
9. Li W, Chen Y, Sun ZP, Cai ZG, Li TT, Zhang L, Huang MX, Hua H, Li M, Hong X, Su JZ, Zhang ZY, Liu YY, He J, Li ZG, Gao Y, Yu GY. Clinicopathological characteristics of immunoglobulin G4-related sialadenitis. *Arthritis Res Ther* 2015;**17**:186.
10. Moriyama M, Furukawa S, Kawano S, Goto Y, Kiyoshima T, Tanaka A, Maehara T, Hayashida JN, Ohta M, Nakamura S. The diagnostic utility of biopsies from the submandibular and labial salivary glands in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. *Int J Oral Maxillofac Surg* 2014;**43**:1276–81.
11. Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjögren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjögren's Syndrome. *Arthritis Rheum* 1999;**42**:1765–72.
12. Christodoulou MI, Kapsogeorgou EK, Moutsopoulos HM. Characteristics of the minor salivary gland infiltrates in Sjögren's syndrome. *J Autoimmun* 2010;**34**:400–7.
13. Tzioufas AG, Kapsogeorgou EK, Moutsopoulos HM. Pathogenesis of Sjögren's syndrome: what we know and what we should learn. *J Autoimmun* 2012;**39**:4–8.
14. Legras F, Martin T, Knapp AM, Pasquali JL. Infiltrating T cells from patients with primary Sjögren's syndrome express restricted or unrestricted T cell receptor V beta regions depending on the stage of the disease. *Eur J Immunol* 1994;**24**:181–5.
15. Singh N, Cohen PL. The T cell in Sjögren's syndrome: force majeure, not spectateur. *J Autoimmun* 2012;**39**:229–33.
16. Yamamoto M, Harada S, Ohara M, Suzuki C, Naishiro Y, Yamamoto H, Takahashi H, Imai K. Clinical and pathological differences between Mikulicz's disease and Sjogren's syndrome. *Rheumatology (Oxford)* 2005;**44**:227–34.
17. Yamamoto M, Takahashi H, Sugai S, Imai K. Clinical and pathological characteristics of Mikulicz's disease (IgG4-related plasmacytic exocrinopathy). *Autoimmun Rev* 2005;**4**:195–200.

18. Hong X, Li W, Xie XY, Zhang ZY, Chen Y, Gao Y, Peng X, Su JZ, Zhang YY, Wang Z, Cai ZG, Zhang L, Liu YY, He J, Ren LM, Li ZG, Yu GY. Differential diagnosis of IgG4-related sialadenitis, primary Sjogren syndrome, and chronic obstructive submandibular sialadenitis. *Br J Oral Maxillofac Surg* 2017;**55**:179–84.
19. Li W, Xie XY, Su JZ, Hong X, Chen Y, Gao Y, Zhang ZY, Yu GY. Ultrasonographic Features of Immunoglobulin G4-Related Sialadenitis. *Ultrasound Med Biol* 2016;**42**:167–75.
20. Strehl JD, Hartmann A, Agaimy A. Numerous IgG4-positive plasma cells are ubiquitous in diverse localised non-specific chronic inflammatory conditions and need to be distinguished from IgG4-related systemic disorders. *J Clin Pathol* 2011;**64**:237–43.
21. Bruhns P, Iannascoli B, England P, Mancardi DA, Fernandez N, Jorieux S, Daeron M. Specificity and affinity of human Fcgamma receptors and their polymorphic variants for human IgG subclasses. *Blood* 2009;**113**:3716–25.
22. Carruthers MN, Khosroshahi A, Augustin T, Deshpande V, Stone JH. The diagnostic utility of serum IgG4 concentrations in IgG4-related disease. *Ann Rheum Dis* 2015;**74**:14–8.
23. Maehara T. IgG4-related disease—mechanistic insights from both clinical and immunologic understanding of this condition. *Nihon Rinsho Meneki Gakkai Kaishi* 2017;**40**:206–12.
24. Mattoo H, Stone JH, Pillai S. Clonally expanded cytotoxic CD4+ T cells and the pathogenesis of IgG4-related disease. *Autoimmunity* 2017;**50**:19–24.
25. Mattoo H, Mahajan VS, Maehara T, Deshpande V, Della-Torre E, Wallace ZS, Kulikova M, Drijvers JM, Daccache J, Carruthers MN, Castelino F, Stone JR, Stone JH, Pillai S. Clonal expansion of CD4 cytotoxic T lymphocytes in patients with IgG-related disease. *J Allergy Clin Immunol* 2016;**138**:825–38.
26. Mattoo H, Mahajan VS, Della-Torre E, Sekigami Y, Carruthers M, Wallace ZS, Deshpande V, Stone JH, Pillai S. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-related disease. *J Allergy Clin Immunol* 2014;**134**:679–87.
27. Haldar D, Hirschfield GM. Deciphering the biology of Ig -related disease: specific antigens and disease? *Gut* 2018;**67**:602–5.
28. Maehara T, Moriyama M, Nakamura S. Pathogenesis of IgG 4-related disease: a critical review. *Odontology* 2018. http://dx.doi.org/10.1007/s10266-018-0377-y. in press.
29. Moriyama M, Tanaka A, Maehara T, Furukawa S, Nakashima H, Nakamura S. T helper subsets in Sjögren's syndrome and IgG4-related dacryoadenitis and sialoadenitis: a critical review. *J Autoimmun* 2014;**51**:81–8.
30. Tanaka A, Moriyama M, Nakashima H, Miyake K, Hayashida JN, Maehara T, Shinozaki S, Kubo Y, Nakamura S. Th2 and regulatory immune reactions contribute to IgG4 production and the initiation of Mikulicz disease. *Arthritis Rheum* 2012;**64**:254–63.
31. Maehara T, Moriyama M, Nakashima H, Miyake K, Hayashida JN, Tanaka A, Shinozaki S, Kubo Y, Nakamura S. Interleukin-21 contributes to germinal centre formation and immunoglobulin G4 production in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. *Ann Rheum Dis* 2012;**71**:2011–9.
32. Maehara T, Mattoo H, Ohta M, Mahajan VS, Moriyama M, Yamauchi M, Drijvers J, Nakamura S, Stone JH, Pillai S. Lesional CD4+ IFN-gamma+ cytotoxic T lymphocytes in IgG4-related dacryoadenitis and sialoadenitis. *Ann Rheum Dis* 2017;**76**:377–85.
33. Tian Y, Sette A, Weiskopf D. Cytotoxic CD4 T cells: differentiation, function, and application to dengue virus infection. *Front Immunol* 2016;**7**:531.
34. Wallace ZS, Mattoo H, Carruthers M, Mahajan VS, Della Torre E, Lee H, Kulikova M, Deshpande V, Pillai S, Stone JH. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis* 2015;**74**:190–5.
35. Della-Torre E, Bozzalla-Cassione E, Sciorati C, Ruggiero E, Lanzillotta M, Bonfiglio S, Mattoo H, Perugino CA, Bozzolo E, Rovati L, Arcidiacono PG, Balzano G, Lazarevic D, Bonini C, Falconi M, Stone JH, Dagna L, Pillai S, Manfredi AA. A CD8alpha- subset of CD4 + SLAMF7+ cytotoxic T cells is expanded in patients with IgG4-related disease and decreases following glucocorticoid treatment. *Arthritis Rheumatol* 2018;**70**:1133–43.
36. Pillai S, Mattoo H, Cariappa A. B cells and autoimmunity. *Curr Opin Immunol* 2011;**23**:721–31.
37. Crotty S. Follicular helper CD4 T cells (TFH). *Annu Rev Immunol* 2011;**29**:621–63.
38. Akiyama M, Suzuki K, Yamaoka K, Yasuoka H, Takeshita M, Kaneko Y, Kondo H, Kassai Y, Miyazaki T, Morita R, Yoshimura A, Takeuchi T. Brief Report: Number of Circulating Follicular Helper 2 T Cells Correlates With IgG4 and Interleukin-4 Levels and Plasmablast Numbers in IgG4-Related Disease. *Arthritis Rheumatol (Hoboken NJ)* 2015;**67**:2476–81.
39. Akiyama M, Yasuoka H, Yamaoka K, Suzuki K, Kaneko Y, Kondo H, Kassai Y, Koga K, Miyazaki T, Morita R, Yoshimura A, Takeuchi T. Enhanced IgG4 production by follicular helper 2 T cells and the involvement of follicular helper 1 T cells in the pathogenesis of IgG4-related disease. *Arthritis Res Ther* 2016;**18**:167.
40. Grados A, Ebbo M, Piperoglou C, Groh M, Regent A, Samson M, Terrier B, Loundou A, Morel N, Audia S, Maurier F, Graveleau J, Hamidou M, Forestier A, Palat S, Bernit E, Bonotte B, Farnarier C, Harle JR, Costedoat-Chalumeau N, Vely F, Schleinitz N. T Cell Polarization toward TH2/TFH2 and TH17/TFH17 in Patients with IgG4-Related Disease. *Front Immunol* 2017;**8**:235.
41. Maehara T, Mattoo H, Mahajan VS, Murphy SJ, Yuen GJ, Ishiguro N, Ohta M, Moriyama M, Saeki T, Yamamoto H, Yamauchi M, Daccache J, Kiyoshima T, Nakamura S, Stone JH, Pillai S. The expansion in lymphoid organs of IL-4(+) BATF(+) T follicular helper cells is linked to IgG4 class switching in vivo. *Life Sci Alliance* 2018;**1**. pii: e201800050.
42. Perugino CA, AlSalem SB, Mattoo H, Della-Torre E, Mahajan V, Ganesh G, Allard-Chamard H, Wallace Z, Montesi SB, Kreuzer J, Haas W, Stone JH, Pillai S. Identification of galectin-3 as an autoantigen in patients with IgG 4-related disease. *J Allergy Clin Immunol* 2018. http://dx.doi.org/10.1016/j.jaci.2018.05.011. in press.
43. Salah A, Yoshifuji H, Ito S, Kitagori K, Kiso K, Yamada N, Nakajima T, Haga H, Tsuruyama T, Miyagawa-Hayashino A. High Expression of Galectin-3 in Patients with IgG4-Related Disease: A Proteomic Approach. *Pathol Res Int* 2017;**2017**:9312142.
44. Li LC, Li J, Gao J. Functions of galectin-3 and its role in fibrotic diseases. *J Pharmacol Exp Ther* 2014;**351**:336–43.
45. Shiokawa M, Kodama Y, Kuriyama K, Yoshimura K, Tomono T, Morita T, Kakiuchi N, Matsumori T, Mima A, Nishikawa Y, Ueda T, Tsuda M, Yamauchi Y, Minami R, Sakuma Y, Ota Y, Maruno T, Kurita A, Sawai Y, Tsuji Y, Uza N, Matsumura K, Watanabe T, Notohara K, Tsuruyama T, Seno H, Chiba T. Pathogenicity of IgG in patients with IgG4-related disease. *Gut* 2016;**65**:1322–32.
46. Shiokawa M, Kodama Y, Sekiguchi K, Kuwada T, Tomono T, Kuriyama K, Yamazaki H, Morita T, Marui S, Sogabe Y, Kakiuchi N, Matsumori T, Mima A, Nishikawa Y, Ueda T, Tsuda M, Yamauchi Y, Sakuma Y, Maruno T, Uza N, Tsuruyama T, Mimori T, Seno H, Chiba T. Laminin 511 is a target antigen in autoimmune pancreatitis. *Sci Transl Med* 2018;**10**. pii: eaaq0997.
47. Kamisawa T, Shimosegawa T, Okazaki K, Nishino T, Watanabe H, Kanno A, Okumura F, Nishikawa T, Kobayashi K, Ichiya T, Takatori H, Yamakita K, Kubota K, Hamano H, Okamura K, Hirano K, Ito T, Ko SB, Omata M. Standard steroid treatment for autoimmune pancreatitis. *Gut* 2009;**58**:1504–7.
48. Masaki YY, Matsui S, Saeki T, Tsuboi H, Hirata S, Izumi Y, Miyashita T, Fujikawa K, Dobashi H, Susaki K, Morimoto H, Takagi K, Kawano M, Origuchi T, Wada Takahashi YN, Horikoshi M, Ogishima H, Suzuki Y, Kawanami T, Kawanami-Iwao H, Sakai T, Fujita Y, Fukushima T, Saito M, Suzuki R, Morikawa Y, Yoshino T, Nakamura S, Kojima M, Kurose N, Sato Y, Tanaka Y, Sugai S, Sumida T. A multicenter phase II prospective clinical trial of glucocorticoid for patients with untreated IgG4-related disease. *Modern Rheumatology/the Japan Rheumatism Association* 2017;**27**:849–54.

49. Hong X, Zhang YY, Li W, Liu YY, Wang Z, Chen Y, Gao Y, Sun ZP, Peng X, Su JZ, Cai ZG, Zhang L, He J, Ren LM, Yang HY, Li ZG, Yu GY. Treatment of immunoglobulin G4-related sialadenitis: outcomes of glucocorticoid therapy combined with steroid-sparing agents. *Arthritis Res Ther* 2018;**20**:12.
50. Masamune A, Nishimori I, Kikuta K, Tsuji I, Mizuno N, Iiyama T, Kanno A, Tachibana Y, Ito T, Kamisawa T, Uchida K, Hamano H, Yasuda H, Sakagami J, Mitoro A, Taguchi M, Kihara Y, Sugimoto H, Hirooka Y, Yamamoto S, Inui K, Inatomi O, Andoh A, Nakahara K, Miyakawa H, Hamada S, Kawa S, Okazaki K, Shimosegawa T. Randomised controlled trial of long-term maintenance corticosteroid therapy in patients with autoimmune pancreatitis. *Gut* 2017;**66**:487–94.
51. Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, Kim MH, Kloppel G, Lerch MM, Lohr M, Notohara K, Okazaki K, Schneider A, Zhang L. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. *Pancreas* 2011;**40**:352–8.
52. Moriyama M, Tanaka A, Maehara T, Ohyama Y, Shimizu M, Nakashima H, Hayashida JN, Shinozaki S, Kubo Y, Furukawa S, Kikuta T, Nakamura S. Clinical characteristics of Mikulicz's disease as an IgG4-related disease. *Clin Oral Investig* 2013;**17**:1995–2002.
53. Mattoo H, Della-Torre E, Mahajan VS, Stone JH, Pillai S. Circulating Th2 memory cells in IgG4-related disease are restricted to a defined subset of subjects with atopy. *Allergy* 2014;**69**:399–402.
54. Furukawa S, Moriyama M, Miyake K, Nakashima H, Tanaka A, Maehara T, Izuka-Koga M, Tsuboi H, Hayashida JN, Ishiguro N, Yamauchi M, Sumida T, Nakamura S. Interleukin-33 produced by M2 macrophages and other immune cells contributes to Th2 immune reaction of IgG4-related disease. *Sci Rep* 2017;**7**:42413.
55. Akiyama M, Suzuki K, Yasuoka H, Kaneko Y, Yamaoka K, Takeuchi T. Follicular helper T cells in the pathogenesis of IgG4-related disease. *Rheumatology* 2018;**1**:236–45.
56. Miyoshi H, Uchida K, Taniguchi T, Yazumi S, Matsushita M, Takaoka M, Okazaki K. Circulating naive and CD4+CD25high regulatory T cells in patients with autoimmune pancreatitis. *Pancreas* 2008;**36**:133–40.
57. Kusuda T, Uchida K, Miyoshi H, Koyabu M, Satoi S, Takaoka M, Shikata N, Uemura Y, Okazaki K. Involvement of inducible costimulator- and interleukin 10-positive regulatory T cells in the development of IgG4-related autoimmune pancreatitis. *Pancreas* 2011;**40**:1120–30.
58. Koyabu M, Uchida K, Miyoshi H, Sakaguchi Y, Fukui T, Ikeda H, Takaoka M, Hirohara J, Nishio A, Uemura Y, Uemoto S, Okazaki K. Analysis of regulatory T cells and IgG4-positive plasma cells among patients of IgG4-related sclerosing cholangitis and autoimmune liver diseases. *J Gastroenterol* 2010;**45**:732–41.
59. Zen Y, Fujii T, Harada K, Kawano M, Yamada K, Takahira M, Nakanuma Y. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. *Hepatology* 2007;**45**:1538–46.
60. Hubers LM, Vos H, Schuurman AR, Erken R, Oude-Elferink RP, Burgering B, van-de-Graaf SFJ, Beuers U. Annexin A11 is targeted by IgG4 and IgG1 autoantibodies in IgG4-related disease. *Gut* 2018;**67**:728–35.

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