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QMR IgG4 Diseases

Pathophysiology of IgG4-related disease: a T follicular helper cells disease?

Benjamin De Sainte Marie[1], Maria Laetizia Urban[1], Frédéric Vély[2], Julie Seguier[1], Aurélie Grados[3], Laurent Daniel[4], Mikael Ebbo[1], Nicolas Schleinitz[1].

[1] Département de médecine interne, Hôpital de la Timone, AP-HM, Aix Marseille Université, Marseille, France.

[2] Aix Marseille Univ, CNRS, INSERM, Centre d'Immunologie de Marseille-Luminy, Marseille, France; Immunology, Marseille Immunopole, Hôpital de la Timone, Assistance Publique des Hôpitaux de Marseille, France.

[3] Service de médecine interne, CH de Niort, France.

[4]Service d'anatomopathologie, Hôpital de la Timone, AP-HM, Aix Marseille Université, Marseille, France.

Corresponding author: Nicolas Schleinitz, Département de médecine interne, Hôpital de la Timone, AP-HM, Marseille. nicolas.schleinitz@ap-hm.fr

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Abstract

IgG4-related disease is a chronic inflammatory disease characterized by clinical, biological and pathological unifying findings. Because these criteria are not always all together available in patients and because biological and pathological markers are not totally specific, the diagnosis should be retained after exclusion of mimickers. Since the individualization of IgG4-RD, several studies have allowed to better characterize immunological abnormalities associated with this particular condition. B and T cell oligoclonal activation is associated with T helper 2 cytokine production leading to IgG4 production and profibrotic cytokine release. A central role for T follicular helper 2 cells is suggested from recent findings. We summarize here recent advances in understanding of immune abnormalities in IgG4-related disease.

Introduction

IgG4-related disease (IgG4-RD) is a chronic fibro-inflammatory condition characterized by mass-forming lesions involving various tissues. The disease more frequently affects males over 50 years of age[1,2]. The unifying findings of the disease are the pathological lesions characterized by dense lymphoplasmacytic infiltrates with numerous $IgG4^{+}$ plasma cells, associated with a typically storiform fibrosis and a risk of organ damage[3]. These characteristics have allowed to unify several previously unrelated syndromes as IgG4-related since more than ten years[4]. The pathological features together with the recognition of frequent ectopic lymphoid structures in diseased tissues suggest an antigen-driven immune response with T cell activation, leading to profibrotic cytokine release and B cell activation with a switch to IgG4

production. Despite important findings these last years, several issues regarding the pathophysiology of IgG4-RD remain unsolved. Important questions to be solved are the nosology with other fibro-inflammatory idiopathic disorders, the identification of antigenic triggers of this aberrant immune response and the precise cells and cytokines that drive the inflammatory and fibrotic process. We review here current knowledge on the pathophysiology of IgG4-RD.

Methodology

We conducted a systematic research from the PubMed database including following search terms "IgG4-related disease" and "type 1 auto-immune pancreatitis" and "IgG4-related sialadenitis". Manuscripts including relevant pathophysiological studies were analyzed and are summarized in this review.

Genetic and environmental factors

There is no reported evidence for ethnical predisposition, but distinctive clinical features have been associated to ethnical background[5]. Familial clustering is reported in two cases in 61 and 62-years-old monozygotic twins presenting with pancreatic and biliary IgG4-related disease[6]. Data regarding HLA-alleles association with IgG4-RD are largely focused on pancreatic involvement of the disease from Asian cohorts. Using association studies by candidate-gene approach and genome-wide association studies, Kawa *et al* demonstrated an association between DRB1*0405-DQB1*0401 haplotype and type 1 (IgG4-related) autoimmune pancreatitis (AIP) in the Japanese population[7]. Moreover, few single nucleotide polymorphisms in genes outside the MHC-region but related to the immune system have been linked to IgG4-RD, such as Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), deletion of fibroblast growth factor binding protein type 2 (FGFBP2) (a protein secreted by cytotoxic T lymphocytes), Fc-

receptor-like 3 (FCRL3) and Potassium Voltage-Gated Channel Subfamily A Member 3 (KCNA3)[8,9,10,11]. More recently, a large genome-wide association study of Japanese individuals (835 IgG4-RD patients and 1789 healthy participants) identified the *HLA-DRB1* and *FCGR2B* regions as susceptibility loci for IgG4-related disease[12], suggesting a central role for *HLA* and *FCGR2B* in the pathogenesis of IgG4-RD, and common molecular pathways with other immune-related diseases, such as systemic lupus erythematosus. The role of possible somatic mutations has not been addressed yet.

Environmental factors have been suggested in few studies. In a case control study comparing IgG4-related cholangitis and/or-pancreatitis with primary sclerosing cholangitis patients, de Buy Wenniger *et al* demonstrated an association with long-term exposure to solvents and other organic agents (industrial and metal dusts, pigments and oils used in the industry), characteristic of "blue-collar" workers[13]. The fact that the disease is anecdotally reported in children and young adults could be another argument to support the role of environmental triggers.

Innate immunity

Only few studies have investigated innate immune cells in IgG4-RD. Immunostaining studies in salivary glands of IgG4-RD patients showed that mast cells are present and release Th2 and profibrotic cytokines (IL-4, IL-10, and TGF-β)[14], as well as IL-13, which could contribute to elevation of serum IgE levels and eosinophil infiltration in IgG4-RD[15]. Because these mast cells strongly express the cell surface high-affinity IgE receptor (FcεRI), this suggest a possible activation of these cells by non-specific IgE, that are elevated in 35% of patients[16]. Another study demonstrated that activation of Toll like Recpetors (TLRs) on basophils can induce IgG4 production by B cells from healthy controls, associated with BAFF and IL-13 release[17]. Because basophils

are known to be an important source of IL-4 in tissues, they could be one of the first step of the Th2 orientation in the disease. Eosinophils are frequently increased in blood[16] and diseased tissues[3] from IgG4-RD patients. Eosinophilia appears to be independent of allergic manifestations in IgG4-RD patients[18] and has been recently identified as a predictor of relapse[19]. The Th2 response (figure 1) may be responsible for eosinophilia in IgG4-RD, and activated eosinophils are able to release cytokines[20], which can promote the production of IgG4[21], and transforming growth factor (TGF)-β[20], with a potential participation in the pathogenesis of fibrosis. Tissue macrophages in IgG4-RD tissues are preferentially M2 macrophages[22]. They could participate to fibrosis through TGF-β production, activate a Th2 immune response through TLR-7/IL-33 axis, and contribute to plasma cell accumulation *via* APRIL release[22,23,24,25]. The role of ILC2, a potential source of Th2 cytokines in tissues, has not yet been addressed.

IgG4, IgG and auto-antibodies

In physiological condition, IgG4 represent the less abundant IgG subclass (1–4% of total IgG). IgG4 are produced after long-term or repeated antigen exposure in response to interleukin IL-4 and IL-10[26]. Not only the IgG4 subclass is increased in serum of IgG4-RD patients, but the fold increase is the highest[2]. About half of the patients present with an increase of the κ/λ light chain ratio related to the fact that most IgG4 harbor the κ light chain[26,27,28].

IgG4 differ from IgG1 by only a few amino acid residues resulting in a more flexible hinge region which confers the ability to Fab-arm exchange and rheumatoid factor (RF)-like activity[26]. RF-like activity mainly consists in binding the Fc portion of other IgG via Fc-Fc interactions. IgG4 Fc has a low affinity for Fc receptors and the C1 complement molecule[26]. For these reasons, IgG4 is considered as a "non-

inflammatory" immunoglobulin with inhibitory functions. Intriguingly, hypocomplementemia with low C3 and/or C4 levels is reported in some IgG4-RD patients, especially those with renal involvement[29]. IgG4 immune complexes have been shown in IgG4-related tubulo-interstitial nephritis[30]. Complement activation and C3 deposits in kidney are correlated with the highest IgG4 serum levels[31]. Patients at diagnosis have high C5 and C5a that correlate negatively with C3 levels[32]. The way of complement activation in IgG4-RD is not completely elucidated but complement activation by IgG4 through the classic pathway rather than through the lectin or alternative pathways is proposed[32,33]. Other IgG subclasses could also be involved. The role of IgG4 and IgG1 was addressed by Shiokawa *et al*. in Balb/c mice[34]. IgG4 from IgG4-RD patients induced a phenotype similar to IgG4-RD with pancreatic and salivary gland injuries, although hemorrhage and necrosis were also observed. In this model, human IgG4-RD IgG1 were found more pathogenic than IgG4[34]. The presence of autoantibodies has been early reported in IgG4-related pancreatitis. Autoantibodies recognizing the pancreatic trypsin inhibitor, amylase α-2A or carbonic anhydrase were described with variable frequency, but their presence was not confirmed in patients with other IgG4-RD organ involvement other than tubulointerstitial nephritis[35,36,37]. More recently several autoantibodies have been documented. Antibodies against laminin 511-E8 (a component of extra-cellular matrix) were found in 51% of IgG4-related AIP vs 1.6% of healthy controls[38]. The immunization of mices with human laminin 511-E8 induced a pancreatitis similar to IgG4-RD and 15% of patients without antibody against laminin 511-E8 have an antibody to integrin α6β1, a laminin 511-E8 ligand[38]. In a study using plasmablast clones from IgG4-RD patients, 28% from 121 patients were found to have anti-galectin-3 antibody[39]. An overexpression of galectin 3 in the pancreas and other organs involved by IgG4-RD was shown by proteomic analysis. From affinity purification with patient serum and

MALDI-TOF/TOF mass spectrometry, antibodies against prohibitin were identified in 73% of patients with IgG4-related pancreatitis, 53% IgG4-related sialadenitis, 54% IgG4-related RPF compared to 13% in pSS and 1% in healthy controls[40]. Eventually nine out of 50 patients with IgG4- related pancreatitis were positive for the antibody against annexin A11 by western blot or ELISA assay[41]. Two epitopes of annexin A11 were shared by IgG1- and IgG4-isotype antibodies. Interestingly, IgG4 antibody against annexin A11 inhibited the binding of IgG1 antibody against annexin A11, which could participate to the regulatory function of IgG4[41]. Recently, the antibodies against prohibitin, annexin A11, and laminin 511-E8 were found in only a small portion of US patients with IgG4-RD, but patients with antibodies against ≥2 autoantigens presented with more severe disease, high IgG subclass elevations, complement consumption, and visceral organ involvement[42].

B cells

The presence of numerous $IgG4^+$ plasma cells in the affected tissues, IgG4 elevation in the serum and effective response to B-cell depletion with rituximab (RTX) suggest an important role of B cells in the pathophysiology of IgG4-RD[43,44,45]. Although total circulating B cell numbers are not abnormal in patients, modification of some B cell subsets have been described. Plasmablasts, characterized as $CD19^+CD27^+CD38^{high}$ (but $CD20^-$) lymphocytes, are expanded in blood of IgG4-RD patients[43,46]. Plasmablast are peripheral cells developed from activated naïve/memory B cells that differentiate into antibody-secreting, tissue resident or long-lived plasma cells. Plasmablasts are increased in peripheral blood of untreated patients compared to healthy controls and patients with other inflammatory diseases. Plasmablast numbers correlate with disease activity (IgG4 levels, IgG4-RD Responder Index and number of involved organs)[46]. Treatment with rituximab led to a decrease of plasmablasts which

again correlate with clinical remission, even in patients who did not normalize serum IgG4 levels following treatment. Analysis of Ig heavy chain genes rearrangement in IgG4$^+$ plasmablast from IgG4-RD patients reveal oligoclonal expansion and extensive somatic hypermutation. The comparison in the same patient of Ig heavy chain genes rearrangement in IgG4$^+$ plasmablasts before and after RTX treatment during a relapse have shown clonally distinct plasmablasts, indicating the recruitment and activation of naïve B-cells by T cells[43]. Beside plasmablast expansion, other B cell subsets variation in blood have been reported in IgG4-RD, some of which correlate with clinical or biological markers of the disease[47,48]. B regulatory IL-10 producing cells have been also addressed in IgG4-RD by analyzing both CD19$^+$CD24^{high}CD38^{high} and CD19$^+$CD24^{high}CD27$^+$ subsets in AIP, but discrepancies between studies do not allow any conclusion on their potential role in the disease[49,50]. Altogether these findings reflect the strong polyclonal activation of the B cell compartment in the disease.

A direct role of plasmablasts in fibroblast activation and fibrosis has been shown recently, suggesting a central role of B cells in the disease[51].

T cells

In IgG4-RD pathophysiology, several observations suggest the critical role of T cells. First, in diseased tissues CD4$^+$ T cells represent a large component of the mononuclear infiltrating cells[52]. These cells are thought to be the major source of cytokines inducing B cell proliferation and switch, in ectopic germinal centers, and to induce fibrosis. Second, the high rate of relapses observed after RTX treatment, together with the observation of clonally different B cell clones during relapses, are strong arguments for the central role of T cells in orchestrating tissue lesions[43].

Th2 cells

T cells subsets have been studied in tissues and blood of patients, initially focusing on Th2 cells. An excessive Th2 response was suggested by the frequent association to allergy, the increase of IgG4 and the presence of eosinophils in tissues lesions. Indeed, high expression of Th2 cytokines (IL-4, IL-13 and IL-5) were found in tissues and blood from IgG4-RD patients[47,53,54]. The role of Th2 cells is still debated. IL-4 production has been shown to be restricted to $CD4^+GATA3^+$ T cells in IgG4-RD patients with known atopy, suggesting that the role of Th2 responses might be confounded by concomitant allergic disease[55,16]. In another study, Th2 and Tfh2 cell numbers, IgE levels, and eosinophil count were not different between atopic and non-atopic IgG4-RD patients[53]. However, there is evidence that other T cell subsets have a central role and probably account for IL-4 release in tissues and blood in the disease. A mutant mouse "Th2" model of IgG4-RD was recently suggested. Loss-of-function of Linker of activation of T cell (LAT, a key signaling hub used by the T cell antigen receptor) displayed increased production of Th2-type IgG1 (a homologue of human IgG4) and developed multiple organ tissue lesions resembling IgG4-RD. This model however was first reported as a model of autoimmunity because of the development of several autoantibodies and glomerulonephritis with IgE deposits, related to polyclonal B cell activation that is far different from typical IgG4-RD[56]. In these mice $CD4^+CD25^+foxp3^+$ regulatory cells are nearly absent in contrary to what is usually observed in IgG4-RD[57].

T follicular helper cells

Ectopic lymphoid structures (ELS) are frequently observed in IgG4-RD. ELS are classically defined as T and B cell aggregates with compartmentalized B cell and T cell-rich zones, development of follicular dendritic cell (FDC) networks and high endothelial venules in non-lymphoid target organs. They are transient structures that

can be triggered by immunization or infection and often resolve after antigen clearance[58]. On an architectural and functional level, these ectopic germinal centers provide an infrastructure to capture and store an antigen, and to direct various B cell and T cell responses, including the induction of effector functions, antibody generation, affinity maturation, class switching and clonal expansion of B cells. ELS can be observed in infections, graft rejection, cancers, autoimmune and inflammatory diseases[59]. They have been studied in several autoimmune diseases and are often associated with poor response to standard therapy and more severe disease course[60]. ELS are dependent on T follicular helper (Tfh) cells which produce IL-21, a major cytokine for germinal center formation. Tfh cells express the transcription factor Bcl-6, and surface cell markers CXCR5, PD-1 and ICOS. Involvement of Tfh in IgG4-RD pathogenesis was suggested early by Zaidan *et al*. in a patient with mildly swollen lymph nodes with follicular hyperplasia, tubulointerstitial nephritis, lymphoplasmacytic sialadenitis, retroperitoneal fibrosis and bile duct involvement. The unusual abundance of interfollicular plasma cells and $CD4^+$ T cells in germinal centers of lymph nodes compared to controls suggested a possible role of Tfh cells in enhancing a skewed B-cell terminal maturation[61]. Maehara *et al* showed elevation of IL-21 mRNA expression in tissues of patients with IgG4-related dacryoadenitis and sialadenitis compared to salivary glands of pSS patients. IL-21 mRNA expression positively correlated with the presence of ELS[62]. An increase in circulating blood $CD4^+CXCR5^+$ Tfh (cTfh) was reported by different groups. Akiyama *et al*. and Grados *et al.* showed that $CD4^+CXCR5^+PD1^+$ cTfh were increased in patients with IgG4-RD when compared to pSS patients and healthy controls. The cTfh were orientated to a Tfh2 $CCR6^-CXCR3^-$ functional phenotype, and Tfh2 cell number positively correlated with serum IgG4 level, IgG4/IgG ratio, number of circulating plasmablasts and disease activity[53,63]. The $PD1^{high}$ circulating Tfh are associated with

an activated state and observed in IgG4-RD[53,64,65]. Tfh2 cells from IgG4-RD patients efficiently secrete IL-4 and IL-21, and Tfh2 efficiently induced the differentiation of naïve B cells to IgG4 producing B cells *in vitro*[64].

More recently, Tfh have been shown and characterized in diseased tissues. Using flow cytometry on fresh tissues from IgG4-RD patients with dacryoadenitis and sialadenitis, Kamekura *et al*. showed a predominance of $CD4^+$ T cells with 72% of these being Tfh cells[66]. Increased number of tissular Tfh cells was correlated with high proportion of PD-1^{high} Tfh activated circulating cells in peripheral blood, disease severity and serum IgG4 levels. Co-culture of Tfh cells from tissues and blood of IgG4-RD patients with allogenic B cells showed a higher capacity of IgG4 production compared to Tfh cells from healthy volunteers[66]. Yang *et al.* also showed that Tfh cells were highly prevalent in tissue and blood of IgG4-RD patients, correlating with high expression of IL-21 in tissues compared to healthy volunteers. Interestingly, frequency and distribution differed according to the organ involved[67]. These observations have demonstrated altogether that IgG4-RD is characterized by an expansion of a Tfh2 orientation in blood and tissues, responsible of ELS formation, tissue IL-4 production and IgG4 class switching[68]. These observations altogether propose a key role for Tfh cells in the disease (figure 1). The way by which they are activated and differentiate to Tfh2 functional cells needs to be further characterized.

CTLs

Circulating effector T $CD4^+$ cells ($CD4^+CD27^{low}CD62^{low}$), also termed $CD4^+$ cytotoxic T lymphocytes ($CD4^+$CTLs), have been described in IgG4-RD lesions and implicated in the pathophysiological process. These CTLS are differentiated antigen experienced (memory) T cell, which expands in situations of chronic antigen simulation. They have a gene signature consisting of both cytolytic and myeloid

genes[69]. It has been shown that they actively secrete profibrotic cytokines such as TGF-β, IL-1β and IFN-γ in tissues of IgG4-RD patients. They are clonally expanded in peripheral blood and in affected organs of IgG4-RD[69]. They have been shown to decline following RTX treatment suggesting that B and some T cells closely interact. The interaction between $CD4^+$CTLs and B cells is suggested to be mediated by the signaling lymphocytic activation molecule 7 (SLAMF7), a surface protein of the SLAM/CD2 family, which acts as a self-ligand and is expressed by both B cells and $CD4^+$CTLs cells[69].

T regulatory cells

T regulatory cells (Treg) expansion in blood and tissues of IgG4-RD patients has been repeatedly shown and is thought to contribute to fibrosis through TGF-β release[53,54]. This contrasts to autoimmune diseases where they are commonly decreased[70]. Their exact role in the disease is unknown.

Conclusion

From the individualization of the disease ten years ago, initially characterized by B cell polyclonal activation and IgG4 production, several important steps have been done toward the understanding of the IgG4-RD pathophysiology. Studies have clearly shown a role for T cells and T cells cytokines. T follicular helper cells orientated functionally to Th2 cytokine production appear as central players, particularly the activated $PD1^{high}$ subset. CTLs and Treg are thought to participate to profibrotic cytokine production. B cell polyclonal activation is T cell driven, but the therapeutic efficacy of rituximab in the disease suggests that B cells participate to T cell activation and potentially to fibrosis. From these results, there is now a reasonable pathophysiological explanation to support the described tissue lesions of the disease.

Hopefully, this will help soon to propose specific biomarkers to better individualize the disease from his mimickers. Functional analysis will further clarify the respective roles of T cells, B cells and innate immunity. Further studies from large cohorts will certainly help to better understand the role of environmental factors and genetic background in the disease. Altogether, the rapid progress in our understanding of IgG4-RD will certainly give soon opportunities to more specifically target cytokines or cells to treat patients.

The authors declare no conflict of interest.

References:

1. Wallace ZS, Deshpande V, Mattoo H, et al. IgG4-Related Disease: Clinical and Laboratory Features in One Hundred Twenty-Five Patients. *Arthritis Rheumatol Hoboken NJ*. 2015;67(9):2466-2475. doi:10.1002/art.39205

2. Ebbo M, Daniel L, Pavic M, et al. IgG4-related systemic disease: features and treatment response in a French cohort: results of a multicenter registry. *Medicine (Baltimore)*. 2012;91(1):49-56. doi:10.1097/MD.0b013e3182433d77

3. Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. *Mod Pathol Off J U S Can Acad Pathol Inc*. 2012;25(9):1181-1192. doi:10.1038/modpathol.2012.72

4. Stone JH, Khosroshahi A, Deshpande V, et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. *Arthritis Rheum*. 2012;64(10):3061-3067. doi:10.1002/art.34593

5. Wallace ZS, Zhang Y, Perugino CA, et al. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. *Ann Rheum Dis*. January 2019. doi:10.1136/annrheumdis-2018-214603

6. Grados A, Vaysse T, Ebbo M, Carbonnel F, Schleinitz N. IgG4-Related Disease in Monozygotic Twins: A Case Report. *Ann Intern Med*. 2017;166(2):153-155. doi:10.7326/L16-0122

7. Kawa S, Ota M, Yoshizawa K, et al. HLA DRB10405-DQB10401 haplotype is associated with autoimmune pancreatitis in the Japanese population. *Gastroenterology*. 2002;122(5):1264-1269. doi:10.1053/gast.2002.33022

8. Chang M-C, Chang Y-T, Tien Y-W, et al. T-cell regulatory gene CTLA-4 polymorphism/haplotype association with autoimmune pancreatitis. *Clin Chem*.

2007;53(9):1700-1705. doi:10.1373/clinchem.2007.085951

9. Umemura T, Ota M, Hamano H, Katsuyama Y, Kiyosawa K, Kawa S. Genetic association of Fc receptor-like 3 polymorphisms with autoimmune pancreatitis in Japanese patients. *Gut*. 2006;55(9):1367-1368. doi:10.1136/gut.2006.095059

10. Ota M, Ito T, Umemura T, et al. Polymorphism in the KCNA3 gene is associated with susceptibility to autoimmune pancreatitis in the Japanese population. *Dis Markers*. 2011;31(4):223-229. doi:10.3233/DMA-2011-0820

11. Newman JH, Shaver A, Sheehan JH, et al. IgG4-related disease: Association with a rare gene variant expressed in cytotoxic T cells. *Mol Genet Genomic Med*. 2019;7(6):e686. doi:10.1002/mgg3.686

12. Terao C, Ota M, Iwasaki T, et al. IgG4-related disease in the Japanese population: a genome-wide association study. *Lancet Rheumatol*. 2019;1(1):e14-e22. doi:10.1016/S2665-9913(19)30006-2

13. de Buy Wenniger LJM, Culver EL, Beuers U. Exposure to occupational antigens might predispose to IgG4-related disease. *Hepatol Baltim Md*. 2014;60(4):1453-1454. doi:10.1002/hep.26999

14. Takeuchi M, Sato Y, Ohno K, et al. T helper 2 and regulatory T-cell cytokine production by mast cells: a key factor in the pathogenesis of IgG4-related disease. *Mod Pathol Off J U S Can Acad Pathol Inc*. 2014;27(8):1126-1136. doi:10.1038/modpathol.2013.236

15. Takeuchi M, Ohno K, Takata K, et al. Interleukin 13-positive mast cells are increased in immunoglobulin G4-related sialadenitis. *Sci Rep*. 2015;5:7696. doi:10.1038/srep07696

16. Della Torre E, Mattoo H, Mahajan VS, Carruthers M, Pillai S, Stone JH. Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease. *Allergy*. 2014;69(2):269-272. doi:10.1111/all.12320

17. Watanabe T, Yamashita K, Sakurai T, et al. Toll-like receptor activation in basophils contributes to the development of IgG4-related disease. *J Gastroenterol*. 2013;48(2):247-253. doi:10.1007/s00535-012-0626-8

18. Zhang X, Zhang P, Li J, et al. Different clinical patterns of IgG4-RD patients with and without eosinophilia. *Sci Rep*. 2019;9(1):16483. doi:10.1038/s41598-019-52847-6

19. Wallace ZS, Mattoo H, Mahajan VS, et al. Predictors of disease relapse in IgG4-related disease following rituximab. *Rheumatol Oxf Engl*. 2016;55(6):1000-1008. doi:10.1093/rheumatology/kev438

20. Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol*. 2006;24:147-174. doi:10.1146/annurev.immunol.24.021605.090720

21. Moriyama M, Nakamura S. Th1/Th2 Immune Balance and Other T Helper Subsets in IgG4-Related Disease. *Curr Top Microbiol Immunol*. 2017;401:75-83. doi:10.1007/82_2016_40

22. Furukawa S, Moriyama M, Tanaka A, et al. Preferential M2 macrophages contribute

to fibrosis in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease. *Clin Immunol Orlando Fla*. 2015;156(1):9-18. doi:10.1016/j.clim.2014.10.008

23. Furukawa S, Moriyama M, Miyake K, et al. Interleukin-33 produced by M2 macrophages and other immune cells contributes to Th2 immune reaction of IgG4-related disease. *Sci Rep*. 2017;7:42413. doi:10.1038/srep42413

24. Ishiguro N, Moriyama M, Furusho K, et al. Activated M2 macrophage contributes to the pathogenesis of IgG4-related disease via TLR7/IL-33 signaling. *Arthritis Rheumatol Hoboken NJ*. July 2019. doi:10.1002/art.41052

25. Kawakami T, Mizushima I, Yamada K, et al. Abundant a proliferation-inducing ligand (APRIL)-producing macrophages contribute to plasma cell accumulation in immunoglobulin G4-related disease. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2019;34(6):960-969. doi:10.1093/ndt/gfy296

26. Aalberse RC, Stapel SO, Schuurman J, Rispens T. Immunoglobulin G4: an odd antibody. *Clin Exp Allergy J Br Soc Allergy Clin Immunol*. 2009;39(4):469-477. doi:10.1111/j.1365-2222.2009.03207.x

27. Grados A, Ebbo M, Boucraut J, et al. Serum Immunoglobulin Free Light Chain Assessment in IgG4-Related Disease. *Int J Rheumatol*. 2013;2013:426759. doi:10.1155/2013/426759

28. Aucouturier P, Preud'Homme JL. Subclass distribution of human myeloma proteins as determined with monoclonal antibodies. *Immunol Lett*. 1987;16(1):55-57.

29. Sugimoto M, Watanabe H, Asano T, et al. Possible participation of IgG4 in the activation of complement in IgG4-related disease with hypocomplementemia. *Mod Rheumatol*. 2016;26(2):251-258. doi:10.3109/14397595.2015.1076924

30. Saeki T, Kawano M. IgG4-related kidney disease. *Kidney Int*. 2014;85(2):251-257. doi:10.1038/ki.2013.393

31. Wang R, He D, Zhao L, et al. Role of complement system in patients with biopsy-proven immunoglobulin G4-related kidney disease. *Hum Pathol*. 2018;81:220-228. doi:10.1016/j.humpath.2018.07.008

32. Fukui S, Fujita Y, Origuchi T, Maeda T, Kawakami A. Serum complement factor C5a in IgG4-related disease. *Ann Rheum Dis*. 2019;78(7):e65. doi:10.1136/annrheumdis-2018-213705

33. Muraki T, Hamano H, Ochi Y, et al. Autoimmune pancreatitis and complement activation system. *Pancreas*. 2006;32(1):16-21. doi:10.1097/01.mpa.0000188308.75043.e4

34. Shiokawa M, Kodama Y, Kuriyama K, et al. Pathogenicity of IgG in patients with IgG4-related disease. *Gut*. 2016;65(8):1322-1332. doi:10.1136/gutjnl-2015-310336

35. Asada M, Nishio A, Uchida K, et al. Identification of a novel autoantibody against pancreatic secretory trypsin inhibitor in patients with autoimmune pancreatitis. *Pancreas*. 2006;33(1):20-26. doi:10.1097/01.mpa.0000226881.48204.fd

36. Endo T, Takizawa S, Tanaka S, et al. Amylase alpha-2A autoantibodies: novel

marker of autoimmune pancreatitis and fulminant type 1 diabetes. *Diabetes*. 2009;58(3):732-737. doi:10.2337/db08-0493

37. Nishi H, Tojo A, Onozato ML, et al. Anti-carbonic anhydrase II antibody in autoimmune pancreatitis and tubulointerstitial nephritis. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2007;22(4):1273-1275. doi:10.1093/ndt/gfl672

38. Shiokawa M, Kodama Y, Sekiguchi K, et al. Laminin 511 is a target antigen in autoimmune pancreatitis. *Sci Transl Med*. 2018;10(453). doi:10.1126/scitranslmed.aaq0997

39. Perugino CA, AlSalem SB, Mattoo H, et al. Identification of galectin-3 as an autoantigen in patients with IgG4-related disease. *J Allergy Clin Immunol*. May 2018. doi:10.1016/j.jaci.2018.05.011

40. Du H, Shi L, Chen P, et al. Prohibitin Is Involved in Patients with IgG4 Related Disease. *PloS One*. 2015;10(5):e0125331. doi:10.1371/journal.pone.0125331

41. Hubers LM, Vos H, Schuurman AR, et al. Annexin A11 is targeted by IgG4 and IgG1 autoantibodies in IgG4-related disease. *Gut*. 2018;67(4):728-735. doi:10.1136/gutjnl-2017-314548

42. Liu H, Perugino CA, Ghebremichael M, et al. Disease severity is linked to an increase in autoantibody diversity in IgG4-related disease. *Arthritis Rheumatol Hoboken NJ*. October 2019. doi:10.1002/art.41140

43. Mattoo H, Mahajan VS, Della-Torre E, et al. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-related disease. *J Allergy Clin Immunol*. 2014;134(3):679-687. doi:10.1016/j.jaci.2014.03.034

44. Ebbo M, Grados A, Samson M, et al. Long-term efficacy and safety of rituximab in IgG4-related disease: Data from a French nationwide study of thirty-three patients. *PloS One*. 2017;12(9):e0183844. doi:10.1371/journal.pone.0183844

45. Carruthers MN, Topazian MD, Khosroshahi A, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. *Ann Rheum Dis*. 2015;74(6):1171-1177. doi:10.1136/annrheumdis-2014-206605

46. Wallace ZS, Mattoo H, Carruthers M, et al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis*. 2015;74(1):190-195. doi:10.1136/annrheumdis-2014-205233

47. Heeringa JJ, Karim AF, van Laar JAM, et al. Expansion of blood IgG4+ B, TH2, and regulatory T cells in patients with IgG4-related disease. *J Allergy Clin Immunol*. 2018;141(5):1831-1843.e10. doi:10.1016/j.jaci.2017.07.024

48. Lanzillotta M, Della-Torre E, Milani R, et al. Increase of circulating memory B cells after glucocorticoid-induced remission identifies patients at risk of IgG4-related disease relapse. *Arthritis Res Ther*. 2018;20(1):222. doi:10.1186/s13075-018-1718-5

49. Sumimoto K, Uchida K, Kusuda T, et al. The role of CD19+ CD24high CD38high and CD19+ CD24high CD27+ regulatory B cells in patients with type 1 autoimmune pancreatitis. *Pancreatol Off J Int Assoc Pancreatol IAP Al*. 2014;14(3):193-200.

doi:10.1016/j.pan.2014.02.004

50. Lin W, Jin L, Chen H, et al. B cell subsets and dysfunction of regulatory B cells in IgG4-related diseases and primary Sjögren's syndrome: the similarities and differences. *Arthritis Res Ther*. 2014;16(3):R118. doi:10.1186/ar4571

51. Della-Torre E, Rigamonti E, Perugino C, et al. B lymphocytes directly contribute to tissue fibrosis in patients with IgG4-related disease. *J Allergy Clin Immunol*. July 2019. doi:10.1016/j.jaci.2019.07.004

52. Stone JH, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med*. 2012;366(6):539-551. doi:10.1056/NEJMra1104650

53. Grados A, Ebbo M, Piperoglou C, et al. T Cell Polarization toward TH2/TFH2 and TH17/TFH17 in Patients with IgG4-Related Disease. *Front Immunol*. 2017;8:235. doi:10.3389/fimmu.2017.00235

54. Zen Y, Fujii T, Harada K, et al. Th2 and regulatory immune reactions are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis. *Hepatol Baltim Md*. 2007;45(6):1538-1546. doi:10.1002/hep.21697

55. 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(3):399-402. doi:10.1111/all.12342

56. Yamada K, Zuka M, Ito K, et al. LatY136F knock-in mouse model for human IgG4-related disease. *PloS One*. 2018;13(6):e0198417. doi:10.1371/journal.pone.0198417

57. Koonpaew S, Shen S, Flowers L, Zhang W. LAT-mediated signaling in CD4+CD25+ regulatory T cell development. *J Exp Med*. 2006;203(1):119-129. doi:10.1084/jem.20050903

58. Jones GW, Jones SA. Ectopic lymphoid follicles: inducible centres for generating antigen-specific immune responses within tissues. *Immunology*. 2016;147(2):141-151. doi:10.1111/imm.12554

59. Pitzalis C, Jones GW, Bombardieri M, Jones SA. Ectopic lymphoid-like structures in infection, cancer and autoimmunity. *Nat Rev Immunol*. 2014;14(7):447-462. doi:10.1038/nri3700

60. Aloisi F, Pujol-Borrell R. Lymphoid neogenesis in chronic inflammatory diseases. *Nat Rev Immunol*. 2006;6(3):205-217. doi:10.1038/nri1786

61. Zaidan M, Cervera-Pierot P, de Seigneux S, et al. Evidence of follicular T-cell implication in a case of IgG4-related systemic disease with interstitial nephritis. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2011;26(6):2047-2050. doi:10.1093/ndt/gfr097

62. Maehara T, Moriyama M, Nakashima H, et al. 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(12):2011-2019. doi:10.1136/annrheumdis-2012-201477

63. Akiyama M, Suzuki K, Yamaoka K, et al. 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(9):2476-2481. doi:10.1002/art.39209

64. Akiyama M, Yasuoka H, Yamaoka K, et al. 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. doi:10.1186/s13075-016-1064-4

65. He J, Tsai LM, Leong YA, et al. Circulating precursor CCR7(lo)PD-1(hi) CXCR5^{+} CD4^{+} T cells indicate Tfh cell activity and promote antibody responses upon antigen reexposure. *Immunity*. 2013;39(4):770-781. doi:10.1016/j.immuni.2013.09.007

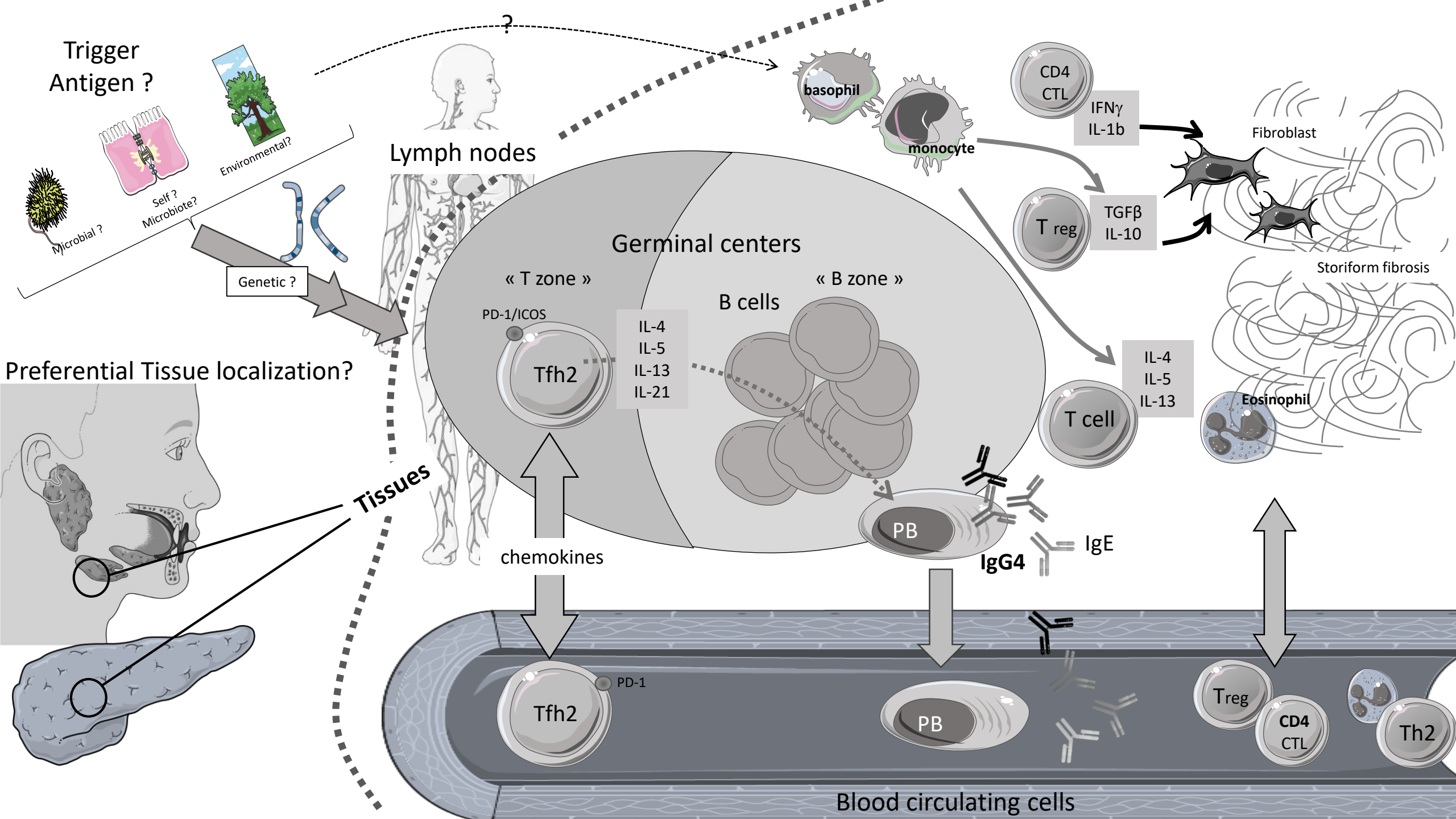
66. Kamekura R, Takano K, Yamamoto M, et al. Cutting Edge: A Critical Role of Lesional T Follicular Helper Cells in the Pathogenesis of IgG4-Related Disease. *J Immunol Baltim Md 1950*. 2017;199(8):2624-2629. doi:10.4049/jimmunol.1601507

67. Yang H, Wei R, Liu Q, Shi Y, Li J. Frequency and distribution of CD4+CXCR5+ follicular B helper T cells within involved tissues in IgG4-related ophthalmic disease. *Mol Med Rep*. 2017;16(6):9512-9520. doi:10.3892/mmr.2017.7780

68. Maehara T, Mattoo H, Mahajan VS, et al. 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(1). doi:10.26508/lsa.201800050

69. Mattoo H, Mahajan VS, Maehara T, et al. Clonal expansion of CD4(+) cytotoxic T lymphocytes in patients with IgG4-related disease. *J Allergy Clin Immunol*. 2016;138(3):825-838. doi:10.1016/j.jaci.2015.12.1330

70. Dominguez-Villar M, Hafler DA. Regulatory T cells in autoimmune disease. *Nat Immunol*. 2018;19(7):665-673. doi:10.1038/s41590-018-0120-4


Trigger
Antigen ?
Environmental?
Self ?
Microbiote?
Microbial ?
Genetic ?
?
Lymph nodes
Preferential Tissue localization?
Tissues
Germinal centers
« T zone »
« B zone »
B cells
PD-1/ICOS
Tfh2
IL-4
IL-5
IL-13
IL-21
PB
IgG4
IgE
chemokines
basophil
monocyte
CD4
CTL
IFNγ
IL-1b
T reg
TGFβ
IL-10
T cell
IL-4
IL-5
IL-13
Fibroblast
Storiform fibrosis
Eosinophil
PD-1
Tfh2
PB
Treg
CD4
CTL
Th2
Blood circulating cells

Pathogenic model for IgG4-related disease

(1) An antigen (self (autoimmunity), environmental (allergy), microbial or microbiote (molecular mimicry)) might act as triggering factor of an immune response

(2) Dendritic and naive/memory B cells might present antigens to CD4+ T lymphocytes triggering their activation in germinal center of lymph nodes or in preferential inflamed organs (for unknown reasons). Local signal from the innate immune system might determine T helper polarization into T follicular helper cell (Tfh), preferentially type 2

(3) Tfh2 cells orchestrate germinal center formation and B cell maturation. Naïve B cells undergo somatic hypermutation (SHM) and affinity maturation (AM) and differentiate mainly into plasmablasts with IgG4/IgE class-switch under the influence of Tfh2 cytokines.

(3’) Hence a fibroinflammatory process is engaged through Th2 cytokines (also responsible of IgE elevation and blood and tissue eosinophilia).

(4) An ineffective compensatory mechanism creates elevation of T regulatory (Treg) cells, or their tissue equivalent T follicular regulatory cells (Tfr) potential drivers of fibrosis concomitantly to macrophagic Tgfβ secretion

(5) A vicious cycle of stimulation and antigen presentation between T and B lymphocytes is engaged and can be disrupted by RTX.

?’ Whether primary antigen presentation and inflammatory response occurs in blood and then migrates the lymphatic system and then to tissues through different chemokines or whether blood anomalies are a consequence of a tissue « overflow » is unknown.

? Genetic predisposition might play a role in a perpetuated cell reaction after an antigenic trigger

Although Tfh2 cells seem to play a central role, IgG4-RD might be characterized by a more complex impairment of the regulatory arm of the immune system