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Review article

Immune dysregulation in immunoglobulin G4–related disease

Takashi Maehara [a,b,1,*], Risako Koga [a,1], Seiji Nakamura [a]

[a] Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, Fukuoka, Japan
[b] Dento-craniofacial Development and Regeneration Research Center, Faculty of Dental Science, Kyushu University, Fukuoka, Japan

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ABSTRACT

(IgG4-RD) is an immune-mediated fibrotic disorder characterized by severe resolution of inflammation and dysregulation of wound healing. IgG4-RD has been considered a unique disease since 2003, and significant progress has been achieved in the understanding of its essential features. The central role of B cells in IgG4-RD has been demonstrated by the robust clinical responsiveness of IgG4-RD to B cell depletion and the identification of multiple self-antigens that promote B cell expansion. Studies have increasingly revealed critical roles of these B cells and T cells in the pathogenesis of IgG4-RD, and we and other authors further identified $CD4^+$ cytotoxic T lymphocytes as the main tissue-infiltrating $CD4^+$ T cell subset in IgG4-RD tissues. Additionally, T follicular helper cell subsets that play a role in IgG4 isotype switching have been identified. In this review, we discuss research on IgG4-RD and the roles of B cell and T cell subsets, as well as the functions of $CD4^+$ cytotoxic T cells in IgG4-RD pathogenesis. We highlight our findings from ongoing research using single-cell analysis of infiltrating $CD4^+$ cytotoxic T cells, $CD4^+$ follicular helper T cells, and infiltrating B cells in IgG4-RD and propose a model for the pathogenesis of IgG4-RD.

Contents

* Correspondence to: Section of Oral and Maxillofacial Oncology, Division of Maxillofacial Diagnostic and Surgical Sciences, Faculty of Dental Science, Kyushu University, 3–1-1 Maidashi, Higashi-ku, Fukuoka 812–8582, Japan.
E-mail address: tmaehara@dent.kyushu-u.ac.jp (T. Maehara).
[1] Co-first authors

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1. Introduction

Immunoglobulin G4–related disease (IgG4-RD) is a progressive condition associated with chronic antigen-driven autoimmune activation, resulting in severe fibrosis [1–3]. IgG4-RD is characterized by multiorgan inflammation, elevated serum IgG4 concentration, tissue infiltration by $IgG4^+$ plasma cells, and storiform fibrosis in various organs, including salivary glands, kidney, pancreas, lung, lymph nodes, bile duct, prostate, retroperitoneum, and lacrimal glands [1–4]. IgG4-RD commonly presents to oral surgeons in the context of Mikulicz's disease (MD), which refers to bilateral, symmetrical, and simultaneous enlargement of both lacrimal and salivary glands. Some patients, however, solely exhibit lacrimal gland disease or even present with unilateral submandibular gland involvement. For many decades, MD had been believed to be a subtype of Sjogren's syndrome [5]. Additionally, for over a century, IgG4-related submandibular gland disease was known in the medical literature as Kuttner's tumor [6]. Both major and minor salivary glands can be affected by IgG4-RD. Among affected tissues, the salivary glands yield a large enough volume of tissue collection to allow for single-cell analysis. In our research to elucidate the pathogenesis of this disease, we have focused our research on infiltrating lymphocytes on various affected organs, including salivary glands, lacrimal glands, kidney, and others, in patients with IgG4-RD.

Important mechanistic insights regarding the pathogenesis of IgG4-RD have gradually been elucidated in recent years. $CD4^+$ T and B cells constitute the major inflammatory cell population in patients with IgG4-RD and likely cause organ damage and disabling tissue fibrosis in patients. Affected patients with active, untreated disease have a marked expansion of IgG4-secreting plasmablasts in the blood. Exploring the role of interactions between $CD4^+$ T and B cells in patients with IgG4-RD is a highly promising field of investigation.

In this review, we focus on some studies of disease-specific T cells and B cells in this disease, and we highlight our findings from ongoing research using single-cell analysis of infiltrating $CD4^+$ T cells in IgG4-RD. Furthermore, we propose a model for the pathogenesis of IgG4-RD.

2. Expansion of antibody-secreting cells (ASCs) in IgG4-RD

B cells are the most abundant cells in the lymphoplasmacytic infiltrate in the lesions of IgG4-RD [1,7]. If a particular treatment significantly inhibits or reverses disease progression, it can provide important clues as to the pathogenesis of the disease. Two therapeutic strategies, systemic corticosteroid administration and B cell depletion, are both significantly effective for IgG4-RD. Although steroids are generally considered "nonspecific," the immune effects of systemic steroid therapy largely target myeloid cells and T cells [8]. In contrast, anti-CD20-mediated B cell depletion, while not directly targeting T cells or myeloid cells, is also a very effective therapy for this disease. These results suggest that T cells, myeloid cells, and B cells may drive the progression of IgG4-RD [9,10].

Mattoo et al. [7,11] described the oligoclonal expansions of IgG4-expressing and non-IgG4-expressing activated B cells including plasmablasts (activated ASCs) in patients with IgG4-RD. Depletion of the B cell lineage with rituximab (anti-CD20 monoclonal therapy) results in striking clinical improvement in IgG4-RD patients [9], suggesting that B cells play a role in the pathogenesis of IgG4-RD. Circulating plasmablasts and activated B cells are heavily somatically hypermutated, implying that these B-lineage cells are derived with the help of disease-specific $CD4^+$ T cells [11]. Pillai et al. [12] showed that B cell depletion therapy is effective in patients with autoimmune disease when somatically hypermutated B cells or plasmablasts at disease sites are likely to be important antigen-presenting cells. This suggests that activated B cells that express MHC class II and high-affinity BCRs are well suited to capture protein autoantigens and process and present peptide antigens on the appropriate MHC class II molecules to disease-specific $CD4^+$ T cells that may contribute to disease [13]. In patients with IgG4-RD, IgG4-secreting plasmablasts or other activated B cells might interact with disease-specific $CD4^+$ cells [14]. These findings imply that this B cell lineage cell is derived with assistance from the $CD4^+$ T cells.

3. Other activated B cells: Double negative (DN) B cells and activated naïve B cells

DN B cells are a B cell population that lacks expression of immunoglobulin D and CD27 memory marker. These cells expand in older healthy individuals, but accumulate early in patients with autoimmune (rheumatic disease, systemic lupus erythematosus:SLE) [15–17] and infectious diseases, including COVID-19 [18]. In SLE, DN B cells respond to TLR7 ligands, IFN-gamma, and IL-21 cytokines and become ASCs [17]. A recent study using single-cell transcriptomics and repertoire analyses of B cells revealed that activated B cell populations (DN B cells and activated naïve B cells) which are precursors of activated ASCs. Here, we describe the DN B cell population and its subsets, as well as the association of DN B cells with other B cells that arise in autoimmune and infectious disease.

Sanz et al. reported that DN B cells were divided into two subgroups depending on the expression of follicular homing marker CXCR5 [17]. The $CXCR5^+$ subgroup, now known as DN1, is the DN subpopulation that expands in older healthy individuals [19], and this population has been shown to be less important in autoimmune and infectious diseases. In contrast, the $CXCR5^-$ subgroup constitutes the extrafollicular (outside germinal centers) DN2 subset and is considered to be of high importance for the induction of autoimmunity and/or the control for the induction of autoimmunity and/or the control of chronic infections [20]. These DN2 cells differentiate from activated naïve B cells that recognize specific self-antigens [17]. DN2 cells then expand dramatically and lead to the generation of autoreactive ASCs. DN2 cells are more marked in activated SLE [20], but they are not as elevated in rheumatoid arthritis, IgG4-RD, primary Sjogren's syndrome, and scleroderma patients as in SLE patients [17]. Thus, the DN2 subset was presumed to be SLE specific. More recent studies have identified a new subset of DN cells other than DN1 and DN2 (DN3 cells), and this new DN subset might be of high importance in the induction of other autoimmune diseases, including IgG4-RD, and in the control of chronic infectious diseases.

The previously unreported DN B cell subset, DN3, was detected in COVID-19 patients. This novel subset is defined by the absence of CD21 and CD11c and is associated with an extrafollicular immune response, similar to DN2 cells [21,22]. Compared with DN2 cells, DN3 cells showed a broader significant correlation pattern with laboratory features associated with critical COVID-19. However, this new subset has not been characterized. Notably, DN3 cells are associated with predominant extrafollicular B cell responses, as they are considered to be newly recruited extrafollicular B cells with low somatic mutations and low affinity maturations [21]. While the germinal center (GC) response remains the focus of B cell research, extrafollicular B cell responses –the development of antibodies outside of the B cell follicles with extrafollicular disease-specific $CD4^+$T cell help – are of great interest to researchers [23,24]. DN B cells have also been implicated in the pathogenesis of IgG4-RD, although only a few reports are available. However, the importance of DN3 cells in IgG4-RD, which is considered to develop antibodies outside of the B cell follicles with the help of extrafollicular disease-specific $CD4^+$T cells, is strongly suggested; more detailed analyses of extrafollicular activated B cells, including DN3 cells and activated naïve B cells, is a theme in IgG4-RD that we are investigating and more studies will be completed in the future.

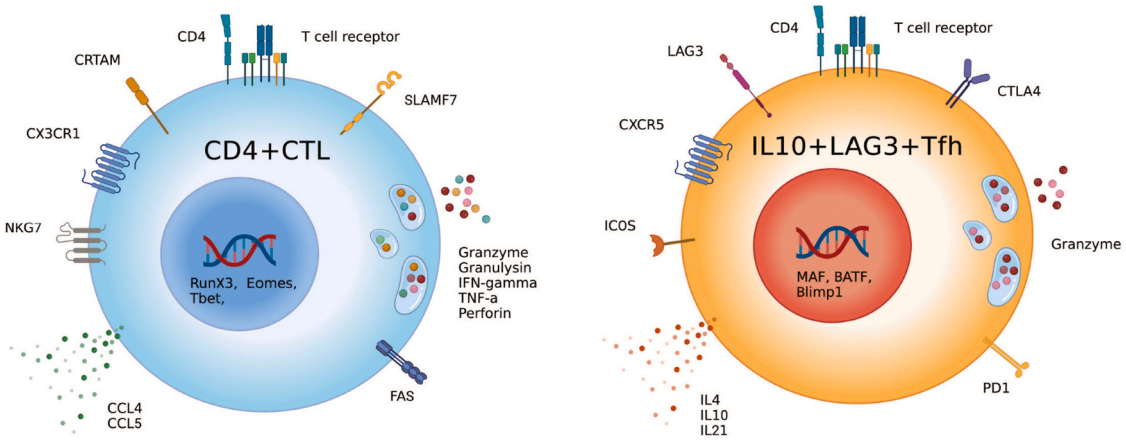

Fig. 1. Schematic illustration of disease-specific CD4$^+$CTLs and IL-10$^+$LAG3$^+$ Tfh cells in IgG4-RD.

4. Analysis of tissue-infiltrating CD4$^+$T cells using single-cell analysis

The heterogeneity of human infiltrating CD4$^+$T cells in tissues has been observed in numerous autoimmune, allergic, and chronic inflammatory diseases [25,26]. CD4$^+$ T cells, orchestrators of adaptive immunity, are divided into Th1, Th2, Th17, follicular helper T (Tfh), peripheral T helper (Tph), CD4$^+$ cytotoxic T lymphocyte (CD4$^+$ CTL), Treg, type 1 regulatory T (Tr1), and follicular regulatory T (Tfr) subsets; these cells express distinct transcription factors and many secrete defined sets of cytokines [27–30]. Improved unbiased methods to identify tissue-infiltrating T cells directed against a causal antigen are needed to focus on disease-specific T cells. Single-cell RNA sequencing (scRNA-seq) has evolved rapidly in recent years. scRNA-seq analyses capture several aspects of T cell states. However, these analyses generally have not demonstrated distinct clusters of paradigmatic T cell effector subsets, such as Th1, Th2, and Th17 cells. Global transcriptomics reliably identifies both proliferating T cells and regulatory T cells (Treg cells) and has helped to identify novel effector subsets in inflammatory tissues such as Tph cells and CD4$^+$ CTLs [25,31]. Analysis of gene expression in disease-linked immune cells, especially T cells obtained from affected tissues of untreated patients, is essential to obtain a more complete picture of the pathogenesis of diseases with tissue inflammation. Few studies thus far have analyzed infiltrating T cell subsets by single-cell analysis in the affected tissues in IgG4-RD. Therefore, scRNA-seq techniques should be used to explore the immunological mechanisms that promote inflammation and fibrosis in lesional T cell- and activated B cell-mediated autoimmune disease in future studies.

5. IgG4 class switch recombination occurs frequently in extrafollicular areas with IL-10$^+$LAG3$^+$T follicular helper T cells in IgG4-RD

The pathogenesis of IgG4-RD is deeply related to B cell activation, and therefore it has been assumed that these are disease-specific CD4$^+$ T cells that act directly on B cells. T follicular (Tfh) cells are a subset of CD4$^+$ T cells that assist B cells during T cell-dependent immune responses and contribute to isotype switching, somatic hypermutation, germinal center formation, and high-affinity B cell selection in germinal centers [32,33]. Tfh cells are distinguished from other CD4$^+$ T cells by their expression of inducible T-cell co-stimulator (ICOS) and B-cell lymphoma 6 (Bcl6). Tfh cells were originally observed in the light zones of germinal centers, but broadly similar cells have also been observed outside follicles at the T cell zone–B cell follicle interface (T-B interface). We and other groups have argued that class-switching events also occur outside the follicle [23,24]. In extrafollicular foci, B cells that are activated by T cells through CD40L may undergo some degree of differentiation into plasma cells and isotype switching [34]. IgG4-RD is an autoimmune

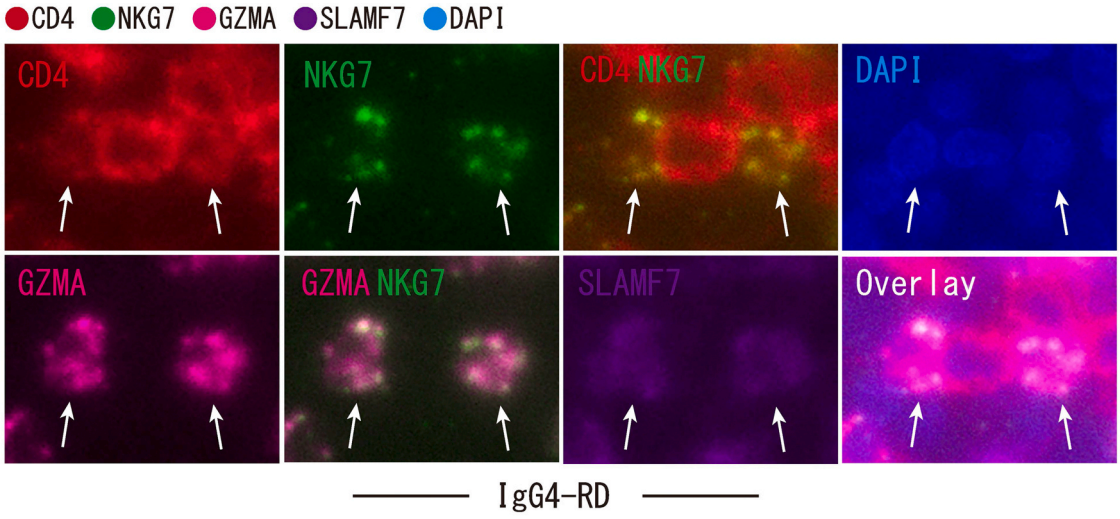

Fig. 2. CD4$^+$ CTLs were abundant in IgG4-RD tissues. Immunofluorescence staining of CD4 (red), GZMA (magenta), NKG7 (green), SLAMF7 (purple), and 4′,6-diamidino-2-phenylindole (DAPI) (blue) in affected salivary gland tissue from an IgG4-RD patient. White arrows show CD4$^+$NKG7$^+$GZMA$^+$SLAMF7$^+$ CTLs.

disease with a characteristic class switching to IgG4, and thus it was assumed that disease-specific Tfh cells are present in the extrafollicular area.

In a study using single-cell RNA-seq analysis of infiltrating lymphocytes [35], infiltrating Tfh cells in secondary lymphoid organs and tertiary lymphoid organs from IgG4-RD patients were investigated [35]. As summarized in Fig. 1, the results showed that the expanded *IL-10*-expressing *CD4*$^+$*CXCR5*$^+$ Tfh cells in affected lesions from IgG4-RD patients co-expressed IL-21, lymphocyte-activation gene 3 (LAG3), cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed cell death protein 1 (PDCD1), and ICOS, but not Foxp3; these cells presumably differed from Treg or regulatory follicular helper T (Tfr) phenotype cells. Consistent with our findings, in a study of IL-10 and IL-21 double-reporter mice, Gang et al. revealed that IL-10$^+$IL-21$^+$CXCR5$^+$PD1$^+$ Tfh cells were distinct from Foxp3-expressing Tfr cells [36]. IL-10$^+$LAG3$^+$Tfh cells were abundant in extrafollicular areas and might suppress cytotoxic T cells (discussed below) and/or activated B cells.

6. Clonal expansions of cytotoxic T cells in IgG4-RD

In our prior studies on the pathogenesis of IgG4-RD, we also demonstrated clonal expansions of CD4$^+$CTLs in the blood [37,38]. CD4$^+$ CTLs have a cytotoxic phenotype, expressing granzymes, perforin, IL-1b, transforming growth factor beta (TGFb), and a surface maker of the signaling lymphocytic activation molecules (SLAM) family, SLAM family member 7 (SLAMF7), which is not expressed on most other CD4$^+$ T cells. We further showed that CD4$^+$ CTLs are the dominant CD4$^+$ T cells that infiltrate IgG4-RD tissues using multicolor immunofluorescence, but these cells are sparse in affected tissue site from Sjogren syndrome [38]. We showed that these CD4$^+$ CTLs express granzyme A, natural killer cell granule protein 7 (NKG7), and SLAMF7 in affected salivary glands in IgG4-RD (Fig. 2). These cells represent activated CD4$^+$ T cells and induced apoptosis in an *ex vivo* context. We consider it likely that activated B cells in disease lesions both secrete profibrotic molecules and present antigenic peptides to CD4$^+$ CTLs, reactivating them and inducing inflammation and fibrosis. Consistent with this notion is our observation that circulating CD4$^+$ CTL numbers decline in response to B cell depleting therapy. Subsequent work by investigators who were the first to report the expansion of CD4$^+$ CTLs [37] reported additional phenotyping of CD4$^+$ CTL; the findings revealed that CD27^{lo}CD28^{lo}CD57^{hi}CD4$^+$SLAMF7$^+$ T cells were the dominant effector subset and exhibited marked clonal expansion and differentially expressed genes relevant to cytotoxicity, activation, and enhanced metabolism [39]. This subset correlated with a more severe clinical phenotype of IgG4-RD and, consistent with the effector phenotype in an anti-viral context, showed upregulated CX3C motif chemokine receptor 1 (CX3CR1) and G protein-coupled receptor 56 (GPR56) and downregulated CD127 in patients with IgG4-RD [39]. We recently demonstrated that recurrent apoptotic cell death, likely following the recognition of self-peptides by autoreactive CD4$^+$ CTL and CD8$^+$ CTL clones, may contribute to cell loss and subsequent extensive tissue remodeling, which promotes fibrosis and organ dysfunction [40]. We also revealed significant correlations between blood CD8$^+$ CTL expansion and serum IgG4 levels, suggesting that B cell responses and CD8$^+$ CTL expansion may be linked [40]. In a recent study, single-cell sequencing was performed on blood from IgG4-RD patients; the expanded T cells associated with the pathogenesis of IgG4-RD were cytotoxic T cells [41]. Fig. 3 shows a schematic of the pathogenesis of this disease.

7. Other human fibrotic diseases linked to cytotoxic CD4$^+$T cells

Fibrosis is the end result of chronic inflammatory reactions such as allergic responses, infections, autoimmune reactions, tissue injury, and radiation [42]. Fibrotic diseases likely have many different etiologies, and they may not all be driven by CD4$^+$ T cells [42]. In any chronic disease that is caused by T cells, the disease-causing T cell population is likely to accumulate in the circulation as oligoclonally expanded effector memory cells [43–45]. Our current results in combination with our recent studies on another fibrotic disease,

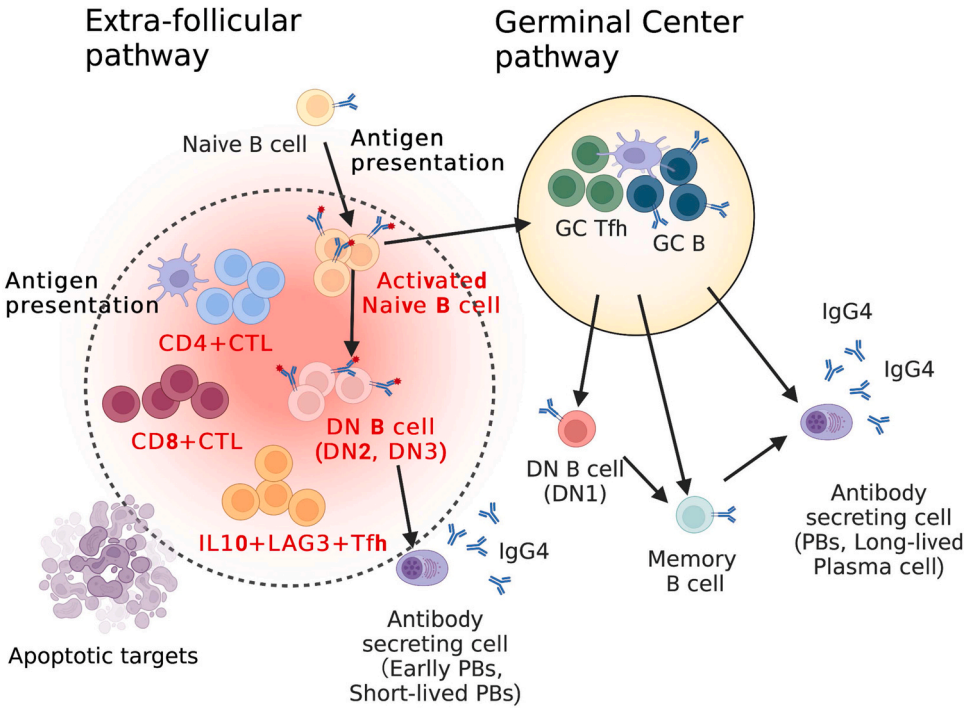

Fig. 3. Schematic illustration of the model for the pathogenesis of IgG4-related disease (IgG4-RD). Tissue infiltration by clonally expanded CD4$^+$ CTLs and CD8$^+$ CTLs likely contribute to inflammation and fibrosis. Activated lineage B cells (activated naïve B cells, DN B cells, and antibody-secreting cells) may capture and present self-antigens on HLA class II molecules to the CD4$^+$ CTLs to reactivate them at tissue sites. Clonally expanded CD4$^+$ CTLs and CD8$^+$ CTLs induce apoptosis of target cells.

systemic sclerosis [46] suggest a model that may mechanistically unify clinically distinct autoimmune fibrotic disorders. Others have provided evidence for $CD4^+$CTLs being of relevance to fibrosis in Grave's orbitopathy [47], *Histoplasma capsulatum* infection [48], and COVID-19 infection [49].

8. Other key cellular mediators of fibrosis in IgG4-RD

Other key cellular mediators of fibrosis include myofibroblasts, notably infiltrating myofibroblasts that secrete primary collagen [42]. We previously found that B cells in IgG4-RD contribute to fibrosis by secreting profibrotic factors that induce collagen production by activated myofibroblasts [50]. We showed that plasmablasts (and likely other activated B cells) in IgG4-RD may regulate extracellular matrix stiffness by secreting enzymes responsible for the cross-linking of collagen molecules, such as lysyl oxidase homolog 2 (LOXL2) [50]. Fibrotic remodeling is characterized by fibroblast/myofibroblast activation and unbalanced extracellular matrix accumulation, resulting in severe fibrosis and structural disorganization of target tissues. We demonstrated that macrophages were activated in IgG4-RD lesions; this may lead to persistent stimulation of processes involved in the resolution of inflammation and tissue fibrosis. Activated CD4/CD8 CTLs may induce apoptosis in the mediastinal space and contribute to overexuberant tissue remodeling and activation of macrophages and myofibroblasts. Inflammatory macrophages and resident tissue macrophages are key regulators of tissue repair, regeneration, and fibrosis [51]. Disturbances in macrophage function can lead to the development of pathological fibrosis. The recruited and resident macrophages proliferate and undergo marked phenotypic and functional changes in response to growth factors and cytokines released in the local tissue microenvironment [51]. Our recent study also demonstrated that Mer receptor tyrosine kinase $(MerTK)^+$ macrophages seem to be linked to the previously established accumulation of activated $CD4^+$ CTLs [52]. They also produce soluble mediators that stimulate local and recruited tissue fibroblasts to differentiate into myofibroblasts, which may lead to severe fibrosis [53].

9. The pathogenesis of Sjogren syndrome

Sjogren syndrome is a systemic autoimmune disease for ductal cells characterized by lymphocytic infiltration of the salivary and lacrimal glands. The histologic hallmark of Sjogren syndrome is lymphocytic infiltration of the affected tissues, in particular by $CD4^+$ T (especially IFN-gamma producing Th1, IL-17-producing Th17 cells, and Tfh cells) and B cells (various pathogenic B cell subsets) [54]. We recently reported that $CD4^+$ CTLs are the dominant $CD4^+$ T cells in affected tissue site from IgG4-RD tissues, but these cells are sparse in those from Sjogren syndrome [38]. It is generally known that $CD4^+$ T cell activation is needed for the establishment of B cell activation in Sjogren syndrome. Restriction of T cell-dependent B cell hyperactivity might therefore be an important target for the treatment of Sjogren syndrome patients. Although the majority of T cells within the glandular infiltrates of Sjogren syndrome patients are $CD4^+$ T cells, $CD8^+$ T cells are also present. Part of these $CD8^+$ T cells show an activated phenotype, as reflected in higher expression levels of HLA-DR. Increased proportions of $HLA\text{-}DR^+CD8^+$ T cells were associated with higher disease severity [55,56]. Recently, Kaneko et al., reported that infiltrating $CD8^+$ CTLs might induce ductal apoptotic cell death in tissues of patients with Sjogren syndrome [57]. In contrast, we recently reported that infiltrating $CD4^+$ CTLs and $CD8^+$ CTLs might induce apoptotic cell death in tissues of patients with IgG4-RD with preferential targeting of nonendothelial, nonimmune cells of mesenchymal origin by using scRNA-seq techniques [39]. Exploring the role of these T cell subsets between Sjogren syndrome and IgG4-RD is a highly promising field of investigation. However, few studies

Table 1
Established and novel potential therapeutic targets for IgG4-RD.

Target	Mechanism of action	Biological agent	Development stage	Trial status/number
B cells [11,44,58–64]	B cell depletion mediated by targeting $CD20^+$ B cells	Rituximab	Open-label, single arm trial	Completed
	B cell depletion mediated by targeting $CD19^+$ B cells	Inebilizumab	Double-blind RCT, Phase 3	NCT04540497
	Plasmablasts and Plasma cell depletion by targeting $CD38^+$ B cells	Daratumumab	–	–
	B cell inhibition mediated by co-ligation of CD19 and FcγRIIb	Obexelimab (XmAb5871)	Open-lavel single arm trial, Phase 2	NCT02725476
	Decrease B cell survival and production of autoantibodies mediated by targeting soluble BLyS	Belimumab	Open lavel, Single arm trial, Phase 4	NCT04660565
T cells [35,58,64]	Prevention of CD28 mediated T cell activation by targeting CD80 and CD86 co-stimulatroy molecules on antigen presenting cells	Abatacept	Open-label single arm trial, Phase 2	NCT03669861
	Depletion of $LAG3^+$T cells	Relatlimab, Fianlimab	–	–
	Depletion of $CD8^+$CTLs mediated by targeting CX3CR1	E6011	–	–
	$CD4^+$CTLs, and $CD8^+$CTLs mediated by targeting NKG7	–	–	–
T and B cells [37–39,44,58]	Depletion of plasmablasts, $CD4^+$CTLs, and $CD8^+$CTLs mediated by targeting SLAMF7	Elotuzumab	Double-blind RCT, Phase 2	NCT04918147
Cytokines and Chemokines [37,65–70]	IL-1b blockade	Canakinumab	–	–
	IL-4 and IL-13 blockade	Dupilumab	–	–
	Tumor necrosis factor α blockade	Infliximab	–	–
	CCL4 blockade	–	–	–
	CCL5 blockade	–	–	–

thus far have analyzed infiltrating T cell subsets by single-cell analysis in the affected tissues in Sjogren syndrome and IgG4-RD. Therefore, scRNA-seq techniques should be used to explore the immunological mechanisms that promote lesional T cell- and B cell-mediated interaction between these diseases.

10. Conclusion

Our single-cell dataset is an unbiased and comprehensive “atlas” of cellular subpopulations represented in IgG4-RD. A new era of biologic therapies is underway as the pathophysiology of IgG4-RD is being elucidated and promising therapeutic targets are rapidly being identified (Table 1). In many autoimmune diseases, it is believed that environmental triggers activate self-active immunological effector mechanisms in genetically susceptible individuals. Although the underlying triggers of autoimmune fibrotic disorder IgG4-RD are unknown, the effector mechanism might involve a combination of clonally expanded cytotoxic T cells and activated B-lineage cells that infiltrate affected tissues.

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Scientific field of dental science

Oral and maxillofacial surgery.

Data availability

Tissue-staining data were shared in TissueGnostics Software at Kyushu University.

Conflict of interest

The authors have no conflicts of interests directly relevant to the content of this article.

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References

[1] Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. Lancet 2015;385:1460–71.
[2] Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details. Mod Rheumatol 2012;22:1–14.
[3] Stone JH, Zen Y, Deshpande V. IgG4-related disease. N Engl J Med 2012;366:539–51.
[4] Wallace ZS, Zhang Y, Perugino CA, Naden R, Choi HK, Stone JH, et al. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. Ann Rheum Dis 2019;78:406–12.
[5] Maehara T, Moriyama M, Nakashima H, Miyake K, Hayashida JN, Tanaka A, 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;71:2011–9.
[6] Furukawa S, Moriyama M, Kawano S, Tanaka A, Maehara T, Hayashida JN, et al. Clinical relevance of Küttner tumour and IgG4-related dacryoadenitis and sialoadenitis. Oral Dis 2015;21:257–62.
[7] Wallace ZS, Mattoo H, Carruthers M, Mahajan VS, Della Torre E, Lee H, et al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. Ann Rheum Dis 2015;74:190–5.
[8] Coutinho AE, Chapman KE. The anti-inflammatory and immunosuppressive effects of glucocorticoids, recent developments and mechanistic insights. Mol Cell Endocrinol 2011;335:2–13.
[9] Khosroshahi A, Bloch DB, Deshpande V, Stone JH. Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG4-related systemic disease. Arthritis Rheum 2010;62:1755–62.
[10] Della-Torre E, Feeney E, Deshpande V, Mattoo H, Mahajan V, Kulikova M, et al. B-cell depletion attenuates serological biomarkers of fibrosis and myofibroblast activation in IgG4-related disease. Ann Rheum Dis 2015;74:2236–43.
[11] Mattoo H, Mahajan VS, Della-Torre E, Sekigami Y, Carruthers M, Wallace ZS, et al. De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-related disease. J Allergy Clin Immunol 2014;134:679–87.
[12] Pillai S, Mattoo H, Cariappa A. B cells and autoimmunity. Curr Opin Immunol 2011;23:721–31.
[13] Mattoo H, Stone JH, Pillai S. Clonally expanded cytotoxic CD4+ T cells and the pathogenesis of IgG4-related disease. Autoimmunity 2017;50:19–24.
[14] Maehara T, Pillai S, Stone JH, Nakamura S. Clinical features and mechanistic insights regarding IgG4-related dacryoadenitis and sialoadenitis: a review. Int J Oral Maxillofac Surg 2019;48:908–16.
[15] Wei C, Anolik J, Cappione A, Zheng B, Pugh-Bernard A, Brooks J, et al. A new population of cells lacking expression of CD27 represents a notable component of the B cell memory compartment in systemic lupus erythematosus. J Immunol 2007;178:6624–33.
[16] Claes N, Fraussen J, Vanheusden M, Hellings N, Stinissen P, Van Wijmeersch B, et al. Age-associated B cells with proinflammatory characteristics are expanded in a proportion of multiple sclerosis patients. J Immunol 2016;197:4576–83.
[17] Jenks SA, Cashman KS, Zumaquero E, Marigorta UM, Patel AV, Wang X, et al. Distinct effector B cells induced by unregulated toll-like receptor 7 contribute to pathogenic responses in systemic lupus erythematosus. Immunity 2018;49:725–39. e6.
[18] Kaneko N, Kuo HH, Boucau J, Farmer JR, Allard-Chamard H, Mahajan VS, et al. Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19. Cell 2020;183:143–57. e13.
[19] Colonna-Romano G, Bulati M, Aquino A, Pellicanò M, Vitello S, Lio D, et al. A double-negative (IgD-CD27-) B cell population is increased in the peripheral blood of elderly people. Mech Ageing Dev 2009;130:681–90.
[20] Maul RW, Catalina MD, Kumar V, Bachali P, Grammer AC, Wang S, et al. Transcriptome and IgH repertoire analyses show that CD11c(hi) B cells are a distinct population with similarity to B cells arising in autoimmunity and infection. Front Immunol 2021;12:649458.
[21] Woodruff MC, Ramonell RP, Nguyen DC, Cashman KS, Saini AS, Haddad NS, et al. Extrafollicular B cell responses correlate with neutralizing antibodies and morbidity in COVID-19. Nat Immunol 2020;21:1506–16.
[22] Sosa-Hernández VA, Torres-Ruíz J, Cervantes-Díaz R, Romero-Ramírez S, Páez-Franco JC, Meza-Sánchez DE, et al. B cell subsets as severity-associated signatures in COVID-19 patients. Front Immunol 2020;11:611004.
[23] Roco JA, Mesin L, Binder SC, Nefzger C, Gonzalez-Figueroa P, Canete PF, et al. Class-switch recombination occurs infrequently in germinal centers. Immunity 2019;51:337–50. e7.
[24] Takashi Maehara HM, Vinay SMahajan, Murphy Samuel JH, Yuen Grace J, Ishiguro Noriko, Ohta Miho, Moriyama Masafumi, Saeki Takako, Yamamoto Hidetaka, Yamauchi Masaki, Daccache Joe, Kiyoshima Tamotsu, Nakamura Seiji, Stone John H, Pillai Shiv. 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.
[25] Rao DA, Gurish MF, Marshall JL, Slowikowski K, Fonseka CY, Liu Y, et al. Pathologically expanded peripheral T helper cell subset drives B cells in rheumatoid arthritis. Nature 2017;542:110–4.
[26] Wen T, Aronow BJ, Rochman Y, Rochman M, Kc K, Dexheimer PJ, et al. Single-cell RNA sequencing identifies inflammatory tissue T cells in eosinophilic esophagitis. J Clin Investig 2019;129:2014–28.
[27] DuPage M, Bluestone JA. Harnessing the plasticity of CD4(+) T cells to treat immune-mediated disease. Nat Rev Immunol 2016;16:149–63.
[28] Linterman MA, Pierson W, Lee SK, Kallies A, Kawamoto S, Rayner TF, et al. Foxp3+ follicular regulatory T cells control the germinal center response. Nat Med 2011;17:975–82.
[29] Takeuchi A, Saito T. CD4 CTL, a cytotoxic subset of CD4+ T cells, their differentiation and function. Front Immunol 2017;8:194.
[30] Zhu X, Zhu J. CD4 T helper cell subsets and related human immunological disorders. Int J Mol Sci 2020;21.
[31] Fonseka CY, Rao DA, Teslovich NC, Korsunsky I, Hannes SK, Slowikowski K, et al. Mixed-effects association of single cells identifies an expanded effector CD4(+) T cell subset in rheumatoid arthritis. Sci Transl Med 2018;10.
[32] Crotty S. Follicular helper CD4 T cells (TFH). Annu Rev Immunol 2011;29:621–63.
[33] Crotty S. A brief history of T cell help to B cells. Nat Rev Immunol 2015;15:185–9.
[34] Vinuesa CG, Sanz I, Cook MC. Dysregulation of germinal centres in autoimmune disease. Nat Rev Immunol 2009;9:845–57.
[35] Munemura R, Maehara T, Murakami Y, Koga R, Aoyagi R, Kaneko N, et al. Distinct disease-specific Tfh cell populations in two different fibrotic diseases: IgG4-related disease and Kimura's disease. J Allergy Clin Immunol 2022.
[36] Xin G, Zander R, Schauder DM, Chen Y, Weinstein JS, Drobyski WR, et al. Single-cell RNA sequencing unveils an IL-10-producing helper subset that sustains humoral immunity during persistent infection. Nat Commun 2018;9:5037.

[37] Mattoo H, Mahajan VS, Maehara T, Deshpande V, Della-Torre E, Wallace ZS, et al. Clonal expansion of CD4(+) cytotoxic T lymphocytes in patients with IgG4-related disease. J Allergy Clin Immunol 2016;138:825–38.
[38] Maehara T, Mattoo H, Ohta M, Mahajan VS, Moriyama M, Yamauchi M, et al. Lesional CD4+ IFN-γ+ cytotoxic T lymphocytes in IgG4-related dacryoadenitis and sialoadenitis. Ann Rheum Dis 2017;76:377–85.
[39] Perugino CA, Kaneko N, Maehara T, Mattoo H, Kers J, Allard-Chamard H, et al. CD4(+) and CD8(+) cytotoxic T lymphocytes may induce mesenchymal cell apoptosis in IgG(4)-related disease. J Allergy Clin Immunol 2021;147:368–82.
[40] Perugino CA, Kaneko N, Maehara T, Mattoo H, Kers J, Allard-Chamard H, et al. CD4(+) and CD8(+) cytotoxic T lymphocytes may induce mesenchymal cell apoptosis in IgG4-related disease. J Allergy Clin Immunol 2020.
[41] Wu X, Peng Y, Li J, Zhang P, Liu Z, Lu H, et al. Single-cell sequencing of immune cell heterogeneity in IgG4-related disease. Front Immunol 2022;13:904288.
[42] Wynn TA. Cellular and molecular mechanisms of fibrosis. J Pathol 2008;214:199–210.
[43] Pillai S. T and B lymphocytes in fibrosis and systemic sclerosis. Curr Opin Rheumatol 2019;31:576–81.
[44] Pillai S, Perugino C, Kaneko N. Immune mechanisms of fibrosis and inflammation in IgG4-related disease. Curr Opin Rheumatol 2020;32:146–51.
[45] Feghali-Bostwick CA, Tsai CG, Valentine VG, Kantrow S, Stoner MW, Pilewski JM, et al. Cellular and humoral autoreactivity in idiopathic pulmonary fibrosis. J Immunol 2007;179:2592–9.
[46] Maehara T, Kaneko N, Perugino CA, Mattoo H, Kers J, Allard-Chamard H, et al. Cytotoxic CD4+ T lymphocytes may induce endothelial cell apoptosis in systemic sclerosis. J Clin Investig 2020;130:2451–64.
[47] Wang Y, Chen Z, Wang T, Guo H, Liu Y, Dang N, et al. A novel CD4+ CTL subtype characterized by chemotaxis and inflammation is involved in the pathogenesis of Graves' orbitopathy. Cell Mol Immunol 2021;18:735–45.
[48] Allard-Chamard H, Alsufyani F, Kaneko N, Xing K, Perugino C, Mahajan VS, et al. CD4(+)CTLs in fibrosing mediastinitis linked to histoplasma capsulatum. J Immunol 2021;206:524–30.
[49] Kaneko N., Boucau J., Kuo H.H., Perugino C., Mahajan V.S., Farmer J.R., et al. Expansion of Cytotoxic CD4+ T cells in the lungs in severe COVID-19. medRxiv. 2021.
[50] Della-Torre E, Rigamonti E, Perugino C, Baghai-Sain S, Sun N, Kaneko N, et al. B lymphocytes directly contribute to tissue fibrosis in patients with IgG4-related disease. J Allergy Clin Immunol 2020;145:968–81. e14.
[51] Wynn TA, Vannella KM. Macrophages in tissue repair, regeneration, and fibrosis. Immunity 2016;44:450–62.
[52] Rovati L, Kaneko N, Pedica F, Monno A, Maehara T, Perugino C, et al. Mer tyrosine kinase (MerTK) as a possible link between resolution of inflammation and tissue fibrosis in IgG4-related disease. Rheumatology 2021.
[53] Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. Nat Rev Immunol 2011;11:723–37.
[54] Verstappen GM, Corneth OBJ, Bootsma H, Kroese FGM. Th17 cells in primary Sjögren's syndrome: pathogenicity and plasticity. J Autoimmun 2018;87:16–25.
[55] Mingueneau M, Boudaoud S, Haskett S, Reynolds TL, Nocturne G, Norton E, et al. Cytometry by time-of-flight immunophenotyping identifies a blood Sjögren's signature correlating with disease activity and glandular inflammation. J Allergy Clin Immunol 2016;137:1809–21. e12.
[56] Zhou H, Yang J, Tian J, Wang S. CD8(+) T lymphocytes: crucial players in Sjögren's syndrome. Front Immunol 2020;11:602823.
[57] Kaneko N, Chen H, Perugino CA, Maehara T, Munemura R, Yokomizo S, et al. Cytotoxic CD8+ T cells may be drivers of tissue destruction in Sjögren's syndrome. Sci Rep 2022;12:15427.
[58] Perugino CA, Mattoo H, Mahajan VS, Maehara T, Wallace ZS, Pillai S, et al. Emerging treatment models in rheumatology: IgG4-related disease: insights into human immunology and targeted therapies. Arthritis Rheumatol 2017;69:1722–32.
[59] Della-Torre E, Rigamonti E, Perugino C, Baghai-Sain S, Sun N, Kaneko N, et al. B lymphocytes directly contribute to tissue fibrosis in patients with IgG(4)-related disease. J Allergy Clin Immunol 2020;145:968–81. e14.
[60] Carruthers MN, Topazian MD, Khosroshahi A, Witzig TE, Wallace ZS, Hart PA, et al. Rituximab for IgG4-related disease: a prospective, open-label trial. Ann Rheum Dis 2015;74:1171–7.
[61] Majumder S, Mohapatra S, Lennon RJ, Piovezani Ramos G, Postier N, Gleeson FC, et al. Rituximab maintenance therapy reduces rate of relapse of pancreaticobiliary immunoglobulin G4-related disease. Clin Gastroenterol Hepatol 2018;16:1947–53.
[62] Urban ML, Maritati F, Palmisano A, Fenaroli P, Peyronel F, Trivioli G, et al. Rituximab for chronic periaortitis without evidence of IgG4-related disease: a long-term follow-up study of 20 patients. Ann Rheum Dis 2020;79:433–4.
[63] Yamamoto M, Aochi S, Suzuki C, Nakamura S, Murakami R, Ogawa Y, et al. A case with good response to belimumab for lupus nephritis complicated by IgG4-related disease. Lupus 2019;28:786–9.
[64] Nakayamada S, Tanaka Y. Development of targeted therapies in IgG4-related disease. Mod Rheumatol 2022.
[65] Jarrell JA, Baker MC, Perugino CA, Liu H, Bloom MS, Maehara T, et al. Neutralizing anti-IL-1 receptor antagonist autoantibodies induce inflammatory and fibrotic mediators in IgG4-related disease. J Allergy Clin Immunol 2022;149:358–68.
[66] Karim F, Paridaens D, Westenberg LEH, Guenoun J, Verdijk RM, van Hagen PM, et al. Infliximab for IgG4-related orbital disease. Ophthalmic Plast Reconstr Surg 2017;33:S162–5.
[67] Simpson RS, Lau SKC, Lee JK. Dupilumab as a novel steroid-sparing treatment for IgG4-related disease. Ann Rheum Dis 2020;79:549–50.
[68] Ebbo M, De Sainte-Marie B, Muller R, Piperoglou C, Grados A, Vély F, et al. Correspondence on: 'Dupilumab as a novel steroid-sparing treatment for IgG(4)-related disease' by Simpson et al. Ann Rheum Dis 2022;81:e26.
[69] Capecchi R, Italiani P, Puxeddu I, Pratesi F, Tavoni A, Boraschi D, et al. IL-1 family cytokines and receptors in IgG4-related disease. Cytokine 2018;102:145–8.
[70] Michailidou D, Schwartz DM, Mustelin T, Hughes GC. Allergic aspects of IgG4-related disease: implications for pathogenesis and therapy. Front Immunol 2021;12:693192.