Clinical Application of Basic Science

EASL EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER | JOURNAL OF HEPATOLOGY

IgG4 cholangiopathy – Current concept, diagnosis, and pathogenesis

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Summary

IgG4 related cholangiopathy, a distinctive type of cholangitis of unknown origin, is characterized by increased serum levels of IgG4, massive infiltration of IgG4-positive plasma cells with storiform fibrosis and/or obliterative phlebitis in the thickened bile duct wall, and good response to steroids. Patients with IgG4-cholangiopathy are frequently associated with autoimmune pancreatitis; IgG4-cholangiopathy is recognized as a biliary manifestation of IgG4-related disease. This condition can be diagnosed by a combination of imaging, serology, histopathology, and steroid responsiveness; however, cholangiographic features are often difficult to differentiate from primary sclerosing cholangitis, pancreatic cancer, or cholangiocarcinoma. The Japanese clinical diagnostic criteria for IgG4-related sclerosing cholangitis established in 2012 are useful in the diagnosis of IgG4-cholangiopathy. Although the precise pathogenic mechanism remains unclear, the development of IgG4-cholangiopathy may involve: susceptible genetic factors, abnormal innate and acquired immunity, decreased naïve regulatory T cells, and specific B cell responses.

Further studies on genetic backgrounds, disease specific antigens, and the role of IgG4 are necessary to clarify the pathogenesis.

Introduction

IgG4 related cholangiopathy is a distinctive type of cholangitis of unknown origin, which is characterized by increased serum levels of IgG4 [1], massive infiltration of IgG4-positive plasma cells with storiform fibrosis and/or obliterative phlebitis in the bile duct wall and good response to steroids [1–3]. Patients with IgG4-cholangiopathy are frequently associated with autoimmune pancreatitis (AIP) [2,3], the concept of which was originally proposed by Yoshida *et al.* [4], and Hamano *et al.* reported increased serum levels of IgG4 in Japanese patients with AIP [1]. Now, it is recognized as a biliary manifestation of IgG4-related disease (IgG4-RD) [2–6]. Clinically, it is important to distinguish IgG4-cholangiopathy from malignancy such as cholangiocarcinoma, pancreas cancer, or a benign counterpart, PSC [2]. The organizing committee of the first international symposium on IgG4-RD in 2009 [6] proposed the nomenclature of "IgG4-related sclerosing cholangitis" (IgG4-SC) instead of "IgG4-associated cholangitis" which was recommended by the European Association for the Study of the Liver (EASL) [6]. Recently, the Japanese clinical diagnostic criteria 2012 for IgG4-SC have been proposed, although the pathogenic mechanisms remain unclear [2]. Here, we introduce the current concept, diagnosis, and recent advances in the pathogenesis of IgG4-SC.

Current concept and diagnosis of IgG4-SC

Classification of sclerosing cholangitis

Sclerosing cholangitis is classified into a primary type of unknown origin such as PSC or IgG4-SC, and secondary type with obvious pathogenesis (e.g., common bile duct (CBD) stone, cholangiocarcinoma, trauma, operation of biliary tract, congenital biliary anatomy, corrosive cholangitis, ischemic bile duct stenosis, AIDS-related cholangitis, or biliary injury of intra-arterial chemotherapy) (Table 1).

Prevalence of IgG4-SC

The prevalence of IgG4-SC still remains unclear. About 80% of AIP patients suffer complications with stenosis of the distal CBD with wall thickness [2,3,5]. This stricture might be due to both the thickening of bile duct and the effect of inflammation and/or edema of pancreas without CBD wall thickness. Based on these propositions, a recent Japanese national study analyzed 197 PSC and 43 IgG4-SC patients without AIP [7]. The male/female ratio was 106:91 (1.16:1) in PSC and 33:10 (3.3:1) in IgG4-SC and the mean age [min–max] was 48.1 [4.0–86.3] in PSC and 69.3

Keywords: IgG4-related disease; IgG4-cholangiopathy; IgG4-related sclerosing cholangitis; Autoimmune pancreatitis.
Received 31 October 2013; received in revised form 23 March 2014; accepted 7 April 2014
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Abbreviations: AIP, autoimmune pancreatitis; ANA, anti-nuclear antibody; CA-II, carbonic anhydrase-II; CBD, common bile duct; *CTLA-4*, cytotoxic T lymphocyte antigen-4; ERCP, endoscopic retrograde cholangio-pancreatography; FCRL, Fc-receptor-like; IFN-γ, interferon-γ; IgG4-RD, IgG4-related disease; IgG4-SC, IgG4-related sclerosing cholangitis; IL-4, interleukin-4; LF, lactoferrin; LPSP, lymphoplasmacytic sclerosing pancreatitis; PSC, primary sclerosing cholangitis.

Table 1. Classification of sclerosing cholangitis.

Sclerosing cholangitis of unknown origin
Primary sclerosing cholangitis (PSC)
IgG4-related sclerosing cholangitis (IgG4-SC)
Secondary sclerosing cholangitis
Biliary lesion in AIDS patients
Cholangiocarcinoma
CBD stone
Postoperative/bile duct injury
Congenital biliary disorders
Chemical agents/drug-induced cholangitis
Ischemic biliary stenosis
Others

[47.6–87.4] in IgG4-SC [7]. Cholangiographic classification of IgG4-SC (Fig. 1) according to the clinical diagnostic criteria of IgG4-SC in 2012 [2] demonstrated that type IV, in which strictures of the bile duct are detected only in the hepatic hilar lesions similar to cholangiocarcinoma was the most common in cases of IgG4-SC without AIP [7].

Bile duct images of IgG4-SC

Cholangiogram

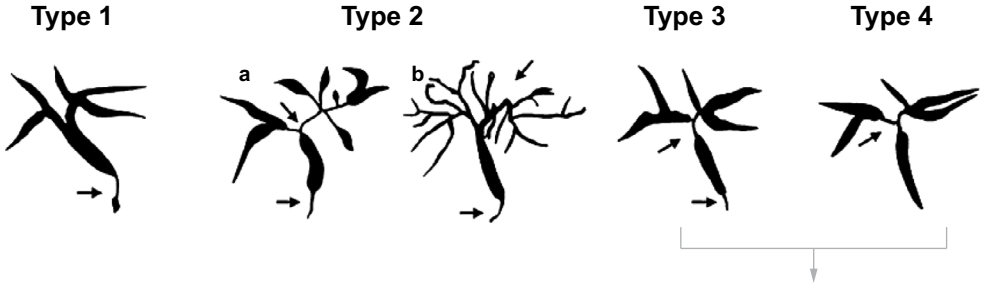
Four types of the characteristic cholangiographic features of IgG4-SC have been proposed based on the regions of stricture (Fig. 1) [2]. Type 1 IgG4-SC shows stenosis only in the distal CBD, which is often observed in pancreas cancer. Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic/proximal bile ducts, should be differentiated from PSC. Type 3 and type 4 of IgG4-SC show stenosis in the hilar hepatic bile duct similar to hepatic hilar cholangiocarcinoma.

Circular/symmetric thickening of the bile duct

Circular and symmetric thickening of the bile duct wall, smooth outer and inner margin, and homogenous internal echo demonstrated by abdominal ultrasonography (US), abdominal computed tomography (CT), abdominal magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), and intraductal ultrasonography (IDUS) are most characteristic images of the bile duct [2]. 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 a cholangiogram [2].

Characteristic hematological findings

More than 80% of the patients with IgG4-SC show elevation of serum hepatobiliary enzymes, total bilirubin in cases of obstructive jaundice, and serum IgG4 levels (higher than the upper limit of normal value (ULN) of 135 mg/dl) [1,2]. However, elevation of serum IgG4 levels is not necessarily specific to IgG4-SC; it is also observed in atopic dermatitis, pemphigus, asthma, and some malignant cholangio-pancreatic diseases [2–6]. Cut-off values of serum IgG4 higher than x 2 ULN may be useful for more precisely differentiating IgG4-SC from PSC or cholangiocarcinoma [2,7].



Differential diagnosis			
	Pancreatic cancer Bile duct cancer Chronic pancreatitis	Primary sclerosing cholangitis	Bile duct cancer Gallbladder cancer
Useful modalities			
	IDUS* (bile duct) EUS-FNA** (pancreas) Biopsy (bile duct)	Liver biopsy Colonoscopy (R/O co-existence of IBD***)	EUS (bile duct, pancreas) IDUS (bile duct) Biopsy (bile duct)

Fig. 1. Classification of cholangiography in IgG4-related sclerosing cholangitis. The characteristic features of IgG4-SC can be classified into 4 types based on the regions of stricture as revealed by cholangiography and differential diagnosis. Type 1 IgG4-SC shows stenosis only in the lower part of the common bile duct, and it should be differentiated from chronic pancreatitis, pancreatic cancer, or cholangiocarcinoma. Type 2 IgG4-SC, in which stenosis is diffusely distributed throughout the intrahepatic and extrahepatic bile ducts, should be differentiated from PSC. Type 2 is further subdivided into 2 types. Type 2a, with narrowing of the intrahepatic bile ducts with prestenotic dilation and Type 2b, with narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches, which is caused by marked lymphocytic and plasmacyte infiltration into the peripheral bile ducts. Type 3 IgG4-SC is characterized by stenosis in both the hilar hepatic lesions and the lower part of common bile duct. Type 4 IgG4-SC shows strictures of the bile duct only in the hilar hepatic lesions. Cholangiographic findings of type 3 and type 4 need to be discriminated from those of cholangiocarcinoma. *IDUS, intraductal ultrasonography; **EUS-FNA, endoscopic ultrasound-guided fine-needle aspiration; ***IBD, inflammatory bowel disease. Modified from Hepatobiliary Pancreat Sci. 2012;19:536–542 [2], Copyright © 2013, with permission.

Other organ involvements (OOIs)

Most cases of IgG4-SC (80–90%) are associated with AIP. It is particularly difficult to accurately diagnose IgG4-SC without AIP [3,5]. Occasionally, IgG4-SC is associated with other systemic IgG4-RD such as IgG4-related symmetrical dacryoadenitis/sialadenitis and IgG4-related retroperitoneal fibrosis [5,6]; these are helpful in the diagnosis of IgG4-SC. Unlike PSC, inflammatory bowel disease (IBD) is rarely observed in patients with IgG4-SC [2,6].

Histopathological findings of bile ducts

In IgG4-SC, massive infiltration of IgG4-positive plasma cells, storiform fibrosis, and/or obliterative phlebitis in the bile duct wall are characteristic and called lymphoplasmacytic sclerosing cholangitis (LPSC) [2,6]. Such fibroinflammatory involvement is mainly observed in the submucosa of the bile duct wall, whereas the epithelium of the bile duct is intact [8]. 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 [2]. Liver biopsy is sometimes useful in the diagnosis of IgG4-SC in cases of intrahepatic bile duct involvement [2].

Effectiveness of steroid therapy

In contrast to PSC or cholangiocarcinoma, the most characteristic feature of IgG4-SC is steroid responsiveness. It is important to make efforts of ruling out malignancy and to take enough biopsy samples. At many institutions, the therapeutic protocol for IgG4-SC follows that for AIP, such as oral prednisolone with the initial dose of 0.5–0.6/kg body weight/day [9]. If lesions do not respond to steroids, re-evaluation to rule out malignancy should be performed. In the refractory cases for oral steroids, it has been reported that steroid mini-pulse therapy [10], immunomodulators [11], and rituximab [12] are useful.

Diagnosis of IgG4-SC

In many cases of IgG4-SC, diagnosis can be made by a combination of characteristic biliary images (MRCP, ERCP, and EUS), increased serum levels of IgG4, coexistence of other organ involvements (OOIs), and characteristic histopathological features; however it is sometimes difficult to distinguish from PSC, cholangiocarcinoma, and pancreas cancer [2]. Based on these findings, the Japanese study group for IgG4-SC proposed the clinical diagnostic criteria for IgG4-SC [2] (Table 2). The effectiveness of steroid therapy is an optional diagnostic criterion to ensure accurate diagnosis of IgG4-SC like AIP only after negative workup of malignancy [2].

Recent advances in the pathogenesis of IgG4-SC

Although the precise pathogenic mechanism remains unclear, susceptible genetic factors, abnormal innate and acquired immunity, decreased naïve regulatory T cells, and specific B cell responses may be involved in the development of IgG4-cholangiopathy [5,3]. The class II antigen haplotype of the human major histocompatibility complex (HLA-DRB1∗0405-DQB1∗0401), polymorphisms of nuclear factor-κB and Fc-receptor-like (FCRL) 3 genes expressed on B cells have been reported in the Japanese patients with AIP [3].

Innate immunity

Recently, abnormal innate immunity has been demonstrated in patients with IgG4-RD. Activation of NOD-2 and TLR ligands on monocytes or basophils from patients with IgG4-related AIP enhance IgG4 responses via B cell activating factor (BAFF) and IL-13, although specific pathogens still remain unclear [13]. In animal models, activation of TLR3 (polyinosinic:polycytidylic acid) or TLR4 (LPS) can induce immune-mediated cholangitis, pancreatitis, and sialadenitis similar to human IgG4-RD [14].

Humoral immunity

Role of IgG4 in IgG4-SC

Although the association of IgE-mediated allergy and IgG4 antibodies is well known, IgG4 characteristics are still poorly understood. IgG4 has non-acting characteristics for immune responses, and is involved in a continuous process referred 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 [3]. While these modified antibodies are hetero-bivalent, they behave as monovalent antibodies. Another aspect of IgG4 is that it mimics IgG rheumatoid factor (RF) activity by interacting with IgG [3]. 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 [3]. In contrast, increased inducible-memory Tregs in the periphery and liver tissues are positively correlated with serum levels of IgG4 [15]. In addition, prominent infiltration of Tregs upregulated IL-10 in livers of the patients with IgG4-SC [16]. These findings suggest that hypersecretory IgG4 from Tregs may be a secondary phenomenon of the development of IgG4-SC, whereas overproduction of IgG4 by BAFF from abnormal innate immunity-related cells such as monocytes or basophils, may be involved with development of IgG4-SC. Further studies are necessary to clarify the role of IgG4 in IgG4-RD.

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 recent study showed that the classical pathway through IgG1 may be involved in activation of the complement system rather than mannose-binding lectin or alternative pathways through IgG4 [17].

Autoantibodies

Some patients with IgG4-related disease have non-specific antibodies such as an anti-nuclear antibody (ANA). From the view of IgG4 function, the big mystery is whether IgG4-related disease is an autoimmune or an allergic disease. However, the occasional coexistence of OOIs leads us to consider that there may be common target antigens in the involved organs, especially the pancreas, because of high incidence. Among candidate antigens

Table 2. The Japanese clinical diagnostic criteria 2012 for IgG4-related sclerosing cholangitis.

Diagnostic items
1. Biliary tract imaging reveals diffuse or segmental narrowing of the intrahepatic and/or extrahepatic bile duct associated with the tickening of the bile duct wall
2. Hematological examination shows elevated serum IgG4 concentrations (≥135 mg/dl)
3. Coexistence of autoimmune pancreatiti, IgG4-related dacryoadenitis/sialadenitis, or IgG4-related retroperitoneal fibrosis
4. Histopathological examination shows:
a. Marked lymphocytic and plasmacyte infiltration and fibrosis
b. Infiltration of IgG4-positive plasma cells: >10 IgG4-positive plasma cells/HPF
c. Storiform fibrosis
d. Obliterative phlebitis
Option: effectiveness of steroid therapy
A specialized facility, in which detailed examinations such as endoscopic biliary biopsy and endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) can be administered, may include in its diagnosis the effectiveness of steroid therapy, once pancreatic or biliary cancers have been ruled out
Diagnosis
Definite diagnosis
1. + 3.
1. + 2. + 4.a., b.
4.a., b., c.
4.a., b., d.
Probable diagnosis
1. + 2. + option
Possible diagnosis
1. + 2.
It is necessary to exclude PSC, malignant diseases such as pancreatic or biliary cancers, and secondary sclerosing cholangitis caused by the diseases with obvious pathogenesis. When it is difficult to differentiate from malignant conditions, a patient must not be treated with facile steroid therapy but should be referred to a specialized medical facility.

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previously reported [18], lactoferrin (LF), carbonic anhydrase (CA)-II, CA-IV, and pancreatic secretory trypsin inhibitor (PSTI) are distributed in the pancreas, salivary glands, biliary duct, lungs, and renal tubules. Immunization with CA-II or LF induced systemic lesions such as pancreatitis, sialadenitis, cholangitis, and interstitial nephritis in the mice models similar to human IgG4-RD [18].

Role of B cells

In addition to steroid and immune-modulators, B cell depletion by rituximab is a useful therapeutic strategy in IgG4-RD. Interestingly, rituximab reduces only the IgG4 subclass but no other subclasses of IgG1, IgG2, or IgG3 [19]. A recent study showed expansion of $IgG4^+$ B cell receptor (BCR) clones in blood and tissue of patients with active IgG4-cholangiopathy, and disappearance by corticosteroid treatment. These findings suggest that specific B cell responses may have a pivotal role in the pathogenesis of IgG4-SC [20].

Th1 and Th2 immune balance

The effector cells in IgG4-related diseases have been poorly understood. The $CD4^+$ T cells differentiate from naïve T cells (Th0) to Th1, Th2, Th17, and regulatory T (Treg) cells [3]. In the livers of IgG4-SC patients, a Th2 type immune reaction [16] is induced in addition to the Th1 responses [18]. Th2 cytokines may be involved in the progression of the disease process, especially the maturation and proliferation of local B cells and plasmacytes.

Regulatory T cells

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 $CD4^+CD25^+$ regulatory T cells (Tregs) classified as naturally occurring $CD4^+CD25^+$ Tregs (nTregs) originating in the thymus and adaptive Tregs (aTregs) induced in the periphery by different antigens [15]. In IgG4-related diseases, circulatory naïve ($CD45RA^+$) Tregs are significantly decreased in the peripheral blood, whereas memory ($CD45RA^-$) Tregs are significantly increased [15]. In addition, prominent infiltration of Tregs with upregulation of IL-10 is observed in the liver of IgG4-SC patients [21]. These findings suggest that increased memory-Tregs in the periphery and local tissues may be an inhibitory immune response against inflammation, although decreased naïve Tregs may be pathogenic. The neonatally thymectomized (nTx)-BALB/c mice with CA-II or LF immunization and WBN/Kob rat models showed depletion of naïve Tregs and multi-organ inflammation similar to human IgG4-RD [5]. These animal models suggested that, in addition to depletion of naïve Tregs, macrophage activation and Th1 immune responses by $CD4^+/CD8^+$ T cells play major roles in the initial development of organ involvement.

Our hypothesis for the pathogenesis of IgG4-SC

Based on the above findings, we propose the pathogenic mechanisms in IgG4-SC/AIP outlined in Fig. 2. The basic concept is the biphasic mechanism of "induction" and "progression." Initially,

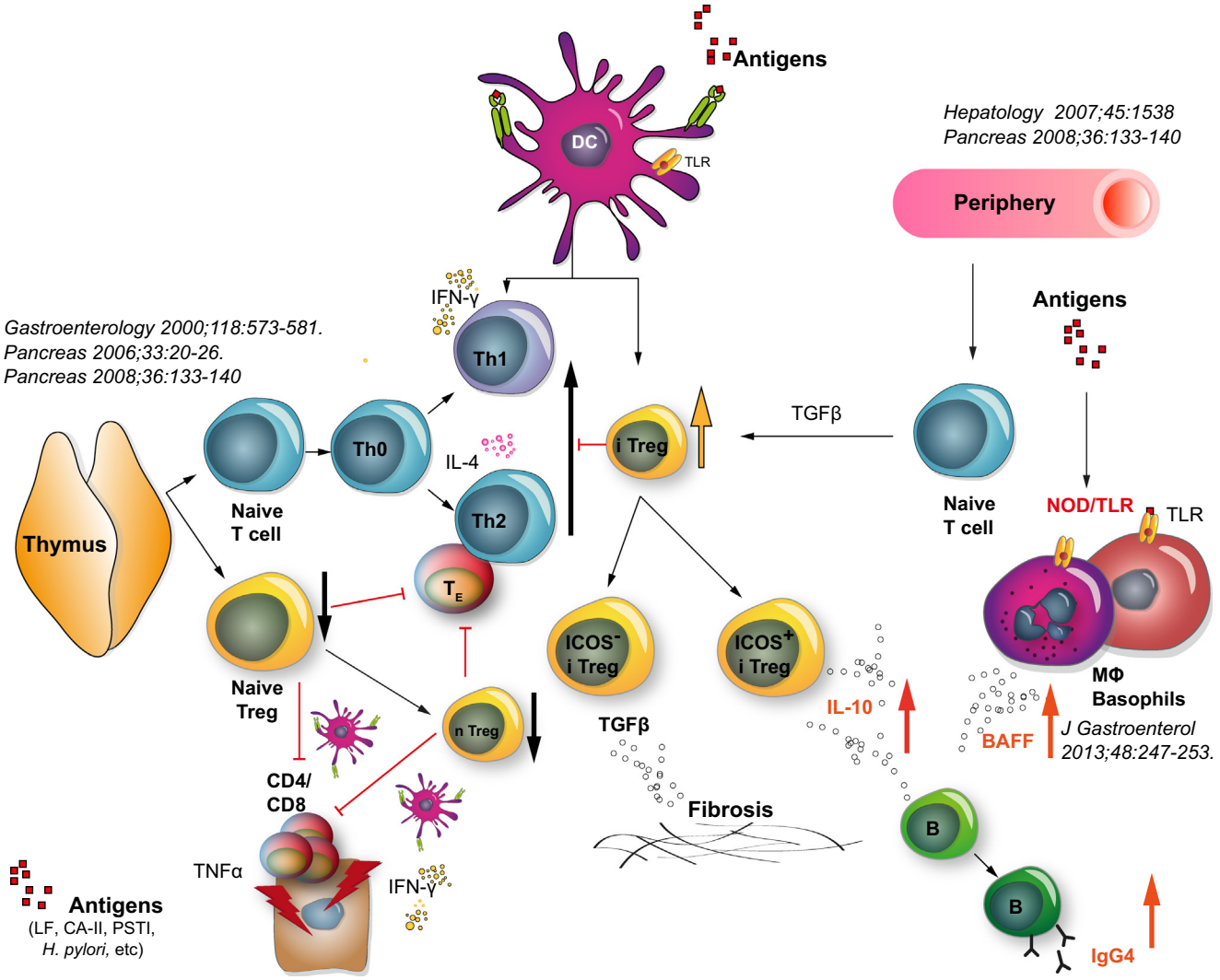

Fig. 2. Hypothesis for the pathogenesis of AIP and IgG4-related disease. In the central tolerance, naïve and natural regulatory T cells (Tregs) derived from the thymus suppress autoreactive CD4 or CD8 cells in the normal state. In the IgG4-related disease, the basic concept is the biphasic mechanism of "induction" and "progression". Initial response to antigens (LF, CA-II, CA-IV, PSTI, amylase-alpha, PBP peptide of *H. pylori*, etc.) might be induced by decreased naïve-Tregs. Th2 immune responses followed by Th1 type immune response with release of proinflammatory cytokines (IFN-γ, IL-1B, IL-2, TNF-α). In progression, Th2 type immune responses with producing IgG, IgG4 and autoantibodies may be involved in pathophysiology. IgG4 and fibrosis may be regulated by increased IL-10 and TGF-β secreted from inducible memory-Tregs, respectively. On the other hand, activation of NOD receptor or TLRs on monocytes or basophils increases IgG4 via upregulation BAFF and IL-13. iTreg, inducible Treg; TE, effector T cell; nTreg, natural Treg; BAFF, B cell activating factor. Modified from J Gastroenterol. 2011;46:277–288 [5], Copyright © 2012, with permission.

decreased naïve-Tregs may induce a Th1 immune response with the release of pro-inflammatory cytokines (IFN-γ, IL-1beta, IL-2, and TNF-α) to unknown antigens such as self-antigens (LF, CA-II, CA-IV, PSTI, and alpha-amylase) or microorganisms (*Helicobacter pylori*, commensal bacteria, and viruses). Subsequently, Th2 type immune responses may be involved in the disease progression. Production of IgG4 may be upregulated by BAFF from monocytes and basophils, and by IL-10 from inducible memory-Tregs. Tumor growth factor (TGF)-beta secreted from inducible memory-Tregs infiltrating into the involved organ may induce fibrosis.

Conclusion

In conclusion, recent advances support the concept of IgG4-SC, a unique clinical entity as a biliary manifestation of IgG4-RD. Although the pathogenic mechanism remains unclear, we proposed a hypothesis of the pathogenic mechanism of IgG4-SC. Further studies are necessary to clarify the pathogenesis including genetic backgrounds, disease specific antigens, and the role of IgG4.

Financial support

This study was partially supported by (1) Grant-in-Aid for Scientific Research (C) of the Ministry of Culture and Science of Japan (20590810, 24591020, 12008507, 26461038), (2) the Research Program on Intractable Diseases, from the Ministry 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.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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