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 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, 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 cellular immune responses.

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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 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 cellular immune responses.

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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 \[2\]. In recent years, several diagnostic criteria have been developed, such as those coming from Japan, South Korea, the United States and Italy \[3\]. 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 \[4\]. 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 \[5,6\] 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% \[10\]. Levels of autoimmune antibodies, including antinuclear antibody, anticalcineurin hydrase 2, antismooth muscle antibody, antihuman lactoferrin and rheumatoid factor and pancreatic secretory trypsin inhibitor may all be elevated in a varying proportion of patients \[11\]. Higher concentrations of circulating leptin \[14\] as well as high levels of peptide AIP \[15\] which showed homology with an amino acid sequence of the plasminogen-binding protein of Helicobacter pylori and with ubiquitin-protein ligase E3 component n-recognition 2, an enzyme highly expressed in acinar cells of the pancreas have been also reported \[16\]. However, it is unclear whether the formation of these antibodies constitutes a pathogenetic event or whether they represent an associated epiphenomenon of AIP \[17,18\]. 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 electrophoretic 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...
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\(^\text{[26]}\) which affects both IgE and IgG4 production\(^\text{[13]}\). In addition, IL-10 is presumably needed to drive the differentiation of IgG4-switched B cells to IgG4-secreting plasma cells\(^\text{[34]}\). In addition to IL-10, IL-21 has also been found to increase IgG4 production \textit{in vitro}\(^\text{[35,36]}\). 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\(^\text{[37]}\). In contrast, IL-21 may function as a co-adjuvant to enhance antibody responses and thereby facilitate host defense to malignances and infectious diseases\(^\text{[37]}\). 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\(^\text{[38]}\), 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\(^\text{[39]}\), and usually produces this phenotype\(^\text{[40,41]}\). Therefore, the modified Th2 response seems to be the typical response to an innocuous antigen\(^\text{[42,43]}\). 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.[46]

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[49], 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 (sCTLA4) 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.[59] 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.[60]. 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.[61]. 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 to 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 polysinosinic: polycytidylic acid may substantially shorten the time course and increase the frequency of both pancreatitis and biliary involvement[62]. The experimental model for inducing inflammatory bowel disease, i.e., IL-10-/- mice, has been also used for developing type 1 AIP[63]. It is also possible induce AIP by immunization with lactoferrin, carbonic anhydrase or other antigens, or by alterations to the intestinal flora[64]. 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[10]. Finally, we also need to investigate whether type 1 or type 2 AIP are different diseases or different presentation of the same illness.

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