Ⅶ. 研究事業報告

厚生労働科学研究費補助金（難治性疾患政策研究事業）
「IgG4 関連疾患の診断基準並びに治療指針の確立を目指した研究」

平成 26 年度 班会議　プログラム

日時：　平成 27 年 1 月 9 日（金）10 時 30 分～17 時 30 分

会場：　京都大学 芝蘭会館

〒 606-8315　京都市左京区吉田近衛町　京都大学医学部構内
TEL: 075-753-9336

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厚生労働科学研究費補助金（難治性疾患政策研究事業）
「IgG４関連疾患の診断基準並びに治療指針の確立を目指した研究」
京都大学医学研究科消化器内科 事務局
TEL:075-751-4302　　FAX:075-751-4303
E-mail: maogawa@kuhp.kyoto-u.ac.jp

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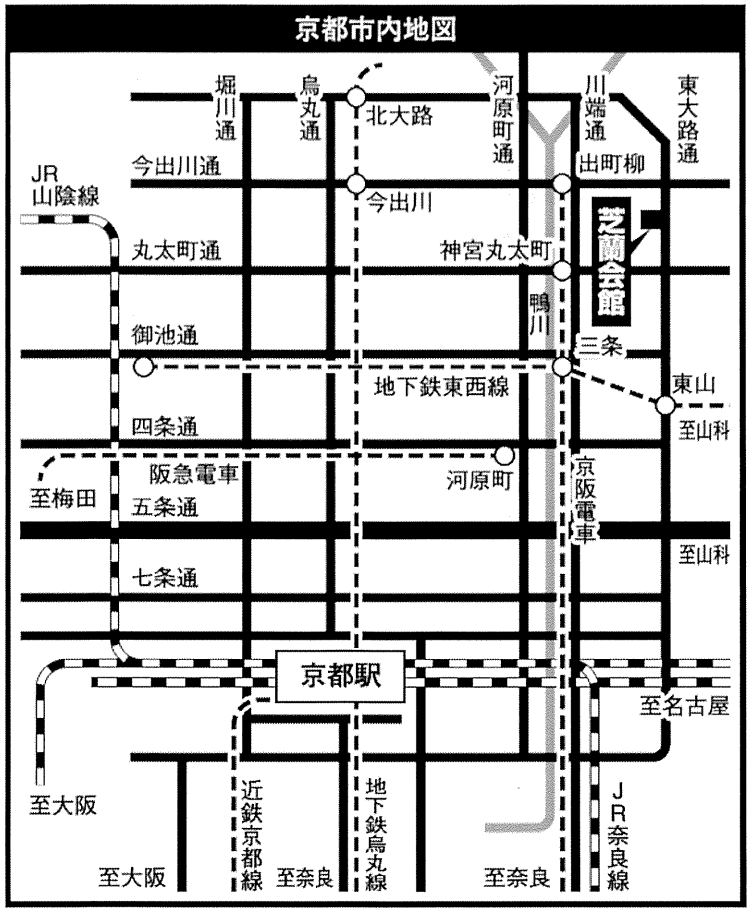
京都市内地図
堀川通
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北大路
河原町通
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今出川通
出町柳
今出川
芝蘭会館
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御池通
三条
東山
地下鉄東西線
至山科
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阪急電車
至梅田
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京阪電車
五条通
七条通
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近鉄京都線
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近隣地図
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川端通
百万遍
今出川通
河原町通
鴨川
小学校
左京区役所
京大正門前
東一条通
精華女子高校
野川通
芝蘭会館（別館）
京大正門前
京阪電車鴨東線
一方通行
京大会館
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東大路通
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薬学部
京大病院
NTT
熊野神社
丸太町通
至京都駅
至三条京阪
至祇園

厚生労働科学研究費補助金（難治性疾患政策研究事業）
「IgG4 関連疾患の診断基準並びに治療指針の確立を目指した研究」

平成 26 年度　プログラム　(敬称略)

日時：平成 27 年 1 月 9 日（金）10 時 30 分～17 時 30 分
会場：京都大学 芝蘭会館

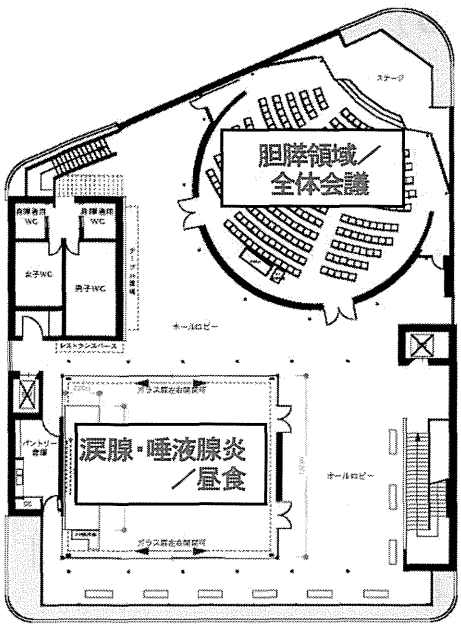
※　10:00 より【芝蘭会館 1 階　班会議受付】にて受付開始　※

【午前】個別分科会　１０：３０～１２：００

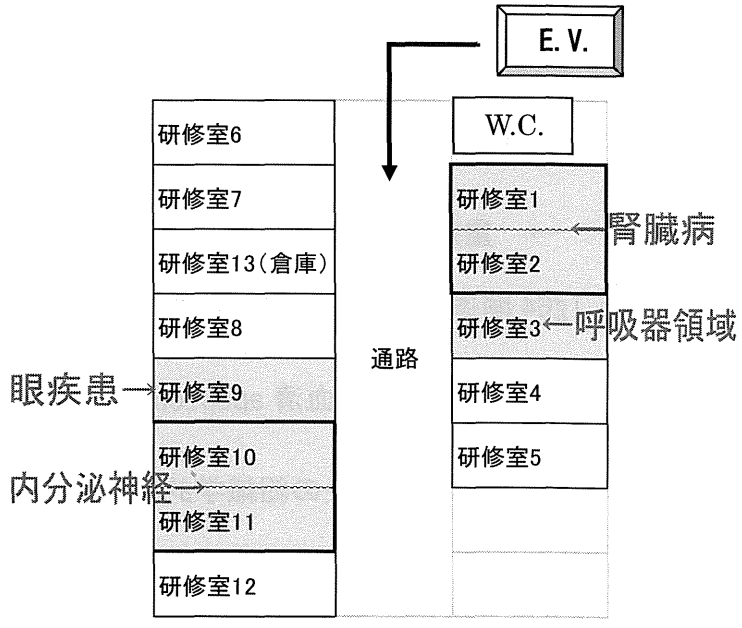
→ 難病指定患者を特定するための臓器別「診断基準」、医療費助成の対象となる重症患者を特定するための「重症度分類」の策定を中心に。

① 内分泌神経領域分科会	地下研修室 10
② IgG4 関連涙腺・唾液腺炎分科会	２階山内ホール
③ 胆膵領域分科会	２階稲盛ホール
④ IgG4関連眼疾患分科会	地下研修室9
⑤ IgG4関連腎臓病分科会	地下研修室1
⑥ 呼吸器領域分科会	地下研修室3

芝蘭会館２階　案内図



芝蘭会館　地下研修室　案内図



休憩・昼食　１２：００～１３：００（２階　山内ホール）

同上昼食時：
研究分担者会議　芝蘭会館別館・会議室
→研究分担者の先生方は、芝蘭会館別館へお集まりください

【午後】合同発表　　１３：００～１７：３０

（１）研究代表者挨拶　（１３：００～１３：０５）

（２）分科会報告　　（１３：０５～１４：５０）　　司会：岡崎和一

→　午前に各領域の分科会で議論された診断基準・重症度分類・治療法を中心に

① 内分泌神経領域分科会	和歌山県立医科大学	赤水尚史
② IgG4 関連涙腺・唾液腺炎分科会	京都大学	三森経世
③ 胆膵領域分科会	関西医科大学	岡崎和一
④ IgG4 関連眼疾患分科会	東京医科大学	後藤　浩
⑤ IgG4 関連腎臓病分科会	金沢大学	川野充弘
⑥ 呼吸器領域分科会	富山大学	松井祥子
⑦ 病理分科会	岡山大学	佐藤康晴

（３）一般演題１（治療に関する各個研究発表）
（１４：５０～１５：０５）　　司会：神澤輝実

① IgG4 関連疾患に対する第 II 相多施設共同前方視的治療研究
金沢医科大学　　正木康史

② ステロイド維持療法中止後の自己免疫性膵炎の予後
東京高輪病院　　平野賢二

（４）難病指定のための IgG4-RD 診断基準・重症度分類の策定

（１５：０５～１５：４０）

【　Coffee break　】

（５）一般演題２（新規共同研究の提案および各個研究発表）
（１６：００～１７：００）　　司会：川野充弘・三森経世

→　重症症例（再燃例・難治例など）の治療方針、新規共同研究の提案など

③ IgG4 関連消化管病変の実態調査
東京都立駒込病院　　神澤輝実

④ IgG4-RD における血清 apoptosis inhibitor of macrophage (AIM)の意義について
鹿児島大学　　井戸章雄

⑤ IgG4 関連唾液腺炎の組織学的診断基準確立に向けた鑑別診断の検討
倉敷中央病院　　能登原憲司

⑥ 自己免疫性膵炎は長期経過で、膵機能障害を呈する慢性膵炎に移行するか？
信州大学　　金井圭太

⑦ IgG4 関連疾患患者末梢血の 8 カラーFACS 解析を用いた治療指針設定への応用
産業医科大学　　田中良哉

（６）国際臨床試験について　（１７：００～１７：３０）

→　International Treatment Consensus をふまえた Rituximab 国際臨床試験について

（７）閉会のあいさつ　　（１７：３０）

抄　　録

1) IgG4 関連疾患に対する第 II 相多施設共同前方視的治療研究

○正木康史、松井祥子、佐伯敬子、坪井洋人、岩男　悠、中島章夫、佐藤智美、藤川敬太、土橋浩章、川野充弘、和田庸子、平田信太郎、宮下賜一郎、折口智樹、森本尚敬、高木和貴、梅原久範

金沢医科大学・血液免疫内科学
厚生労働科学研究難治性疾患克服研究事業研究奨励分野　旧「新規疾患,IgG4 関連多臓器リンパ増殖性疾(IgG4+MOLPS)の確立のための研究 」班

【目的】IgG4 関連疾患にはステロイドが著効する事が経験的に知られているが、前方視研究によるエビデンスが存在しなかった。そのため本邦における前方視研究を行った。
【方法】「IgG4 関連疾患のステロイド治療指針を決定するための第 II 相多施設共同前方視的臨床研究（UMIN :000002311)」は、５年間で 57 例の目標登録症例数で開始した。20 施設の IRB 承認を受け、うち 12 施設から予想を上回る積極的な症例登録があり、４年間で 61 例にて登録終了となった。CRF は全て回収され、今後病理中央診断の後に最終データとする予定である。
【結果】施設診断に基づく、完全寛解率は 60.7%（37/61)、奏効率は 82.0%（50/61）であった。一方、不変＋無効が 13.1%（8/61）あり、これらの症例も含めて診断妥当性を病理中央診断会にて検討予定である。
最も多い有害事象は耐糖能異常であり 27.9%（17/61）で、新たな糖尿病の出現が 16.4%、元々の糖尿病の増悪 11.5%で、うち５例にインスリン投与を要した。その他、様々な感染症 16.4%、脂質異常 24.6%、病的骨折 13.1%、神経症 3.3%、緑内障 3.3%、筋力低下 3.3%、大腿骨頭壊死 1.6%、白内障 1.6%を認めた。予期せぬ有害事象として、血栓性血小板減少性紫斑病、振戦（パーキンソン様症状)、がん再発、アロプリノールによる薬剤起因性過敏症症候群を各々１例ずつ認めた。prednisolone 維持量の中央値は 7mg、維持投与後の再発再増悪は 12%に認めた。
【結語】IgG4 関連疾患に対するステロイド治療は優れた寛解導入率および奏効率を認めたが、ステロイド治療に伴う有害事象、減量維持後の再発再燃が問題となる。欧米で汎用されている rituximab を含め、再発再燃例に対する二次治療につき本邦でも多施設共同研究の検討が必要である。国際的な共同研究も重要であるが、海外の症例は診断やデータの信用性などを検証する必要がある。

2) ステロイド維持療法中止後の自己免疫性膵炎の予後

○平野賢二 1,2)、多田稔 2)、伊佐山浩通 2)、小池和彦 2)

1)東京高輪病院消化器内科、2)東京大学消化器内科

【研究目的】AIP の維持療法期間はガイドラインに記載されている 3 年で十分か否かを検証する。【患者と方法】3 年以上維持療法を継続している患者のち 1)臨床再燃歴がない 2)IgG<1600mg/dl を直近 1 年以上維持している、1 型 AIP21 症例を対象とした。ステロイドを徐々に減量、中止し前向きに経過を追った。症状、画像所見からステロイド再開が必要と判断したものを臨床再燃、無症状ながら IgG>1600mg/dl を示したものを血液学的再燃と定義した。【結果】平均 27 カ月の観察で臨床再燃が 10 例（膵 4 例、冠動脈 2 例、他 4 例）にみられた。無再燃は 6 例であった。血液学再燃は 12 例に認められ、臨床再燃と同時が 3 例、臨床再燃に先行が 4 例、血液再燃のみが 5 例であった。中止前のステロイド投与期間が有意な非再燃予測因子であった（ハザード比 0.969/月、95%信頼区間 0.940-0.998、P=0.038)。【結論】3 年以上の維持療法を行っても中止後の臨床再燃率は高く、維持療法中止は基本的には推奨できない。

3）IgG4 関連消化管病変の実態調査

○神澤輝実[1)]、能登原憲司[2)]、岡崎和一[3)]、児玉裕三[4)]、千葉　勉[4)]

[1)]東京都立駒込病院内科、[2)]倉敷中央病院病理診断科、[3)]関西医科大学消化器肝臓内科、[4)]京都大学消化器内科

IgG4 関連消化管病変が IgG4 関連疾患の一つの entity として認められるかを明らかにするために、本研究班の施設等より IgG4 に関連する消化管病変と思われる症例を集積し、それらの病理組織像および臨床像について検討する。さらに IgG4 関連消化管病変が存在するのであれば、その診断基準も提唱したい。病理組織標本（手術検体あるいは診断可能な内視鏡切除材料）の利用可能な IgG4 関連消化管病変と思われる症例を対象とする。対象とする IgG4 関連消化管病変は、食道、胃、十二指腸、小腸、大腸、腸間膜等に腫瘤、著しい壁肥厚、狭窄、ポリープ、潰瘍などの病変を呈し、病理組織標本において、多数（少なくても 10/hpf 以上）の IgG4 陽性形質細胞浸潤を認める例である。組織検体解析施設において、収集された組織スライド（HE, EVG 染色、IgG 染色、IgG4 染色）の組織学的検討を行う。病理組織学的な診断に従い、臨床情報解析施設において収集された臨床情報を解析する。

4）「IgG4-RD における血清 apoptosis inhibitor of macrophage (AIM)の意義について」

井戸章雄、藤田俊浩、○小田耕平、橋元慎一、上村修司、沼田政嗣、宇都浩文

鹿児島大学大学院　消化器疾患・生活習慣病学

アポトーシス抑制因子（Apoptosis inhibitor of Macrophage ; AIM）はマクロファージのアポトーシスを抑制する分子であるが、我々は、AIM が C 型慢性肝炎や非アルコール性脂肪性肝疾患（NAFLD）の肝線維化と関連する可能性を明らかにしている。

一方、IgG4 関連疾患（IgG4-RD）の病態にはマクロファージが関与する可能性が報告されており、IgG4-RD において組織の線維化進展は重要な要素である。しかし、IgG4-RD における AIM の意義については未だ明らかにされていない。本研究では IgG4-RD と AIM との関連を明らかにすることを目的とする。

5) IgG4 関連唾液腺炎の組織学的診断基準確立に向けた鑑別診断の検討

○能登原憲司

倉敷中央病院病理診断科

IgG4 関連唾液腺炎（IgG4-SA）、唾石症、Sjogren 症候群（SjS）の組織学的鑑別点を明らかにする目的で、1）顎下腺切除術の施行された IgG4-SA 17 例と唾石症 26 例、および 2）口唇腺生検で口唇腺が採取できた IgG4-SA 10 例と SjS 18 例を比較検討した。1）小葉内を主体に高度の細胞浸潤をきたす IgG4-SA と、導管の炎症が高度で小葉内では炎症の弱い唾石症の鑑別は、大多数の症例で容易であった。小葉内にリンパ濾胞の形成が顕著で、IgG4-SA に類似した唾石症が 2 例あった。2）免疫染色（IgG4+ >10/hpf、かつ IgG4+/IgG+ >40%）を併用することにより 4 例の IgG4-SA を診断することが可能であった。SjS は 7 例(39%)で導管上皮にリンパ球浸潤、破壊がみられ、診断可能であったが、それ以外の症例は形質細胞浸潤のみで IgG4-SA と差がなかった。【結語】IgG4-SA、唾石症、SjS は組織学的に鑑別可能なことが多いが、例外もある。口唇腺生検の診断には免疫染色が必須である。

6) 自己免疫性膵炎は長期経過で、膵機能障害を呈する慢性膵炎に移行するか？

○金井 圭太、浅野 純平、小口 貴也、伊藤 哲也、浜野 英明、 新倉 則和、川 茂幸

信州大学医学部付属病院　消化器内科

【背景】自己免疫性膵炎（AIP）は長期経過で通常の慢性膵炎（CP）と同様に膵石灰化を呈することがあるが、AIP の膵機能が CP と同様に低下するか否かは十分に検討されていない。【目的】AIP が長期経過で CP 同様膵機能低下を来すかどうかを明らかにする。【方法】1992 年～2014 年の間に 3 年以上経過観察が可能であった AIP 確診例を、慢性膵炎臨床診断基準 2009 を満たす膵石灰化群と非石灰化群の 2 群に分け、CP 群、正常コントロール群を対照とし、便中エラスターゼ値測定による膵外分泌機能を評価した。【結果】AIP 膵石灰化群(n=9)の便中エラスターゼ濃度は CP 群(n=27)に次いで低く、AIP 非石灰化群(n=33)よりも低い傾向にあった。AIP 非石灰化群の便中エラスターゼ濃度は、CP 群に比し有意に保たれていた($p<0.005$)。【結論】AIP は、長期経過で膵機能低下を呈する CP に移行しうる。他の IgG4 関連疾患についても長期経過で機能障害を呈する慢性期の病態に移行しうるか検討する必要があると思われる。

7) IgG4 関連疾患患者末梢血の 8 カラーFACS 解析を用いた治療指針設定への応用

○田中良哉、平田信太郎、久保智史、中山田真吾、齋藤和義

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IgG4 関連疾患（IgG4-RD）は IgG4 陽性形質細胞やリンパ球の浸潤と線維化を特徴とする全身性疾患であるが、末梢血リンパ球の細胞分類は未検討である。そこで当科で治療導入前の IgG4-RD 8 例、原発性 Sjögren 症候群（pSS）4 例、健常人（HC）8 名の末梢血単核細胞を用い Human Immunology Project に基づく 8 カラーFACS 分類を試みた。Umehara 基準にて診断した IgG4-RD 患者 8 例の背景(平均)は、年齢 56 歳，罹病期間 16.3 ヶ月，血清 IgG4 628 mg/dl。IgG4-RD では他群と比べ B 細胞中の $CD19^{+}IgD^{+}CD27^{+}$ IgM memory B 細胞の割合が低く（IgG4-RD 9.9%, pSS 20.3%, HC 27.9%, p=0.0065）、$CD19^{+}CD20^{-}CD38^{+}$ plasmablasts の割合が高かった(各 19.5%, 3.5%, 4.6%, p=0.0085)。クラスター解析により、plasmablasts の割合は $CD3^{+}CD4_{+}CCR7^{-}$ effector memory T 細胞の割合と相関した。以上より IgG4-RD では、末梢での effector memory T 細胞による B 細胞の分化誘導が示唆され、B 細胞標的療法の妥当性、及び、末梢血 FACS 解析の治療方針設定への有用性が示された。

Ⅷ. 研究成果の刊行物・別刷

REVIEW

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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.*[1] 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.*[2] 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).[3] 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.[4] 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 obliterative fibrosis,[5,6] which is also called lymphoplasmacytic sclerosing pancreatitis (LPSP).[7] 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.*[8] first suggested that AIP showing LPSP is a systemic sclerosing disease based on the concept of multifocal fibrosclerosis proposed by Comings *et al.*,[9] 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).[10] Type 2 AIP, unlike type 1 AIP, is thought to be a specific pancreatic disease with occasional coexistence with ulcerative colitis.[10,11]

On the other hand, in 1892, Mikulicz[12] 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-

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

Author (Year)	Evidences/Contents
Mikulicz (1892)[12]	Mikulicz's disease *(Z Chir Fesrschr)*
Sarles *et al.* (1961)[1]	Hypergammaglobulinemia in CP *(Am J Dig Dis)*
Comings *et al.* (1967)[9]	Familial multifocal fibrosclerosis *(Ann Intern Med)*
Küttner (1972)[13]	Küttner tumor *(Beitr Klin Chir)*
Kawaguchi *et al.* (1991)[7]	Lymphoplasmacytic sclerosing pancreatitis *(Hum Pathol)*
Yoshida *et al.* (1995)[2]	Autoimmune pancreatitis *(Dig Dis Sci)*
Hamano *et al.* (2001)[4]	High IgG4 levels in sclerosing pancreatitis *(N Eng J Med)*
Kamisawa *et al.* (2003)[8]	IgG4-related sclerosing disease *(J Gastroenterol)*
Kamisawa *et al.* (2006)[14]	IgG4-related sclerosing disease *(J Gastroenterol)*
Yamamoto *et al.* (2006)[15]	IgG4-related plasmacytic disease *(Mod Rheumatol)*
Masaki *et al.* (2009)[16]	IgG4-multiorgan lymphoproliferative syndrome (MOLPS) *(Ann Rheum Dis)*
Shimosegawa *et al.* (2011)[11]	International Consensus Diagnostic Criteria for AIP *(Pancreas)*
Umehara *et al.*[3,17]	Concept and comprehensive diagnostic criteria for IgG4-related disease *(Mod Rheumatol)*
Deshpande *et al.* (2012)[18]	International Pathological Consensus for IgG4-RD *(Mod Pathol)*
Stone *et al.* (2012)[19]	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[18]

The three major histopathological features associated with IgG4-RD

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

1. Characteristic histopathological findings with an elevated IgG4t plasma cells and IgG4-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.

drome, which also presents with bilateral, painless, and symmetrical swelling of the lachrymal, parotid, and submandibular glands. Küttner[13] reported a tumor-like enlargement of the submandibular gland that was sometimes a result of stones in the Wharton duct. These patients, lacking anti-SS-A/Ro or anti-SS-B/La antibodies, often show other systemic organ involvement with elevated serum levels of IgG4, infiltration of IgG4-positive plasma cells into the glands, and recovery of secretion with steroid treatment similar to AIP.[4-6] Referring to the original concept of multifocal fibrosclerosis, recent studies led us to develop a novel concept of a systemic disease such as IgG4-related systemic sclerosing disease,[14] systemic IgG4-related plasmacytic syndrome,[15] or IgG4-positive multiorgan lymphoproliferative syndrome,[16] all of which may refer to the same conditions. Based on these findings, although it is unclear whether the pathogenetic mechanisms in individual organs are same or not,[3,17] the comprehensive term "IgG4-related disease IgG4-RD," which was internationally endorsed with the proposal of nomenclatures for individual organ lesions as well as pathological consensus, and diagnostic criteria have been proposed from the Japanese investigators.[17] In this review, we discussed the current concepts of hepato-bilio-pancreatic lesions and recent advances in our understanding of the pathogenesis of IgG4-RD.

CURRENT CONCEPTS OF IgG4-RD IN THE HEPATO-BILIO-PANCREATIC SYSTEM

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.[3,5,14] 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.[5,14-19] Clinical symptoms vary depending on the organ in which the lesions are located, but many cases are treated effectively by steroid therapy. All of

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.[18] Storiform fibrosis and obliterative phlebitis are characteristic in pancreatic and biliary tract lesions, but rarely observed in the salivary or lymphnodes.[18] Although most patients have multiorgan lesions synchronously or metachronously, about 10% to 20% of the patients have solitary organ involvement.[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-biliopancreatic system.[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.[5,21] Recent studies have suggested that "AIP" manifests two distinct subtypes, type 1 and type 2 AIP (Table 3).[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 ($IgG4^+$ 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 obliterative 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 $IgG4^+$ plasma cells. Patients with type 1 AIP often have obstructive jaundice in elderly males, and the pancreatic and extrapancreatic manifestations respond to steroid therapy.[21] Therefore, it is a pancreatic manifestation of a systemic disorder, IgG4-RD.[19,21]

2. IgG4-SC

About 60% to 80% of patients with type 1 AIP are associated with IgG4-SC,[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.[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,	Normal IgG,
	IgG4, autoAbs (+)	normal IgG4, autoAbs (-)
OOI	Sclerosing cholangitis	Unrelated with OOI
	Sclerosing sialadenitis	
	Reteroperitoneal 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).[22] 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 colangiocarcinoma.[22] In addition to stenosis of bile ducts, circular and symmetric thickening of the bile duct wall, smooth outer and inner margin, and homogenous internal echo demonstrated by abdominal ultrasonography, abdominal computed tomography, abdominal magnetic resonance imaging, endoscopic ultrasonography, and intraductal ultrasonography are most characteristic images.[22] 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.[20-22] 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.[20-22]

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.[19,22] Such fibroinflammatory involvement is mainly observed in the submucosa of the bile duct wall, whereas the epithelium of the bile duct is intact.[23] 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.[22] Liver biopsy is sometimes useful in the diagnosis of IgG4-SC in cases of intrahepatic bile duct involvement.[22]

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.[24] 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.[25,26] 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

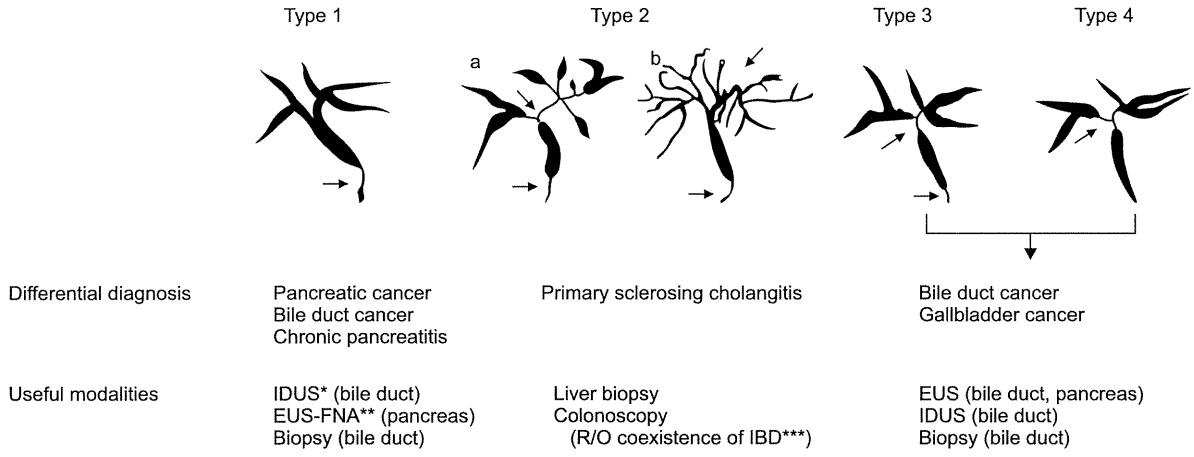

Fig. 1. Classification of cholangiography in IgG4-related sclerosing cholangitis (IgG4-SC). The characteristic features of IgG4-SC can be classified into four types, based on the regions of stricture as revealed by cholangiography and differential diagnosis. Type 1 IgG4-SC shows stenosis only in the lower part of the common bile duct, which should be differentiated from chronic pancreatitis, pancreatic cancer, or cholangiocarcinoma. Type 2 IgG4-SC, in which stenosis 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 dilation, and Type 2b has a narrowing of the intrahepatic bile ducts without prestenotic dilation and reduced bile duct branches, 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 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.[22]
IDUS, intraductal 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),[27] polymorphism of nuclear factor-κB and Fc-receptor-like 3 genes expressed on B cells.[28] 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.[29,30] 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.[5]

2. Innate immunity

Recently, abnormal innate immunity has been demonstrated in some patients with IgG4-RD.[5,21] 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.[31,32] 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.[33]

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.[34] 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.[35] 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.[36] A most 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.[37]

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.[38-42] Increased peripheral inducible-memory Tregs are positively correlated with serum levels of IgG4.[39] In addition, prominent infiltration of Tregs upregulated IL-10 in livers of the patients with IgG4-SC.[40] These findings suggest that IgG4 do not act as a pathogenic factor, but as an anti-inflammartory 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.[43] 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.[43]

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),[44,45] carbonic anhydrase (CA)-II,[44-47] CA-IV,[48] and pancreatic secretory trypsin inhibitor (PSTI)[49] 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.[50] Amylase α-2A,[51] HSP-10,[52] and *Helicobacter pylori*[53-56] 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.[5,20,21] 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,[57] and the biliary tree-derived stem cells may be involved in a pancreatic organogenesis in mice.[58] Nakanuma *et al.*[59] 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.[60,61] 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.[62] A recent study showed that the increased $CD19^+CD24^{high}CD38^{high}$ Bregs may suppress the disease activity of type 1 AIP, whereas the decreased $CD19^+CD24^{high}CD27^+$ Bregs might be involved in the development of type 1 AIP.[63] 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[38,42] is induced in addition to the Th1 responses.[45,50] 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.[64] In type 1 AIP, circulatory naive ($CD45RA^+$) Tregs are significantly decreased in the peripheral blood, whereas memory ($CD45RA^-$)-Tregs are significantly increased.[39] In addition, prominent infiltration of Tregs with upregulation of IL-10 is observed in the liver of type 1 AIP and IgG4-SC patients.[40,41] 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 sialadenitis similar to human IgG4-RD.[50] 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.[65] These animal models suggest that $CD4^+$/$CD8^+$ 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).[5] 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

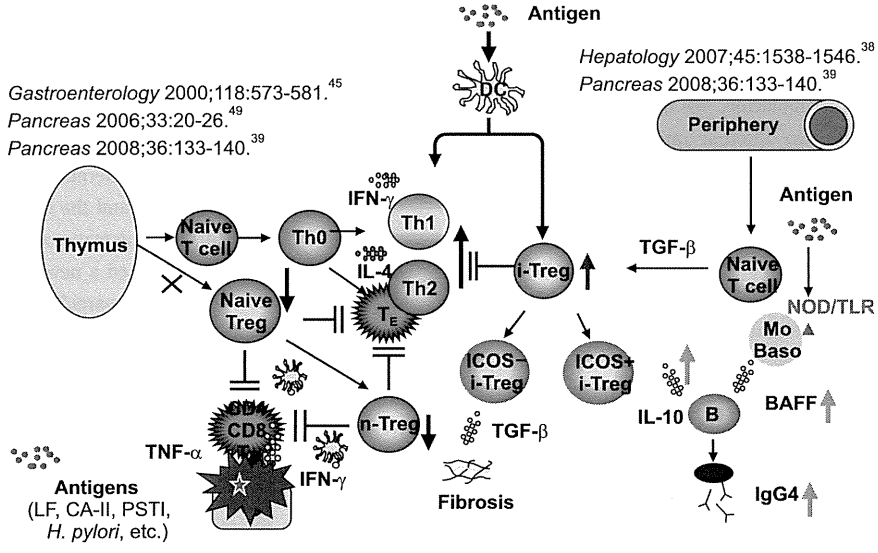

Fig. 2. Hypothesis for the pathogenesis of autoimmune pancreatitis (AIP) and IgG4-related disease. In central tolerance, naturally occurring naive regulatory T cells (n-Tregs) derived from the thymus suppress autoreactive CD4 or CD8 cells in the normal state. In the IgG4-related disease, the basic concept is a 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]-1b, 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.[5]
DC, ductal cell; TE, effector T cell.

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 costimulator (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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