Clinical Immunology 198 (2019) 1–10

Contents lists available at ScienceDirect

Clinical Immunology

journal homepage: www.elsevier.com/locate/yclim

Review Article

New insights into immune cells cross-talk during IgG4-related disease

Fahd Touzani[a,b,*], Agnieszka Pozdzik[b,c]

[a] Internal medicine department, Hospital Brugmann, Brussels, Belgium
[b] Nephrology and dialysis clinic, Hospital Brugmann, Brussels, Belgium
[c] Faculty of Medicine, Université Libre de Bruxelles (ULB), Brussels, Belgium

ARTICLE INFO

Keywords:
IgG4-related disease
IgG4 subclass
Plasmablasts
T-follicular helper cells
Innate immune system
Tertiary lymphoid organs
Rituximab

ABSTRACT

Immunoglobulin G4-related disease (IgG4-RD) is a newly acknowledged entity, characterized by an immune-mediated fibro-inflammatory process affecting virtually all organs, with infiltration of $IgG4^+$ bearing plasma cells. Until today the pathogenesis of IgG4-RD remains unknown. Treatment with anti-CD20 monoclonal antibodies efficiently induced remission and attenuated the secretory phenotype of myofibroblasts responsible of uncontrolled collagen deposition. This supports the pathogenic role of the adaptive immunity, particularly B cell compartment and B cell/T cell interaction. Latest studies have also highlighted the importance of innate immune system that has been underestimated before and the key role of a specific T cell subset, T follicular helper cells that are involved in IgG4-class-switching and plasmablast differentiation. In this review, we aim to review the most recent knowledge of innate immunity, T and B cells involvement in IgG4-RD, and introduce tertiary lymphoid organs (TLO) as a potential marker of relapse in this condition.

1. Introduction

Immunoglobulin G4-related disease (IgG4-RD) is a newly acknowledged entity, characterized by an immune-mediated fibro-inflammatory process affecting all organs, synchronously or metachronously [1]. In 1961, Sarles and al. first described a sclerosing pancreatitis with polyclonal hypergammaglobulinaemia [2], that has been recognized as “type 1 autoimmune pancreatitis” (AIP) in 1995 [3]. Six years later, Hamano and colleagues (coll.) reported a specific elevation of serum IgG4 (sIgG4) levels in AIP patients [4]. In 2002, the same team identified concomitant retroperitoneal fibrosis in patients treated for sclerosing pancreatitis and found the same histological pattern in both pancreatic and ureteral lesions, demonstrating the systemic nature of this disease [5]. Since these first descriptions, several diseases believed to be isolated, such as Mikulicz's disease (MD), became a part of IgG4-RD [6–12].

In 2012, recommendations for a unified nomenclature for the disease have been published [13]. In parallel, the “Japan Research Team for IgG4-RD” proposed a Comprehensive Diagnostic Criteria in Japan for IgG4-RD, for practical use. Clinical, serological and histopathological features are the main criteria to make a definite, probable or possible diagnosis of IgG4-RD [14,15] (Table 1). Specific guidelines for the diagnosis of AIP, MD, IgG4-related kidney disease and IgG4-related cholangiopathy exist [16–19]. The annual incidence is estimated at 0.28–1.08/100,000 in Japan [20], and little is known about its epidemiology in Europe, however the incidence seems to be lower [21,22]. IgG4-RD usually occurs after 50 years of age, but some cases have been also reported in children [23]. Except for sialadenitis and dacryoadenitis, the disease shows a male predominance [24].

Organ involvement varies between studies [25]. Virtually all organs can be affected, however some patterns of association have been reported [26]. Patients generally present with organ-specific complaints related to organ swelling or non-specific symptoms such as abdominal pain, asthenia or pruritus [1]. Histological examination of tissue biopsy specimen is the cornerstone for the diagnosis of IgG4-RD and in order to rule out other etiologies, in particular cancer. The four major findings include lymphoplasmatic cells infiltration containing several $IgG4^+$ plasma cells, storiform fibrosis, obliterative phlebitis, and tissue eosinophilia [27]. The presence of abundant $IgG4^+$ plasma cells should raise the suspicion for IgG4-RD, but other autoimmune diseases could also present this pattern [28–30]. The $IgG4^+$/total IgG^+ ratio is than used, with a variable cut-off dependent on the involved organ (from > 30% to > 50%) [31,32], but then again, a recent meta-analysis revealed a low sensitivity with a high specificity as a diagnostic biomarker for this disease [33].

Until today the pathogenesis of IgG4-RD remains unknown.

* Corresponding author at: Nephrology and dialysis clinic, Hospital Brugmann, Université Libre de Bruxelles (ULB), Place A. Van Gehuchten 4, 1020 Brussels, Belgium.
E-mail address: fahd.touzani@ulb.ac.be (F. Touzani).

https://doi.org/10.1016/j.clim.2018.11.004
Received 28 June 2018; Received in revised form 25 September 2018; Accepted 9 November 2018
Available online 10 November 2018
1521-6616/

Table 1
Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011.

1- Clinical examination shows characteristic diffuse/localized swelling or masses in single or multiple organs
2- Serum IgG4 level ≥ 135 mg/dL
3- Histopathologic examination with:
- Marked lymphocyte and plasma cells infiltration and fibrosis
- Infiltration of IgG4-positive plasma cells: ratio of IgG4/IgG positive cells > 40% and > 10 IgG4-positive plasma cells/high power field

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

Treatment with anti-CD20 monoclonal antibodies efficiently induced remission and attenuated the secretory phenotype of myofibroblasts responsible of uncontrolled collagen deposition [34,35], supporting thus the pathogenic role of the adaptive immunity, particularly B cells compartment and B cells/T cells interactions.

We aim to review the most recent knowledge on T and B cells involvement in IgG4-RD, and introduce tertiary lymphoid organs (TLO) as a potential marker of relapse and resistance to treatment in this condition.

2. Pathophysiology

2.1. Humoral immunity

2.1.1. The role of IgG4 subclass

Humoral immunity is characterized by production of antibodies (Abs). The five classes of immunoglobulins (Ig); IgA, IgD, IgE, IgG and IgM are defined by their heavy chain constant domain sequences [36]. There are four subclasses of IgG Abs, IgG1 to IgG4, and the latter represents the least abundant one in healthy people, accounting for < 10% of total IgG. The normal levels in human varies from 0.08 to 1.4 mg/dL [37]. Contrary to the IgG1 and IgG3 subclasses, IgG4 Abs bind less to Fc receptors but their affinity for the inhibitory receptor FcγRIIB is preserved [38]. Structurally, the core IgG4 hinge has a serine amino acid at position 228, instead of proline (as seen in IgG1). This difference results in inefficient disulphide bonds. IgG4 Abs can then undergo half-antibody exchange, in which every half IgG4 molecule dissociate from each other and reassociate with another half one with distinct antigen-combining site, resulting in the formation of a bispecific IgG4 antibody. This process prevents immune complex formation [39]. For those reasons, the IgG4 subclass is regarded as a non-inflammatory, even as an anti-inflammatory molecule. This is supported by observations in desensitizing immunotherapy [40].

The role of IgG4 subclass in the pathophysiology of IgG4-RD is still debated. It is unclear whether its arise reflects a protective process in response to anti-inflammatory cytokine production, or if it directly mediates the disorder. Indeed, the direct pathogenic role of IgG4 has been demonstrated in patients with pemphigus, an autoimmune skin disease, where IgG4 directed against desmoglein cause blister formation by acantholysis. In mice, injection of human desmoglein-specific IgG4 Abs causes bullous lesions [41–43]. It is also established that IgG4 are implicated in the pathogenesis of primary membranous nephropathy and it was recently shown that they could act by activating alternative and lectine complement pathway [44]. IgG4 have been implicated in the pathogenesis of other diseases such as thrombotic thrombocytopenic purpura [45] and in myasthenia gravis [46]. Also, chronic infusion of factor VIII in patients with haemophilia results in an IgG4 response that counteracts its effect [47]. It seems therefore that IgG4 can assume a double role. This is illustrated in a neonatal mouse model of AIP, where injection of patient's IgG1 or IgG4 resulted in pancreatic injury, more pronounced with IgG1 injection alone. The toxic properties of IgG1 were attenuated by simultaneous injection of IgG4 [48]. Finally, it should be highlighted that even if a specific elevation of IgG4 subclass is still the main characteristic of IgG4-RD, serum IgG4 level of patients with this disease can be under the normal range at presentation in about one third and even half percent, adding complexity about it pathogenic role [49–53]. In conclusion, whether IgG4 are pathogenic or play a counter-regulatory response in IgG4-RD remains a mystery.

2.1.2. The role of B cells and plasmablasts

During their development, B cells undergo various stages of maturation and differentiation characterized by the expression of specific combinations of surface cell markers. After an immune challenge, antigen specific B cells proliferate and differentiate into antibody secreting cells or into memory B cells [36]. Short-lived plasmablasts are proliferating antibody-secreting B cells that mature into plasma cells, the long-lived mediators of sustained humoral immunity. Plasmablasts are identified as $CD19^{low}CD20^{-}CD27^{+}CD38^{bright}$ cells by flow cytometry [54]. Although they usually disappear after few days following activation, chronic inflammation or infection increase their lifespan [55–57]. They can be also induced after vaccination [58]. In healthy people, circulating plasmablasts are mainly IgA^{+} derived from mucosal responses, whereas during infection and reinfection, they are mainly IgG^{+} derived from non-mucosal secondary lymphoid organs and memory B cells, respectively [59]. Plasma cells express the adhesion molecule CD138, preventing them from migration. They are more frequently present in the bone marrow and represent < 1% of the cells in peripheral lymphoid organs.

B cells are involved in the pathogenesis of IgG4-RD. This statement comes from the observation of abundant $IgG4^{+}$ bearing plasma cells in biopsies of affected organs, and from the efficacy of B cells depletion therapy by anti-CD20 antibodies [rituximab: (RTX)] in this condition [35]. The CD20 molecule, a transmembrane signalling molecule, part of the BCR complex- is expressed by the majority of the B cells lineage, except the early B cells precursor, pro B cells, plasmablasts and plasma cells. Administration of RTX, a chimeric monoclonal antibody that targets CD20 is often associated with a prompt and profound depletion of circulating B cells [60]. As haematopoietic stem cells lack CD20 expression, a course of this therapy is followed by reappearance of B cells in peripheral blood – starting after few months, usually 6 to 9 months- mainly by transitional and naïve B cells [61]. Efficacy of RTX has been reported in several auto-immune diseases, transplantation and hematologic malignancies [62–65]. Circulating plasmablasts positively correlate with systemic lupus erythematosus disease activity [66], anti-citrullinated protein antibodies levels in rheumatoid arthritis, and myasthenia gravis relapses [67,68].

The critical role of B cells in the pathogenesis of IgG4-RD has been reported. In a study of 15 patients with active, untreated IgG4-RD, the percentage of plasmablasts was significantly higher compared to the 23 healthy controls (HC) [69]. In the same way, studies by Mattoo and coll. and by Lin and coll. have shown a significant rise in their absolute number in 84 and 42 patients respectively, compared to HC [70,71]. These cells are elevated even in patients with normal IgG4 serum levels and re-emerge during relapse [50]. Using high-resolution next generation sequencing methods, de Buy Wenniger and coll. showed in 6 patients suffering from IgG4-related cholangitis, that IgG4 positive B cells were clonally expanded [72]. In the same way, during relapse after a RTX course, re-emergent plasmablasts were clonally distinct from those initially present and somatically hypermutated within the variable rearranged regions, supporting an antigen-driven immune response [70]. One hypothesis is that newly generated naïve B cells are recruited from the bone marrow by interacting with T-cells leading to somatically mutated B cells and plasmablasts. However, it is unknown if re-emerging plasmablasts differentiate de novo from naive B cells or from memory B cells that survive RTX therapy and that could thus de novo present antigens to naïve T cells, favouring disease relapse. Indeed, memory B cells are more resistant to depletion than naïve B cells and this can be illustrated in influenza vaccination studies in patients previously treated with RTX, where specific IgM B cells were decreased compared with controls, while IgA B cells and IgG B cells levels were

similar [73].

Circulating plasmablasts correlate well with disease activity and with the number of organ involved, making them a useful biomarker of IgG4-RD, even in presence of normal level of IgG4. Indeed, Wallace and coll. found that plasmablasts count were significantly higher in patients with multi-organ involvement compared with those with 2 or < 2 organs involved (median 7370/mL and 3435/mL, respectively) [50]. Contrary to circulating IgG4, RTX induced significant decline of plasmablasts during complete or part remission. Thus, circulating plasmablasts emerged as a new very attractive biomarker of IgG4-RD activity. Moreover plasmablasts count of 2000/mL differentiate patients with IgG4-RD from those without this condition, but its sensitivity and specificity were modest (87% and 91%, respectively). Plasmablasts and plasma cells are not directly depleted by anti-CD20 antibodies because they lack the CD20 molecule. This could explain the persistence of serum immunoglobulin elevations after treatment with one course of RTX. In IgG4-RD, serum IgG4 levels decline after B cells depletion but do not normalise, probably because of the long-lived plasma cells that continue to produce it [74]. Furthermore, the fact that plasmablasts rapidly decline following RTX course can be explained by the depletion of their circulating $CD20^+$ precursors and by their short lifespan.

2.2. The role of T cells (Fig. 1)

T cells are the dominant cell type in the lymphoplasmacytic infiltrate in IgG4-RD [1]. $CD4^+$ T helper (Th) cells play a critical role in the adaptive immune system by secreting cytokines that will orchestrate the activity of other immune cells, including B cells, other T cells and macrophages. Following a polarizing signal induced by cytokines, naïve $CD4^+$ Th cells will differentiate into a Th subpopulation. $CD4^+$ Th cell subsets were first described by Mosmann and Coffman in 1986, who distinguished Th1 from Th2 cells based on their mutually exclusive production of either interferon-gamma (IFN-γ) or interleukin (IL)-4, respectively [75]. Other subsets were subsequently described and there are now 5 main Th subpopulations, with distinct regulating factors, different secreted cytokines and functions. Globally, Th1 and Th17 regulate cell-mediated immunity (CD8 cells and macrophages) and Th2 and T follicular helper (Tfh) cells regulate humoral immunity (involving B cells). Th2 cells produce IL-4, IL-5, IL-13 and are involved in allergy. Regulatory T cells (Treg) are crucial for maintaining self-tolerance. They modulate T and B cells responses by the secretion of anti-inflammatory cytokines IL-10 and transforming growth factor-beta (TGF-β) and by direct interaction with effector immune cells. Th subpopulations are self-regulating. Each class secretes a cytokine that favour it differentiation and expansion while inhibiting it differentiation in another Th type. This is particularly true for the subset Th1/Th2 and Th17/Treg. Thus, Th2 responses can counteract Th1-mediated action [36].

Th1-mediated immune reactions have been reported to participate in the mechanism of IgG4-RD as circulating Th1 cells are increased in

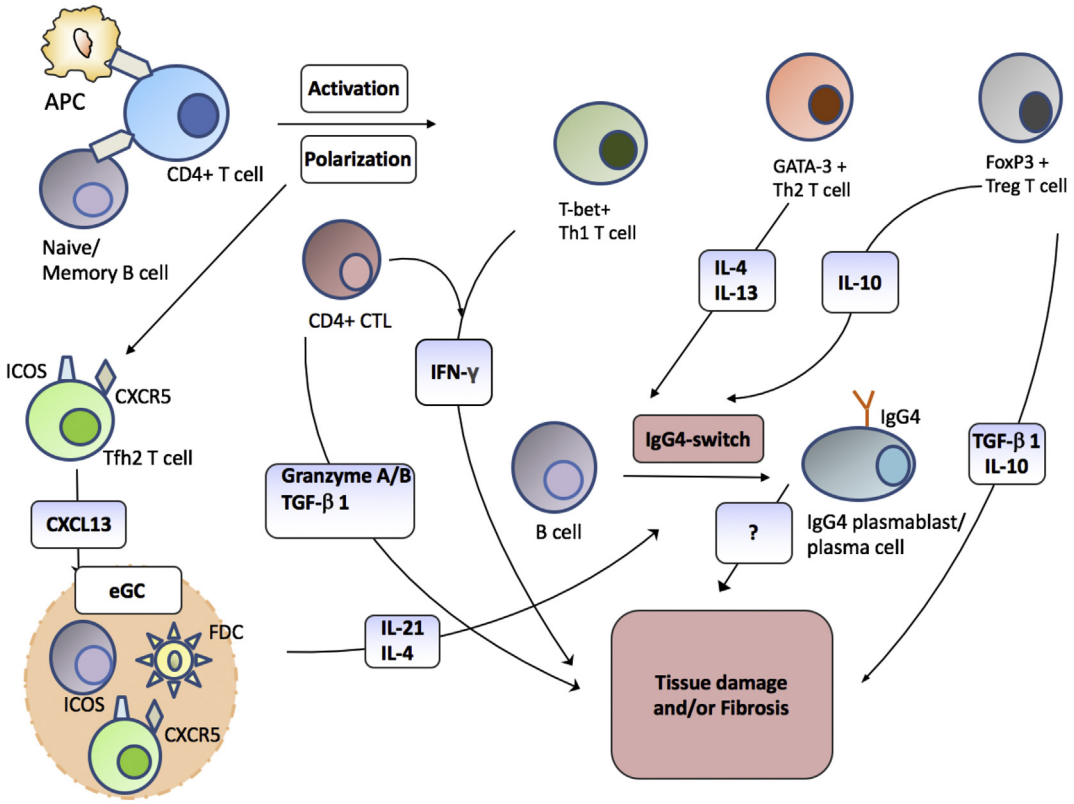

Fig. 1. Cellular T immunity and IgG4-RD. Chronic exposure to unknown antigens activates antigen presenting cells (APC) and naive or memory B cells that can in turn trigger $CD4^+$ T cell activation and polarization under local signals and cytokines from the innate immune system. T regulatory cells (Treg) might induce fibroblast activation and extracellular matrix accumulation through secretion of profibrotic cytokines TGF-β 1 and IL-10, the latter also inducing the differentiation of B cells IgG4 producing plasmablasts and plasma cells. Activated Th2- T cells also promote IgG4-class switch via secretion of Th2-derived cytokines IL-4 and IL-13. Th1 T cells might play a role in IgG4-RD pathophysiology via their production of IFN-γ that activate macrophages and cytotoxic cells. However, it seems that this production is derived from $CD4^+$ cytotoxic lymphocytes that secrete also Granzyme and TGF-β1 leading to tissue lesions. In the T-cell rich zone of tertiary lymphoid organ (TLO), APCs induce the differentiation of Tfh2 cells, that upregulate inducible T-cell co-stimulator (ICOS) and CXC-chemokine receptor 5 (CXCR5), thus migrating to the B-cell rich zone where CXCR5 interacts with CXC-chemokine ligand 13 (CXCL13). This chemokine can be produced by follicular dendritic cells (FDCs), resulting in the formation of ectopic germinal centre (eGC) in the involved organ. Within eGC, Tfh2 provide cognate help for B cells and secrete high levels of IL21, which induce IgG4 class-switching, affinity maturation and somatic hypermutation, in synergy with IL-4 release. Whether IgG4 itself contribute to tissue damage is actually unknown.

patients with this condition. Indeed, among 10 patients with IgG4-related sialadenitis, the percentage of blood IFN-γ expressing $CD4^+$ Th1-like cells and IFN-γ concentrations were significantly higher compared to HC, contrary to Th2 cells (see below for Th2 involvement in IgG4-RD) [76]. In line with this, circulating $CD4^+$ Th1 lymphocytes levels from patients with AIP were also greater than those from controls and IL-4 levels were not increased [77]. These studies used a single colour staining to characterize $CD4^+$ T cells. However, recent data that used multi-colour immunofluorescence staining of the tissues found that in patients with IgG4-related dacryosialadenitis (DS)- or MD- secretion of IFN-γ was mainly linked to infiltration by another type of T cells, $CD4^+$ IFN-γ^+ cytotoxic T lymphocytes (CTL) which also produce granzyme A. Granzyme A^-Th1 cells and $CD4^+GATA3^+$ Th2 cells were rarely found [78]. Thus, whether $CD4^+$ T cells identified in previous reports by single colour staining were in fact CD4 + CTL or "true" Th1 cells or both remains unknown. Apart from Th1 and $CD4^+$CTL cells, IFN-γ production which is enhanced in IgG4-RD can be achieved by another Th subset: Tfh and a recent report indicated elevated amounts of activated Tfh1 in this disease [79–81].

Organs affected by IgG4-RD are characterized by fibrosis and $IgG4^+$ bearing plasma cells infiltration. This condition is regarded as a consequence of a Th2-driven immunological response thorough the production of Th2 associated cytokines – IL-4 and IL-13 and a T regulatory-driven mechanism thorough the secretion of the Treg cytokines TGFβ and IL-10. Indeed, IL-13 and TGFβ favour fibrogenesis by myofibroblasts differentiation and production of type 1 collagen, fibronectin and periostin [82,83], while IL-4 and IL-10 induced IgG4 class-switch in naïve B cells. IL-13 can modulate collagen homeostasis, induce fibrosis by local activation of TGFβ [84,85], suppress matrix metalloproteinase-1 (MMP-1) induction, enzyme involved in collagen degradation [86]. Overexpression of TGFβ and periostin has been reported without IL-13 + cells in IgG4-RD patients [87].

Immunohistochemical analysis of labial salivary gland sections from patients with MD showed infiltration by Treg cells and increased expression of messenger RNA (mRNA) for IL4, IL5, IL10, TGF-beta and FoxP3 – the hallmark of Treg- compared to controls and to patients with SS. In addition, it was positively correlated with the IgG4 + /IgG ratio. This suggests promotion of B cells to produce IgG4 by Th2 and regulatory mediated immune responses [88]. The increased proportion of Th2 and Treg cells or their subsequent cytokines is also reported in IgG4-related TIN [89], in AIP, IgG4-related cholangitis and IgG4-related lung disease [90,91]. In peripheral blood, increased T helper subsets, particularly Th2 and Treg are reported in IgG4-RD patients [92]. IL-10 is implicated in T cell tolerance, but it also suppresses allergen-specific IgE while increasing IgG4 production. Blockage of the IL-10 receptor on Treg cells diminishes the suppression effect on IgE and the induction effect on IgG4, supports this fact [93]. IL-10 potentiate IL-4 induced IgG4 switch [94]. Although those findings suggesting Treg cells involvement in IgG4 class-switching is not such obvious. Indeed, despite increase in serum IgG4 levels, patients suffering from eosinophilic granulomatosis with polyangiitis display decreased circulating Treg [95,96].

The relative frequency of an atopic history, peripheral blood eosinophilia and serum IgE elevation supports the role of Th2 cells in the IgG4-RD pathophysiology as atopic features are generally induced by Th2 derived cytokines [71,81,97]. However, Mattoo and coll. have recently demonstrated that circulating GATA-3^+ Th2 memory cells were increased only in IgG4-RD patients with a history of atopy, indicating thus that expanded Th2 responses may in fact result from the concomitant atopic condition, inducing a bias [98]. In the same way, conflicting results are found among the prevalence of atopy in IgG4-RD. According to a study by Della Torre and coll., only 31% of the 70 patients with IgG4-RD were atopic, 35% had elevated serum IgE levels and 27% had blood eosinophilia and those elevations were more frequent in atopic patients [99]. This is against the notion of allergic-driven immune response in IgG4-RD patients. However, among atopic and non-atopic patients with serum IgE elevations and/or peripheral blood eosinophilia, there was no significant difference in the mean value, suggesting that this increase is not related to the atopic manifestation but to the IgG4-RD itself. Another controversial result regarding the role of Th2 cells comes from the observation in the involved organ of an enhanced expression of IL-4 mRNA in IgG4-RD despite a lower $GATA3^+$ Th2 mRNA expression, suggesting that this cytokine is produced by non-Th2 cells [78]. Concerning Treg, we also find discrepancies as a recent report by Mattoo and coll. related only a minimal increase in circulating Treg in IgG4 patients that was not statistically significant compared to controls [100]. Taken together, the hypothesis is that the presence of Th2 derived cytokines (IL-4 and IL-13) and Treg derived cytokines (IL-10 and TGFβ) promote a switch to the IgG4 subclass and fibrogenesis. This concept is evolving as new Th subsets – particularly T follicular helper- appear to play a critical role in the pathophysiology of IgG4-RD (see below).Under the influence of TGFβ, IL-6 and IL-23, naïve $CD4^+$ T helper cells differentiate in the Th17 subset. These lymphocytes produce IL-17, a potent pro-inflammatory cytokine, and play a major role in anti-infectious, inflammatory immune responses and auto-immunity [101–103]. Indeed, IL-17 was not found in labial salivary gland sections of patients with MD contrary to those with SS [88]. However, in a recent prospective study [53] comparing 28 patients with untreated IgG4-RD and different affected organs to patients with SS and healthy individuals, analysis of peripheral lymphocytes has shown that IL-17^+producing $CD4^+$ T cells were significantly increased in patients with IgG4-RD compared to HC. T cell polarization toward Th17 may then be implicated in the disease pathophysiology but this requires further evaluation.

2.2.1. The role of T follicular helper cells

Interestingly, ectopic germinal centers (GC) are usually found in IgG4-RD affected tissues [104,105]. We distinguish 2 compartments in mature GC based on their histologic appearance: the dark zone with high density of proliferating B cells who undergo somatic hypermutation before moving to the light zone where their density is lower where follicular dendritic cells (FDC) and $CD4^+$ Tfh cells are located [106]. Both are crucial for induction of GC, generation of affinity-matured antibodies, isotype switching, somatic hypermutation and plasmablast and plasma-cell genesis even if they represent only 5% to 20% of GC cells in secondary lymphoid organs [107,108]. Tfh cells were initially described based on the expression of the B cells homing chemokine receptor CXCR5 in the GC of human tonsils, where they induced antibody production by B-cells [109,110]. CXCR5 interacts with its ligand CXCL13 in the follicle. They also differ from other Th populations by expressing a unique combination of other molecules and cell-surface proteins [111,112].

Tfh cells surface molecules interact with ligands located on the surface of B cells then could be implicated in IgG4-RD pathophysiology. They produce mainly IL-21, hallmark cytokine allowing B cell differentiation toward plasmablasts [113] as well as IL-4 in lesser amounts [114], both interleukins enable class-switch of IgG4 [115,116]. In IgG4-RD patients, Tissue expression of IL-21 within germinal center is crucial for GC maintenance. Indeed levels of IL-21 mRNA expression in labial salivary glands of MD patients positively correlated with the number of ectopic GC and the IgG4 + /IgG ratio [117]. Tfh population can be divided in at least three functionally distinct subsets depending on their pattern of surface antigens CXCR3 and CCR6: $CXCR3^+CCR6^-$Tfh1 cells, $CXCR3^-CCR6^-$Tfh2, and $CXCR3^-CCR6^+$ Tfh17 cells [79]. Tfh1 cells secrete IFN-γ and have limited class switching activity whereas Tfh2 and Tfh17 cells induce the switching of immunoglobulin isotypes. The role of Tfh cells can also be assessed by studying their presence in peripheral blood. Circulating Tfh cells (cTfh) share similar markers and function with Tfh cells in GCs [118]. It has been shown that Tfh are involved in several immune-mediated diseases and cTfh can represent a potential biomarker for the monitoring of disease activity and in allergy [119–124]. In IgG4-RD, higher circulating levels of cTfh1 and cTfh2

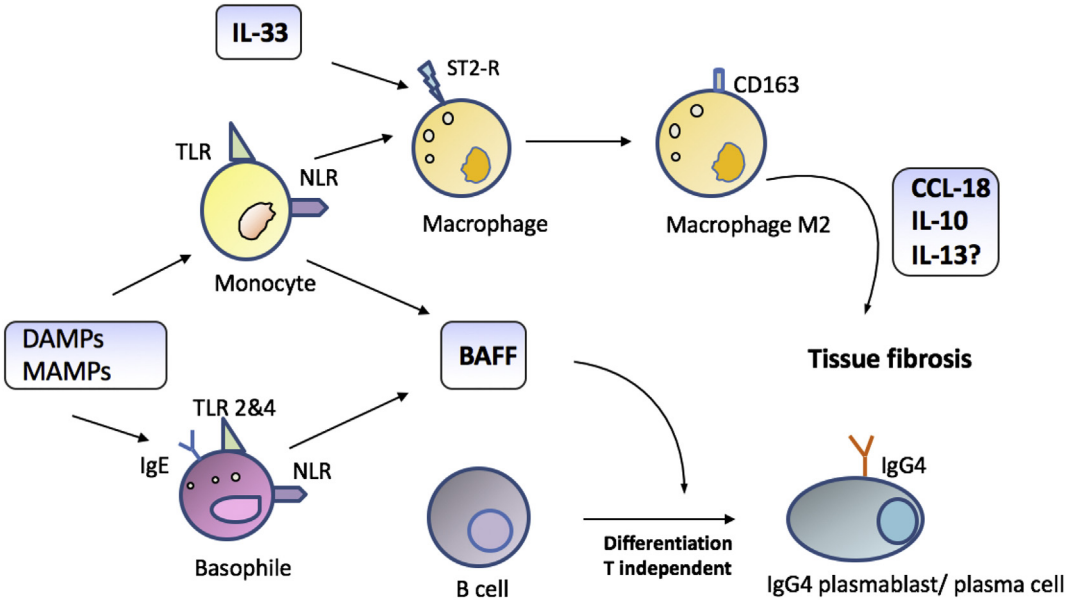

Fig. 2. Innate immunity and IgG4-RD. Exposure to an unknown antigen- microbial, environmental or self-antigen-, activates the innate immune system through interaction between Damage-associated molecular patterns (DAMPs) and microbe-associated molecular patterns (MAMPs) and their receptors, mainly Toll-like receptors (TLRs) and NOD-like receptors (NLRs), expressed in monocytes and basophiles. This interaction activates nuclear factor κB (NFκB), leading to production of B-cell-activating factor (BAFF) which enables expansion of IgG4-switched B cells and production of IgG4 antibodies in a T independent pathway. When activated, monocytes migrate to tissue and become tissue-resident macrophage. IL-33, a member of the IL-1 superfamily, binds to ST2-receptor expressed in macrophage and can induce polarization toward the M2 phenotype with the expression of CD163. These M2 macrophages might induce tissue fibrosis via production of CCL-18, IL-10 and maybe IL-13.

subsets and not cTfh17 as compared to primary SS (pSS) patients, Castelman's disease patients or HC have been reported. In vitro experiments Tfh2 cells induce differentiation of naïve B cells into plasmablasts and IgG4 + /IgG ratio [81]. Recently, infiltrating Tfh cells in submandibular glands positively correlated with sIgG4 levels in 6 patients with IgG4-related dacryosialadenitis (DS) [125].

In parallel, in a larger cohort of 46 patients with IgG4-RD, Tfh were significantly expanded in peripheral blood and in involved tissues of IgG4-RD patients compared with HC, with a higher expression in affected tissues than blood and a positive correlation between cTfh and serum IgG4 concentrations, the IgG4 + /IgG ratio was found, in line with previous studies.

Interestingly, mRNA expression of IL-21 in circulating mononuclear cells of IgG4-RD was also higher compared with HC, and positively correlated with serum levels of IgG4 and IgG4/IgG ratio. Furthermore, analysis of subsets has demonstrated a higher elevation in cTfh1 and cTfh2 and those cells favoured B cells differentiate into IgG4 producing plasma cells [126]. Glucocorticoids significantly decrease circulating activated Tfh2 and plasmablasts levels leading to clinical improvement. Conversely, disease relapse coincides with their reappearance [53]. Azathioprine combined to RTX also induced a cTfh decrease and disease remission [81]. Although, if activated Tfh1 cells (able to induce fibrosis via IFN-γ production) can favour IgG4-RD remains still unclear [127]. Interestingly, abatacept might affect Tfh cells in GC in RTX resistant IgG4-RD patient [128] and decreased circulating Tfh cells in RA patients [129].

Taken together, these findings underline the more likely the pivotal involvement of activated Tfh2 than Tfh1 in plasmablasts expansions and IgG4 class-switching in IgG4-RD placing them as a useful biomarker for monitoring IgG4-RD activity.

2.2.2. The role of $CD4^+$ cytotoxic T cells

Recent advances involved another $CD4^+$ T cell type recognized as $CD4^+$ $CD28^-$ T cells ($CD4^+$ CTLs), with cytotoxic capacities as they transcribe the perforin and granzyme genes [130]. They constitute a population of effector memory T cells and their expansion in the peripheral blood and/or affected tissues have been reported in several immune disorders [131–134], in chronic viral infections and malignancies [135,136]. These cells are able to produce pro-inflammatory and Th1-like cytokine as IFN-γ [137]. One study have reported clonally expanded circulating and tissue $CD4^+$ CTLs in IgG4-RD patients with various organ involvement, with secretion of profibrotic cytokines IFN-γ, TGFβ and IL-1β. Their number decreased following B-cell depletion therapy in parallel with clinical improvement. These observations suggest that the dysregulation of these cells might play a role in the pathophysiology of IgG4-RD, mainly by contributing to fibrosis [100]. This is in line with another study demonstrating tissue infiltration by CTLs producing IFN-γ in IgG4-DS patients and where number of $CD4^+$ CTLs in affected tissues correlated with serum IgG4 levels and also with the total number of disease lesions [78]. More studies on this cell population are necessary to well understand their pathogenic role.

2.2.3. The role of $CD8^+$ T cells

$CD8^+$ T cells play a key role in maintaining the integrity of the host by lysing targeted cells through an MHC (major histocompatibility complex)- I dependent process or by inducing cell's death via interaction of death-inducing ligands expressed by $CD8^+$ T cells with their corresponding receptors on the cell surface [138]. Their implication in the pathophysiology of IgG4-RD is still unclear, but probably limited, however one study in a small sample reported an enhanced percentage of peripheral IFN-γ^+CD8^+ T cell in IgG4-related sialadenitis compared to HC [76] but the frequency of cytotoxic perforin and/or granzyme positive $CD8^+$ T cells was lower in IgG4-related sialadenitis compared to SS patients [139]. Furthermore, $PD1^+$ CTLs cells were found significantly more frequently in salivary glands of IgG4-related sialadenitis than in SS patients and this inhibitory receptor is known to dampen lymphocyte responses, inducing an exhaustion state or even anergy [140,141]. The authors of this study suggested in MD that CTLs are functionally inactivated by PD1 signals like in the exhaustion state.

2.3. The role of innate immune system (Fig. 2)

2.3.1. The role of macrophages

Recent investigations have focused on the importance of the innate immunity in the pathogenesis of IgG4-RD and it interaction with the adaptive immune responses. Initiation of innate immunity begins by the recognition through pathogen recognition receptors (PRR) of microbe-associated molecular patterns (MAMPs) or non-microbial damage-associated molecular patterns (DAMPs). There are four types of PRR: Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), RIG-I-like receptors, and C-type lectin-like receptors [142–145]. In monocytes from HCs, stimulation of NOD-2-LR by muramyldipeptide (MDP)-a small fragment of bacterial cell wall-induced IgG4 production by B cells in a T-cell independent way. This interaction activated nuclear factor κB (NFκB), leading to B-cell-activating factor (BAFF)-dependent induction of IgG4 production [146]. In patients with AIP, production of IgG4 was enhanced upon stimulation with both NLR and TLR ligands. They concluded that the immunopathogenesis of AIP might be related to an abnormal innate immune response to microbial antigens [147]. Macrophages can play various roles in tissue injury as well as repair and fibrosis [148]. There are two types of macrophages, based on their in vitro stimulation by cytokines: M1-activated macrophages - classically activated- with pro-inflammatory and antimicrobial functions as attested by their production of inducible nitric oxide synthase (iNOS) and cytokines TNF-α, IL-6, and IL-12 and M2-activated macrophages- alternatively activated-with anti-inflammatory properties as they are induced by Th2 cytokines IL-4 and IL-13 and can produce pro-fibrotic factors such as CCL-18, IL-10 and IL-13. However, overlaps exist [149–151]. As IgG4-RD is characterized by fibrosis, macrophages could contribute to the pathogenesis. In line with this, Furukawa and coll. have shown an over-expression of macrophage markers in submandibular glands (SMG) of IgG4-DS patients compared to SS and HC. These cells were localized in and around areas of fibrosis and were mainly M2 macrophages regarding their CD163 expression. M2 macrophages co-localized with pro-fibrotic factors IL-10 and CCL-18 (but not IL-13) suggesting thus that fibrosis might be promoted by enhanced production of these cytokines by M2 macrophages. Moreover, the fibrosis score positively correlated with the CD163/CD68 ratio in SMGs from IgG4-DS patients. These observations were not limited to SMG but were also found in other involved organs of IgG4-DS patients. The same group has recently shown that the newly identified member of the IL-1 superfamily of cytokines, IL-33, a potent innate immune system activator can polarize macrophages towards the M2 phenotype via it binding to ST2 receptor, thus enhancing Th2 immune responses [152]. The expression of IL-4 and ST2 receptor were significantly higher in IgG4-DS than SS patients and HC and IL-33 seemed to be produced by M2 macrophages in salivary glands specimen. mRNA expression of IL-33 positively correlated with that of Th2 cytokines these patients [153]. M2 macrophages were also detected in high proportion in IgG4-related sclerosing pancreatitis [154,155]. In conclusion, M2 macrophages are thought to contribute to “Th2 mediated immune response” described in IgG4-RD, but more evidence is needed.

2.3.2. The role of basophils and eosinophils

Growing interest is also concerning the role of basophils and eosinophils in IgG4-RD. Basophils are recruited in the peripheral tissue in case of an immunologic or pathologic event, especially host responses to parasitic infection and IgE-associated allergic inflammatory responses. However, their accumulation has been reported in other numerous diseases, including autoimmune conditions, rejection or hematologic malignancies. They produce Th2 type cytokines when activated and can also act as antigen-presenting cells for Th2 responses [156, 157]. Their contribution in IgG4-RD has been recently evaluated upon activation of their TLRs and NLRs [158]. One has observed an IgG4 production by B-cells under stimulation of basophils with TLR2 & 4 ligands in HCs as well as production of BAFF and IL-13 after activation of TLR4. IgG4 production was dependent from a BAFF signalling pathway. Furthermore, basophils from patients with AIP induced a more pronounced IgG4 production than those from HCs, suggesting that TLR-mediated innate immunity represented here by basophils might contribute to the development of IgG4-RD in a T-independent process involving BAFF signals, as observed previously with macrophages. However, the sites where basophil activation occurs remains unclear. Eosinophilia has been described in IgG4-RD. In blood, eosinophilia is found in approximately 30-40% of IgG4 patients [159–161]. As explained, IgG4-RD was thought to be driven by an allergic process, as a substantial proportion of IgG4-RD patients is atopic, but eosinophilia is not limited to atopic patients. Eosinophils secrete type 2 cytokines and TGFβ1 and have been linked to the development of fibrosis in various organs, such as liver, lung or skin [162–164], but results are conflicting, such as in liver fibrosis where eosinophils have recently been found to correlate with severity of fibrosis in non-alcoholic fatty liver disease (NAFLD) [165] while promoting tissue regeneration in the same organ in other conditions [166]. As eosinophils may express MHC class II [167,168], they can act as antigen presenting cells to $CD4^+$ T-cells [169] and this function may play a role in IgG4-RD pathophysiology, but all these speculations remains actually vague.

2.3.3. The role of complement system

Complement system is a critical component of the innate immunity. Activation can be achieved through 3 recognized pathways that all lead to the cleavage of C5: the classical pathway, the mannose-binding lectin (MBL) pathway and the alternative pathway [170]. Hypocomplementemia is regularly reported in IgG4-RD [105,161]. In 44 patients with AIP, Muraki and coll. observed hypocomplementemia in 36% of cases [171]. As the C4 fraction was decreased, activation through the alternative pathway seems doubtful. The classical and the MBL mediated complement pathway might then be involved as it is established in several auto-immune diseases [172–174]. In AIP patients, serum MBL levels were increased compared to controls and chronic pancreatitis patients. However, one would expect low concentrations in case of activation through this way. Furthermore, there was no correlation with disease activity and no significant variation after steroid based therapy [171]. Taken together, MBL pathway seemed to be not involved in pathophysiology of IgG4-related sclerosing pancreatitis, contrary to the classical pathway which seemed to be activated by IgG1 as attested by significant association between elevated levels of circulating immune complex, high serum IgG1 concentrations and low C3 and C4 levels [171]. In line with this, in the study by Wallace and coll. [25] patients with hypocomplementemia and elevated serum IgG4 concentrations tended to present raised levels of other serum IgG subclasses, suggesting that one of these IgG could be implicated in low complement levels. On the other hand, by analysing which IgG subtypes could contribute to the activation of the complement in three IgG4-RD patients –with various affected organs- with hypocomplementemia, Sugimoto and coll. [175] have observed reduced complement activity in all pathways in such patients. In addition, the serum levels of C1q-binding IgG4 were high in IgG4-RD patients with hypocomplementemia and immune complexes (ICs) in polyethylene glycol (PEG) precipitates were formed with IgG4 regardless of hypocomplementemia. Normal human serum (NHS) incubated with PEG-IC isolated from IgG4RD patients with hypocomplementemia resulted in a marked reduction of CH50 and reduced complement activity in the classical and MBL complement pathway. The authors concluded that IgG4 could participate in the complement activation through different pathways, which is contradictory to report from Muraki and coll. where IgG1-type IC was supposed to activate of the classical complement pathway [171]. According to the authors, this might be explained by the difference in methods applied: indirect observation in the AIP study and direct one in the latter. Another reason could be differences in affected organs, although there are components of the same disorder – AIP versus MD. In

conclusion, knowledge about complement activation in IgG4-RD remains limited in view of controversy on what complement pathway is involved. Recently described in RA, anti-IgG4 hinge antibodies were directed against the IgG4 F(ab')2 fragment of anti-citrullinated protein antibody and could activate complement through formation of ICs [176]. Their presence among IgG4-RD should be evaluated to provide new insights into mechanisms of complement activation.

2.4. The role of tertiary lymphoid organs

Tertiary lymphoid organs (TLOs) are accumulations of lymphoid and stromal cells that develop in response to inflammatory signals. These structures are also known as ectopic lymphoid follicles or ectopic lymphoid structures as they develop outside of secondary LOs [177]. TLOs include compartmentalized T cells with CD4 and CD8 subsets, compartmentalized B cells and plasma cells who may organize into germinal centers and dendritic and follicular dendritic cells (FDC) who are part of antigen presenting cells. There is expression of lymphoid chemokines CXCL13, CCL19 and CCL21 who regulate localization of GC B cells and are necessary for the recruitment of T cells and dendritic cells [178]. TLOs are described in various conditions such as auto-immune diseases, graft rejections, chronic infections or malignancies. Whether they are pathogenic or protective is still unclear [179–186]. As IgG4-RD is characterized by an inflammatory process, TLOs at affected sites are a frequent finding. Indeed, Maehara and coll. have observed ectopic lymphoid structures with germinal centers in 12 of 20 patients with IgG4-DS [104]. TLOs were reported in 13 of 22 patients with IgG4-RD in other report [187]. They seem to be more frequent in head and neck affected organs than others [32]. However, the diagnostic value of tissue TLO as a biomarker of IgG4-RD activity is until now unknown. It has been hypothesized that these structures could contribute to therapy resistance in inflammatory processes [188,189]. Administration of anti-CD20 monoclonal antibodies is actually guided by peripheral circulating B cells depletion, but this could be inappropriate because it may not reflect its impact regarding what is happening in the targeted organ, in particular what is the effect of this therapy on TLOs [190]. Indeed, despite a complete disappearance of circulating B-cells after administration of RTX in patients with chronically rejected allografts, functional TLOs were still detected within the graft, with local production of alloantibodies [191]. In patients with SS, incomplete B cell depletion was seen in repeated salivary gland biopsies after RTX therapy [189]. Thus, niches of B cells and plasma cells that escape depletion are frequently observed in TLOs. This resistance might be due to survival signals to B lymphocytes provided by inflammatory microenvironment [192].

2.5. Interactions between the immune system and the epithelium of target organs in the pathogenesis of IgG4-RD

Strikingly IgG4-RD mainly targets exocrine glands such as pancreas, bile ducts, salivary and lacrimal gland. Therefore, the interaction(s) between the immune system and the epithelium could be involved in the pathogenesis of this disease. Indeed, subcutaneous injection of IgG from patients with IgG4-RD induced pancreatic and lower bile duct injury in mice, but no pathological change in prostate, heart, lung or liver [48]. In this in vivo experiment, IgG deposits, especially IgG1 and IgG4, colocalised with collagen IV - the main collagen component of the basement membrane (BM) suggesting a possibility of interaction between antibodies and molecules of BM and/or other cell adhesion molecules. However, until today no autoantigen within the extract of proteins from BM has been identified. Interestingly, Detlefsen et al. [193] found also complement C3c deposits along BM of pancreatic ducts and acini in patients with AIP as well as BM of the peribiliary tubular glands in a patient with IgG4-related sclerosing cholangitis, reinforcing the hypothesis of immune-complex mediated pathway in the pathophysiology of IgG4-RD. The importance of the epithelial cells is moreover underlined by the presence of IgG4 deposits within BM of renal tubules in patients IgG4-TIN [194]. Beside *Helicobacter pylori* associated antigens, lactoferrin (localised within the cells membrane) and carbonic anhydrase II (localised within carboxysome in cytoplasm) have been proposed as the antigens but are not associated with the BM. Both are produced by the secretory cells of exocrine glands and renal tubules [195–197]. Recently, a new 13.1kDa protein - not yet identified, has been detected in the serum of all patients presenting with AIP, MD or TIN [198]. and might constitute one candidate of the antigens involved in the immune response during IgG4-RD.

3. Conclusion

IgG4-RD is a recent acknowledged complex entity through its numerous presentation that can mimic various conditions, making diagnosis challenging especially in the absence histopathological proof. Awareness of this disease is growing, especially in Europe where its epidemiology is still lacking. The mechanism of IgG4-RD is still not well defined as well as the target antigen, but recent advances that we tried to review in the present work highlight the interplay between innate and adaptive immune responses as well as collaboration between B cells and T cells and involvement of Tfh cells, leading to IgG4 class switching, tissue fibrosis, GC formation and plasmablasts differentiation. Thus, circulating Tfh2, plasmablasts and tissue TLO have emerged as the most promising biomarkers reflecting IgG4 RD activity. Targeting TLOs in the inflamed tissues could constitute a novel approach to minimize relapses but further studies are needed to better understand their pathogenic and/or protective role and to confirm their value in every day clinical practice to monitor the immunologically active diseases and to better adapt immunosuppressive therapies.

Conflict of interest

No conflict of interest to declare.

Acknowledgments

We thank R. Karmali, Professor of Internal medicine at Brugmann Hospital, University of Brussels, for his constructive criticism of the discussion.

References

[1] V.S. Mahajan, H. Mattoo, V. Deshpande, et al., IgG4-related disease, Annu. Rev. Pathol. 9 (2014) 315–347.
[2] H. Sarles, J.C. Sarles, R. Muratore, et al., Chronic inflammatory sclerosis of the pancreas-an autonomous pancreatic disease? Am. J. Dig. Dis. 6 (1961) 688–698.
[3] K. Yoshida, F. Toki, T. Takeuchi, et al., Chronic pancreatitis caused by an autoimmune abnormality. Proposal of the concept of autoimmune pancreatitis, Dig. Dis. Sci. 40 (1995) 1561–1568.
[4] H. Hamano, S. Kawa, A. Horiuchi, et al., High serum IgG4 concentrations in patients with sclerosing pancreatitis, N. Engl. J. Med. 344 (2001) 732–738.
[5] H. Hamano, S. Kawa, Y. Ochi, et al., Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis, Lancet 359 (9315) (2002 Apr 20) 1403–1404.
[6] T. Kamisawa, H. Nakajima, N. Egawa, et al., IgG4-related sclerosing disease incorporating sclerosing pancreatitis, cholangitis, sialadenitis and retroperitoneal fibrosis with lymphadenopathy, Pancreatology 6 (1-2) (2006) 132–137.
[7] J.T. Geyer, J.A. Ferry, N.L. Harris, et al., Chronic sclerosing sialadenitis (Küttner tumor) is an IgG4-associated disease, Am. J. Surg. Pathol. 34 (2) (2010 Feb) 202–210.
[8] M. Dahlgren, A. Khosroshahi, G.P. Nielsen, et al., Riedel's thyroiditis and multifocal fibrosclerosis are part of the IgG4-related systemic disease spectrum, Arthritis Care Res. 62 (9) (2010 Sep) 1312–1318.
[9] A. Dyer, P.M. Sadow, E. Bracamonte, et al., Immunoglobulin G4- related retroperitoneal fibrosis of the pelvis, Rev. Urol. 16 (2014) 92–94.
[10] M. Yamamoto, H. Takahashi, M. Ohara, et al., A new conceptualization for Mikulicz's disease as an IgG4-related plasmacytic disease, Mod. Rheumatol. 16 (6) (2006) 335–340.
[11] A. Kleger, T. Seufferlein, M. Wagner, et al., IgG4-related autoimmune diseases: polymorphous presentation complicates diagnosis and treatment, Dtsch. Arztebl. Int. 112 (8) (2015) 128–135.

[12] H. Umehara, K. Okazaki, Y. Masaki, et al., A novel clinical entity, IgG4-related disease (IgG4RD): general concept and details, Mod. Rheumatol. 22 (2012) 1–14.
[13] J.H. Stone, A. Khosroshahi, V. Deshpande, et al., Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations, Arthritis Rheum. 64 (10) (2012 Oct) 3061–3067.
[14] K. Okazaki, H. Umehara, Are classification criteria for IgG4-RD now possible? The concept of IgG4-related disease and proposal of comprehensive diagnostic criteria in Japan, Int. J. Rheumatol. 2012 (2012) 357071.
[15] H. Umehara, K. Okazaki, Y. Masaki, et al., Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011, Mod. Rheumatol. 22 (1) (2012) 21–30.
[16] Y. Masaki, S. Sugai, H. Umehara, IgG4-related diseases including Mikulicz's disease and sclerosing pancreatitis: diagnostic insights, J. Rheumatol. 37 (7) (2010) 1380–1385.
[17] T. Shimosegawa, S.T. Chari, L. Frulloni, et al., International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the international association of pancreatology, Pancreas 40 (3) (2011) 352–358.
[18] M. Kawano, T. Saeki, H. Nakashima, et al., Proposal for diagnostic criteria for IgG4-related kidney disease, Exp. Nephrol. 15 (5) (2011) 615–626.
[19] H. Ohara, K. Okazaki, H. Tsubouchi, et al., Clinical diagnostic criteria of IgG4-related sclerosing cholangitis 2012, J. Hepatobiliary Pancreat. Sci. 19 (2012) 536–542.
[20] D. Inoue, K. Yoshida, N. Yoneda, et al., IgG4-related disease: dataset of 235 consecutive patients, Medicine 94 (15) (2015) e680.
[21] M. Ebbo, A. Grados, M. Samson, 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 12 (9) (2017 Sep 15) e0183844.
[22] A. Fernández-Codina, F. Martínez-Valle, B. Pinilla, et al., IgG4-related disease: results from a multicenter Spanish registry, Medicine 94 (32) (2015) e1275.
[23] F. Karim, J. Loeffen, W. Bramer, et al., IgG4-related disease: a systematic review of this unrecognized disease in pediatrics, Pediatr. Rheumatol. Online J. 14 (2016) 18, https://doi.org/10.1186/s12969-016-0079-3.
[24] J.H. Stone, Y. Zen, V. Deshpande, IgG4-RD, N. Engl. J. Med. 366 (6) (2012 Feb 9) 539–551.
[25] Wallace, et al., IgG4-related disease: clinical and laboratory features in one hundred twenty-five patients, Arthritis Rheumatol. 67 (2015) 2466–2475.
[26] S. Koizumi, T. Kamisawa, S. Kuruma, et al., Organ correlation in IgG4-related diseases, J. Korean Med. Sci. 30 (6) (2015) 743–748.
[27] T. Kamisawa, Y. Zen, S. Pillai, J.H. Stone, IgG4-related disease, Lancet 385 (2015) 1460–1471.
[28] D.C. Houghton, M.L. Trioxell, An abundance of IgG4+ plasma cells is not specific for IgG4-related tubulointerstitial nephritis, Mod. Pathol. 24 (2011) 1480–1487.
[29] N. Ayuzawa, Y. Ubara, S. Keiichi, et al., Churg-Strauss syndrome with a clinical condition similar to IgG4-related kidney disease: a case report, Intern. Med. 51 (2012) 1233–1238.
[30] M. Yahata, S. Takahashi, I. Nakaya, et al., Possible IgG4-related kidney disease requiring a differential diagnosis of membranous lupus nephritis, Intern. Med. 51 (2012) 1731–1736.
[31] Y. Masaki, L. Dong, N. Kurose, et al., Proposal for a new clinical entity, IgG4-positive multiorgan lymphoproliferative syndrome: analysis of 64 cases of IgG4-related disorders, Ann. Rheum. Dis. 68 (2009) 1310–1315.
[32] Y. Zen, Y. Nakanuma, IgG4-related disease: a cross-sectional study of 114 cases, Am. J. Surg. Pathol. 34 (12) (2010 Dec) 1812–1819.
[33] C. Deng, W. Li, S. Chen, et al., Histopathological diagnostic value of the IgG4+/IgG+ ratio of plasmacytic infiltration for IgG4-related diseases: a PRISMA-compliant systematic review and meta-analysis, Medicine (Baltimore) 94 (9) (2015 Mar) e579.
[34] E. Della-Torre, E. Feeney, V. Deshpande, et al., B-cell depletion attenuates serological biomarkers of fibrosis and myofibroblast activation in IgG4-related disease, Ann. Rheum. Dis. 74 (12) (2015) 2236–2243.
[35] A. Khosroshahi, D. Bloch, V. Deshpande, J.H. Stone, Rituximab therapy leads to rapid decline of serum IgG4 levels and prompt clinical improvement in IgG-related systemic disease, Arthritis Rheum. 62 (2010) 1755–1762.
[36] J. Owen, J. Punt, S. Stranford, Immunology, 7th edition, (2013).
[37] E. Della-Torre, M. Lanzillotta, C. Doglioni, Immunology of IgG4-related disease, Clin. Exp. Immunol. 181 (2) (2015) 191–206.
[38] P. Bruhns, B. Iannascoli, P. England, et al., Specificity and affinity of human Fcgamma receptors and their polymorphic variants for human IgG subclasses, Blood 113 (2009) 3716–3725.
[39] A. Nirula, S.M. Glaser, S.L. Kalled, et al., What is IgG4? A review of the biology of a unique immunoglobulin subtype, Curr. Opin. Rheumatol. 23 (2011) 119–124.
[40] R. Aalberse, The role of IgG antibodies in allergy and immunotherapy, Allergy 66 (Suppl. 95) (2011) 28–30.
[41] C. Sitaru, S. Mihai, D. Zillikens, The relevance of the IgG subclass of autoantibodies for blister induction in autoimmune bullous skin diseases, Arch. Dermatol. Res. 299 (2007) 1–8.
[42] C. Sitaru, D. Zillikens, Mechanisms of blister induction by autoantibodies, Exp. Dermatol. 14 (2005) 861–875.
[43] Y. Shirakata, S. Shiraishi, K. Sayama, Y. Miki, Subclass characteristics of IgG autoantibodies in bullous pemphigoid and pemphigus, J. Dermatol. 17 (11) (1990) 661–666.
[44] Y. Yang, C. Wang, L. Jin, et al., IgG4 anti-phospholipase A2 receptor might activate lectin and alternative complement pathway meanwhile in idiopathic membranous nephropathy: an inspiration from a cross-sectional study, Immunol. Res. 64 (4) (2016 Aug) 919–930.
[45] S. Ferrari, G.C. Mudde, M. Rieger, et al., IgG subclass distribution of anti-ADAMTS13 antibodies in patients with acquired thrombotic thrombocytopenic purpura, J. Thromb. Haemost. 7 (10) (2009) 1703–1710.
[46] R. Klooster, J.J. Plomp, M.G. Huijbers, et al., Muscle-specific kinase myasthenia gravis IgG4 autoantibodies cause severe neuromuscular junction dysfunction in mice, Brain 135 (Pt 4) (2012 Apr) 1081–1101.
[47] P.M.W. van Helden, H.M. van den Berg, S.C. Gouw, et al., IgG subclasses of anti-FVIII antibodies during immune tolerance induction in patients with hemophilia a, Br. J. Haematol. 142 (2008) 644–652.
[48] M. Shiokawa, Y. Kodama, K. Kuriyama, et al., Pathogenicity of IgG in patients with IgG4-related disease, Gut 65 (8) (2016 Aug) 1322–1332.
[49] N. Takahashi, A. Kawashima, Fletcher Jg, et al., Renal involvement in patients with autoimmune pancreatitis: CT and MR imaging findings, Radiology 242 (2007 Mar) 791–801.
[50] Z.S. Wallace, H. Mattoo, M. Carruthers, et al., Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations, Ann. Rheum. Dis. 74 (1) (2015) 190–195.
[51] M.N. Carruthers, M.D. Topazian, A. Khosroshahi, et al., Rituximab for IgG4-related disease: a prospective, open-label trial, Ann. Rheum. Dis. 74 (6) (2015 Jun) 1171–1177.
[52] Z.S. Wallace, H. Mattoo, V.S. Mahajan, et al., Predictors of disease relapse in IgG4-related disease following rituximab, Rheumatology 55 (6) (2016) 1000–1008.
[53] A. Grados, M. Ebbo, C. Piperoglou, et al., T cell polarization toward $T_H2/T_{FH}2$ and $T_H17/T_{FH}17$ in patients with IgG4-related disease, Front. Immunol. 8 (2017) 235.
[54] S.L. Nutt, P.D. Hodgkin, D.M. Tarlinton, et al., Nat. Rev. Immunol. 15 (3) (2015 Mar) 160–171.
[55] M.C. Hsu, K.M. Toellner, C.G. Vinuesa, I.C. Maclennan, B cell clones that sustain long-term plasmablast growth in T-independent extra-follicular antibody responses, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 5905–5910.
[56] K. Fink, Origin and function of circulating plasmablasts during acute viral infections, Front. Immunol. 3 (2012 Apr 17) 78.
[57] G. Blanchard-Rohner, A.S. Pulickal, C.M. Jol-van der Zijde, M.D. Snape, A.J. Pollard, Appearance of peripheral blood plasma cells and memory B cells in a primary and secondary immune response in humans, Blood 114 (24) (2009) 4998–5002.
[58] Y. Qian, C. Wei, F.E.-H. Lee, et al., Elucidation of seventeen human peripheral blood b cell subsets and quantification of the tetanus response using a density-based method for the automated identification of cell populations in multi-dimensional flow cytometry data, Cytometry B Clin. Cytom. 78 (Suppl. 1) (2010) S69–S82.
[59] H.E. Mei, T. Yoshida, W. Sime, et al., Blood-borne human plasma cells in steady state are derived from mucosal immune responses, Blood 113 (11) (2009 Mar 12) 2461–2469.
[60] M.E. Re, K. Carner, K.S. Chambers, et al., Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20, Blood 83 (1994) 435–445.
[61] M. Bemark, J. Holmqvist, J. Abrahamsson, K. Mellgren, Translational mini-review series on B cell subsets in disease. Reconstitution after haematopoietic stem cell transplantation – revelation of B cell developmental pathways and lineage phenotypes, Clin. Exp. Immunol. 167 (1) (2012) 15–25.
[62] C.C. Mok, Rituximab for the treatment of rheumatoid arthritis: an update, Drug Des. Dev. Ther. 8 (2013 Dec 27) 87–100.
[63] G.L. Plosker, D.P. Figgitt, Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia, Drugs 63 (8) (2003) 803–843.
[64] S.C. Liossis, C. Staveri, B Cell-based treatments in SLE: past experience and current directions, Curr. Rheumatol. Rep. 19 (12) (2017 Nov 4) 78.
[65] T. Castillo-Trivino, D. Braithwaite, P. Bacchetti, E. Waubant, Rituximab in relapsing and progressive forms of multiple sclerosis: a systematic review, PLoS One 8 (7) (2013) e66308.
[66] A.M. Jacobi, M. Odendahl, K. Reiter, et al., Correlation between circulating CD27high plasma cells and disease activity in patients with systemic lupus erythematosus, Arthritis Rheum. 48 (5) (2003 May) 1332–1342.
[67] P.F. Kerkman, Y. Rombouts, E.L. van der Voort, et al., Circulating plasmablasts/plasma cells as a source of anti-citrullinated protein antibodies in patients with rheumatoid arthritis, Ann. Rheum. Dis. 72 (2013) 1259–1263.
[68] P. Stathopoulos, A. Kumar, R.J. Nowak, K.C. O'Connor, Autoantibody-producing plasmablasts after B cell depletion identified in muscle-specific kinase myasthenia gravis, JCI Insight 2 (17) (2017) e94263.
[69] M. Akiyama, K. Suzuki, K. Yamaoka, 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. 67 (9) (2015 Sep) 2476–2481.
[70] H. Mattoo, V. Mahajan, E. Della-Torre, et al., De novo oligoclonal expansions of circulating plasmablasts in active and relapsing IgG4-related disease, J. Allergy Clin. Immunol. 134 (2014) 679–687.
[71] W. Lin, P. Zhang, H. Chen, et al., Circulating plasmablasts/plasma cells: a potential biomarker for IgG4-related disease, Arthritis Res. Ther. 19 (2017) 25.
[72] Maillette De Buy Wenniger Lj, Doorenspleet Me, Klarenbeek Pl, Et Al., Immunoglobulin G4 clones identified by next-generation sequencing dominate the B cell receptor repertoire in immunoglobulin G4 associated cholangitis, Hepatology 57 (6) (2013) 2390–2398.
[73] M. Rehnberg, M. Brisslert, S. Amu, et al., Vaccination response to protein and carbohydrate antigens in patients with rheumatoid arthritis after rituximab treatment, Arthritis Res. Ther. 12 (2010) R111.
[74] M.J. Leandro, B-cell subpopulations in humans and their differential susceptibility to depletion with anti-CD20 monoclonal antibodies, Arthritis Res. Ther. 15 (Suppl. 1) (2013) S3.
[75] T.R. Mosmann, H. Cherwinski, M.W. Bond, et al., Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins, J. Immunol. 136 (1986) 2348–2357.

[76] N. Ohta, S. Makihara, M. Okano, et al., Roles of IL-17, Th1, and Tc1 cells in patients with IgG4-related sclerosing sialadenitis, Laryngoscope 122 (2012) 2169–2174.
[77] K. Okazaki, K. Uchida, M. Ohana, et al., Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2-type cellular immune response, Gastroenterology 118 (2000) 573–581.
[78] T. Maehara, H. Mattoo, M. Ohta, et al., Lesional CD4+ IFN-g+ cytotoxic T lymphocytes in IgG4-related dacryoadenitis and sialoadenitis, Ann. Rheum. Dis. 76 (2017) 377–385.
[79] R. Morita, N. Schmitt, S.E. Bentebibel, et al., Human blood CXCR5(+)CD4(+) T cells are counterparts of T follicular cells and contain specific subsets that differentially support antibody secretion, Immunity 34 (2011) 108–121.
[80] J.L. Cannons, K.T. Lu, P.L. Schwartzberg, T follicular helper cell diversity and plasticity, Trends Immunol. 34 (5) (2013) 200–207.
[81] M. Akiyama, H. Yasuoka, K. Yamaoka, 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. 18 (2016) 167.
[82] S.J. Conway, T. Doetschman, M. Azhar, The inter-relationship of periostin, TGF beta, and BMP in heart valve development and valvular heart diseases, Sci. World J. 11 (2011) 1509–1524.
[83] L. Li, C. Wang, J.Y. Wang, et al., Angiotensin II increases periostin expression via Ras/p38 MAPK/CREB and ERK1/2/TGF-b1 pathways in cardiac fibrosis, Cardiovasc. Res. 91 (2011) 80–89.
[84] C.G. Lee, R.J. Homer, Z. Zhu, et al., Interleukin-13 Induces tissue fibrosis by selectively stimulating and activating transforming growth factor β_1, J. Exp. Med. 194 (6) (2001) 809–822.
[85] A. Oriente, N.S. Fedarko, S.E. Pacocha, et al., Interleukin-13 modulates collagen homeostasis in human skin and keloid fibroblasts, J. Pharmacol. Exp. Ther. 292 (3) (2000) 988–994.
[86] M.L. Brown Lobbins, B.R. Shivakumar, A.E. Postlethwaite, et al., Chronic exposure of interleukin-13 suppress the induction of matrix metalloproteinase-1 by tumour necrosis factor α in normal and scleroderma dermal fibroblasts through protein kinase B/Akt, Clin. Exp. Immunol. 191 (1) (2018 Jan) 84–95.
[87] N. Ohta, K. Kurakami, A. Ishida, et al., Roles of TGF-beta and periostin in fibrosclerosis in patients with IgG4-related diseases, Acta Otolaryngol. 133 (2013) 1322–1327.
[88] A. Tanaka, M. Moriyama, H. Nakashima, et al., Th2 and regulatory immune reactions contribute to IgG4 production and the initiation of Mikulicz disease, Arthritis Rheum. 64 (1) (2012 Jan) 254–263.
[89] H. Nakashima, K. Miyake, M. Moriyama, et al., An amplification of IL-10 and TGF-beta in patients with IgG4-related tubulointerstitial nephritis, Clin. Nephrol. 73 (2010) 385–391.
[90] Y. Zen, T. Fujii, K. Harada, M. Kawano, et al., Th2 and regulatory immune reaction are increased in immunoglobin G4-related sclerosing pancreatitis and cholangitis, Hepatology 45 (2007) 1538–1546.
[91] H. Yamamoto, M. Yasuo, T. Ichiyama, et al., Cytokine profiles in the BAL fluid of IgG4-related respiratory disease compared with sarcoidosis, ERJ Open Res. 23 (2015 Oct) 1(2).
[92] J.J. Heeringa, A.F. Karim, J.A.M. van Laar, et al., Expansion of blood IgG4+ B, TH2, and regulatory T cells in patients with IgG4-related disease, J. Allergy Clin. Immunol. 19 (2017 Aug).
[93] F. Meiler, S. Klunker, M. Zimmermann, et al., Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors, Allergy 63 (2008) 1455–1463.
[94] P. Jeannin, S. Lecoanet, Y. Delneste, et al., IgE versus IgG4 production can be differentially regulated by IL-10, J. Immunol. 160 (7) (1998 Apr 1) 3555–3561.
[95] N. Tsurikisawa, H. Saito, C. Oshikata, et al., Decreases in the numbers of peripheral blood regulatory T cells, and in- creases in the levels of memory and activated B cells, in patients with active eosinophilic granulomatosis and polyangiitis, J. Clin. Immunol. 33 (2013) 965–976.
[96] M. Yamamoto, H. Takahashi, C. Suzuki, et al., Analysis of serum IgG subclasses in Churg-Strauss syndrome—the meaning of elevated serum levels of IgG4, Intern. Med. 49 (2010) 1365–1370.
[97] H. Chen, W. Lin, Q. Wang, et al., IgG4-related disease in a Chinese cohort: a prospective study, Scand. J. Rheumatol. 43 (1) (2014) 70–74.
[98] H. Mattoo, E. Della-Torre, V. Mahajan, J. Stone, S. Pillai, Circulating Th2 memory cells in IgG4 related disease are restricted to a defined subset of subjects with atopy, Allergy 69 (3) (2014) 399–402.
[99] E.D. Torre, H. Mattoo, V.S. Mahajan, M. Carruthers, S. Pillai, J.H. Stone, Prevalence of atopy, eosinophilia, and IgE elevation in IgG4-related disease, Allergy 69 (2) (2014) 269–272.
[100] H. Mattoo, V.S. Mahajan, T. Maehara, et al., Clonal expansion of CD4+ cytotoxic T lymphocytes in patients with IgG4-related disease, J. Allergy Clin. Immunol. 138 (2016) 825 38.
[101] H. Park, Z. Li, X.O. Yang, et al., A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17, Nat. Immunol. 6 (2005) 1133–1141.
[102] M. Chabaud, J.M. Durand, N. Buchs, et al., Human interleukin-17: a T cell-derived proinflammatory cytokine produced by the rheumatoid synovium, Arthritis Rheum. 42 (1999) 963–970.
[103] S. Fujino, A. Andoh, S. Bamba, et al., Increased expression of interleukin 17 in inflammatory bowel disease, Gut 52 (2003) 65–70.
[104] T. Maehara, M. Moriyama, H. Nakashima, 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. 71 (2012) 2011–2019.
[105] M. Ebbo, L. Daniel, M. Pavic, et al., IgG4-related systemic disease: features and treatment response in a French cohort: results of a multicenter registry, Medicine 91 (1) (2012 Jan) 49–56.
[106] D. Gatto, R. Brink, The germinal center reaction, J. Allergy Clin. Immunol. 126 (5) (2010 Nov) 898–907.
[107] H. Ueno, J. Banchereau, C.G. Vinuesa, Pathophysiology of T follicular helper cells in humans and mice, Nat. Immunol. 16 (2015) 142–152.
[108] N.M. Haynes, C.D. Allen, R. Lesley, et al., Role of CXCR5 and CCR7 in follicular Th cell positioning and appearance of a programmed cell death gene-1high germinal center-associated subpopulation, J. Immunol. 179 (2007) 5099–5108.
[109] D. Breitfeld, L. Ohl, E. Kremmer, et al., Follicular B helper T cells express Cxc chemokine receptor 5, localize to B cell follicles, and support immunoglobulin production, J. Exp. Med. 192 (11) (2000) 1545–1552.
[110] D.J. Campbell, C.H. Kim, E.C. Butcher, Separable effector T cell populations specialized for B cell help or tissue inflammation, Nat. Immunol. 2 (2001) 876–881.
[111] S. Crotty, Follicular helper CD4 T cells (TFH), Annu. Rev. Immunol. 29 (2011) 621–663.
[112] Wataru Ise, Development and function of follicular helper T cells, Biosci. Biotechnol. Biochem. 80 (1) (2016) 1–6.
[113] Rosanne Spolski, Warren J. Leonard, IL-21 and T follicular helper cells, Int. Immunol. 22 (1) (2010) 7–12.
[114] C.G. Vinuesa, S.G. Tangye, B. Moser, C.R. Mackay, Follicular B helper T cells in antibody responses and autoimmunity, Nat. Rev. Immunol. 5 (2005) 853–865.
[115] N. Wood, K. Bourque, D.D. Donaldson, et al., IL-21 effects on human IgE production in response to IL-4 or IL-13, Cell. Immunol. 231 (2004) 133–145.
[116] A. Suto, H. Nakajima, K. Hirose, et al., Interleukin 21 prevents antigen-induced IgE production by inhibiting germ line C (epsilon) transcription of IL-4-stimulated B cells, Blood 100 (2002) 4565–4573.
[117] H. Yajima, M. Yamamoto, Y. Shimizu, et al., Loss of interleukin-21 leads to atrophic germinal centers in multicentric Castleman's disease, Ann. Hematol. 95 (1) (2016 Jan) 35–40.
[118] X. Zhang, E. Lindwall, C. Gauthier, et al., Circulating CXCR5+CD4+helper T cells in systemic lupus erythematosus patients share phenotypic properties with germinal center follicular helper T cells and promote antibody production, Lupus 24 (9) (2015 Aug) 909–917.
[119] Q. Li, Z. Liu, E. Dang, et al., Follicular helper T cells (Tfh) and IL-21 involvement in the pathogenesis of bullous pemphigoid, PLoS One 8 (7) (2013) e68145.
[120] J.-Y. Choi, J.H. Ho, S.G. Pasoto, et al., Circulating follicular helper-like T cells in systemic lupus erythematosus: association with disease activity, Arthritis Rheumatol. 67 (4) (2015) 988–999.
[121] Y. Wang, L. Wang, H. Yang, W. Yuan, J. Ren, Y. Bai, Activated circulating T follicular helper cells are associated with disease severity in patients with psoriasis, J Immunol Res 2016 (2016) 7346030.
[122] Y. Zhang, Y. Li, T.T. Lv, et al., Elevated circulating Th17 and follicular helper CD4(+) T cells in patients with rheumatoid arthritis, APMIS 123 (8) (2015 Aug) 659–666.
[123] S. Crotty, T follicular helper cell differentiation, function, and roles in disease, Immunity 41 (2014) 529–542.
[124] R. Kamekura, K. Shigehara, S. Miyajima, et al., Alteration of circulating type 2 follicular helper T cells and regulatory B cells underlies the comorbid association of allergic rhinitis with bronchial asthma, Clin. Immunol. 158 (2015) 204–211.
[125] R. Kamekura, K. Takano, M. Yamamoto, et al., Cutting edge: a critical role of lesional T follicular helper cells in the pathogenesis of IgG4-related disease, J. Immunol. 199 (8) (2017 Oct 15) 2624–2629.
[126] Y. Chen, W. Zhang, P. Zhang, et al., Aberrant expression and function of human circulating T follicular helper cells and its subsets in IgG4 related disease [abstract], Arthritis Rheumatol. 69 (Suppl. 10) (2017).
[127] K. Chen, Y. Wei, G.C. Sharp, H. Braley-Mullen, Balance of proliferation and cell death between thyrocytes and myofibroblasts regulates thyroid fibrosis in granulomatous experimental autoimmune thyroiditis (G-EAT), J. Leukoc. Biol. 77 (2005) 166–172.
[128] M. Yamamoto, H. Takahashi, K. Takano, et al., Efficacy of abatacept for IgG4-related disease over 8 months, Ann. Rheum. Dis. 75 (2016) 1576–1578.
[129] S. Iwata, S. Nakayamada, S. Fukuyo, et al., Activation of Syk in peripheral blood B cells in patients with rheumatoid arthritis: a potential target for abatacept therapy, Arthritis Rheumatol. 67 (2015) 63–73.
[130] T. Namekawa, U.G. Wagner, J.J. Goronzy, et al., Functional subsets of CD4 T cells in rheumatoid synovitis, Arthritis Rheum. 41 (1998) 2108–2116.
[131] M. Allez, V. Tieng, A. Nakazawa, et al., CD4+NKG2D+ T cells in Crohn's disease mediate inflammatory and cytotoxic responses through MICA interactions, Gastroenterology 132 (2007) 2346–2358.
[132] D. Capraru, A. Muller, E. Csernok, et al., Expansion of circulating NKG2D+ effector memory T-cells and expression of NKG2D-ligand MIC in granulomatous lesions in Wegener's granulomatosis, Clin. Immunol. 127 (2008) 144–150.
[133] D. Schmidt, J.J. Goronzy, C.M. Weyand, CD4+ CD7– CD28– T cells are expanded in rheumatoid arthritis and are characterized by autoreactivity, J. Clin. Invest. 97 (1996) 2027–2037.
[134] D. Yang, H. Wang, B. Ni, et al., Mutual activation of CD4+ T cells and monocytes mediated by NKG2D-MIC interaction requires IFN-gamma production in systemic lupus erythematosus, Mol. Immunol. 46 (2009) 1432–1442.
[135] V. Appay, J.J. Zaunders, L. Papagno, et al., Characterization of CD4(þ) CTLs ex vivo, J. Immunol. 168 (2002) 5954–5958.
[136] D. Martorelli, E. Muraro, A. Merlo, et al., Role of CD4þ cytotoxic T lymphocytes in the control of viral diseases and cancer, Int. Rev. Immunol. 29 (2010) 371–402.
[137] A. Komocsi, P. Lamprecht, E. Csernok, et al., Peripheral blood and granuloma $CD4^+CD28^-$ T cells are a major source of interferon-gamma and tumor necrosis factor- alpha in Wegener's granulomatosis, Am. J. Pathol. 160 (2002) 1717 24.
[138] M.H. Andersen, D. Schrama, P. Thor Straten, J.C. Becker, Cytotoxic T Cells, J.

Investig. Dermatol. 126 (2006) 32–41.
[139] T. Tabeya, M. Yamamoto, Y. Naishiro, et al., The role of cytotoxic T cells in IgG4-related dacryoadenitis and sialadenitis, the so-called Mikulicz's disease, Mod. Rheumatol. 24 (2014) 953 60.
[140] L. Trautmann, L. Janbazian, N. Chomont, et al., Upregulation of PD-1 expression on HIV-specific CD8 T cells leads to reversible immune dysfunction, Nat. Med. 12 (10) (2006) 1198–1202.
[141] Blank C. Zha Yy, T.F. Gajewski, Negative regulation of T-cell function by PD-1, Crit. Rev. Immunol. 24 (4) (2004) 229–237.
[142] H. Kono, K.L. Rock, How dying cells alert the immune system to danger, Nat. Rev. Immunol. 8 (2008) 279–289.
[143] E. Elinav, T. Strowig, J. Henao-Mejia, et al., Regulation of the antimicrobial response by NLR proteins, Immunity 34 (2011) 665.
[144] M. Fukata, A.S. Vamadevan, M.T. Abreu, Toll-like receptors (TLR) and Nod-like receptors (NLR) in inflammatory disorders, Semin. Immunol. 21 (2009) 242.
[145] T. Kawai, S. Akira, The role of pattern recognition receptors in innate immunity: update on toll-like receptors, Nat. Immunol. 11 (2010) 373.
[146] T. Watanabe, K. Yamashita, S. Fujikawa, et al., Involvement of activation of toll-like receptors and nucleotide binding oligomerization domain-like receptors in enhanced IgG4 responses in autoimmune pancreatitis, Arthritis Rheum. 64 (2012) 914–924.
[147] T.A. Wynn, K.M. Vannella, Macrophages in tissue repair, regeneration, and fibrosis, Immunity 44 (2016) 450–462.
[148] S.C. Huen, L.G. Cantley, Macrophages in renal injury and repair, Annu. Rev. Physiol. 79 (2017 Feb 10) 449–469.
[149] S. Gordon, Alternative activation of macrophages, Nat. Rev. Immunol. 3 (2003) 23–35.
[150] F.O. Martinez, S. Gordon, M. Locati, A. Mantovani, Transcriptional profiling of the human monocyte-to-macrophage differentiation and polarization: new molecules and patterns of gene expression, J. Immunol. 177 (2006) 7303–7311.
[151] S. Furukawa, M. Moriyama, A. Tanaka, et al., Preferential M2 macrophages contribute to fibrosis in IgG4-related dacryoadenitis and sialoadenitis, so-called Mikulicz's disease, Clin. Immunol. 156 (2014) 9–18.
[152] A.M. Miller, Role of IL-33 in inflammation and disease, J. Inflamm. 8 (2011) 22.
[153] S. Furukawa, M. Moriyama, K. Miyake, et al., Interleukin-33 produced by M2 macrophages and other immune cells contributes to Th2 immune reaction of IgG4-related disease, Sci. Rep. 7 (2017 Feb 13) 42413.
[154] Y. Fukui, K. Uchida, Y. Sakaguchi, et al., Possible involvement of Toll-like receptor 7 in the development of type 1 autoimmune pancreatitis, J. Gastroenterol. 50 (4) (2015 Apr) 435–444.
[155] K. Notohara, Y. Wani, M. Fujisawa, Proliferation of CD163+ spindle-shaped macrophages in IGG4-related sclerosing disease: analysis of lymphoplasmacytic sclerosing pancreatitis and sclerosing sialadenitis, Mod. Pathol. 23 (2010) 367A.
[156] M.C. Sirakusa, B.S. Kim, J.M. Spergel, D. Artis, Basophils and allergic inflammation, J. Allergy Clin. Immunol. 132 (4) (2013 October) 789–798.
[157] C.L. Sokol, R. Medzhitov, Role of basophils in the initiation of Th2 responses, Curr. Opin. Immunol. 22 (1) (2010 February) 73–77.
[158] T. Watanabe, K. Yamashita, T. Sakurai, et al., Toll-like receptor activation in basophils contributes to the development of IgG4-related disease, J. Gastroenterol. 48 (2013) 247–253.
[159] E.L. Culver, R. Sadler, A.C. Bateman, et al., Increases in IgE, eosinophils, and mast cells can be used in diagnosis and to predict relapse of IgG4-related disease, Clin. Gastroenterol. Hepatol. 15 (9) (2017 Sep) 1444–1452.e6.
[160] Y. Raissian, S.H. Nasr, C.P. Larsen, et al., Diagnosis of IgG4-related tubulointerstitial nephritis, J. Am. Soc. Nephrol. 22 (2011) 1343–1352.
[161] T. Saeki, S. Nishi, N. Imai, et al., Clinicopathological characteristics of patients with IgG4-related tubulointerstitial nephritis, Kidney Int. 78 (10) (2010) 1016–1023.
[162] R.M. Reiman, R.W. Thompson, C.G. Feng, et al., Interleukin-5 (IL-5) augments the progression of liver fibrosis by regulating IL-13 activity, Infect. Immun. 74 (2006) 1471–1479.
[163] E.J. Lee, J.W. Kim, H. Yoo, et al., Single high-dose irradiation aggravates eosinophil-mediated fibrosis through IL-33 secreted from impaired vessels in the skin compared to fractionated irradiation, Biochem. Biophys. Res. Commun. 464 (2015) 20–26.
[164] C.M. Percopo, Z. Qiu, S. Phipps, et al., Pulmonary eosinophils and their role in immunopathologic responses to formalininactivated pneumonia virus of mice, J. Immunol. 183 (2009) 604–612.
[165] K.M. Hart, T. Fabre, J.C. Sciurba, et al., Type 2 immunity is protective in metabolic disease but exacerbates NAFLD collaboratively with TGF-β, Sci. Transl. Med. 9 (2017) eaal3694.
[166] Y.P. Goh, N.C. Henderson, J.E. Heredia, et al., Eosinophils secrete IL-4 to facilitate liver regeneration, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 9914–9919.
[167] H.B. Wang, I. Ghiran, K. Matthaei, P.F. Weller, Airway eosinophils: allergic inflammation recruited professional antigen-presenting cells, J. Immunol. 179 (2007) 7585–7592.
[168] H. Yamamoto, J.B. Sedgwick, R.F. Vrtis, W.W. Busse, The effect of transendothelial migration on eosinophil function, Am. J. Respir. Cell Mol. Biol. 23 (2000) 379–388.
[169] S.D. Mawhorter, J.W. Kazura, W.H. Boom, Human eosinophils as antigen-presenting cells: relative efficiency for superantigen- and antigen-induced CD4+ T-cell proliferation, Immunology 81 (1994) 584–591.
[170] M. Noris, G. Remuzzi, Overview of complement activation and regulation, Semin. Nephrol. 33 (6) (2013) 479–492.
[171] T. Muraki, H. Hamano, Y. Ochi, et al., Autoimmune pancreatitis and complement activation system, Pancreas 32 (1) (2006) 16–21.
[172] S. Saevarsdottir, T. Vikingsdottir, A. Vikingsson, et al., Low mannose binding lectin predicts poor prognosis in patients with early rheumatoid arthritis. A prospective study, J. Rheumatol. 28 (4) (2001) 728–734.
[173] E. Ballanti, C. Perricone, E. Greco, et al., Complement and autoimmunity, Immunol. Res. 56 (2–3) (2013) 477–491.
[174] J.Y. Kwok, F. Vaida, R.M. Augst, et al., Mannose binding lectin mediated complement pathway in multiple sclerosis, J. Neuroimmunol. 239 (1-2) (2011 October 28) 98–100.
[175] M. Sugimoto, H. Watanabe, T. Asano, et al., Possible participation of IgG4 in the activation of complement in IgG4-related disease with hypocomplementemia, Mod. Rheumatol. 26 (2) (2016) 251–258.
[176] L.A. van de Stadt, H. de Vrieze, N.I. Derksen, et al., Antibodies to IgG4 hinge can be found in rheumatoid arthritis patients during all stages of disease and may exacerbate chronic antibody-mediated inflammation, Arthritis Rheumatol. 66 (5) (2014) 1133–1140.
[177] F. Aloisi, R. Pujol-Borrell, Lymphoid neogenesis in chronic inflammatory diseases, Nat. Rev. Immunol. 6 (2006) 205–217.
[178] N.H. Ruddle, High endothelial venules and lymphatic vessels in tertiary lymphoid organs: characteristics, functions, and regulation, Front. Immunol. 7 (2016) 491.
[179] R.M. Thurlings, C.A. Wijbrandts, R.E. Mebius, et al., Synovial lymphoid neogenesis does not define a specific clinical rheumatoid arthritis phenotype, Arthritis Rheum. 58 (2008) 1582–1589.
[180] F. Humby, M. Bombardieri, A. Manzo, et al., Ectopic lymphoid structures support ongoing production of class-switched autoantibodies in rheumatoid synovium, PLoS Med. 6 (1) (2009) e1.
[181] C. Hsieh, A. Chang, D. Brandt, et al., Predicting outcomes of lupus nephritis with tubulointerstitial inflammation and scarring, Arthritis Care Res. 63 (6) (2011) 865–874.
[182] A. Chang, S.G. Henderson, D. Brandt, et al., In situ B cell-mediated immune responses and tubulointerstitial inflammation in human lupus nephritis, J. Immunol. 186 (3) (2011) 1849–1860.
[183] L. Martinet, I. Garrido, T. Filleron, et al., Human solid tumors contain high endothelial venules: association with T- and B-lymphocyte infiltration and favourable prognosis in breast cancer, Cancer Res. 71 (17) (2011) 5678–5687.
[184] N. Hiraoka, Y. Ino, R. Yamazaki-Itoh, et al., Intratumoral tertiary lymphoid organ is a favourable prognosticator in patients with pancreatic cancer, Br. J. Cancer 112 (11) (2015) 1782–1790.
[185] M.C. Dieu-Nosjean, M. Antoine, C. Danel, et al., Long-term survival for patients with non-small-cell lung cancer with intratumoral lymphoid structures, J. Clin. Oncol. 26 (2008) 4410–4417.
[186] D. Coppola, M. Nebozhyn, F. Khalil, et al., Unique ectopic lymph node-like structures present in human primary colorectal carcinoma are identified by immune gene array profiling, Am. J. Pathol. 179 (2011) 37–45.
[187] T. Satoh-Nakamura, N. Kurose, T. Kawanami, et al., CD14+ follicular dendritic cells in lymphoid follicles may play a role in the pathogenesis of IgG4-related disease, Biomed. Res. 36 (2) (2015) 143–153.
[188] W.D. Shipman, D.C. Dasoveanu, T.T. Lu, Tertiary lymphoid organs in systemic autoimmune diseases: pathogenic or protective? F1000Research 6 (F1000 Faculty Rev) (2017) 196.
[189] J. Pijpe, J.M. Meijer, H. Bootsma, et al., Clinical and histological evidence of salivary gland restoration supports the efficacy of rituximab treatment in Sjogren's syndrome, Arthritis Rheum. 60 (2009) 3251–3256.
[190] A. Kratz, A. Campos-Neto, M.S. Hanson, et al., Chronic inflammation caused by lymphotoxin is lymphoid neogenesis, J. Exp. Med. 183 (1996) 1461.
[191] O. Thaunat, N. Patey, C. Gautreau, et al., B cell survival in intragraft tertiary lymphoid organs after rituximab therapy, Transplantation 85 (2008) 1648–1653.
[192] Q. Gong, Q. Ou, S. Ye, et al., Importance of cellular microenvironment and circulatory dynamics in B cell immunotherapy, J. Immunol. 174 (2005) 817.
[193] V. Deshpande, S. Chicano, D. Finkelberg, et al., Autoimmune pancreatitis: a systemic immune complex mediated disease, Am. J. Surg. Pathol. 30 (2006) 1537–1545.
[194] S. Detlefsen, J.H. Brasen, G. Zamboni, P. Capelli, G. Kloppel, Deposition of complement C3c, immunoglobulin (Ig)G4 and IgG at the basement membrane of pancreatic ducts and acini in autoimmune pancreatitis, Histopathology 57 (2010) 825–835.
[195] K. Okazaki, K. Uchida, M. Ohana, et al., Autoimmune-related pancreatitis is associated with autoantibodies and a Th1/Th2- type cellular immune response, Gastroenterology 118 (2000) 573–581.
[196] F.R. Korsrud, P. Brandtzaeg, Characterization of epithelial elements in human major salivary glands by functional markers: localization of amylase, lactoferrin, lysozyme, secretory component, and secretory immunoglobulins by paired immunofluorescence staining, J. Histochem. Cytochem. 30 (7) (1982 Jul) 657–666.
[197] M. Abrink, E. Larsson, A. Gobl, L. Hellman, Expression of lactoferrin in the kidney: implications for innate immunity and iron metabolism, Kidney Int. 57 (5) (2000 May) 2004–2010.
[198] M. Yamamoto, Y. Naishiro, C. Suzuki, et al., Proteomics analysis in 28 patients with systemic IgG4-related plasmacytic syndrome, Rheumatol. Int. 30 (2010) 565–568.