Table 4 Subtypes of autoimmune pancreatitis (AIP) [33]

Subtype of AIP other nomenclatures	Type 1 AIP without GEL IgG4-related, LPSP	Type 2 AIP with GEL IgG4-unrelated IDCP
Prevalence	Asia > USA, Europe	Europe > USA > Asia
Age	High age	Younger
Gender	Male ≫ female	Male = female (NS)
Symptoms	Often obstructive jaundice	Often obstructive jaundice
Jaundice	Rare abdominal pain	Abdominal pain like acute pancreatitis
Pancreas images	Swelling/diffuse	Swelling/diffuse
	Segmental/focal	Segmental/focal
	Mass-forming	Mass-forming
Serology	High serum IgG	Normal IgG
	High serum IgG4	Normal IgG4
	Auto antibodies (+)	Auto antibodies (−)
Other organ involvement (OOI)	Sclerosing cholangitis	Unrelated to OOI
	Sclerosing sialadenitis	
	Retroperitoneal fibrosis	
	Other characteristics	
Ulcerative colitis	Rare	Often
Steroid response	Responsive	Responsive
Relapse	High rate	Rare

GEL, granulocyte epithelial lesion; *LPSP*, lymphoplasmacytic sclerosing pancreatitis; *IDCP*, idiopathic duct-centric chronic pancreatitis; *NS*, not significant

irregular narrowing of the pancreatic duct (sclerosing pancreatitis on endoscopic retrograde cholangiopancreatography [ERCP] images); (7) lymphocyte and IgG4-positive plasmacyte infiltration and fibrosis, and obliterative phlebitis; (8) occasional association with extrapancreatic lesions, such as sclerosing cholangitis similar to primary sclerosing cholangitis (PSC), sclerosing cholecystitis, sclerosing sialoadenitis, RPF, interstitial renal tubular disorders, enlarged celiac and hilar lymph nodes, chronic thyroiditis, and pseudotumor of the pancreas, liver, or lung; and (9) responsiveness to steroid therapy. Older males with IgG-related AIP often have obstructive jaundice, with both pancreatic and extrapancreatic manifestations responding to steroid therapy [12–15, 21, 33, 34].

Histological examination by American and European pathologists of the resected pancreases of patients with chronic non-alcoholic pancreatitis revealed another histopathological pattern, called idiopathic duct-centric pancreatitis (IDCP) or AIP with granulocytic epithelial lesions (GELs), later called type 2 AIP [35, 36]. Type 2 AIP is characterized primarily by these GELs, often accompanied by destruction and obliteration of the pancreatic duct [36]. Patients with type 2 AIP show swelling of the pancreas, but no or very few IgG4-positive plasma cells. Type 2 AIP has different clinicopathological features than type 1 AIP. Type 2 AIP shows no elevations in serum IgG4 or IgG, no autoantibodies, and no involvement of other organs, except for inflammatory bowel disease. Inflammatory bowel disease has been observed in approximately 30% of patients with type 2 AIP. Although type 1, or IgG4-related, AIP (LPSP type) often occurs in older men and is accompanied by a variety of extrapancreatic lesions, type 2, or neutrophil-related pancreatitis (IDCP/GEL type), has no gender bias, younger age at onset (often <40 years), and is frequently associated with inflammatory bowel disease. Thus, after a worldwide debate over the diagnostic criteria for AIP, IgG4-related pancreatitis has been defined as type 1 (LPSP type) and neutrophil-related pancreatitis has been defined as type 2 (IDCP/GEL type) [34].

IgG4-related sclerosing cholangitis (IgG4-related SC)

Extrapancreatic bile duct lesions are frequently associated with AIP. For example, 73% of patients with AIP have shown wall thickening or sclerosing changes in extrapancreatic bile ducts on endoscopic ultrasonography (EUS) and intraductal ultrasonography (IDUS), though only 26% of patients with AIP demonstrated sclerosing changes by ERCP [37]. However, many individuals without AIP have shown IgG4-related SC with isolated biliary tract involvement [38, 39]. In IgG4-related SC, stenosis is usually observed in the lower part of the common bile duct. The cholangiographic appearance of stenosis in the intrahepatic or hilar hepatic bile duct is very similar to that observed in PSC [40], a progressive disease of unknown etiology that ultimately results in liver cirrhosis. IgG4-related SC is associated with older age, male predominance, obstructive jaundice, weight loss, and abdominal discomfort [40]. Although steroid therapy has shown mixed results in patients with PSC, IgG4-related SC

responds dramatically to steroid therapy, as does IgG4RD [41]. The histopathological features of IgG4-related SC are similar to those of AIP and include diffuse plasmacytic infiltration, marked interstitial fibrosis with a focal storiform-like pattern, and obliterative phlebitis.

IgG4-related kidney disease (IgG4-related KD)

The kidney is a frequent target organ in IgG4RD, with tubulointerstitial nephritis (TIN) and fibrosis and abundant IgG4-positive plasma cell infiltration being diagnostically important histopathological features of this disease [42–44]. Recently, the clinicopathological features of 23 patients with IgG4-related TIN were reported to be quite uniform and similar to those observed in patients with IgG4-AIP, including high serum concentrations of IgG4 and IgE, hypocomplementemia, and TIN with infiltration of large numbers of IgG4-positive plasma cells plus fibrosis [45].

Kidney diseases in IgG4RD include conditions other than renal parenchymal lesions, such as hydronephrosis associated with RPF and tumors of the renal pelvis and urethra. However, IgG4-related TIN is considered to be representative of IgG4 renal parenchymal lesions [19]. Compared with other types of interstitial nephritis, IgG4-related TIN is often associated with extrarenal lesions, such as pancreatitis, sialadenitis, and lymphadenitis, and a high incidence of hypocomplementemia [46]. Imaging often shows heterogeneous shadows in the kidneys, such as a mass or multiple nodules (findings that are not observed in other types of interstitial nephritis). Histopathologically, the renal tubulointerstitium shows the infiltration of many lymphocytes and plasmacytes, as well as fibrosis, and IgG4 immunostaining shows a number of IgG4-positive plasma cells [47]. Although many studies have found no significant changes in the glomeruli, others have reported an association with glomerular lesions, including membranous nephropathy [46]. In the near future, the Japanese Kidney Society expects to develop diagnostic criteria for IgG4-related KD.

IgG4-related pulmonary diseases (IgG4-related PD)

IgG4-related PD has been described as inflammatory pseudotumor, interstitial pneumonitis, organizing pneumonia, and lymphomatoid granulomatosis [48]. Most (81%) patients with IgG4-related PD have been reported to be men, with a median age at diagnosis of 69 years [48], features similar to those of IgG4RD. Some patients present initially with respiratory symptoms, such as dry cough or dyspnea, whereas 75% of patients are asymptomatic and the disease is found incidentally by abnormal shadows on chest X-rays. Although IgG4-related PD is associated with a variety of radiologic abnormalities [49], diffuse lymphoplasmacytic infiltration has been observed in all lesions, with irregular fibrosis and obliterative vascular changes being more common in solid areas [48]. Hilar and pancreatic accumulation of gallium-67 has been reported as characteristic of the active stage of AIP when serum IgG4 concentrations are high [50].

Radiographically, IgG4-related PD can be divided into two types, inflammatory pseudotumors and interstitial pneumonitis. Inflammatory pseudotumors have been described as nodular or mass lesions, or infiltration, and are characterized by radiating reticular shadows surrounding the tumor. Interstitial pneumonitis presents in most patients with reticular shadows, ground-glass opacity, and interstitial fibrosis in both lower lung fields [17].

Histopathologically, inflammatory pseudotumor is a plasma cell granuloma, with infiltration mainly by plasma cells and lymphocytes, irregular fibrosis, lymphoid follicle formation, findings of interstitial pneumonitis at the periphery of the nodule, obliterating phlebitis and arteritis, and eosinophilic infiltration [17]. Interstitial pneumonitis is characterized by thickening of the alveolar septa due to infiltration by plasma cells and lymphocytes, and by diffuse fibrosis. Histopathologically, interstitial pneumonitis often shows a pattern previously classified as non-specific interstitial pneumonia (NSIP) [51]. The diagnostic criteria for IgG4-related PD are now under consideration by the Japanese Respiratory Association.

IgG4-related Hashimoto's thyroiditis (IgG4-related HT)

Hashimoto's thyroiditis (HT) has been considered a well-defined clinicopathological entity, characterized by the presence of goiter and serum thyroid autoantibodies. Recently, a unique subtype of HT was described, characterized by the presence of prominent fibrosis such as storiform fibrosis and swirling fibrosis, numerous IgG4-positive plasma cells, and elevated serum IgG4 [52], and called IgG4-related HT [53]. Among 23 patients with HT who underwent total thyroidectomy, 14 cases (60.8%) were IgG4-related HT, but there were no significant differences in positivity for thyroid and microsome tests between IgG4-related HT and non-IgG4 HT [54].

Riedel's thyroiditis was first described in 1896 in two patients with hard goiter and tracheal compressive symptoms. One-third of patients with Riedel's thyroiditis have multifocal fibrosclerosis, including sclerosing cholangitis, salivary gland fibrosis, RPF, or fibrotic orbital pseudotumor. Therefore, despite the lack of immunohistochemical staining for IgG4, certain proportions of Riedel's thyroiditis were considered a type of IgG4RD. Although one patient with IgG4RD showed involvement of the lachrymal gland and pulmonary and biliary tracts as well as Riedel's

thyroiditis [32], it is still unclear whether Riedel's thyroiditis is a type of IgG4RD.

IgG4-related lymphadenopathy and Castleman's disease

Concomitant lymphadenopathy is common in patients with IgG4RD, and there have been several reports dealing with the morphological and immunohistological findings of lymph node lesions [55–57]. Although IgG4-related lymphadenopathy is occasionally characterized by systemic lymphadenopathy, polyclonal hyperimmunoglobulinemia, especially elevated IgG and IgE concentrations, and positivity for various autoantibodies, patients with IgG4RD with generalized lymphadenopathy should only be evaluated for lymphoma, sarcoidosis, multicentric Castleman's disease, and other malignancies.

IgG4-related lymphadenopathy can be characterized into five histological subtypes: Castleman's disease-like morphology (type I), reactive follicular hyperplasia (type II), interfollicular plasmacytosis and immunoblastosis (type III), progressive transformation of germinal center-like (type IV), and inflammatory pseudotumor-like morphology (type V) [57]. In addition, IgG4-related lymphadenopathy can be classified into two types based on the infiltrative patterns of IgG4-positive cells: interfollicular plasmacytosis (types I, II, III, and V) and intragerminal center plasmacytosis (type IV). Patients with systemic IgG4-related lymphadenopathy were significantly older (68.8 vs. 43.3 years) and had significantly lower C-reactive protein (0.29 vs. 8.71 mg/dl) and interleukin (IL)-6 (8.45 vs. 34.82 pg/ml) concentrations than patients with multicentric Castleman's disease [56].

IgG4-related retroperitoneal fibrosis (IgG4-related RPF)

RPF is a chronic inflammatory condition with marked fibrosis in retroperitoneal tissue. In patients with advanced RPF a retroperitoneal mass covers the abdominal aorta and compresses the ureters, leading to urinary obstruction. Its etiology is unknown, but it has many causes, including infection, radiation, drugs, malignant tumor, and trauma. Three patients with RPF and elevated serum IgG4 have been described [58], and the histology of all 12 patients with RPF was reported to be similar to that seen in AIP, including fibrosis, intense inflammatory cell infiltration with plasma cells, venulitis, and obliterative arteritis [59]. Of 17 patients with RPF, 10 had both elevated serum IgG4 and histopathological features typical of IgG4RD, suggesting that RPF could be categorized as IgG4-related [60]. However, in RPF, fibrosis gradually progresses during chronic inflammation, with lymphocyte infiltration predominant during the early stages and a fibroinflammatory process occurring later. Therefore, determining the stage of illness seems important for diagnosis and prediction of response to steroid treatment [61].

IgG4-related aortitis

There have been several recent reports of inflammatory aneurysms in the abdominal or thoracic aorta [62–64]. For example, 40% of inflammatory abdominal aortic aneurysms (AAAs) were IgG4RD, with elevated IgG4 in serum and abundant infiltration of IgG4+ plasma cells and obliterative phlebitis [62]. These findings suggested that inflammatory AAAs can be classified into 2 groups: IgG4-related and IgG4-unrelated [62]. Although IgG4RD shows good response to steroid therapy, treatment with the anti-CD20 monoclonal antibody, rituximab, may result not only in clinical improvement, but in the tapering or discontinuation of steroids or other drugs [65].

Pathogenesis and pathophysiology of IgG4RD

At present, the pathogenetic mechanism and underlying immunological abnormalities in IgG4RD remain unclear. The elevated serum IgG4 concentration and tissue infiltration of IgG4-positive plasma cells are characteristic features of IgG4RD. Because IgG4 antibodies are dynamic molecules that can exchange Fab arms by swapping a heavy chain and attached light chain, IgG4 can form bi-specific antibodies, as well as functioning as a monovalent molecule [66, 67]. These properties may protect against type I allergy by inhibiting IgE functions, and may prevent type II and III allergy by blocking the Fc-mediated effector functions of IgG1 and inhibiting the formation of large immune complexes. The predominant expression of IgG4 under conditions of chronic antigen exposure is compatible with the clinical features of IgG4RD, including its slow progression and relatively weak immune response.

Some autoantibodies, including those to pancreatic trypsin inhibitor (PSTI), lactoferrin (LF), and carbonic anhydrase (CA), have been detected in patients with IgG4RD, especially in those with IgG4-related AIP [34]. Although IgG4 from the patients was able to bind the normal epithelia of the pancreatic ducts, gallbladder, and salivary gland ducts [68], IgG4-type autoantibodies have not been detected in patients with IgG4RD.

Aberrant immunological findings have been observed in patients with IgG4RD. For example, the Th2-dominant immune response and the production of Th2-type cytokines, such as IL-4, IL-5, IL-10, and IL-13, are increased [69–71]. Furthermore, the numbers of regulatory T cells (Treg) expressing CD4+CD25+Foxp3 are significantly higher in the affected tissues and peripheral blood of

patients with IgG4RD than the numbers in patients with autoimmune and nonautoimmune diseases [72–74]. Overexpression of the regulatory cytokines IL-10 and transforming growth factor β (TGF-β) has also been reported in patients with IgG4RD [74, 75]. IL-10 and TGF-β have potent activities in directing B cells to produce IgG4 and induce fibroplasia, respectively. IL-4, IL-5, and IL-13 are important for class switching to IgE production and eosinophil migration. Therefore, abnormalities in the production of these cytokines may be involved in the pathogenesis of IgG4RD.

Perspectives on IgG4RD

Although IgG4RD is a novel clinical entity, it is not a rare disease. Despite the effectiveness of steroid therapy, for IgG4RD, the condition has often been misdiagnosed as a malignant tumor, lymphoma, Sjögren's syndrome, or other diseases. To date, the clinical diagnostic criteria for IgG4RD have not been established. Because IgG4RD may occur in a variety of organs throughout the body, comprehensive discussions with the cooperation of many clinicians from various specialized fields is needed to establish uniform diagnostic criteria. At present, the diagnostic criteria for IgG4-MD (Table 2) [8] and those for IgG4-AIP type 1 (Table 5) [14] have been established.

Consensus has been reached on two diagnostic criteria for IgG4RD: (1) serum IgG4 concentration >135 mg/dl, and (2) >40% of IgG-positive plasma cells being IgG4-positive. The MHLW Japan team has proposed guidelines for the diagnosis of IgG4RD; these are shown in Table 3. The formulation of organ-specific (i.e., kidney and pulmonary) diagnostic criteria for IgG4RD requires cooperation with the relevant societies. Although IgG4RD responds well to steroid therapy, recurrence and relapse occur following the early reduction or withdrawal of prednisone. Therefore, it is necessary to develop treatment guidelines to establish initial doses of steroids, tapering procedures, and maintenance doses. The MHLW Japan team is currently pursuing a "Prospective study for creating IgG4-related disease treatment guidelines", and unified clinical guidelines are expected in the near future.

Table 5 Clinical diagnostic criteria of autoimmune pancreatitis; revised proposal in Japan (2006) [79]

1. Diffuse or segmental narrowing of the main pancreatic duct with irregular wall and diffuse or localized enlargement of the pancreas on imaging modalities, such as abdominal ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI)
2. High-serum F-globulin, IgG, or IgG4, or the presence of autoantibodies, such as antinuclear antibodies and rheumatoid factor
3. Marked interlobular fibrosis and prominent infiltration of lymphocytes and plasma cells into the periductal area, with occasional lymphoid follicles in the pancreas

For diagnosis, criterion 1 must be present, together with criteria 2 and/or 3

However, it is necessary to exclude malignant diseases such as pancreatic and biliary cancers

Acknowledgments This work was supported by the Research Program for Intractable Diseases, Health and Labor Sciences Research Grants from the Ministry of Health, Labor and Welfare, Japan. We sincerely thank the many contributing researchers and collaborators who participated in the MHLW Japan G4 team.

Conflict of interest None.

Appendix

The authors thank the many patients who participated in this registry. In addition to the listed authors, other professional collaborators in the Research Program for Intractable Disease supported by the Ministry of Health, Labor and Welfare (MHLW) Japan G4 team, include: Keita Fujikawa (Isahaya Hospital); Hideaki Hamano, Keiji Kubo, and Hiroshi Yamamoto (Shinshu University); Mitsuyosi Hirokawa (Kuma Hospital); Kunihiko Itoh (Shizuoka Prefectural University); Terumi Kamisawa (Tokyo Metropolitan Research Institute); Daisuke Kawabata (Kyoto University); Morio Matsumoto (Nishi Gunma Hospital); Seijiro Minamoto (Osaka Respiratory and Allergy Center); Kayoko Murayama (Gunma Cancer Institute); Susumu Nishiyama (Kurashiki Hospital); Yoko Ogawa (Keio University); Tomoki Origuchi (Nagasaki University); Norihide Oyama (Niigata University); Yasuharu Sato (Okayama University); Masao Seto (Aichi Cancer Center); Susumu Sugai (Kudou Hospital); Norifumi Tsukamoto (Gunma University); Masayuki Takahira (Kanazawa University); Hiroki Takahashi (Sapporo Medical University); Hiroto Tsuboi (Tsukuba University); Yuko Waseda (Kanazawa University); and Kazuko Kitagawa, Takayuki Nojima, Hitoshi Yokoyama, Hisao Tonami, Toshihiro Fukushima, Masao Tanaka, Yoshimasa Fujita, Toshioki Sawaki, Takafumi Kawanami, Miyuki Miki, Haruka Iwao, Akio Nakajima, and Takuji Nakamura (Kanazawa Medical University).

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J Gastroenterol (2011) 46:277–288
DOI 10.1007/s00535-011-0386-x

REVIEW

Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease

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Received: 6 February 2011 / Accepted: 7 February 2011 / Published online: 11 March 2011

Abstract Recent studies have suggested the existence of two subtypes of autoimmune pancreatitis (AIP): type 1 AIP, related to IgG4 (lymphoplasmacytic sclerosing pancreatitis); and type 2 AIP, related to a granulocytic epithelial lesion (idiopathic duct-centric chronic pancreatitis). Compared with type 2 AIP, the clinicopathological features of type 1 AIP, with increased serum IgG4/IgE levels, abundant infiltration of IgG4 + plasmacytes and lymphocytes, autoantibodies, and steroid responsiveness, are more suggestive of abnormal immunity such as allergy or autoimmunity. Moreover, patients with type 1 AIP often have extrapancreatic lesions, such as sclerosing cholangitis, sclerosing sialadenitis, or retroperitoneal fibrosis, showing pathological features similar to those of the pancreatic lesions. Based on these findings, an international concept of and diagnostic criteria for AIP have been proposed recently. Of interest, many synonyms have been proposed for the conditions of AIP and extrapancreatic lesions associated with IgG4, such as "multifocal idiopathic fibrosclerosis," "IgG4-related autoimmune disease," "IgG4-related sclerosing disease," "systemic IgG4-related plasmacytic syndrome (SIPS)," and "IgG4-related multiorgan lymphoproliferative syndrome," all of which may refer to the same conditions. Therefore, the Japanese Research Committee for "Systemic IgG4-Related Sclerosing Disease" proposed a disease concept and clinical diagnostic criteria based on the concept of multifocal fibrosclerosing disease, in 2009, in which the term "IgG4-related disease" was agreed upon as a minimal consensus to cover these conditions. Although the significance of IgG4 in the development of "IgG4-related disease" remains unclear, we have proposed a hypothesis for the development of type 1 AIP, one of the IgG4-related diseases. The concept and diagnostic criteria of "IgG4-related disease" will be changed in accordance with future studies.

Keywords IgG4 · IgG4-related disease · Autoimmune pancreatitis · Mikulicz disease · Regulatory T cell (Treg)

Abbreviations

AIP	Autoimmune pancreatitis
ANA	Anti-nuclear antibody
CA-II	Carbonic anhydrase-II
CTLA-4	Cytotoxic T lymphocyte antigen-4
ERCP	Endoscopic retrograde cholangiopancreatography
FCRL	Fc-receptor-like
IFN-γ	Interferon-γ
IL-4	Interleukin-4
LF	Lactoferrin
LPSP	Lymphoplasmacytic sclerosing pancreatitis
MD	Mikulicz disease
MHC	Major histocompatibility complex
MOLPS	Multiorgan lymphoproliferative disease
PBP	Plasminogen-binding protein
SjS	Sjögren's syndrome
PSC	Primary sclerosing cholangitis
RF	Rheumatoid factor
SIPS	Systemic IgG4 plasmacytic syndrome
SLE	Systemic lupus erythematosus
Treg	Regulatory T cell
UBR2	Ubiquitin-protein ligase E3 component n-recognin 2

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Introduction

In 1961, Sarles et al. [1] first observed a case of particular pancreatitis with hypergammaglobulinemia. Yoshida et al. [2] first proposed the concept of autoimmune pancreatitis (AIP). Hamano et al. [3] reported increased serum levels of IgG4 in Japanese patients with AIP. Thereafter, many studies of AIP were reported, mainly by Japanese investigators. The histopathological findings of AIP are characterized by the periductal localization of predominantly CD4-positive T cells, IgG4-positive plasma cells, storiform fibrosis with acinar cell atrophy frequently resulting in stenosis of the main pancreatic duct, and obliterative fibrosis [4–6], which is also called lymphoplasmacytic sclerosing pancreatitis (LPSP) [7]. In 2003, Kamisawa et al. [8] suggested that AIP is a systemic sclerosing disease, based on the findings that the pancreas and other involved organs have fibrosis with abundant infiltration of IgG4-positive plasma cells, which is similar to the concept of multifocal fibrosclerosis proposed by Comings et al. [9]. Further histological and clinical profiling of patients with "AIP" reveals two distinct subtypes, type 1 and type 2 AIP [10, 11]. Type 1 AIP is classified as a pancreatic manifestation of IgG4-related disease, probably a systemic disease with an autoimmune process, whereas type 2 AIP is regarded as a specific pancreatic disease with a granulocytic epithelial lesion (GEL) [12, 13] and occasional coexistence with ulcerative colitis [10, 11].

Of note, patients with Mikulicz's disease (MD) –originally classified as an atypical type of Sjögren's syndrome– who usually have bilateral, painless, and symmetrical swelling of the lachrymal, parotid, and submandibular glands [14], show elevated serum levels of IgG4, infiltration of IgG4-positive plasma cells into the glands, and recovery of secretion with steroid treatment. Similar to patients with AIP, these patients often show other organ involvement (OOI) such as AIP, sclerosing cholangitis, retroperitoneal fibrosis, enlarged celiac and hilar lymph nodes, chronic thyroiditis, and interstitial nephritis [4–6, 14–16]. Recently, however, MD has been considered to be completely different from Sjögren's syndrome because of the lack of anti-SS-A/Ro or anti-SS-B/La antibodies, and the showing of steroid responsiveness [2–6]. The steroid responses and the prognoses of AIP patients with sclerosing cholangitis differ from these features in patients with primary sclerosing cholangitis (PSC), which suggests different pathological conditions. These findings led us to the concept of "IgG4-related disease" such as IgG4-related systemic sclerosing disease [8, 17], systemic IgG4-related plasmacytic syndrome (SIPS) [18], and IgG4-positive multiorgan lymphoproliferative syndrome (IgG4-MOLPS) [19]. Although the pathogenesis and pathophysiology of AIP remain unclear, we will discuss the most recent advances in the concept of AIP, especially IgG4-related type 1 AIP, and the advances in the novel concept of "IgG4-related disease."

Subtypes of autoimmune pancreatitis: type 1 and type 2 AIP

Recent studies have suggested that "AIP" manifests as two distinct subtypes, type 1 and type 2 AIP (Table 1) [10, 11]. Hypergammaglobulinemia, the deposition of immunoglobulins, the presence of autoantibodies, and steroid efficacy in Type 1 AIP confirm the definition of autoimmune disease proposed by Mackay [20]. Different from type 1 AIP, patients with type 2 AIP have no serological markers of autoimmunity. Therefore, it is still in debate as to whether or not type 2 AIP should be classified as a clinical entity of AIP, but the deposition of C3c and IgG in the basement membrane of pancreatic ducts and acini suggests an immune complex-mediated destruction of ducts and acini in type 2 AIP as well as type 1 AIP [21]. The nomenclature of the two subtypes of AIP and international consensus diagnostic criteria were proposed at the meeting of the International Association of Pancreatology held at Fukuoka in 2010 (Tables 2, 3) [22].

Type 1 AIP

In type 1 AIP, whose histological description is called LPSP, the pancreatic histopathology shows the following characteristic features: (1) abundant infiltration of plasma cells ($IgG4^+$ cells; high-power field [hpf], IgG4/IgG cells; >40%) and lymphocytes, (2) peculiar storiform or swirling fibrosis, and (3) perivenular infiltration with lymphocytes and plasma cells often leading to obliterative phlebitis. Clinically, type 1 AIP seems to be the pancreatic manifestation of the recently proposed IgG4-related disease, characterized by swelling of the pancreas, elevated serum IgG4 levels, and extrapancreatic lesions (e.g., sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis) associated with the infiltration of abundant IgG4 + plasma cells. Patients with type 1 AIP are often elderly males who have obstructive jaundice, and the pancreatic and extrapancreatic manifestations respond to steroid therapy.

Extrapancreatic lesions in type 1 AIP

A variety of extrapancreatic lesions have been noted in patients with AIP, including lachrymal and salivary gland lesions [23], pulmonary lesions including hilar lymphadenopathy [24], sclerosing cholangitis [25, 26], retroperitoneal fibrosis [27], and tubulointerstitial nephritis (TIN) [15, 28, 29]. Associations were also reported with hypophysitis

Table 1 Subtypes of autoimmune pancreatitis (AIP)

Subtype of AIP	Type 1	Type 2
Other nomenclatures	AIP without GEL	AIP with GEL
	IgG4-related LPSP	IgG4-unrelated IDCP
Prevalence	Asia > USA, Europe	Europe > USA > Asia
Age	High age	Younger
Gender	Male ≫ female	Male = female (NS)
Symptoms	Often obstructive jaundice rare abdominal pain	Often obstructive jaundice abdominal pain like acute pancreatitis
Pancreas images	Swelling (diffuse/segmental/focal)/ mass-forming	Swelling (diffuse/segmental/focal)/mass-forming
Serology	High serum IgG, IgG4, autoAbs (+)	Normal IgG, normal IgG4, autoAbs (−)
Other organ involvement (OOI)	Sclerosing cholangitis	Unrelated to OOI
	Sclerosing sialadenitis	
	Retroperitoneal fibrosis	
	Others	
Ulcerative colitis	Rare	Often
Steroid	Responsive	Responsive
Relapse	High rate	Rare

GEL granulocytic epithelial lesion, *LPSP* lymphoplasmacytic sclerosing pancreatitis, *IDCP* idiopathic duct-centric chronic pancreatitis, *Abs* antibodies, *NS* not significant

[30], chronic thyroiditis [16, 31], and prostatitis [32]. Other extrapancreatic involvements have been reported in a few cases [33–36]. Though it is not certain that all of these involvements have a relation with AIP, extrapancreatic lesions are prevalent systemically in various organs (Table 4) [29–41], suggesting that type 1 AIP, but not type 2 AIP, may be a pancreatic manifestation of IgG4-related disease. The extrapancreatic lesions appear synchronously or metachronously with the pancreatic lesion(s), share the same pathological conditions, and show favorable responses to steroid therapy; these characteristics suggest a common pathophysiological background. The lesions are usually detected by imaging and blood tests (computed tomography [CT], magnetic resonance imaging [MRI], gallium scintigraphy, fluorodeoxyglucose positron emission tomography [FDG-PET], and IgG4); however, such findings should be confirmed by histological findings. Extrapancreatic lesions sometimes mimic, or are misdiagnosed as, primary lesions of the corresponding organs: lachrymal and salivary gland lesions for Sjögren's syndrome, respiratory lesions for sarcoidosis, and sclerosing cholangitis for PSC. Therefore, it is necessary to differentiate between IgG4-related diseases and inherent diseases of the corresponding organs. Patients with IgG4-related sialodacryoadenitis, synonymous with IgG4-related MD [13, 41], usually have symmetrical enlargement of the salivary and lacrimal glands. The IgG4-related central nervous system lesions include infundibulohypophysitis, hypertrophic pachymeningitis, intracranial inflammatory pseudotumor, and orbital pseudotumor [21–41].

Type 2 AIP

Type 2 AIP was proposed from histological examination of pancreases resected from patients with chronic non-alcoholic pancreatitis by American and European pathologists, who reported another histopathological pattern, named idiopathic duct-centric pancreatitis (IDCP) or AIP with GEL [11–13]. The most characteristic feature of type 2 AIP is the GEL, often with destruction and obliteration of the pancreatic duct. Type 2 AIP has swelling of the pancreas, but none or very few IgG4-positive plasma cells, and clinical features show a distinctly different profile from that of type 1 AIP, with no associated serum IgG4, IgG elevation, presence of autoantibodies, or other organ involvement, except for inflammatory bowel disease (approximately 30%).

The concept of IgG4-related disease and proposal of the clinical diagnostic criteria

Patients with IgG4-related disease show diffuse/focal organ enlargement, with mass-forming or nodular/thickened lesions in various organs, occurring synchronously or metachronously, due to the prominent infiltration of lymphocytes and plasmacytes with fibrosis [21–41]; however, the causes of the disease are still not clear. The organs known to be affected include the pancreas, biliary duct, lacrimal/salivary glands, retroperitoneum, central nervous system, thyroid gland, lungs, liver, gastrointestinal tract, kidneys, prostate gland, and lymph nodes [21–41]. Clinical

Table 2 Diagnosis of definitive and probable type 1 AIP using international consensus diagnostic criteria (ICDC) [22]

Diagnosis	Primary basis for diagnosis	Imaging evidence	Collateral evidence
Definitive type 1 AIP	Histology	Typical/indeterminate	Histologically confirmed LPSP (level 1 H)
	Imaging	Typical	Any non-D level 1/level 2
		Indeterminate	Two or more from level 1 (+level 2 D*)
	Response to steroid	Indeterminate	Level 1 S/OOI + Rt or level 1 D + level 2 S/OOI/H + Rt
Probable type 1 AIP		Indeterminate	Level 2 S/OOI/H + Rt

	Criterion	Level 1	Level 2
P	Parenchymal imaging	*Typical*	*Indeterminate* (*including atypical**):
		Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the MPD) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size <5 mm)
S	Serology	IgG4 > 2× upper limit of normal value	IgG4 1–2× upper limit of normal value
OOI	Other organ involvement	a or b	a or b
		a. Histology of extrapancreatic organs	**a. Histology of extrapancreatic organs including endoscopic biopsies of bile duct****
		Any three of the following	*Both of the following*
		Marked lymphoplasmacytic infiltration with fibrosis and without granulocytic infiltration	Marked lymphoplasmacytic infiltration without granulocytic infiltration
		Storiform fibrosis	Abundant (>10 cells/hpf) IgG4-positive cells
		Obliterative phlebitis	**b. Physical or radiological evidence**
		Abundant (>10 cells/hpf) IgG4 positive cells	*At least one*
		b. Typical radiological evidence	Symmetrically enlarged salivary/lacrimal glands
		At least one	Radiological evidence of renal involvement described in association with AIP
		Segmental/multiple proximal (hilar/intra hepatic) or proximal and distal bile duct stricture	
		Retroperitoneal fibrosis	
H	Histology of the pancreas	LPSP (core biopsy/resection)	LPSP (core biopsy)
		At least 3 of the following	*Any 2 of the following*
		Periductal lymphoplasmacytic infiltrate without granulocytic infiltration	Periductal lymphoplasmacytic infiltrate without granulocytic infiltration
		Obliterative phlebitis	Obliterative phlebitis
		Storiform fibrosis	Storiform fibrosis
		Abundant (>10 cells/hpf) IgG4-positive cells	Abundant (>10 cells/hpf) IgG4positive cells
Diagnostic steroid trial			
Response to steroid (Rt)[#]		Rapid (≤2 weeks) radiologically demonstrable resolution or marked improvement in pancreatic/extrapancreatic manifestations	

hpf high-power field, *MPD* main pancreatic duct, *D* ductal imaging, *Rt* response to steroid treatment, *S* serology, *H* histology, *ERP* endoscopic retrograde pancreatography

Table 3 Diagnosis of definitive and probable type 2 AIP using international consensus diagnostic criteria (ICDC) [22]

Diagnosis	Imaging evidence	Collateral evidence
Definitive type 2 AIP	Typical/ indeterminate	Histologically confirmed IDCP (level 1 H) or clinical IBD + level 2 H + Rt
Probable type 2 AIP	Typical/ indeterminate	Level 2 H/clinical IBD + Rt

	Criterion	Level 1	Level 2
P	Parenchymal imaging	*Typical*	*Indeterminate (including atypical*)*
		Diffuse enlargement with delayed enhancement (sometimes associated with rim-like enhancement)	Segmental/focal enlargement with delayed enhancement
D	Ductal imaging (ERP)	Long (>1/3 length of the MPD) or multiple strictures without marked upstream dilatation	Segmental/focal narrowing without marked upstream dilatation (duct size <5 mm)
OOI	Other organ involvement		Clinically diagnosed inflammatory bowel disease
H	Histology of the pancreas (core biopsy/resection)	IDCP:	
		Both of the following	*Both of the following*
		Granulocytic infiltration of duct wall (GEL) with or without granulocytic acinar inflammation	Granulocytic and lymphoplasmacytic acinar infiltrate
		Absent or scant (0–10 cells/hpf) IgG4-positive cells	Absent or scant (0–10 cells/hpf) IgG4-positive cells
Diagnostic steroid trial			
Response to steroid (Rt)[#]		Rapid (<2 weeks) resolution or marked improvement in manifestations	

IBD inflammatory bowel disease, *D* ductal imaging, *Rt* response to steroid treatment, *H* histology, *ERP* endoscopic retrograde pancreatography

symptoms vary depending on the organ in which the lesions are located, but many cases are treated effectively by steroid therapy [21–41]. The prognosis is not clear; however, some patients develop serious complications such as obstructive jaundice due to hepatic, gallbladder, or pancreatic lesions; hydronephrosis due to retroperitoneal fibrosis; or respiratory symptoms due to "pulmonary lesions" [17–19, 26–29]. Although the infiltration of IgG4-positive cells and increased serum levels of IgG4 are characteristic of IgG4-related disease, the severity of fibrosis seems to be different among the individual involved organs. These conditions are quite similar to multifocal idiopathic fibrosclerosis (MIF) [9].

In addition to MIF, there are many synonyms, such as IgG4-related autoimmune disease [8], "IgG4-related sclerosing disease" [17], SIPS [18], and "IgG4 + MOLPS" [19], all of which may refer to the same conditions. It has been debated which term is the most appropriate. Storiform fibrosis and obliterative phlebitis are characteristic in the pancreatic and biliary tract lesions, but the degree varies depending on the individual organs, e.g., these features are very seldom found in lachrymal/salivary gland lesions or lymph node lesions. The term "IgG4-related sclerosing disease" is mainly based on fibrous swollen organs, whereas the terms "IgG4-SIPS" and "IgG4 + MOLPS" are based on lymphoplasmacytic proliferation and swollen lymph nodes without fibrosis.

Although most patients with type 1 AIP have multiorgan lesions that occur synchronously or metachronously, about 10–20% of the patients show a solitary organ involved without confirmation of other organ involvement. Therefore, it is unclear whether or not the pathogenetic mechanism is the same in individual organs. Based on these findings, the members of the Japanese Research Committees for "Systemic IgG4-Related Sclerosing Disease" (chaired by Professor K. Okazaki) [40] and "IgG4-MOLPS" (chaired by Professor H. Umehara) [41], both of which Committees were supported by the "Research for Intractable Disease Program from the Ministry of Health, Labor and Welfare of Japan", have agreed that the term "IgG4-related disease" be regarded as minimally accepting these conditions at present. To study these conditions, the Japanese Research Committee for "Systemic IgG4-Related Sclerosing Disease" (chaired by Professor K. Okazaki) proposed a disease concept and clinical diagnostic criteria of "systemic IgG4-related sclerosing disease" in 2009 (Table 5) [40]. However, the concept and diagnostic criteria should be changed in accordance with the findings of the future studies.

Table 4 Extrapancreatic lesions complicated with autoimmune pancreatitis. (from Ref. [38])

Close association
Lachrymal gland inflammation
Sialoadenitis
Hilar lymphadenopathy
Interstitial pneumonitis
Sclerosing cholangitis
Retroperitoneal fibrosis
Tubulointerstitial nephritis
Possible association
Hypophysitis
Autoimmune neurosensory hearing loss
Uveitis
Chronic thyroiditis
Pseudotumor (breast, lung, liver)
Gastric ulcer
Swelling of papilla of Vater
IgG4 hepatopathy
Aortitis
Prostatitis
Schonlein-Henoch purpura
Autoimmune thrombocytopenia

Immunological approaches to the pathophysiology of AIP and IgG4-related disease

The pathogenesis and pathophysiology of AIP have been studied mainly from immunological approaches and

Table 5 Clinical diagnostic criteria 2009 for IgG4-related disease (proposed by the Japanese Research Committee for "Systemic IgG4-related Sclerosing Disease") [40]

(1) Clinically, diffuse/focal enlargement, or mass-forming, nodular/thickened lesions in one or more organs

(2) Elevated levels of serum IgG4 (>135 mg/dl)

(3) Histopathological findings

① Prominent infiltration of lymphocytes and plasmacytes with fibrosis, but no neutrophilic infiltration

② Abundant infiltration of IgG4-positive plasmacytes (>10/hpf) and/or a ratio of IgG4/IgG-positive cells of >40%

③ Storiform/swirling fibrosis

④ Obliterative phlebitis

Diagnosis of IgG4-related disease: (1) + (2), (1) + (3)①②, (2) + (3)①②, or (3)①②③④

The following cases must be excluded from the diagnosis: malignant tumors developed in organs (e.g., cancers, malignant lymphomas) or similar diseases (e.g., Sjögren's syndrome, primary sclerosing cholangitis), bronchial asthma, and Castleman's disease

studies have focused mainly on IgG4-related type 1 AIP, because little evidence of abnormal immunity has been reported in type 2 AIP.

Humoral immunity

IgG4 and its possible role in IgG4-related diseases

In healthy subjects, IgG1 usually accounts for most of the total IgG [42]. Generally, the amount of IgG4 does not vary with sex or age, and the quantity of IgG4 as well as the IgG4/total IgG ratio tends to remain constant [42]. The ratios for each IgG subclass are 65% of IgG1, 25% of IgG2, 6% of IgG3, and 4% of IgG4 [42]. In IgG4-related diseases, total IgG, IgG1, IgG2, IgG4, and IgE ratios are usually increased compared with healthy subjects, while IgM, IgA, and the ratios of IgG to IgM or IgA, are decreased compared with findings in healthy subjects or those with other diseases [3, 15, 19, 43]. Ratios of IgG subclasses other than IgG4 are somewhat different among individual diseases; in AIP, all subclasses (IgG1-G4) of IgG are increased compared with findings in other types of pancreatitis. In contrast, IgG_1 and IgG_3 in MD show significantly lower negative correlations with IgG4 than those shown in typical Sjögren's syndrome.

Although the association of IgE-mediated allergy and IgG4 antibodies is well known [44], IgG4 characteristics are still poorly understood. Basically, IgG4 has non-active characteristics for immune responses involved in a continuous process referred to as 'Fab-arm exchange', which occurs by the swapping of a heavy chain and attached light chain (half-molecule) with a heavy-light chain pair from another molecule [45], which usually results in asymmetric antibodies with two different antigen-combining sites. While these modified antibodies are hetero-bivalent, they behave as monovalent antibodies [45]. Another aspect of IgG4 mimics IgG rheumatoid factor (RF) activity by interacting with IgG on a solid support [46]. In contrast to conventional RF, which binds via its variable domains, the activity of IgG4 is located in its constant domains, but is inefficient in activating potentially dangerous effector systems due to its low affinity for C1q and the classical Fcγ-receptors.

IgG4 seems to be associated with a pathogenic effect in a few situations. In pemphigus, recognition of skin autoantigens (desmogleins) by IgG4 is at the origin of the disease process [47]. IgG4 Fc–Fc binding may have a pathological role within the inflammatory process, or may even induce inflammation through the aggregation of immunoglobulins, as occurs in a mouse lupus model [48]. Although some earlier reports of AIP suggested the presence of autoantibodies against the systemically distributed antigens described above, it remains unclear whether or not IgG4-type autoantibodies have a direct role in the pathogenesis of IgG4-related diseases. To date, there have been few reports indicating IgG4 deposition in IgG4-related renal diseases [15, 29]. Therefore, in some IgG4-related diseases, the infiltration of IgG4 + plasma cells might have an association with pathological roles, similar to those in pemphigoid diseases, through IgG4 Fc–IgG Fc binding.

On the other hand, although IgG4 is associated with several clinical conditions, it is generally considered to be a benign, non-pathogenic antibody [49]. Some of these associations suggest a protective effect, such as in allergen-specific immunotherapy, tolerance induction after food avoidance [50], and protection from allergic effects during parasitosis [51, 52]. Recent data on the regulation of IgG4 showed that IgG4-related diseases may reflect an excessive production of anti-inflammatory cytokines such as interleukin (IL)-10, triggering an overwhelming expansion of IgG4-producing plasma cells. In AIP, increased peripheral inducible-memory regulatory T cells (Tregs) are positively correlated with serum levels of IgG4 [53]. In addition, prominent infiltration of Tregs upregulated IL-10 in the livers of patients with IgG4-related sclerosing cholangitis [54]. These findings suggest that IgG4 or IgG4-immune complexes do not act as a pathogenetic factor, but act as an anti-inflammatory factor in IgG4-related diseases [46]. Further studies are necessary to clarify the role of IgG4 in IgG4-related diseases.

The complement system

Patients in active stages of AIP occasionally show decreased complement (C3, C4) with elevated circulating immune complex as well as elevated serum levels of IgG4 and the IgG4 subclass of immune complexes [3, 55]. However, a recent study showed that the classical pathway of complement activation through IgG1 may be involved in the development of AIP, rather than mannose-binding lectin or alternative pathways through IgG4 [56]. Moreover, IgG4 is bound to other isotypes such as IgG1, 2, and 3 with an Fc–Fc interaction immune complex in patients with AIP [46], and thus IgG4 may contribute to the clearance of immune complexes or termination of the inflammatory process by preventing the formation of large immune complexes by blocking the Fc-mediated effector functions of IgG1. Compared with findings in systemic lupus erythematosus (SLE), TIN is more often observed in the renal lesions of IgG4-related disease. But, in acute TIN associated with AIP, the deposition of immune complex (IgG and C3) was observed in the glomerular basement membrane but not in the tubular basement membrane, which suggests that membranous glomerulonephritis is also associated with severe TIN associated with IgG4-related disease [15, 29]. Recently, the deposition of C3 and IgG in the basement membrane of pancreatic ducts have been identified in both type 1 and 2 AIP [21].

Autoantibodies

Patients with IgG4-related diseases generally show several autoantibodies in addition to increased IgG and IgG4 [4, 5]. Although some patients with IgG4-related disease have non-specific antibodies such as anti-nuclear antibody (ANA), the association of IgG4-related disease and well-known autoimmune diseases such as Sjögren's syndrome and SLE is rare. From the viewpoint of IgG4 function, the big mystery is whether IgG4-related disease is an autoimmune or an allergic disease. However, the occasional coexistence of other organ involvement leads us to the concept that there may be common target antigens in the involved organs such as the pancreas, salivary glands, biliary tract, lungs, and renal tubules. Although disease-specific antibodies have not been identified at present, several disease-related antibodies such as anti-lactoferrin (LF) [57, 58], anti-carbonic anhydrase (CA)-II [57–60], anti-CA-IV [61], anti-pancreatic secretory trypsin inhibitor (PSTI) [62], anti-amylase-alpha [63], anti-heat-shock protein (HSP)-10 [64], and anti-plasminogen-binding protein (PBP) peptide autoantibodies [65] have been reported. Although the patients show increased serum levels of IgG4, the major subclass of these autoantibodies is not necessarily IgG4, but is often IgG1 [62]. CA-II [59], CA-IV [61], LF [58], and PSTI [62] are distributed in the ductal cells of several exocrine organs, including the pancreas, salivary glands, biliary duct, lungs, and renal tubules. Although not all peptides have been studied, immunization with CA-II or LF induced systemic lesions such as pancreatitis, sialadenitis, cholangitis, and interstitial nephritis in mouse models similar to human IgG4-related diseases [66, 67]. The high prevalence of the above antibodies suggests that they may be candidates for the target antigens in AIP [58].

Molecular mimicry among microbes and target antigens may be a possible mechanism for breaking down immune tolerance. This hypothesis is based on the concept that infectious agents share one or more epitopes with self-components, or infectious agents cause bystander activation of immune cells with autoaggressive potential [68–70]. Guarneri and colleagues showed significant homology between human CA-II and alpha-CA of *Helicobacter pylori*, a fundamental enzyme for bacterial survival and proliferation in the stomach [70]. Moreover, the homologous segments contained the binding motif of DRB1*0405 [71], which confers a risk for AIP development [70]. The PBP peptide newly identified in European patients with AIP shows homology with an amino acid sequence of PBP of *H. pylori* and with the ubiquitin-protein ligase E3 component n-recognin 2 (UBR2), an enzyme highly expressed in acinar cells of the pancreas, while European patients with AIP did not necessarily show LPSP as the typical histopathology of type 1 AIP in IgG4-related diseases [65]. These findings suggest that gastric *H. pylori* infection might trigger AIP in genetically predisposed subjects [68–70].

Diabetes mellitus (DM) complications exist in 43–68% of AIP patients, but autoantibodies against glutamic acid decarboxylase, beta-cell, or tyrosine phosphatase-like protein [67] associated with type 1A DM are rarely observed. These findings suggest that islet cells may not be targeted in the development of DM associated with AIP.

No disease-specific autoantibodies have been identified in IgG4-related disease. The rare association of IgG4-related disease and well-known autoimmune diseases such as Sjögren's syndrome and SLE must be discussed.

Cellular immunity

Th1 and Th2 immune balance

The effector cells in IgG4-related diseases have been poorly understood. The presence of autoantibodies, the predominant infiltration of $CD4^+$ and $CD8^+$ T cells, and the expression of HLA-DR antigens in the pancreas [57] suggest that, as well as the infiltration of plasmacytes and B cells, an immunological mechanism may be involved in the development of AIP. $CD4^+$ T cells differentiate from naïve T cells (Th0) to Th1, Th2, Th17, and Treg cells [72]. IL-12 induces Thl cells, which produce IL-2, tumor necrosis factor (TNF)-alpha, and interferon (IFN)-gamma, and mediate cellular immunity, macrophage activation, and cytotoxicity, as well as helping B-cell production of opsonizing and complement fixing antibodies [4]. IL-4 induces Th2 cells, which produce IL-4, IL-5, IL-6, and IL-10, promoting humoral and allergic responses [4]. Transforming growth factor (TGF)-beta, IL-6, IL-21, and IL-23 induce Th17 cells, which secrete IL-17, and may be involved in inflammation in mice [73].

In some patients with AIP, Th1 cells are predominant over Th2 type cells in the periphery [58, 74]. On the other hand, a Th2-type immune reaction, as well as the Th1 responses, is induced in the livers of patients with IgG4-related sclerosing cholangitis [54]. This discrepancy may be explained by the shift of Th2 cells from the periphery to local tissues, or by different disease stages. Mouse models with depletion of Tregs induced by neonatal thymectomy (nTx) support the hypothesis that Th1 cells act mainly as effectors in the initial early stage [75]. In Sjögren's syndrome [76] and PSC [77], the major infiltrating cells in the tissue are $CD4^+$HLA-DR^+Th1 cells, although $CD8^+$ and B cells are also present. Similar to Sjögren's syndrome, Th1 cytokines may be essential in the induction of AIP, while Th2 cytokines may be involved in the progression of the

disease process, especially the maturation and proliferation of local B cells and plasmacytes [4].

Regulatory T cells

From naïve Th0 cells, TGF-beta can induce $CD4^+CD25^+$ Tregs, which have a potent inhibitory function, via the transcription factor Foxp3, to show $CD4^+$ T cell-mediated immune responses such as Th1, Th2, and Th17 [73]. Foxp3 is a member of the forkhead/winged-helix family of transcriptional regulators, and functions as the master regulator in the development and function of Tregs. This suppressive function is mediated by TGF-beta and IL-10, and/or cell-to-cell contact via ligation of cytotoxic T lymphocyte antigen-4 (CTLA-4). Recent studies have clarified several subtypes of Tregs [78]. Tregs originating in the thymus are naturally occurring $CD4^+CD25^+$ Tregs (nTregs), which are different from adaptive Tregs (aTregs) induced in the periphery by different antigens [78]. As Tregs expressing Foxp3 are critical in the transfer of immune tolerance, Treg deficiency has been shown to induce various autoimmune diseases in animal experimental models [73]. However, in humans, an increased prevalence of circulating $CD4^+CD25^+$ T cells or a similar level of peripheral $CD4^+CD25^+$ T cells was observed in patients with rheumatoid arthritis, Sjögren's syndrome, and inflammatory bowel disease, compared with healthy controls [79]. Therefore, the evidence of decreased circulating Tregs as shown in the animal studies may not be a general finding in human autoimmune diseases. In IgG4-related diseases, the role of Tregs remains unclear. In AIP, in addition to increased soluble CTLA4, circulatory naïve (CD45RA+) Tregs are significantly decreased in the peripheral blood of patients with AIP, whereas the major population of memory (CD45RA−)-Tregs is significantly increased [53]. In addition, prominent infiltration of Tregs with upregulation of IL-10 is observed in the livers of patients with IgG4-related sclerosing cholangitis [58]. These findings suggest that increased memory-Tregs in the periphery and local tissues may be inhibitory immune responses against inflammation in patients with AIP, although decreased naïve Tregs may be pathogenetic.

Our hypothesis for the pathogenesis of AIP as IgG4-related disease

In nTx-BALB/c mouse models immunized with CA-II or LF, $CD4^+$ T cells, rather than B cells, are the predominant infiltrates in pancreatitis, sialoadenitis, and cholangitis, which is similar to human AIP [75]. These findings suggest

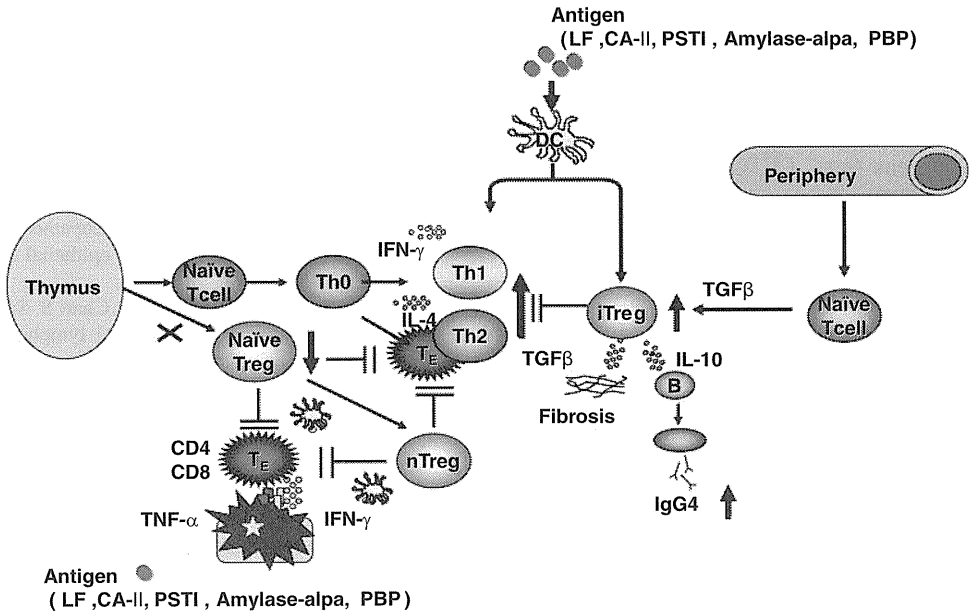

Fig. 1 Hypothesis for the pathogenesis of autoimmune pancreatitis (AIP) in IgG4-related disease. In regard to central tolerance, naïve and natural regulatory T cells (*Tregs*) derived from the thymus suppress autoreactive CD4 or CD8 cells in the normal state. In IgG4-related disease, the basic concept is a biphasic mechanism of "induction" and "progression". Initial response to self-antigens (e.g., lactoferrin [*LF*], carbonic anhydrase II [*CA-II*], CA-IV, pancreatic secretory trypsin inhibitor [*PSTI*], amylase-alpha, and plasminogen-binding protein [*PBP*] peptide of *Helicobacter pylori*) might be induced by decreased naïve Tregs. Th2 immune responses are followed by a Th1-type immune response with the release of proinflammatory cytokines (interferon-γ [*IFN-γ*], interleukin [*IL*]-1beta, IL-2, tumor necrosis factor-α [*TNF-α*]). Th2-type immune responses, producing IgG, IgG4, and autoantibodies may be involved in the pathophysiology of progression. IgG4 and fibrosis may be regulated by increased IL-10 and transforming growth factor-β (*TGF-β*), respectively, secreted from inducible memory Tregs. *DC* ductal cell, *iTreg* inducible Treg, *TE* effector T cell, *nTreg* natural Treg

that the depletion of naïve Tregs in the periphery [80] and major histocompatibility complex (MHC)-class II restricted-autoreactive $CD4^+$ T cells that escape from positive selection in the thymus, may play important roles in the induction of systemic organ lesions. These $CD4^+$ T cells probably induce macrophage activation and further proinflammatory reactions during the early stage of AIP as direct cytotoxic effects through Fas ligand expression [81]. On the other hand, $CD8^+$ T cells may play roles as effector cells in the MHC class II-deficient mouse [82] and in WBN/Kob rat models [83]. WBN/Kob rats with congenitally decreased peripheral Tregs spontaneously develop sialadenitis, thyroiditis, sclerotic cholangitis, and TIN. Although the target antigens remain unclear, $CD8^+$ cells also seem to be effectors. Although rodents lack the IgG4 subclass, deposits of tissue-specific IgG2b, in electrophoretic position similar to human IgG4, were observed in the injured pancreas and lachrymal glands in WBN/Kob rats [83]. These animal models suggest that although $CD8^+$ T cells may be partially involved, $CD4^+$ T cells play major roles in the development of experimental systemic lesions, which are similar to the lesions in human IgG4-related diseases [4, 58], although the counterpart of IgG4 in mouse IgG subclasses has not been identified. As TGF-beta is an important regulatory factor in maintaining immune homeostasis [84], TGF-beta-dominant negative mutant mice suggest that the loss of TGF-beta signaling may contribute to AIP [85].

From the above findings, we propose a hypothesis for the pathogenesis of AIP (Fig. 1). The basic concept is a biphasic mechanism of "induction" and "progression." An initial response to self-antigens (e.g., LF, CA-II, CA-IV, PSTI, amylase-alpha, and PBP peptide of *H. pylori*) might be induced by decreased naïve Tregs, followed by a Th1-type immune response with the release of proinflammatory cytokines (IFN-gamma, IL-1-beta, IL-2, TNF-alpha). Then Th2-type immune responses producing IgG, IgG4, and autoantibodies may be involved in the pathophysiology of progression. IgG4 and fibrosis may be regulated by increased IL-10 and TGF-beta, respectively, secreted from inducible memoryTregs. The classical pathway of the complement system may be activated by the IgG1 immune complex.

Conclusion

In conclusion, recent advances support the concept of IgG4-related disease, a unique clinical entity, as a systemic disease. As Tregs seem to play important roles in the progression as well as the induction of the disease, further studies are necessary to clarify the pathogenesis, including studies of genetic backgrounds, disease-specific antigens, and the role of IgG4.

Acknowledgments This study was partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Culture and Science of Japan (20590810), and a Grant-in-Aid for the "Research for Intractable Disease" Program from the Ministry of Health, Labor and Welfare of Japan.

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Involvement of Inducible Costimulator– and Interleukin 10–Positive Regulatory T Cells in the Development of IgG4-Related Autoimmune Pancreatitis

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Objectives: Immunoglobulin G4 (IgG4)–related autoimmune pancreatitis (AIP) is a new clinical entity of pancreatic disorder. There are immunologic and histological abnormalities, including increased serum IgG4 levels and the infiltration of IgG4-positive plasmacytes. However, the role of IgG4 is unclear. Recently, regulatory T cells (Tregs) were reported to contribute to the development of various autoimmune diseases as well as in B-cell shifting to IgG4-producing plasmacytes. We studied Tregs in the pancreas and peripheral blood.

Methods: We recruited 44 patients with IgG4-related AIP. For comparison, we recruited 37 patients with other pancreatic diseases and 27 healthy subjects as controls. We studied infiltrating cells in the pancreas by immunohistochemistry and analyzed inducible costimulator–positive Tregs and interleukin 10–positive Tregs in the peripheral blood by flow cytometry.

Results: The ratio of Foxp3-positive cells to infiltrated mononuclear cells (Foxp3/Mono) in AIP patients was significantly higher than in patients with alcoholic chronic pancreatitis. In AIP, Foxp3/Mono and IgG4/Mono were positively correlated. Inducible costimulator–positive Tregs were significantly higher in AIP patients than in the patients with other pancreatic diseases and the healthy control group. Interleukin 10–positive Tregs were significantly higher in AIP patients than in the healthy control group.

Conclusions: Increased quantities of inducible costimulator–positive Tregs may influence IgG4 production in IgG4-related AIP.

Key Words: IgG4-related disease, autoimmune pancreatitis (AIP), regulatory T cells (Tregs), IgG4, IL-10, inducible costimulator (ICOS)

(*Pancreas* 2011;40: 1120–1130)

In 1961, Sarles et al[1] observed the first case of idiopathic chronic pancreatitis (CP) with hypergammaglobulinemia, in which an autoimmune mechanism was supposedly involved. In 1991, Kawaguchi et al[2] reported 2 cases of an unusual lymphoplasmacytic sclerosing inflammatory disease involving the total pancreas, common bile duct, gallbladder, and, in 1 patient, the lip. In addition, 2 patients presented mass-like enlargement of the pancreatic head. Histopathologic characteristics included diffuse lymphoplasmacytic infiltration, marked interstitial fibrosis, acinar atrophy, and obliterative phlebitis of the pancreatic and portal veins, which was termed as lymphoplasmacytic sclerosing pancreatitis (LPSP). In 1995, Yoshida et al[3] first proposed the concept of "autoimmune pancreatitis (AIP)," in which patients showed a diffusely enlarged pancreas, a narrowing pancreatogram, increased serum immunoglobulin G (IgG), the presence of autoantibodies, fibrotic changes with lymphocytic infiltration, and steroidal efficacy. In 2001, Hamano et al[4] reported that elevated serum IgG4 levels were highly specific and sensitive for the diagnosis of AIP. In 2003, Kamisawa et al[5] suggested that AIP is a systemic disease, based on the findings that the pancreas and other involved organs have abundant infiltration of IgG4-positive plasma cells. Thereafter, many AIP cases have been reported by Japanese investigators, and AIP has been accepted as a new clinical entity.[6–11]

On the other hand, reports from Europe[12] and the United States[13] described unique histological patterns in the resected pancreata of patients with mass-forming, chronic, nonalcoholic pancreatitis with epithelial destruction by granulocytes, which is now supposed to be distinguishable from IgG4-related AIP (or type 1 AIP) and called idiopathic duct centric pancreatitis (IDCP) or AIP with granulocyte epithelial lesions (AIP with GELs) or type 2 AIP.[14] Most of the Japanese AIP cases are LPSP, whereas those concerning IDCP are very few. Although we recently reported the first case of IDCP in Japan with full radiological and histopathologic findings,[15] it still remains unclear whether the clinical manifestations of the Japanese patients with IDCP are similar to those of Western countries. Therefore, Japanese consensus clinical guidelines have focused on IgG4-related AIP (LPSP).[9–11] An overlap in the histological features of the 2 patterns may exist in some patients. Although the pathogenesis is still unclear, the most important issue in managing AIP is to differentiate it from pancreas and biliary malignancy.

Great attention has been focused on the relation between various autoimmune diseases and regulatory T cells (Tregs), which are present in human peripheral blood,[16–21] intestinal lamina propria,[22] and the thymus.[20,21] Recent reports have shown that Tregs can be classified into 2 groups: (1) naturally occurring Tregs expressing $CD4^+CD25^{high}$ and (2) naive Tregs expressing the naive T-cell marker CD45RA in addition to CD4 and CD25. Naive Tregs also expressed very high levels of mRNA for Foxp3 and manifested equivalent suppressive activity in vitro.[23,24] We have previously reported that increased quantities of $CD4^+$ $CD25^{high}$ Tregs may influence IgG4 production, and naive Tregs may be involved in the development of AIP.[25] Patients with IgG4-related AIP often show high serum levels of IgG4, but the pathologic significance and mechanism are unknown. Immunoglobulin 4 is well known as a T-helper 2 (T_H2)–dependent isotype. Interleukin (IL) 4 directs naive human B cells to switch to IgG4 and IgE production.[26] Interleukin 10 promotes isotype switching from IgM to IgG1, IgG3, IgG4, and/or IgE. Interleukin 10 also stimulates IgG4 production.[27] The association with the IL-10 response still holds and has strengthened, with the

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Received for publication September 21, 2010; accepted April 14, 2011.

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This study was partially supported by (1) Grant-in-Aid for Scientific Research (C) of the Ministry of Culture and Science of Japan (20590810, 23591017-0001), (2) Intractable Diseases, the Health and Labor Sciences Research Grants (KO) from the Minister of Labor and Welfare of Japan, and (3) grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan, from CREST Japan Science and Technology Agency.