Recent Advances in the Concept and Pathogenesis of IgG4-Related Disease in the Hepato-Bilio-Pancreatic System

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Recent studies have proposed nomenclatures of type 1 autoimmune pancreatitis (AIP) (IgG4-related pancreatitis), IgG4-related sclerosing cholangitis (IgG4-SC), IgG4-related cholecystitis, and IgG4-related hepatopathy as IgG4-related disease (IgG4-RD) in the hepato-bilio-pancreatic system. In IgG4-related hepatopathy, a novel concept of IgG4-related autoimmune hepatitis (AIH) with the same histopathological features as AIH has been proposed. Among organs involved in IgG4-RD, associations with pancreatic and biliary lesions are most frequently observed, supporting the novel concept of “biliary diseases with pancreatic counterparts.” Targets of type 1 AIP and IgG4-SC may be periductal glands around the bile and pancreatic ducts. Based on genetic backgrounds, innate and acquired immunity, Th2-dominant immune status, regulatory T (Treg) or B cells, and complement activation via a classical pathway may be involved in the development of IgG4-RD. Although the role of IgG4 remains unclear in IgG4-RD, IgG4-production is upregulated by interleukin 10 from Treg cells and by B cell activating factor from monocytes/basophils with stimulation of toll-like receptors/nucleotide-binding oligomerization domain-like receptors. Based on these findings, we have proposed a hypothesis for the development of IgG4-RD in the hepato-bilio-pancreatic system. Further studies are necessary to clarify the pathogenic mechanism of IgG4-RD. (Gut Liver 2014;8:462-470)

Key Words: IgG4-related disease; Autoimmune pancreatitis; IgG4-related sclerosing cholangitis; IgG4-related hepatopathy

INTRODUCTION

In 1961, Sarles et al. observed a case of particular pancreatitis with hypergammaglobulinaemia, which is supposed to be a prototype of autoimmune pancreatitis (AIP) (Table 1). In 1995, Yoshida et al. proposed a novel concept of AIP, which has been accepted as type 1 AIP (IgG4-related pancreatitis), the pancreatic manifestation of IgG4-related disease (IgG4-RD). IgG4-RD is recognized worldwide as a novel clinical entity following the epoch-making evidence of increased serum levels of IgG4 in the history of AIP. The histopathological findings are characterized by the periductal localization of predominantly CD4 positive T cells, IgG4-positive plasma cells, storiform fibrosis with acinar cell atrophy, and obliterator fibrosis, which is also called lymphoplasmacytic sclerosing pancreatitis (LPSP). On the other hand, mainly in the Western countries, histological analyses using resected pancreatic samples in patients with chronic non-alcoholic pancreatitis demonstrated a different histological pattern of pancreatitis from LPSP, so called idiopathic duct-centric pancreatitis (IDCP) or AIP with granulocytic epithelial lesion. In 2003, Kamisawa et al. first suggested that AIP showing LPSP is a systemic sclerosing disease based on the concept of multifocal fibrosclerosis proposed by Comings et al., because the pancreas and other involved organs have fibrosis with abundant infiltration of IgG4-positive plasma cells. On the other hand, patients with IDCP, rarely observed in Japan, are not associated with either serum IgG4 elevation or with other organ involvement typically seen in LPSP. AIP is subclassified according to the International Consensus of Diagnostic Criteria for AIP as either type 1 (LPSP) or type 2 (IDCP). Type 2 AIP, unlike type 1 AIP, is thought to be a specific pancreatic disease with occasional coexistence with ulcerative colitis.

On the other hand, in 1892, Mikulicz first observed a patient with symmetrical swelling of the lachrymal, parotid and submandibular glands, with massive infiltration of mononuclear cells. The condition was called Mikulicz’s disease; however, it has since been classified as an atypical type of Sjögren’s syn-
The patients with IgG4-RD show diffuse or focal organ enlargement and mass-forming or nodular/thickened lesions in various organs, either synchronously or metachronously. This is due to the prominent infiltration of lymphocytes and plasmacytes with fibrosis. The causes are still unclear; however, some abnormal immunological mechanisms are involved. The organs known to be affected include the pancreas, biliary duct, lacrimal/salivary glands, retroperitoneum, central nervous system, thyroid gland, lungs, liver, gastrointestinal tracts, kidneys, prostate gland, and lymph nodes. Clinical symptoms vary depending on the organ in which the lesions are located, but many cases are treated effectively by steroid therapy. All of

### Table 1. Transition of the Concept of IgG4-Related Disease

| Author (Year) | Evidences/Contents |
|---------------|--------------------|
| Mikulicz (1892) | Mikulicz’s disease (Z Chir Fessler) |
| Sarles et al. (1961) | Hypergammaglobulinemia in CP (Am J Dig Dis) |
| Comings et al. (1967) | Familial multifocal fibrosclerosis (Ann Intern Med) |
| Küttner (1972)6,13 | Küttner tumor (Beitr Klin Chir) |
| Kawaguchi et al. (1991) | Lymphoplasmacytic sclerosing pancreatitis (Hum Pathol) |
| Yoshida et al. (1995) | Autoimmune pancreatitis (Dig Dis Sci) |
| Hamano et al. (2001) | High IgG4 levels in sclerosing pancreatitis (N Engl J Med) |
| Kamisawa et al. (2003) | IgG4-related sclerosing disease (J Gastroenterol) |
| Kamisawa et al. (2006) | IgG4-related sclerosing disease (J Gastroenterol) |
| Yamamoto et al. (2006) | IgG4-related plasmacytic disease (Mod Rheumatol) |
| Masaki et al. (2009) | IgG4-multiorgan lymphoproliferative syndrome (MOLPS) (Ann Rheum Dis) |
| Shimosegawa et al. (2011) | International Consensus Diagnostic Criteria for AIP (Pancreas) |
| Umehara et al.17 | Concept and comprehensive diagnostic criteria for IgG4-related disease (Mod Rheumatol) |
| Deshpande et al. (2012) | International Pathological Consensus for IgG4-RD (Mod Pathol) |
| Stone et al. (2012) | Nomenclatures of individual organ manifestation of IgG4-RD (Arthritis Rheum) |

CP, chronic pancreatitis; AIP, autoimmune pancreatitis.

### Table 2. The Three Major Histopathological Features Associated with IgG4-Related Disease and the Minimal Criteria in a New Organ/Site in the International Pathological Consensus

The three major histopathological features associated with IgG4-RD are:
1. Dense lymphoplasmacytic infiltrate
2. Fibrosis, arranged at least focally in a storiform pattern
3. Obliterative phlebitis

Other histopathological features associated with IgG4-RD are:
1. Phlebitis without obliteration of the lumen
2. Increased numbers of eosinophils

Minimal criteria for IgG4-RD in a new organ/site are:
1. Characteristic histopathological findings with an elevated IgG4/t-to-IgG ratio
2. High serum IgG4 concentrations
3. Effective response to glucocorticoid therapy
4. Reports of other organ involvement that is consistent with IgG4-RD

IgG4-RD, IgG4-related disease.
them show similar pathological findings with abundant infiltration of IgG4-positive cells and fibrosis, and international minimum histological consensus was proposed (Table 2). Although the infiltration of IgG4-positive cells and increased serum levels of IgG4 are characteristic in IgG4-RD, the severity of fibrosis seems to be different among the individual involved organs.\textsuperscript{18} Storiform fibrosis and obliterator phlebitis are characteristic in pancreatic and biliary tract lesions, but rarely observed in the salivary or lymphnodes.\textsuperscript{18} Although most patients have multiorgan lesions synchronously or metachronously, about 10\% to 20\% of the patients have solitary organ involvement.\textsuperscript{20} Therefore, it is unclear whether the pathogenetic mechanism is same among individual organs or not. Type 1 AIP (IgG4-related pancreatitis), IgG4-related sclerosing cholangitis (IgG4-SC), IgG4-related cholecystitis, and IgG4-related hepatopathy are recommended as the nomenclatures of IgG4-RD in the hepato-bilio-pancreatic system.\textsuperscript{19}

1. Type 1 AIP (IgG4-related pancreatitis)

AIP is a distinct form of pancreatitis clinically characterized by frequent presentation with obstructive jaundice with or without a pancreatic mass, histologically by a lymphoplasmacytic infiltrate and fibrosis and therapeutically by a dramatic response to steroids.\textsuperscript{5,21} Recent studies have suggested that “AIP” manifests two distinct subtypes, type 1 and type 2 AIP (Table 3).\textsuperscript{10,11} Type 1 AIP (IgG4-related pancreatitis) is more prevalent in Japan and Korea, whereas type 2 AIP, with granulocytic epithelial lesion, is more commonly observed in Europe and the United States.

In type 1 AIP, the pancreatic histopathology shows the following characteristic features of LPSP: 1) abundant infiltration of plasma cells (IgG4\textsuperscript{+} cells; >10/hpf, 40\%>IgG4/IgG cells) and lymphocytes, 2) peculiar storiform or swirling fibrosis, and 3) perivenular infiltration with lymphocytes and plasma cells often leading to obliterator phlebitis. Clinically, it is characterized by swelling of the pancreas, elevated serum IgG4 levels and extrapancreatic lesions (e.g., sclerosing cholangitis, sclerosing sialadenitis, and retroperitoneal fibrosis) associated with infiltration of abundant IgG4\textsuperscript{+} plasma cells. Patients with type 1 AIP often have obstructive jaundice in elderly males, and the pancreatic and extrapancreatic manifestations respond to steroid therapy.\textsuperscript{21} Therefore, it is a pancreatic manifestation of a systemic disorder, IgG4-RD.\textsuperscript{19,21}

2. IgG4-SC

About 60\% to 80\% of patients with type 1 AIP are associated with IgG4-SC,\textsuperscript{5,20-22} in which cholangiographic features are similar to those of primary sclerosing cholangitis (PSC), pancreatic cancer, and cholangiocarcinoma. The steroid responses and the prognoses of IgG4-SC differ from patients with PSC, which suggests different pathological conditions.\textsuperscript{5,20-22} Four types of the characteristic cholangiographic features of IgG4-

| Table 3. Subtypes of Autoimmune Pancreatitis |
|-----------------------------------------------|
| Subtype of AIP | Type 1 | Type 2 |
|----------------|--------|--------|
| Other nomenclatures | AIP without GEL | AIP with GEL |
|                  | IgG4-related | IgG4-unrelated |
|                  | LPSP | IDCP |
| Prevalence | Asia>USA, EU | EU>USA>Asia |
| Age | High aged | Younger |
| Gender | Male>>Female | Male=Female (NS) |
| Symptoms | | |
| Obstructive jaundice | Often | Often |
| Abdominal pain | Rare | Common |
| Pancreas swelling | Common | Common |
| Serology | High serum IgG, IgG4, autoAbs (+) | Normal IgG, normal IgG4, autoAbs (-) |
| OOI | Sclerosing cholangitis | Unrelated with OOI |
| | Sclerosing sialadenitis | |
| | Retroperitoneal fibrosis | |
| Others | | |
| Ulcerative colitis | Rare | Often |
| Steroid | Responsive | Responsive |
| Relapse | High rate | Rare |

AIP, autoimmune pancreatitis; GEL, granulocytic epithelial lesion; LPSP, lymphoplasmacytic sclerosing pancreatitis; IDCP, idiopathic duct-centric chronic pancreatitis; NS, not significant; OOI, other organ involvement.
SC have been proposed based on the regions of stricture (Fig. 1). IgG4-SC with only stenosis of the distal common bile duct (type 1) is difficult to differentiate from pancreatic cancer. This stricture might be due to both the thickening of bile duct and the effect of inflammation and/or edema of pancreas without wall thickness. IgG4-SC with diffuse stenosis throughout the intrahepatic/proximal bile ducts (type 2) is similar to PSC. IgG4-SC with stenosis in the hilar hepatic bile duct (type 3 and 4) is difficult to differentiate from hepatic hilar cholangiocarcinoma. In addition to stenosis of bile ducts, circular and symmetric thickening of the bile duct wall, smooth outer and inner margin, and homogenenous internal echo demonstrated by abdominal ultrasonography, abdominal computed tomography, abdominal magnetic resonance imaging, endoscopic ultrasonography, and intraductal ultrasonography are most characteristic images. These characteristic features are recognized not only in the stenotic areas or occasionally in the gallbladder but also in areas without stenosis that appear normal in cholangiogram. Most cases of IgG4-SC (80% to 90%) are associated with AIP. It is particularly difficult to accurately diagnose IgG4-SC without AIP. In contrast to PSC, inflammatory bowel disease is rarely observed in the patients with IgG4-SC.

Histopathologically, similar to LPSP in type 1 AIP, massive infiltration of IgG4-positive plasma cells, storiform fibrosis and/or obliterative phlebitis in the bile duct wall are characteristic and called as lymphoplasmacytic sclerosing cholangitis. Such fibroinflammatory involvement is mainly observed in the submucosa of the bile duct wall, whereas the epithelium of the bile duct is intact. Endoscopic transpapillary bile duct biopsy or cytological examinations are useful for differential diagnosis of cholangiocarcinoma, although it is difficult to take enough biopsy samples for characteristic histopathological findings of IgG4-SC. Liver biopsy is sometimes useful in the diagnosis of IgG4-SC in cases of intrahepatic bile duct involvement.

3. IgG4-related hepatopathy

Liver dysfunction is frequently observed in AIP patients and most of them show various pathological changes with infiltration of IgG4-bearing plasma cells in the liver; portal inflammation with or without interface hepatitis, large bile duct obstructive features, portal sclerosis, lobular hepatitis, and canalicular cholestasis. As a very few of IgG4-RD patients without AIP or IgG4-SC show the same histological features as autoimmune hepatitis (AIH), a novel concept of IgG4-related AIH has been proposed. To establish the concept of IgG4-related AIH, further studies are required.

RECENT ADVANCES IN THE PATHOGENIC MECHANISMS OF IgG4-RD IN THE HEPATO-BILIO-PANCREATIC SYSTEM

1. Immunogenic backgrounds

Although immunogenic backgrounds of IgG4-RD are not well understood, Japanese patients with AIP, most of whom are

**Fig. 1.** Classification of cholangiography in IgG4-related sclerosing cholangitis (IgG4-SC). The characteristic features of IgG4-SC can be classified into four types, based on the regions of stricture as revealed by cholangiography and differential diagnosis. Type 1 IgG4-SC shows sclerosis only in the lower part of the common bile duct, which should be differentiated from chronic pancreatitis, pancreatic cancer, or cholangiocarcinoma. Type 2 IgG4-SC, in which sclerosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from primary sclerosing cholangitis. Type 2 is further subdivided into two types. Type 2a has a narrowing of the intrahepatic bile ducts with prestenotic dilatation, and Type 2b has a narrowing of the intrahepatic bile ducts without prestenotic dilatation and reduced bile duct branches, caused by marked lymphocytic and plasmacyte infiltration into the peripheral bile ducts. Type 3 IgG4-SC is characterized by sclerosis in both the hilar hepatic lesions and the lower portion of the common bile duct. Type 4 IgG4-SC shows strictures of the bile duct only in the hilar hepatic lesions. Cholangiographic findings of types 3 and 4 need to be discriminated from those of cholangiocarcinoma. From Ohara H, et al. J Hepatobiliary Pancreat Sci 2012;19:536-542, with permission from Springer.

IDUS, intraocular ultrasonography; EUS, endoscopic ultrasonography; EUS-FNA, EUS-guided fine-needle aspiration; IBD, inflammatory bowel disease.
IgG4-related, may be associated with class II antigen haplotype of the major histocompatibility complex (HLA-DRB1*0405-DQB1*0401), polymorphism of nuclear factor-κB and Fc-receptor-like 3 genes expressed on B cells. An inhibitory molecule, cytotoxic T lymphocyte antigen-4 (CTLA-4; CD152) expressed on the activated memory T cells or CD4+CD25+ regulatory T cells (Tregs), was independently reported as a susceptibility factor. Based on immunogenic backgrounds, abnormal conditions of immune responses may be involved in the development of type 1 AIP, although the precise pathogenic mechanisms remain unclear.

2. Innate immunity

Recently, abnormal innate immunity has been demonstrated in some patients with IgG4-RD. Activation of NOD-2 and TLR ligands on monocytes or basophils from patients with IgG4-related AIP enhances IgG4 responses via B cell activating factor (BAFF) and interleukin (IL)-13, although specific pathogens still remain unclear. In animal models, activation of TLR3 by polyinosinic-polycytidylic acid or TLR4 by lipopolysaccharide can induce immune-mediated cholangitis, pancreatitis and sialadenitis similar to human IgG4-RD.

3. Possible roles of IgG4 in IgG4-RD

Although the association of IgE-mediated allergy and IgG4 antibodies is well known, IgG4 characteristics are still poorly understood. IgG4 is involved in an immune process referring to as ‘Fab-arm exchange,’ which is a swapping of a heavy chain and attached light chain (half-molecule) with a heavy-light chain pair from another molecule; this usually results in asymmetric antibodies with two different antigen-combining sites. While these modified antibodies are hetero-bivalent, they behave as monovalent antibodies. Another aspect of IgG4 is that it mimics IgG rheumatoid factor activity by interacting with IgG, namely Fc-mediated aggregation. 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. A recent study of structural determinants of human IgG4-Fc by crystallography suggested that Fc-Fc interactions are compatible with intact IgG4 molecules and may provide a model for the formation of aggregates of IgG4 that can cause disease pathology in the absence of antigen.

Another recent data on regulation of IgG4 showed that IgG4-RD may reflect an excessive production of anti-inflammatory cytokines such as IL-10 that triggers an overwhelming expansion of IgG4-producing plasma cells. Increased peripheral inducible-memory Tregs are positively correlated with serum levels of IgG4. In addition, prominent infiltration of Tregs up-regulated IL-10 in livers of the patients with IgG4-SC. These findings suggest that IgG4 do not act as a pathogenic factor, but as an anti-inflammatory factor in IgG4-RD. Further studies are necessary to clarify the precise role of IgG4 in IgG4-RD.

4. The complement system

Patients in active stages of AIP occasionally show decreased complement (C3, C4) with elevated circulating immune complex as well as serum levels of IgG4 and the IgG4 subclass of immune complexes. However, a previous 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.

5. Autoantibodies and candidate of target antigens

Although some patients with IgG4-RD have nonspecific antibodies such as an antinuclear antibody, there is scarce association of IgG4-RD. From the view of IgG4 function, the big mystery is whether IgG4-RD is an autoimmune or an allergic disease. Although disease-specific targets are unknown, the occasional coexistence of multiorgan involvements leads us to consider that there may be common target antigens. Among candidate antigens previously reported, lactoferrin (LF), carbonic anhydrase (CA)-II, carbonic anhydrase (CA)-IV, and pancreatic secretory trypsin inhibitor (PSTI) are expressed in the pancreas, salivary glands, biliary duct, lungs, renal tubules, and so forth. Immunization with CA-II or LF induced systemic lesions such as pancreatitis, sialadenitis, cholangitis, interstitial nephritis in the mice models similar to human IgG4-RD. Amylase α-2A, HSP-10, and Helicobacter pylori are also candidates of disease-associated antigens. Among the involved organs in IgG4-RD, recent studies suggest an extremely high association of pancreatic and biliary lesions. As both peribiliary glands in the biliary tract and pancreatic duct glands associated with pancreatic ducts in human are intermingled with small amounts of pancreatic exocrine acini, and the biliary tree-derived stem cells may be involved in a pancreatic organogenesis in mice. Nakamura et al. have proposed a new concept of the “biliary diseases with pancreatic counterparts,” in which targets of type 1 AIP and IgG4-SC may be periductal glands around the bile and pancreatic ducts. Further studies of the biliary tract’s pathophysiology based on its similarity to pancreatic counterparts are warranted.

6. Role of B cells

In addition to steroid and immune-modulators, the B cell depletion by rituximab, which reduces only IgG4, but not IgG1, IgG2, or IgG3, is useful in the therapeutic strategy in IgG4-RD. A recent study showed expansion of IgG4+ B cell receptor clones in blood and tissue of patients with active IgG4-cholangiopathy, and disappearance by corticosteroid treatment. A recent study showed that the increased CD19+CD24hiCD38lo Bregs may suppress the disease activity of type 1 AIP, whereas the decreased CD19+CD24hiCD38hi Bregs might be involved in the development of type 1 AIP. These findings suggest that
specific B cell responses may have a pivotal role in the pathogenesis of IgG4-RD such as type 1 AIP and IgG4-SC.

7. Th1 and Th2 immune balance

The effector cells in IgG4-RD have been poorly understood. The CD4+ T cells differentiate from naive T cells (Th0) to Th1, Th2, Th17, and Treg cells. In the livers of IgG4-SC patients, a Th2 type immune reaction is induced in addition to the Th1 responses. Th2 cytokines may be involved in the progression of the disease process, especially the maturation and proliferation of local B cells and plasmacytes.

8. Tregs

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 CD4+/CD25+ Tregs classified as naturally occurring naive-Tregs originating in the thymus and adaptively induced memory-Tregs in the periphery by different antigens. In type 1 AIP, circulatory naive (CD45RA+) Tregs are significantly decreased in the peripheral blood, whereas memory (CD45RA−)-Tregs are significantly increased. In addition, prominent infiltration of Tregs with upregulation of IL-10 is observed in the liver of type 1 AIP and IgG4-SC patients. These findings suggest that increased memory-Tregs in the periphery and local tissues may be an inhibitory immune response against inflammation, although decreased naive Tregs may be pathogenic.

9. Our hypothesis for the pathogenesis of IgG4-SC

The neonatally thymectomized (nTx)-BALB/c mice models showed that immunization with CA-II or LF induced pancreatitis, cholangitis, and salalenditis similar to human IgG4-RD. These findings suggest that depletion of naive Tregs may induce macrophage/T cell activation and further proinflammatory reactions during the early stage of the disease as direct cytotoxicity effects through Fas ligand expression. WBN/Kob rat models with congenital decreased peripheral Tregs spontaneously develop sclerotic cholangitis, sialadenitis, thyroiditis, and tubulointerstitial nephritis. These animal models suggest that CD4+ and CD8+ T cells play major roles in the development of primary lesions similarly to human IgG4-RD; however, the counterpart of IgG4 in mice IgG subclasses has not been identified.

Based on these findings, we proposed the pathogenesis of type 1 AIP (Fig. 2). The basic concept is the biphasic mechanism of "induction" and "progression." An initial response to unknown disease specific antigens including self-antigens (LF, CA-II, CA-IV, and PSTI) or microorganisms (bacteria or virus) might be induced by decreased naive-Tregs followed by a Th1 response against inflammation, although decreased naive Tregs may be pathogenic.

Fig. 2. Hypothesis for the pathogenesis of autoimmune pancreatitis (AIP) and IgG4-related disease. In central tolerance, naturally occurring naive regulatory T cells (n-Tregs) derived from the thymus suppress autoreactive CD4 or CD8 cells in the normal state. In the IgG4-related disease, the basic concept is the biphasic mechanism of "induction" and "progression." Initial response to antigens (lactoferrin [LF], carbonic anhydrase II [CA-II], CA-IV, pancreatic secretory trypsin inhibitor [PSTI], α-amylase, plasminogen binding protein peptide of Helicobacter pylori, etc.) might be induced by decreased n-Tregs. Th2 immune responses were followed by Th1-type immune responses, with releases of proinflammatory cytokines (interferon γ [IFN-γ], interleukin [IL]-1β, IL-2, tumor necrosis factor α [TNF-α]). In progression, Th2-type immune responses producing IgG, IgG4 and autoantibodies may be involved in pathophysiology. IgG4 and fibrosis may be regulated by increased IL-10 and transforming growth factor β (TGF-β) secreted from inducible memory-Tregs (i-Tregs), respectively. However, activation of nucleotide-binding oligomerization domain (NOD) receptor or TLRs on monocytes or basophils increases IgG4 via the upregulation of B cell activating factor belonging to the tumor necrosis factor family (BAFF) and IL-13. From Okazaki K, et al. J Gastroenterol 2011;46:277-288, with permission from Springer.
type immune response with the release of proinflammatory cytokines (interferon γ, IL-1β, IL-2, tumor necrosis factor α). In progression, Th2 type immune responses producing IgG, IgG4, and autoantibodies may be involved in pathophysiology. IgG4 and fibrosis may be regulated by increased IL-10 and transforming growth factor β secreted from inducible T cell co-stimulator (ICOS)-positive and ICOS-negative inducible adaptive Tregs, respectively. Production of IgG4 may be also upregulated by BAFF from monocytes and basophils.

CONCLUSIONS

Recent advances support the concept of IgG4-RD, a unique clinical entity, in the hepato-bilio-pancreas system. Although the pathogenic mechanism remains unclear, innate and acquired immunity, Tregs, and B cells may be involved in the development of these lesions. Further studies are necessary to clarify the pathogenesis including genetic backgrounds, disease-specific antigens, and the role of IgG4.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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