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Clonally expanded cytotoxic CD4⁺ T cells and the pathogenesis of IgG4-related disease

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Abstract

IgG4-related disease (IgG4-RD) is a systemic condition of unknown cause characterized by highly fibrotic lesions, with dense lymphoplasmacytic infiltrates containing a preponderance of IgG4-expressing plasma cells. CD4⁺ T cells and B cells constitute the major inflammatory cell populations in IgG4-RD lesions. IgG4-RD patients with active, untreated disease show a marked expansion of plasmablasts in the circulation. Although the therapeutic depletion of B cells suggests a role for these cells in the disease, a direct role for B cells or IgG4 in the pathogenesis of IgG4-RD is yet to be demonstrated. Among the CD4⁺ T-cell subsets, Th2 cells were initially thought to contribute to IgG4-RD pathogenesis, but many previous studies were confounded by the concomitant history of allergic diseases in the patients studied and the failure to use multi-color staining to definitively identify T-cell subsets in tissue samples. More recently, using an unbiased approach to characterize CD4⁺ T-cell subsets in patients with IgG4-RD – based on their clonal expansion and ability to infiltrate affected tissue sites – CD4⁺ CTLs have been identified as the major CD4⁺ T-cell subset in disease lesions as well as in the circulation. CD4⁺ CTLs in affected tissues secrete pro-fibrotic cytokines including IL-1 β , TGF- β 1, and IFN- γ as well as cytolytic molecules such as perforin and granzymes A and B. In this review, we examine possible mechanisms by which activated B cells and plasmablasts may collaborate with the expanded CD4⁺ CTLs in driving the fibrotic pathology of the disease and describe the lacunae in the field and in our understanding of IgG4-RD pathogenesis.

Keywords

IgG4-RD; CD4⁺ CTL; fibrosis; lymphoplasmacytic infiltrate

Introduction

IgG4-related disease (IgG4-RD) emerged as a distinct clinical entity in the early part of the twenty-first century [1]. Hamano, Kamisawa, and others had observed that several seemingly unrelated chronic inflammatory fibrotic conditions, all with tumefactive lesions, and affecting a wide range of organs, often present with elevations in serum IgG4 concentrations and exhibit a set of unique histopathological features [2–6]. The hallmark

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Declaration of interest

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histologic characteristics of IgG4-RD are a lymphoplasmacytic infiltrate, storiform fibrosis, obliterative phlebitis, and the presence of a high proportion of IgG4-expressing plasmablasts or plasma cells in affected tissues [6,7]. Mild to moderate tissue eosinophilia has also been described in some subjects but this is a variable feature whose significance remains unclear [8,9].

IgG4-RD can involve every organ of the body. The clinical, radiologic, and histopathologic features of the disorder in the pancreas, biliary tree, salivary glands, periorbital tissues, kidneys, lungs, lymph nodes, meninges, aorta, breast, prostate, thyroid, pericardium, and skin have been cataloged. This diagnosis today unifies many diverse conditions including autoimmune pancreatitis, many cases of orbital pseudotumor, Ormond's disease (retroperitoneal fibrosis), Riedel's thyroiditis, Küttner's tumor, Mikulicz's disease, and multifocal fibrosclerosis, as well as subsets of interstitial lung disease, tubulointerstitial nephritis, hypertrophic pachymeningitis, and other entities [1–8].

IgG4 antibodies and T follicular helper cells that drive the IgG4 class switch

IgG4 is an antibody isotype that is generally considered to be non-inflammatory; it does not bind to activating Fc receptors and does not fix complement and undergoes a process of virtual monomerization called "Fab arm exchange" [9]. These properties make it unlikely that IgG4 antibodies are responsible for the fibro-inflammatory pathology seen in IgG4-RD. However, the degree to which IgG4 undergoes Fab arm exchange *in vivo* is very difficult to assess, so it is possible that some IgG4 participates in immune complexes, likely with IgG1 antibodies as well. Thus, IgG4 could in theory contribute to inflammation because of the associated IgG1. It is possible that IgG4 may undergo altered glycosylation in disease and may acquire the ability to bind activating Fc receptors. IgG4-containing immune complexes could also potentially recruit mannose-binding lectin and thus activate complement [10]. In a recent study by Shiokawa et al., purified human IgG1 and IgG4 from IgG4-RD subjects was found to induce pancreatic lesions in infant mice [10]. IgG1 caused more damage than IgG4 and IgG4 could attenuate the lesions caused by IgG1. Whether these antibodies actually contained immune complexes or not is unclear and the mechanism by which the pancreatic lesions were generated in this study remains obscure.

IgG4 may have evolved as an antibody that dampens inflammation rather than induces it. In the context of IgE-mediated allergy, it is accepted that the acquisition of tolerance is accompanied by an increase in IgG4 levels [11–17]. It is conceivable that the IgG4 response in IgG4-RD is an ineffectual attempt to sequester the disease-causing antigen and thus dampen inflammation. Clearly while enhancing IgG4 levels in the context of allergy may tamp down IgE-mediated inflammation, in IgG4-RD, high levels of antibodies of this isotype fail to attenuate the disease process.

Given the uncertainty regarding the role, if any, of IgG4 antibodies in the causation of IgG4-RD, the relevance of the cells that drive the IgG4 class switch remains unclear. T follicular helper (T_{FH}) cells provide help to B cells during T-dependent immune responses and they contribute to the processes of isotype switching, somatic hypermutation, germinal center formation, and the selection of high affinity B-cell germinal centers [18–20]. Some, albeit

indirect, evidence for specialized T_{FH} subsets comes from studies of circulating human T_{FH} cells defining three subclasses separated on the basis of chemokine receptor expression. The relationship between blood T_{FH}-cell subsets and T_{FH} cells in secondary or tertiary lymphoid organs remains unclear. In the studies of Ueno et al. on blood T_{FH}-cell subsets [21,22], T_{FH1} cells secrete IFN- γ upon activation and have limited isotype-switching activity when examined in *in vitro* co-culture experiments. T_{FH2} cells secrete IL-4 after *in vitro* stimulation and can mediate class switching to IgA, IgE and essentially all IgG isotypes including IgG4; T_{FH17} cells secrete IL-17 following activation and are also promiscuous. Isotype switching occurs in secondary and tertiary lymphoid organs and not in blood, and so far all attempts to identify corresponding subsets of T_{FH} cells in human tonsils and lymph nodes have failed. The actual biological significance therefore of the blood T_{FH} subsets as defined by Ueno and colleagues remains unclear [21,22]. These BCL-6^{low} blood cells express chemokine receptors that cannot be used to subset bona fide BCL-6^{hi} tonsillar T_{FH} cells. It has been suggested that the IgG4 class switch depends on both IL-4 and IL-10, but it is not clear if the blood T_{FH2}-cell subset makes both cytokines [23], and no evidence exists to suggest that the promoter upstream of the $\gamma 4$ switch region in humans has a binding site that must be occupied by a protein generated by IL-10 signaling.

Nevertheless, the studies of Akiyama et al. in IgG4-RD patients have suggested a potential role for circulating T_{FH2} cells in IgG4-RD [24]. While these studies are of interest, it would be helpful to establish whether circulating T_{FH2} cells in IgG4-RD subjects are clonally expanded. Of even greater significance would be the demonstration of a specific population of T_{FH} cells in secondary or tertiary lymphoid organs of patients with this disease.

Although a role for IgG4 itself in IgG4-RD pathogenesis, and as a consequence of specialized T_{FH} cells that drive IgG4 class switching, cannot be excluded, other hypotheses need to also be considered to explain the disease process.

Plasmablast expansions in IgG4-RD

Our studies using Next Generation Sequencing have established that oligoclonal expansions of IgG4 and non-IgG4 expressing plasmablasts can be visualized in the peripheral blood of IgG4-RD patients [25,26]. We suspect that these plasmablasts are generated by B-cell activation in germinal centers as we showed that IgG4 and IgG1 antibodies in patients are extensively somatically hypermutated [25]. Cloning of Ig heavy and light chain genes from single cells allowed the generation of patient-derived human monoclonal antibodies that are auto-reactive, supporting the view that this disease has an autoimmune component [25]. The strongest evidence supporting the relevance of B cells to the pathogenic process is that depletion of cells of the B lineage with rituximab results in striking clinical improvement [27]. As we have argued elsewhere, it is likely that B-cell depletion works in some autoimmune disorders as somatically mutated B cells or plasmablasts at disease sites are likely to be crucial antigen presenting cells [28]. This implies that at disease sites activated B cells may present antigens to some disease causing T cells. A role for B cells in sustaining memory B-cell responses has been established in rodents [29,30].

CD4⁺ CTLs are clonally expanded and infiltrate disease tissues

What T cells are crucial to the pathogenesis of IgG4-RD? In previous studies, a potential role for Th2 cells in this disease had been suggested, but no direct identification or quantitation of Th2 cells in disease tissues has ever been reported [31–33]. In order to define that one is looking at a Th2 cell in a tissue, it is important to use multi-color staining approaches and this had previously not been done in IgG4-RD. We established that circulating Th2 cells do accumulate in a fraction of patients but not in the majority of disease subjects [34]. However only about 30% of patients with IgG4-RD have a history of allergic disease and it is only in this subset of patients that circulating Th2 cells are relatively abundant in the circulation, suggesting that Th2 cells are probably not important in the disease process [34,35].

We therefore used an unbiased approach to identify disease-related T cells. We gated on effector CD4⁺ T cells and discovered that this population of CD4⁺ CD45RO⁺ CD27⁺ T cells accumulated in the blood of patients with active disease. We used Next Generation Sequencing of the T-cell receptor (TCR) β chain to show that these cells were clonally expanded [36]. These cells were found by gene expression analyses to have the phenotype of CD4⁺ cytotoxic T lymphocytes (CTLs) – they expressed granzyme A, perforin, and a cell surface protein of the SLAM family called SLAMF7 [36]. These CD4⁺ CTLs surprisingly secrete IL-1 β , as well as TGF- β and IFN- γ . The examination of affected tissues by multi-color immunofluorescence revealed that tissues contained very few Th2 cells, but the dominant infiltrating T cells in the tissue were CD4⁺ CTLs [36]. These CD4⁺ CTLs in the tissue sites actively secrete IL-1 β , IFN- γ , and TGF- β [36,37], suggesting that they are reactivated *in vivo* in disease tissues. These data therefore suggest to us that in IgG4-RD, specific CD4⁺ CTLs clonally expand, infiltrate disease sites and are re-activated locally presumably by activated cognate B cells that capture the driving antigen through the BCR, internalize it and present it to the CD4⁺ CTLs causing them to drive the inflammatory and fibrotic processes that characterize the disease. This overall model explains why rituximab-based B-cell depletion is a successful therapy and implicate CD4⁺ CTLs as the drivers of the disease (Figure 1).

The number of CD4⁺ CTLs in disease tissues correlates with the serum IgG4 levels in patients and also correlates with the total number of disease lesions [37]. Treatment of patients with rituximab results not only in clinical improvement but also in a reduction of plasmablasts in weeks and months after B-cell depletion is initiated. Reduction of circulating CD4⁺ CTLs also occurs, is indirect, and exhibits a slower time course.

Although these reports [36,37] were the first to establish a role for CD4⁺ CTLs in an inflammatory disease, evidence has previously existed supporting the contribution of CD4⁺ CTLs to anti-viral immunity, and even to protection against tumors. Protective responses are mediated by CD4⁺ CTLs in the context of influenza and CMV infections and in controlling melanoma [38–46]. There may therefore be some redundancy between CD8⁺ and CD4⁺ T cells in the cytolytic elimination of infected cells and tumors. Indeed, while viral escape may also occur in HIV in a CD4/HLA class II context, the combined activity of cytolytic CD4⁺ and CD8⁺ T cells has been suggested to be potentially less susceptible to evasion [42].

There are many reports in the literature of unusual but incompletely characterized, CD4⁺ CD28⁻ T cells accumulating in chronic inflammatory and autoimmune diseases including Wegener's granulomatosis, systemic lupus erythematosus, atherosclerosis, and rheumatoid arthritis [47–52]. These cells, that are likely similar or identical to CD4⁺ CTLs in IgG4-RD [36,37], have also been reported to be clonally expanded in rheumatoid arthritis [53]. CD4⁺ CTLs as well as CD4⁺ CD28⁻ T cells express CD11b and CD57 as well as killer Ig-like receptors like KIR2DS2 and KIR3DL2 [36,54–56]. These studies, although fragmented, do provide circumstantial evidence that the CD4⁺ CD28⁻ T cells reported in rheumatoid arthritis and atherosclerosis are very likely to be CD4⁺ CTLs.

CD4⁺ CTLs, cytokines, and the mechanism of fibrosis in IgG4-RD

Storiform fibrosis is an important feature of IgG4-RD. We have established that Th2 cells are not expanded in IgG4-RD, and they are not prominent in affected tissues [34,36,37]. It is not clear exactly how fibrosis occurs in the context of IgG4-RD but there are a number of candidate mechanisms. T cells that have been repeatedly activated by self or microbial antigens can undergo many rounds of division, resulting in large numbers of clonal progeny, and in many cases may yield CD4⁺ CD28⁻ cells [47]. These cells may in turn secrete cytokines and chemokines that activate and/or recruit successive waves of other immune effectors (macrophages, neutrophils, dendritic cells, etc.). These second- and third waves of effector cells may contribute to a highly inflammatory and sometimes fibrotic lymphoplasmacytic infiltrate [48]. In a study on idiopathic pulmonary fibrosis (IPF) an accumulation of CD4⁺ CD28⁻ cells was observed in lung biopsies and the cells produced several pro-inflammatory mediators such as IL-1 β , IL-6, TNF- α , and G-CSF which have the potential to initiate or amplify immune responses both constitutively, and also in conjunction with TCR stimulation [49]. Moreover, these CD4⁺ CD28⁻ cells also synthesized perforin and granzyme B in IPF disease lesions, and potentially could have contributed to the pulmonary epithelial apoptosis observed in this disorder. In the murine model of bleomycin-induced pulmonary fibrosis, inflammasome activation and IL-1 receptor/myeloid differentiation primary response gene-88 (MyD88) signaling are critical aspects of the profibrotic activity of IL-1 β [50]. Transient expression of IL-1 β alone in the rat lung has been shown to result in tissue damage and progressive fibrosis [51]. Transgenic overexpression of IL-1 β in the murine pancreas also results in fibrotic pancreatitis [52]. Although the exact mechanisms driving the onset and progression of this model of pancreatic disease are yet to be elucidated, these findings on IL-1 β -mediated fibrosis may be relevant in IgG4-RD and may provide insights as to how CD4⁺ CTLs could contribute to pathogenesis. We have demonstrated recently that CD4⁺ CTLs in IgG4-related dacryoadenitis and sialoadenitis secrete large amounts of IFN- γ and TGF- β 1 [37]. Depending upon the surrounding milieu, IFN- γ and TGF- β 1 can also be pro-fibrotic cytokines as has been demonstrated in murine models of thyroiditis [57–59]. In these models, IFN- γ is not necessary for the induction of experimental autoimmune thyroiditis, but progression to full-blown disease depends on the action of this cytokine.

Potential interplay between activated B cells and CD4⁺ CTLs

Patients with active, untreated IgG4-RD show marked expansions of IgG4⁺ as well as IgG1 plasmablasts in peripheral blood as well as within disease lesions [60]. These plasmablasts express high levels of MHC class II molecules and are depleted by B-cell depletion therapy (using rituximab). It is possible that these plasmablasts or other activated B cells play an important role in the reactivation of the CD4⁺ CTLs and induce them to either make cytokines including IL-1 β , TGF β 1, IFN- γ , and other mediators of adaptive and innate immune infiltration. In addition, the B cell–CD4-CTL interaction may also mediate the killing of parenchymal cells potentially expressing the disease driving auto-antigen(s) or a microbially/environmentally derived antigen. CD4⁺ CTLs are selectively depleted in IgG4-RD subjects – including the expanded clones after rituximab-mediated B-cell depletion therapy. These findings have broad relevance and imply that in humans, as in rodents, B cells play an important role in the maintenance of effector/memory CD4⁺ T cells, including disease-associated, “pathogenic” T-cell clones [29,61]. These findings are consistent with those demonstrating effective remission in patients with T-cell-mediated diseases like relapsing–remitting multiple sclerosis following B-cell depletion therapy [62]. We speculate that activated B cells and plasmablasts that have the unique ability to bind to specific auto-antigens may act as potent antigen-presenting cells at low antigen concentrations, and may thus provide efficient access to T-cell epitopes. It can be concluded that in T-cell-mediated autoimmune disorders that are responsive to rituximab therapy, the effector/memory CD4⁺ T-cell response is maintained by activated B cells and/or plasmablasts.

Specific antigens that drive the IgG4-RD disease process have yet to be identified. While no specific auto-antigen has been found, the evidence for environmental antigens driving the disease process also remains weak. Some evidence exists for polyclonal IgG4 antibodies against food antigens [63], but this may be a reflection of enhanced class switching to IgG4 in this disease whether or not this isotype switching event is of pathogenic relevance. Similarly evidence for responses to environmental antigens lacks strong support [64].

A schematic model for the pathogenesis of IgG4-RD is shown in Figure 1. The clonal expansion of CD4⁺ CTLs and their infiltration into tissue sites may be the cause of this syndrome. The formal possibility remains that the induction of T_{FH} cells and class switching to IgG4 may also contribute to this disease. Reactivation of CD4⁺ CTL cells may require antigen presentation by plasmablasts or other activated B cells in tissue sites. Activated CD4⁺ CTLs presumably mediate fibrosis and inflammation as a result of cytokine and chemokine secretion or possibly the induction of cell death. The association of CD4⁺ CTLs with IgG4-RD pathogenesis is significant, but the mechanism of action remains speculative. A mouse model is desirable to address all the mechanistic questions in depth.

Conclusions and lacunae in our understanding

The relatively small numbers of subjects with IgG4-RD has so far precluded detailed studies on genetic susceptibility. We assume that there is some contribution of genetics and that in this context some unknown environmental trigger induces epigenetic alterations in immune cells that triggers disease. While we have concluded that plasmablasts in subjects with active

disease are specific for auto-antigens, an aberrant response to self-antigens, resulting in clonal CD4⁺ CTL expansion, remains a hypothetical cause of this disease. A number of autoantibodies have been described in the context of autoimmune pancreatitis. The prevalence of these auto-antibodies may reflect a broad break in immunological tolerance, but the identity of the antigens that drive T_{FH} cells and class switching to IgG4 remains unknown. Whether it is the same or different antigens that contribute to clonal expansions of CD4⁺ CTLs and plasmablasts also remains to be experimentally determined. The tools of modern molecular biology and immunology will likely help provide answers to some of these questions in the coming decade.

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Figure 1.

A schematic model depicting the role of CD4⁺ CTLs, T_H cells, and plasma-blasts in IgG4-RD pathogenesis.