World Journal of Gastrointestinal Pathophysiology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.4291/wjgp.v5.i1.11

World J Gastrointest Pathophysiol 2014 February 15; 5(1): 11-17
ISSN 2150-5330 (online)

TOPIC HIGHLIGHT

WJGP 5th Anniversary Special Issues (3): Pancreatitis

Pathophysiology of autoimmune pancreatitis

Raffaele Pezzilli, Nico Pagano

Raffaele Pezzilli, Nico Pagano, Department of Digestive Diseases and Internal Medicine, Sant'Orsola-Malpighi Hospital, 40138 Bologna, Italy
Author contributions: Pezzilli R and Pagano N acquired, analyzed and interpreted the data in the literature; they drafted the manuscript and approved the version of the paper to be published.
Correspondence to: Raffaele Pezzilli, MD, Department of Digestive Diseases and Internal Medicine, Sant'Orsola-Malpighi Hospital, Via Massarenti 9, 40138 Bologna, Italy. raffaele.pezzilli@aosp.bo.it
Telephone: +39-51-6364148 Fax: +39-51-6364148
Received: October 21, 2013 Revised: November 5, 2013
Accepted: November 15, 2013
Published online: February 15, 2014

Abstract

Autoimmune pancreatitis (AIP) is a recently discovered form of pancreatitis and represents one of the diseases of the pancreas which can be cured and healed medically. International consensus diagnostic criteria have been developed, and the clinical phenotypes associated with the histopathologic patterns of lymphoplasmacytic sclerosing pancreatitis and idiopathic duct-centric pancreatitis should be referred to as type 1 and type 2 AIP, respectively. Most importantly, in type 1 AIP, the pancreatic manifestations are associated with other extrapancreatic disorders, resembling an immunoglobulin G4 (IgG4)-related disease. In addition, the pancreas of a patient with AIP is often infiltrated by various types of immune cells; the cluster of differentiation (CD) 4 or CD8 T lymphocytes and IgG4-bearing plasma cells have been found in the pancreatic parenchyma and other involved organs in AIP and factors regulating T-cell function may influence the development of AIP. From a genetic point of view, it has also been reported that *DRB1*0405* and *DQB1*0401* mutations are significantly more frequent in patients with AIP when compared to those with chronic calcifying pancreatitis, and that only *DQB1*0302* had a significant association with the relapse of AIP. Finally, it has been found that the polymorphic genes encoding cytotoxic T lymphocyte-associated antigen 4, a key negative regulator of the T-cell immune response, are associated with AIP in a Chinese population. Even if these data are not concordant, it is possible that physiological IgG4 responses are induced by prolonged antigen exposure and controlled by type 2 helper T cells. We reviewed the current concepts regarding the pathophysiology of this intriguing disease, focusing on the importance of the humoral and cellular immune responses.

Key words: Autoimmune disease; Immune system disease; Immunoglobulin G4; Meta-analysis; Pancreatitis; Pancreatic neoplasms

Core tip: Autoimmune pancreatitis (AIP) is a recently discovered form of pancreatitis and represents one of the diseases of the pancreas which can be cured and healed medically. Two types of AIP have been recognized: type 1 (usually associated with other extrapancreatic disorders) and type 2. The pancreas of a patient with AIP is often infiltrated by various types of immune cells, including cluster of differentiation 4-positive T cells and granulocytes in type 2 AIP or immunoglobulin G4 -producing plasma cells in type 1 AIP. We reviewed the current concepts regarding the pathophysiology of this intriguing disease, focusing on the importance of the humoral and the cellular immune responses.

Pezzilli R, Pagano N. Pathophysiology of autoimmune pancreatitis. *World J Gastrointest Pathophysiol* 2014; 5(1): 11-17 Available from: URL: http://www.wjgnet.com/2150-5330/full/v5/i1/11.htm DOI: http://dx.doi.org/10.4291/wjgp.v5.i1.11

INTRODUCTION

Autoimmune pancreatitis is a recently discovered form

of pancreatitis and represents one of the diseases of the pancreas which can be cured and healed medically[1]. In recent years, several diagnostic criteria have been developed, such as those coming from Japan, South Korea, the United States and Italy[2]. The Japanese criteria are mainly based on radiological appearance while, in addition to imaging, the American and South Korean criteria are based on extra-pancreatic organ involvement and response to steroids, and the Italian diagnostic criteria are based on pathological findings. International consensus diagnostic criteria have subsequently been developed and, although a complete consensus has not yet been achieved, most experts agreed that the clinical phenotypes associated with the histopathologic patterns of lymphoplasmacytic sclerosing pancreatitis (LPSP) [Autoimmune pancreatitis (AIP) without granulocytic epithelial lesions (GELs)] and idiopathic duct-centric pancreatitis (IDCP) (AIP with GELs) should be referred to as type 1 and type 2 AIP, respectively[3]. The main characteristics of the two types of AIP are reported in Table 1. This will allow additional study of and the identification of specific markers of both forms of AIP; at present, the disease associated with IDCP can be definitively diagnosed only by histological examination since steroid trials cannot differentiate diseases associated with LPSP from those associated with IDCP. Type 1 AIP predominantly in Japan[4-6] whereas type 2 AIP was proposed and developed predominantly in Europe on the basis of its histopathological features[7]. Most importantly, in type 1 AIP the pancreatic manifestation is associated with other extrapancreatic disorders resembling an immunoglobulin G4 (IgG4)-related disease (IgG4-RD)[8,9]. We reviewed the current concepts regarding the pathophysiology of this intriguing disease, focusing on the importance of the humoral and the cellular immune responses.

PATHOGENESIS

Although both subtypes undergo remission when treated with corticosteroids[10,11], there is little agreement regarding their pathogenesis. The categorization of AIP as an autoimmune disorder is based on the observation that the disease is associated with the infiltration of immune cells into pancreatic tissue, and that the disease dramatically responds to steroid therapy. The pancreas of a patient with AIP is often infiltrated by various types of immune cells, including cluster of differentiation (CD) 4-positive T cells and granulocytes in type 2 AIP or IgG4-producing plasma cells and B-lymphocyte antigen CD20 in type 1 AIP[12].

SERUM IMMUNOLOGICAL FEATURES

Even if high circulating serum IgG4 levels have been proposed as a marker of AIP with good accuracy in differentiating between AIP and the overall controls, pancreatic cancer and other autoimmune diseases[13], other substances have also been reported in AIP. Hypergammaglobulinemia has been reported with a frequency ranging from 37% to 76%[1]. Levels of autoimmune antibodies, including antinuclear antibody, anticarboanhydrase 2, antismooth muscle antibody, antihuman lactoferrin and rheumatoid factor and pancreatic secretory trypsin inhibitor may all be elevated in a varying proportion of patients[1]. Higher concentrations of circulating leptin[14] as well as high levels of peptide AIP$_{1-7}$ which showed homology with an amino acid sequence of the plasminogen-binding protein of Helicobacter pylori and with ubiquitin-protein ligase E3 component n-recognin 2, an enzyme highly expressed in acinar cells of the pancreas have been also reported[15]. However, it is unclear whether the formation of these antibodies constitutes a pathogenetic event or whether they represent an associated epiphenomenon of AIP[16-18]. From a practical point of view, only IgG4 seems to be an interesting molecule for understanding the pathophysiology of type 1 AIP whereas altered cellular immune response is an interesting tool for understanding the pathophysiology of type 2 AIP.

IGG4: ITS PROPERTIES AND ROLE IN AIP

Human IgG subclasses are numbered according to their concentration in plasma; thus, IgG1 is the most abundant (greater than 50% of total IgG) while the amount of IgG4 is scarce, usually less than 5%. A polyclonal antiserum to one Ig class does not cross-react with other Ig classes, but antibodies to an Ig subclass will usually cross-react extensively with other subclasses of the same class. For the most part, IgG antibodies to bacterial polysaccharides belong to the human IgG2 subclass and a similar association was discovered between IgG antibodies to allergens and the IgG4 subclass[19,20].

It has been demonstrated that IgG4 antibodies are non-precipitating and behave like monovalent antibodies[21]. An unusual feature of IgG4 may explain its monovalency[22]; upon eelectrophoretic analysis, a substantial part of IgG4 was found to lack interchain disulphide bonds and, thus, to be a half-molecule of one heavy chain plus one light chain. This phenomenon was shown to be due to a single amino acid located at the site of the bond which differs between IgG1 and IgG4; a proline in IgG1 is replaced by a serine in IgG4. Mutating this serine into proline abolished the appearance of half-molecules on sodium dodecyl sulfate electrophoresis[23]. However, no half-molecules were found upon size exclusion chromatography, and this exchange process seems to be irrelevant *in vivo*.

There is also a peculiar characteristic of IgG4, namely its tendency to interact with other immunoglobulins. This has been studied in relation to the IgG rheumatoid factor[24]. IgG4 was found to possess an intrinsic affinity for IgG coated to a solid phase. This binding activity was not located in its variable domains, but in its constant domain. However, using labeled IgG4, it can be shown that IgG4 will also bind to coated IgG4. To further com-

Table 1 Epidemiological, laboratory, pathological and clinical characteristics of type 1 and type 2 autoimmune pancreatitis

	Type 1 AIP	Type 2 AIP
Age	Adult	Child and adult
Gender	Usually male	Equal
Serum IgG4 levels	Elevated	Normal
Histology	Lymphoplasmacytic sclerosing pancreatitis	Idiopathic duct-centric pancreatitis
IgG4 plasma cells	Well represented	Rare
Granulocytic epithelial lesions	Absent	Present
Relapse rate	High	Low
Extra-pancreatic lesions	IgG4-related disease: hypophysitis, pachymeningitis, perineural mass, chronic sclerosing dacryoadenitis, chronic sclerosing sialadenitis, lymphadenopathy, thyroiditis or hypothyroidism, pseudolymphoma, breast inflammatory pseudotumor or mastitis, pulmonary inflammatory pseudotumor, nodular pleuritis, chronic gastritis, Vater's ampulla pseudotumor, sclerosing cholangitis, lymphoplasmacytic sclerosing cholecystitis, hepatic inflammatory pseudotumor, autoimmune hepatitis, retroperitoneal fibrosis, periaortitis/periarteritis, inflammatory aneurysm, tubulointerstitial nephritis	Inflammatory bowel disease

AIP: Autoimmune pancreatitis; IgG4: Immunoglobulin G4.

plicate the situation, IgG4 with irrelevant specificity was found to bind to IgG4 antibody bound to its antigen[25]; this is a potential source of artifacts in analytical assays, not only for the measurement of bi-specific IgG4, but also for the measurement of the IgG4 antibody in general. In the case of the measurement of the bispecificity of IgG4, this "non-specific" binding was blocked by adding pooled immunoglobulins to the incubation buffer.

Total IgG4 levels are low in infancy and, thereafter, tend to increase; this presumably reflects a dependency on the maturity of accessory cells (macrophages, dendritic cells, *etc*.) which are important producers of interleukin (IL)-10. Moreover, some of the IL-10 effects are mediated via such accessory cells[26]. In fact, it has been suggested that AIP patients may be exposed to high doses of unknown disease-specific antigens, resulting in the activation of both Th1-type immune cells and regulatory T cells *via* IL-10[27].

The slow kinetics of IgG4-expressing cells is also reflected in IgG4-specific antibody levels. The IgG4/IgG1 ratio of antibodies to common foods is lower in infancy than in adolescence. This shift in the IgG4/IgG1 antibody may be related to the chronic stimulation requirement for IgG4 production, as previously discussed. This shift to IgG4 is, however, only partially due to an earlier appearance of IgG1 antibodies; it also reflects an earlier decline of IgG1 antibodies[28].

The requirements for the class switch to IgG4 are similar to those for IgE because both depend on IL-4/IL-13 induction[29-32]. Both are therefore considered to be part of the Th2 immune response. In relation to allergen-specific immunotherapy, it is sometimes suggested that a switch occurs from IgE production to IgG4 production. While a B cell can switch sequentially, such a sequential switch can transform an IgG4-producing B cell into an IgE-producing B cell, but not the other way around as a consequence of the sequence order in which the genes for the isotypes are arranged on the chromosome[30-32].

One of the effects of this common dependency on Th2 cells is that antigens which induce IgE responses are also good inducers of IgG4 responses. There are probably some regulatory differences before the class switch because the occurrence of IgG4 antibodies without IgE antibodies is not uncommon. One type of regulation is particularly important: the effects of IL-10 and related cytokines. Interleukin-10 interferes with the class switch[26] which affects both IgE and IgG4 production[33]. In addition, IL-10 is presumably needed to drive the differentiation of IgG4-switched B cells to IgG4-secreting plasma cells[34]. In addition to IL-10, IL-21 has also been found to increase IgG4 production *in vitro*[35,36]. Increased IL-21 production is characteristic of certain autoimmune diseases and is likely to contribute to autoantibody production as well as to the pathologic features of autoimmune disease[37]. In contrast, IL-21 may function as a co-adjuvant to enhance antibody responses and thereby facilitate host defense to malignances and infectious diseases[37]. Thus, the critical role of IL-21 in promoting humoral immune responses makes it an important focus of potential therapeutic interventions under conditions characterized by either the overproduction of pathogenic autoantibodies or the underproduction of protective antibodies.

The "modified Th2 response" was first used in relation to the antibody response to cat allergen[38], and it refers to subjects with IgG4 antibodies without demonstrable IgE antibodies. As the presence of IgG4 antibodies indicates a Th2 response, the absence of IgE antibodies is unexpected. However, this situation is quite common and it is seen in most beekeepers and in individuals having occupational exposure to protein antigens, such as rodent allergens in the animal house and/or exposure to mammalian serum albumin in the animal blood processing industry[39], and usually produces this phenotype[40,41]. Therefore, the modified Th2 response seems to be the typical response to an innocuous antigen[42,43]. It is intriguing that this type of response is not found in all situations where allergen exposure does not

result in IgE production. This is true not only for IgG4, but also for IgG1. The presence of high-affinity IgG antibodies (IgG1 and/or IgG4) to pollen- or mite allergens is much more common in subjects with allergen-specific IgE than in IgE-negative subjects; this difference is more marked for some allergens than for others which suggests that not all allergens are equal. However, some allergens do not induce an IgG antibody response at all whereas others induce an IgG (IgG1 and/or IgG4) response without IgE[44].

An important aspect of the IgG4 response is the slow manifestation of IgG4 antibodies. It usually takes many months of repeated antigen exposure before IgG4 responses become prominent. This is well known in the sequential analysis of sera from novice bee-keepers[45], and the analysis of sequential samples from patients who received subcutaneous allergen-specific immunotherapy shows the same pattern. It is likely that the production of sufficient IL-10 is a rate-limiting step.

CELLULAR IMMUNE ACTIVATION

CD4 or CD8 T lymphocytes and IgG4-bearing plasma cells have been found in the pancreatic parenchyma and other involved organs in AIP[46-49]. It seems that factors regulating T-cell function influence the development of AIP. The cytotoxic T-lymphocyte antigen 4 gene is an inhibitory receptor expressed on the cell surface of activated memory T cells and on $CD4^+$ $CD25^+$ regulatory T cells, and acts largely as a negative regulator of T-cell responses[50]. CTLA4 may modulate positive T-cell costimulatory signals by competing with the CD28 molecule for engagement with the B7 molecules CD80 and CD86 localized on antigen-presenting cells. In addition, and *CTLA4* + 49A/G single nucleotide polymorphisms (SNPs) have been associated with susceptibility to autoimmune diseases, such as type 1 diabetes, autoimmune thyroid disease, autoimmune hepatitis, and primary biliary cirrhosis[50]. Another form of *CTLA4*, secreted by resting T cells, can suppress T-cell activation and this soluble isoform of *CTLA4* (s*CTLA4*) is present in human serum, and it is elevated in patients with autoimmune diseases, such as autoimmune thyroid disease[51], systemic lupus erythematosus[52], and myasthenia gravis[53]. The + 6230G/A SNP in the 3' untranslated region of *CTLA4* has been also found in Graves' disease, type 1 diabetes[54] and Umemura *et al*[55] have demonstrated that AIP is closely associated with the *CTLA4* + 6230 SNP and serum sCTLA4 levels and that *CTLA4* gene plays an important role in the pathogenesis of AIP.

It has also been reported that *DRB1*0405* and *DQB1*0401* mutations are significantly more frequent in patients with AIP when compared to those with chronic calcifying pancreatitis[56], even if these initial and promising findings were not confirmed by two recent studies[57,58]. Furthermore, Park *et al*[57] found that only *DQB1*0302* had a significant association with the relapse of AIP. Finally, it has been found that the polymorphic genes (CTLA-4 49A polymorphism and -318C/+ 49A/CT60G haplotype) encoding cytotoxic T lymphocyte-associated antigen 4, a key negative regulator of the T-cell immune response, are associated with AIP in a Chinese population[59]. Even if these data are not concordant, it is possible that physiological IgG4 responses are induced by prolonged antigen exposure and controlled by type 2 helper T cells[18]. A possible explanation may come from genetically-modified animals which were produced to mimic AIP.

ANIMAL MODELS FOR STUDYING THE PATHOPHYSIOLOGY OF AIP

We believe that due the no high incidence of AIP, the animal models are important in helping the researchers to test new pathogenetic hypotheses on AIP and also new drugs able to treat this disease.

It has been demonstrated that MRL/Mp mice develop a form of autoimmune pancreatitis and that the administration of polyinosinic: polycytidylic acid may substantially shorten the time course and increase the frequency of both pancreatitis and biliary involvement[60]. The experimental model for inducing inflammatory bowel disease, *i.e.*, *IL-10*$^{-/-}$ mice, has been also used for developing type I AIP[61]. It is also possible induce AIP by immunization with lactoferrin, carbonic anhydrase or other antigens, or by alterations to the intestinal flora[62,63]. When applied, these models may answer the question regarding the first events which may lead to AIP, and to test novel therapeutic modalities, especially those regarding cellular immune activation.

CONCLUSION

Several questions remain open in the pathophysiology of AIP. The interrelationship with allergies and the multivisceral involvement in patients with AIP should be better evaluated in order to answer the question of whether IgG4 disease is initiated by allergens. In this respect, we would point out that we have recently reported an association between anisakis infection and AIP[64], and worms are well-known inducers of allergic phenomena [31]. Finally, we also need to investigate whether type 1 or type 2 AIP are different diseases or different presentation of the same illness.

REFERENCES

1 **Pezzilli R**. Acute recurrent pancreatitis: an autoimmune disease? *World J Gastroenterol* 2008; **14**: 999-1006 [PMID: 18286678 DOI: 10.3748/wjg.14.999]
2 **Fantini L**, Zanini N, Fiscaletti M, Calculli L, Casadei R, Campana D, Pezzilli R. Autoimmune pancreatitis: the classification puzzle. *Adv Med Sci* 2007; **52**: 71-75 [PMID: 18217393]
3 **Chari ST**, Kloeppel G, Zhang L, Notohara K, Lerch MM, Shimosegawa T. Histopathologic and clinical subtypes of autoimmune pancreatitis: the Honolulu consensus document. *Pancreas* 2010; **39**: 549-554 [PMID: 20562576 DOI: 10.1097/MPA.0b013e3181e4d9e5]

4 **Kawaguchi K**, Koike M, Tsuruta K, Okamoto A, Tabata I, Fujita N. Lymphoplasmacytic sclerosing pancreatitis with cholangitis: a variant of primary sclerosing cholangitis extensively involving pancreas. *Hum Pathol* 1991; **22**: 387-395 [PMID: 2050373 DOI: 10.1016/0046-8177(91)90087-6]

5 **Hamano H**, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, Fukushima M, Nikaido T, Nakayama K, Usuda N, Kiyosawa K. High serum IgG4 concentrations in patients with sclerosing pancreatitis. *N Engl J Med* 2001; **344**: 732-738 [PMID: 11236777 DOI: 10.1056/NEJM200103083441005]

6 **Kamisawa T**, Funata N, Hayashi Y, Eishi Y, Koike M, Tsuruta K, Okamoto A, Egawa N, Nakajima H. A new clinicopathological entity of IgG4-related autoimmune disease. *J Gastroenterol* 2003; **38**: 982-984 [PMID: 14614606]

7 **Ectors N**, Maillet B, Aerts R, Geboes K, Donner A, Borchard F, Lankisch P, Stolte M, Lüttges J, Kremer B, Klöppel G. Non-alcoholic duct destructive chronic pancreatitis. *Gut* 1997; **41**: 263-268 [PMID: 9301509 DOI: 10.1136/gut.41.2.263]

8 **Stone JH**, Khosroshahi A, Deshpande V, Chan JK, Heathcote JG, Aalberse R, Azumi A, Bloch DB, Brugge WR, Carruthers MN, Cheuk W, Cornell L, Castillo CF, Ferry JA, Forcione D, Klöppel G, Hamilos DL, Kamisawa T, Kasashima S, Kawa S, Kawano M, Masaki Y, Notohara K, Okazaki K, Ryu JK, Saeki T, Sahani D, Sato Y, Smyrk T, Stone JR, Takahira M, Umehara H, Webster G, Yamamoto M, Yi E, Yoshino T, Zamboni G, Zen Y, Chari S. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. *Arthritis Rheum* 2012; **64**: 3061-3067 [PMID: 22736240 DOI: 10.1002/art.34593]

9 **Umehara H**, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S, Yoshino T, Nakamura S, Kawa S, Hamano H, Kamisawa T, Shimosegawa T, Shimatsu A, Nakamura S, Ito T, Notohara K, Sumida T, Tanaka Y, Mimori T, Chiba T, Mishima M, Hibi T, Tsubouchi H, Inui K, Ohara H. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012; **22**: 21-30 [PMID: 22218969 DOI: 10.1007/s10165-011-0571-z]

10 **Kamisawa T**, Chari ST, Giday SA, Kim MH, Chung JB, Lee KT, Werner J, Bergmann F, Lerch MM, Mayerle J, Pickartz T, Lohr M, Schneider A, Frulloni L, Webster GJ, Reddy DN, Liao WC, Wang HP, Okazaki K, Shimosegawa T, Kloeppel G, Go VL. Clinical profile of autoimmune pancreatitis and its histological subtypes: an international multicenter survey. *Pancreas* 2011; **40**: 809-814 [PMID: 21747310 DOI: 10.1097/MPA.0b013e3182258a15]

11 **Pickartz T**, Mayerle J, Lerch MM. Autoimmune pancreatitis. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4**: 314-323 [PMID: 17541445 DOI: 10.1038/ncpgasthep0837]

12 **Hart PA**, Topazian MD, Witzig TE, Clain JE, Gleeson FC, Klebig RR, Levy MJ, Pearson RK, Petersen BT, Smyrk TC, Sugumar A, Takahashi N, Vege SS, Chari ST. Treatment of relapsing autoimmune pancreatitis with immunomodulators and rituximab: the Mayo Clinic experience. *Gut* 2013; **62**: 1607-1615 [PMID: 22936672 DOI: 10.1136/gutjnl-2012-302886]

13 **Morselli-Labate AM**, Pezzilli R. Usefulness of serum IgG4 in the diagnosis and follow up of autoimmune pancreatitis: A systematic literature review and meta-analysis. *J Gastroenterol Hepatol* 2009; **24**: 15-36 [PMID: 19067780 DOI: 10.1111/j.1440-1746.2008.05676.x]

14 **Pezzilli R**, Barassi A, Corsi MM, Morselli-Labate AM, Campana D, Casadei R, Santini D, Corinaldesi R, D'Eril GM. Serum leptin, but not adiponectin and receptor for advanced glycation end products, is able to distinguish autoimmune pancreatitis from both chronic pancreatitis and pancreatic neoplasms. *Scand J Gastroenterol* 2010; **45**: 93-99 [PMID: 19883273 DOI: 10.3109/00365520903358907]

15 **Frulloni L**, Lunardi C, Simone R, Dolcino M, Scattolini C, Falconi M, Benini L, Vantini I, Corrocher R, Puccetti A. Identification of a novel antibody associated with autoimmune pancreatitis. *N Engl J Med* 2009; **361**: 2135-2142 [PMID: 19940298 DOI: 10.1056/NEJMoa0903068]

16 **Okazaki K**, Uchida K, Miyoshi H, Ikeura T, Takaoka M, Nishio A. Recent concepts of autoimmune pancreatitis and IgG4-related disease. *Clin Rev Allergy Immunol* 2011; **41**: 126-138 [PMID: 21170607 DOI: 10.1007/s12016-010-8214-2]

17 **Okazaki K**, Uchida K, Koyabu M, Miyoshi H, Takaoka M. Recent advances in the concept and diagnosis of autoimmune pancreatitis and IgG4-related disease. *J Gastroenterol* 2011; **46**: 277-288 [PMID: 21452084 DOI: 10.1007/s00535-011-0386-x]

18 **Stone JH**, Zen Y, Deshpande V. IgG4-related disease. *N Engl J Med* 2012; **366**: 539-551 [PMID: 22316447 DOI: 10.1056/NEJMra1104650]

19 **Devey ME**, Wilson DV, Wheeler AW. The IgG subclasses of antibodies to grass pollen allergens produced in hay fever patients during hyposensitization. *Clin Allergy* 1976; **6**: 227-236 [PMID: 939035 DOI: 10.1111/j.1365-2222.1976.tb01901.x]

20 **van der Giessen M**, Homan WL, van Kernbeek G, Aalberse RC, Dieges PH. Subclass typing of IgG antibodies formed by grass pollen-allergic patients during immunotherapy. *Int Arch Allergy Appl Immunol* 1976; **50**: 625-640 [PMID: 773842 DOI: 10.1159/000231566]

21 **van der Zee JS**, van Swieten P, Aalberse RC. Serologic aspects of IgG4 antibodies. Ⅱ. IgG4 antibodies form small, nonprecipitating immune complexes due to functional monovalency. *J Immunol* 1986; **137**: 3566-3571 [PMID: 3782791]

22 **King DJ**, Adair JR, Angal S, Low DC, Proudfoot KA, Lloyd JC, Bodmer MW, Yarranton GT. Expression, purification and characterization of a mouse-human chimeric antibody and chimeric Fab' fragment. *Biochem J* 1992; **281** (Pt 2): 317-323 [PMID: 1736881]

23 **Angal S**, King DJ, Bodmer MW, Turner A, Lawson AD, Roberts G, Pedley B, Adair JR. A single amino acid substitution abolishes the heterogeneity of chimeric mouse/human (IgG4) antibody. *Mol Immunol* 1993; **30**: 105-108 [PMID: 8417368 DOI: 10.1016/0161-5890(93)90432-B]

24 **Zack DJ**, Stempniak M, Wong AL, Weisbart RH. Localization of an Fc-binding reactivity to the constant region of human IgG4. Implications for the pathogenesis of rheumatoid arthritis. *J Immunol* 1995; **155**: 5057-5063 [PMID: 7594514]

25 **Rispens T**, Ooievaar-De Heer P, Vermeulen E, Schuurman J, van der Neut Kolfschoten M, Aalberse RC. Human IgG4 binds to IgG4 and conformationally altered IgG1 via Fc-Fc interactions. *J Immunol* 2009; **182**: 4275-4281 [PMID: 19299726 DOI: 10.4049/jimmunol.0804338]

26 **Punnonen J**, de Waal Malefyt R, van Vlasselaer P, Gauchat JF, de Vries JE. IL-10 and viral IL-10 prevent IL-4-induced IgE synthesis by inhibiting the accessory cell function of monocytes. *J Immunol* 1993; **151**: 1280-1289 [PMID: 8393044]

27 **Miyoshi H**, Uchida K, Taniguchi T, Yazumi S, Matsushita M, Takaoka M, Okazaki K. Circulating naïve and CD4+CD25high regulatory T cells in patients with autoimmune pancreatitis. *Pancreas* 2008; **36**: 133-140 [PMID: 18376303 DOI: 10.1097/MPA.0b013e3181577553]

28 **Calkhoven PG**, Aalbers M, Koshte VL, Griffioen RW, Van Nierop JC, Van Der Heide D, Aalberse RC. Relationship between IgG1 and IgG4 antibodies to foods and the development of IgE antibodies to inhalant allergens. Ⅰ. Establishment of a scoring system for the overall food responsiveness and its application to 213 unselected children. *Clin Exp Allergy* 1991; **21**: 91-98 [PMID: 2021884 DOI: 10.1111/j.1365-2222.1991.tb00809.x]

29 **Punnonen J**, Aversa G, Cocks BG, McKenzie AN, Menon S, Zurawski G, de Waal Malefyt R, de Vries JE. Interleukin 13 induces interleukin 4-independent IgG4 and IgE synthesis and CD23 expression by human B cells. *Proc Natl Acad Sci USA* 1993; **90**: 3730-3734 [PMID: 8097323 DOI: 10.1073/pnas.90.8.3730]

30 **Jabara HH**, Loh R, Ramesh N, Vercelli D, Geha RS. Sequential switching from mu to epsilon via gamma 4 in human B cells stimulated with IL-4 and hydrocortisone. *J Immunol*

1993; **151**: 4528-4533 [PMID: 8409416]
31 **Vercelli D**, De Monte L, Monticelli S, Di Bartolo C, Agresti A. To E or not to E? Can an IL-4-induced B cell choose between IgE and IgG4? *Int Arch Allergy Immunol* 1998; **116**: 1-4 [PMID: 9623503 DOI: 10.1159/000023918]
32 **Agresti A**, Vercelli D. Analysis of gamma4 germline transcription in human B cells. *Int Arch Allergy Immunol* 1999; **118**: 279-281 [PMID: 10224410 DOI: 10.1159/000024099]
33 **Meiler F**, Klunker S, Zimmermann M, Akdis CA, Akdis M. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. *Allergy* 2008; **63**: 1455-1463 [PMID: 18925882 DOI: 10.1111/j.1398-9995.2008.01774.x]
34 **Satoguina JS**, Weyand E, Larbi J, Hoerauf A. T regulatory-1 cells induce IgG4 production by B cells: role of IL-10. *J Immunol* 2005; **174**: 4718-4726 [PMID: 15814696]
35 **Wood N**, Bourque K, Donaldson DD, Collins M, Vercelli D, Goldman SJ, Kasaian MT. IL-21 effects on human IgE production in response to IL-4 or IL-13. *Cell Immunol* 2004; **231**: 133-145 [PMID: 15919378 DOI: 10.1016/j.cellimm.2005.01.001]
36 **Avery DT**, Bryant VL, Ma CS, de Waal Malefyt R, Tangye SG. IL-21-induced isotype switching to IgG and IgA by human naive B cells is differentially regulated by IL-4. *J Immunol* 2008; **181**: 1767-1779 [PMID: 18641314]
37 **Ettinger R**, Kuchen S, Lipsky PE. The role of IL-21 in regulating B-cell function in health and disease. *Immunol Rev* 2008; **223**: 60-86 [PMID: 18613830 DOI: 10.1111/j.1600-065X.2008.00631.x]
38 **Platts-Mills T**, Vaughan J, Squillace S, Woodfolk J, Sporik R. Sensitisation, asthma, and a modified Th2 response in children exposed to cat allergen: a population-based cross-sectional study. *Lancet* 2001; **357**: 752-756 [PMID: 11253969 DOI: 10.1016/S0140-6736(00)04168-4]
39 **Krop EJ**, Stapel SO, De Vrieze H, Van der Zee JS. Immunoglobulin E and G4 antibody responses in occupational airway exposure to bovine and porcine plasma proteins. *Int Arch Allergy Immunol* 2006; **139**: 237-244 [PMID: 16446546 DOI: 10.1159/000091169]
40 **Matsui EC**, Diette GB, Krop EJ, Aalberse RC, Smith AL, Curtin-Brosnan J, Eggleston PA. Mouse allergen-specific immunoglobulin G and immunoglobulin G4 and allergic symptoms in immunoglobulin E-sensitized laboratory animal workers. *Clin Exp Allergy* 2005; **35**: 1347-1353 [PMID: 16238795 DOI: 10.1111/j.1365-2222.2005.02331.x]
41 **Krop EJ**, Matsui EC, Sharrow SD, Stone MJ, Gerber P, van der Zee JS, Chapman MD, Aalberse RC. Recombinant major urinary proteins of the mouse in specific IgE and IgG testing. *Int Arch Allergy Immunol* 2007; **144**: 296-304 [PMID: 17652940 DOI: 10.1159/000106318]
42 **Akdis CA**, Blaser K. Role of IL-10 in allergen-specific immunotherapy and normal response to allergens. *Microbes Infect* 2001; **3**: 891-898 [PMID: 11564436 DOI: 10.1016/S1286-4579(01)01449-6]
43 **Akdis M**. Healthy immune response to allergens: T regulatory cells and more. *Curr Opin Immunol* 2006; **18**: 738-744 [PMID: 17023149 DOI: 10.1016/j.coi.2006.06.003]
44 **Aalberse RC**. Structural features of allergenic molecules. *Chem Immunol Allergy* 2006; **91**: 134-146 [PMID: 16354955 DOI: 10.1159/000090277]
45 **Aalberse RC**, van der Gaag R, van Leeuwen J. Serologic aspects of IgG4 antibodies. I. Prolonged immunization results in an IgG4-restricted response. *J Immunol* 1983; **130**: 722-726 [PMID: 6600252]
46 **Hamano H**, Kawa S, Ochi Y, Unno H, Shiba N, Wajiki M, Nakazawa K, Shimojo H, Kiyosawa K. Hydronephrosis associated with retroperitoneal fibrosis and sclerosing pancreatitis. *Lancet* 2002; **359**: 1403-1404 [PMID: 11978339 DOI: 10.1016/S0140-6736(02)08359-9]
47 **Zen Y**, Harada K, Sasaki M, Sato Y, Tsuneyama K, Haratake J, Kurumaya H, Katayanagi K, Masuda S, Niwa H, Morimoto H, Miwa A, Uchiyama A, Portmann BC, Nakanuma Y. IgG4-related sclerosing cholangitis with and without hepatic inflammatory pseudotumor, and sclerosing pancreatitis-associated sclerosing cholangitis: do they belong to a spectrum of sclerosing pancreatitis? *Am J Surg Pathol* 2004; **28**: 1193-1203 [PMID: 15316319 DOI: 10.1097/01.pas.0000136449.37936.6c]
48 **Umemura T**, Zen Y, Hamano H, Kawa S, Nakanuma Y, Kiyosawa K. Immunoglobin G4-hepatopathy: association of immunoglobin G4-bearing plasma cells in liver with autoimmune pancreatitis. *Hepatology* 2007; **46**: 463-471 [PMID: 17634963 DOI: 10.1002/hep.21700]
49 **Kamisawa T**, Funata N, Hayashi Y, Tsuruta K, Okamoto A, Amemiya K, Egawa N, Nakajima H. Close relationship between autoimmune pancreatitis and multifocal fibrosclerosis. *Gut* 2003; **52**: 683-687 [PMID: 12692053 DOI: 10.1136/gut.52.5.683]
50 **Gough SC**, Walker LS, Sansom DM. CTLA4 gene polymorphism and autoimmunity. *Immunol Rev* 2005; **204**: 102-115 [PMID: 15790353 DOI: 10.1111/j.0105-2896.2005.00249.x]
51 **Oaks MK**, Hallett KM. Cutting edge: a soluble form of CTLA-4 in patients with autoimmune thyroid disease. *J Immunol* 2000; **164**: 5015-5018 [PMID: 10799854]
52 **Liu MF**, Wang CR, Chen PC, Fung LL. Increased expression of soluble cytotoxic T-lymphocyte-associated antigen-4 molecule in patients with systemic lupus erythematosus. *Scand J Immunol* 2003; **57**: 568-572 [PMID: 12791095 DOI: 10.1046/j.1365-3083.2003.01232.x]
53 **Wang XB**, Kakoulidou M, Giscombe R, Qiu Q, Huang D, Pirskanen R, Lefvert AK. Abnormal expression of CTLA-4 by T cells from patients with myasthenia gravis: effect of an AT-rich gene sequence. *J Neuroimmunol* 2002; **130**: 224-232 [PMID: 12225905 DOI: 10.1016/S0165-5728(02)00228-X]
54 **Ueda H**, Howson JM, Esposito L, Heward J, Snook H, Chamberlain G, Rainbow DB, Hunter KM, Smith AN, Di Genova G, Herr MH, Dahlman I, Payne F, Smyth D, Lowe C, Twells RC, Howlett S, Healy B, Nutland S, Rance HE, Everett V, Smink LJ, Lam AC, Cordell HJ, Walker NM, Bordin C, Hulme J, Motzo C, Cucca F, Hess JF, Metzker ML, Rogers J, Gregory S, Allahabadia A, Nithiyananthan R, Tuomilehto-Wolf E, Tuomilehto J, Bingley P, Gillespie KM, Undlien DE, Rønningen KS, Guja C, Ionescu-Tîrgovişte C, Savage DA, Maxwell AP, Carson DJ, Patterson CC, Franklyn JA, Clayton DG, Peterson LB, Wicker LS, Todd JA, Gough SC. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature* 2003; **423**: 506-511 [PMID: 12724780 DOI: 10.1038/nature01621]
55 **Umemura T**, Ota M, Hamano H, Katsuyama Y, Muraki T, Arakura N, Kawa S, Kiyosawa K. Association of autoimmune pancreatitis with cytotoxic T-lymphocyte antigen 4 gene polymorphisms in Japanese patients. *Am J Gastroenterol* 2008; **103**: 588-594 [PMID: 18341485 DOI: 10.1111/j.1572-0241.2007.01750.x]
56 **Kawa S**, Ota M, Yoshizawa K, Horiuchi A, Hamano H, Ochi Y, Nakayama K, Tokutake Y, Katsuyama Y, Saito S, Hasebe O, Kiyosawa K. HLA DRB10405-DQB10401 haplotype is associated with autoimmune pancreatitis in the Japanese population. *Gastroenterology* 2002; **122**: 1264-1269 [PMID: 11984513]
57 **Park do H**, Kim MH, Oh HB, Kwon OJ, Choi YJ, Lee SS, Lee TY, Seo DW, Lee SK. Substitution of aspartic acid at position 57 of the DQbeta1 affects relapse of autoimmune pancreatitis. *Gastroenterology* 2008; **134**: 440-446 [PMID: 18155707 DOI: 10.1053/j.gastro.2007.11.023]
58 **Hirano K**, Asaoka Y, Tada M, Isayama H, Sasahira N, Tsujino T, Kawabe T, Omata M. No significant relation between relapse of autoimmune pancreatitis and substitution of aspartic acid at position 57 of DQbeta1. *J Gastroenterol* 2009; **44**: 799-800 [PMID: 19468670 DOI: 10.1007/s00535-009-0080-4]
59 **Chang MC**, Chang YT, Tien YW, Liang PC, Jan IS, Wei SC, Wong JM. T-cell regulatory gene CTLA-4 polymorphism/

haplotype association with autoimmune pancreatitis. *Clin Chem* 2007; **53**: 1700-1705 [PMID: 17712006 DOI: 10.1373/clinchem.2007.085951]

60 **Qu WM**, Miyazaki T, Terada M, Okada K, Mori S, Kanno H, Nose M. A novel autoimmune pancreatitis model in MRL mice treated with polyinosinic: polycytidylic acid. *Clin Exp Immunol* 2002; **129**: 27-34 [PMID: 12100019 DOI: 10.1046/j.1365-2249.2002.01881.x]

61 **Yamashina M**, Nishio A, Nakayama S, Okazaki T, Uchida K, Fukui T, Okazaki K. Comparative study on experimental autoimmune pancreatitis and its extrapancreatic involvement in mice. *Pancreas* 2012; **41**: 1255-1262 [PMID: 22836854 DOI: 10.1097/MPA.0b013e31824a0e58]

62 **Uchida K**, Okazaki K, Nishi T, Uose S, Nakase H, Ohana M, Matsushima Y, Omori K, Chiba T. Experimental immune-mediated pancreatitis in neonatally thymectomized mice immunized with carbonic anhydrase Ⅱ and lactoferrin. *Lab Invest* 2002; **82**: 411-424 [PMID: 11950899 DOI: 10.1038/labinvest.3780435]

63 **Haruta I**, Shimizu K, Yanagisawa N, Shiratori K, Yagi J. Commensal Flora, is it an Unwelcomed Companion as a Triggering Factor of Autoimmune Pancreatitis? *Front Physiol* 2012; **3**: 77 [PMID: 22485093 DOI: 10.3389/fphys.2012.00077]

64 **Pezzilli R**, Casadei R, Santini D. Autoimmune pancreatitis associated with anisakis infection. *Dig Liver Dis* 2007; **39**: 273 [PMID: 17267310 DOI: 10.1016/j.dld.2006.10.006]

P- Revieweras: Machado MCC, Rakonczay Z
S- Editor: Ma YJ **L- Editor**: A **E- Editor**: Liu XM

百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**
Flat C, 23/F., Lucky Plaza,
315-321 Lockhart Road, Wan Chai, Hong Kong, China
Telephone: +852-6555-7188
Fax: +852-3177-9906
E-mail: bpgoffice@wjgnet.com
http://www.wjgnet.com