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Editorial Board Member of *World Journal of Gastroenterology*, Paola De Nardi, MD, FASCRS, Doctor, Surgeon, Surgical Oncologist, Division of Gastrointestinal Surgery, IRCCS San Raffaele Scientific Institute, via Olgettina 60, Milan 20132, Italy. denardi.paola@hsr.it

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MINIREVIEWS

Autoimmune pancreatitis and pancreatic cancer: Epidemiological aspects and immunological considerations

Dimitri Poddighe

ORCID number: Dimitri Poddighe 0000-0001-6431-9334.

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Dimitri Poddighe, Department of Medicine, School of Medicine, Nazarbayev University, Nur-Sultan 010000, Kazakhstan

Dimitri Poddighe, Department of Pediatrics, National Research Institute for Maternal and Child Health (NRCMCH), University Medical Center (UMC) Nur-Sultan 010000, Kazakhstan

Corresponding author: Dimitri Poddighe, MD, MSc, PhD-Eq., Associate Professor, Department of Medicine, School of Medicine, Nazarbayev University, Kerei-Zhanibek Str. 5/1, Nur-Sultan 010000, Kazakhstan. dimitri.poddighe@nu.edu.kz

Abstract

Ordinary chronic pancreatitis is a well-known risk factor for pancreatic cancer, whereas such an association with autoimmune pancreatitis (AIP) is widely debated. Due to the rarity of the latter disorder, there are few specific clinical and epidemiological studies investigating the relation between AIP and pancreatic cancer, which do not seem to support it. However, these studies are affected by several limitations and, therefore, a link between AIP (and, specifically, type 1 AIP) and pancreatic cancer cannot be ruled out definitively on this basis. Moreover, several immunopathological aspects of type 1 AIP and, in general, immunoglobulin G4-related disease can create an immunological context that may impair the tumoral immunosurveillance and promote the pancreatic carcinogenesis and its progression. In detail, Th2 immunological dominance, type 2 macrophage polarization and basophil infiltration observed in type 1 AIP, may play a permissive role in creating a favorable immunological environment for pancreatic carcinogenesis, in addition to the immunosuppressive therapies that can be used in these patients.

Key Words: Autoimmune pancreatitis; Chronic pancreatitis; Pancreatic cancer; Immunoglobulin G4-related disease; Epidemiology; Immunology; Basophils; Macrophages; Th2 cells; Systemic lupus erythematosus

Core Tip: This mini-review discusses the debated issue of autoimmune pancreatitis (type 1) as a potential risk factor for pancreatic cancer. After summarizing the few

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available (low-quality) epidemiological evidence that does not clearly support this role, the immunopathological characteristics of type 1 autoimmune pancreatitis (including Th2 immunological dominance, type 2 macrophage polarization and basophil infiltration) are discussed as potential factors that may actually create a tolerogenic immunological environment favorable to pancreatic carcinogenesis and/or tumor progression.

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INTRODUCTION

Autoimmune pancreatitis: Definition, pathology, and epidemiology

Chronic pancreatitis (CP) is a persistent inflammatory disease of the exocrine pancreas leading to progressive fibrotic tissue damage. CP prevalence varies between 13.5-98.7 cases per 100000 people with an incidence of around 4-5 new cases per 100000 people every year. Most cases of CP (also defined as "ordinary" or "generic") are triggered by the repeated and/or persistent activation of intrapancreatic digestive enzymes, due to the variable combination of some environmental factors (*e.g.*, excessive alcohol consumption, regular tobacco use, hypertriglyceridemia, *etc.*) and/or genetic factors (*e.g.*, Chymotrypsin C mutations)[1].

Autoimmune Pancreatitis (AIP), which represents < 5%-10% of pancreatitis cases and has an estimated prevalence of approximately 1-2/100000 people, is much rarer[1,2]. However, the real incidence of AIP is currently unknown: indeed, it is diagnosed in around 2% of patients who have undergone pancreas surgical resection for presumed pancreatic cancer and, therefore, this condition may be underdiagnosed[3].

The term AIP was originally introduced by Yoshida *et al*[4] in 1995 to describe a patient diagnosed with pancreatitis who "had hyperglobulinemia, was autoantibody-positive, and responded to steroid therapy". Currently, AIP diagnosis must be supported by well-defined and specific clinical, radiological, serological and histopathological criteria[3]. Importantly, based on histopathological aspects (according to the Honolulu classification), AIP is classified into two main subtypes that are mainly distinguished by the absence (type 1 AIP) or presence (type 2 AIP) of one peculiar finding, called "granulocytic epithelial lesion"(GEL), consisting of the neutrophilic infiltration of medium/small-sized ducts and often acini[5]. Thus, type 1 AIP is characterized by a substantial lymphoplasmacytic infiltration, where eosinophils may be relatively frequent and neutrophils are rare. Indeed, it was originally described as lymphoplasmacytic sclerosing pancreatitis[5,6]. Moreover, it is much more frequent than type 2 AIP, which accounts for 10%-20% and no more than 5% of all AIP cases in Western and Eastern countries, respectively. Importantly, type 1 AIP is now accepted as a clinical-pathological aspect of immunoglobulin G4 (IgG4)-related disease (IgG4-RD)[6,7].

IgG4-RD is a multisystem immune-mediated fibroinflammatory condition where several organs can be involved and, most frequently, pancreas, bile ducts, salivary glands, lacrimal glands, kidneys, retroperitoneum, and lungs. Pancreas is involved in at least 45% of IgG4-RD patients as type 1 AIP[8]. Therefore, unlike ordinary CP, type 1 AIP is usually the pancreatic manifestation of a systemic immunological disorder, in which several alterations of the innate and acquired immune system contribute to the lympho-plasmocytic inflammatory infiltration of the pancreas[9].

IgG4-RD pathogenesis is complex and involves both the innate and adaptive immune system; as regards the latter one, Th2 (specifically, follicular Th2 cells, Tfh2) and Treg lymphocytes (and related cytokines) have been clearly and mainly implicated in this pathologic process characterized by altered B cell and plasma cell activation, enhancement of IgG4 class switch recombination and, finally, development of ectopic germinal centers and induction of fibrosis[9,10].

Type 2 AIP pathogenesis is more elusive and, indeed, is also called idiopathic duct-centric pancreatitis. It is not characterized by IgG4 increase and other specific extra-pancreatic manifestations, except for an association with inflammatory bowel diseases

in 20%-30% cases[6,7].

Type 1 and type 2 AIP cannot be certainly differentiated by radiological imaging and share similar clinical presentations. However, the diagnostic differentiation is very important since the prognosis is quite different. Indeed, type 1 AIP is usually more aggressive, showing a much higher rate of relapse after steroid therapy, and is characterized by synchronous or metachronous extra-pancreatic organs involvement, as previously mentioned[11].

Both AIP types are almost exclusively adulthood diseases with a median age at diagnosis between 40-50 years, even though patients with type 1 AIP are 10-15 years older on average. AIP has been rarely described in the pediatric population, where the few reported cases were consistent with type 2 AIP in most cases[7,12].

PANCREATIC CANCER AND AIP: EPIDEMIOLOGICAL ASPECTS

Pancreatic cancer is represented by adenocarcinoma in > 85% of cases. Nowadays the overall incidence of pancreatic cancer is estimated to be around 11.0 per 100,000 people per year in the United States, where it accounts for 3% of all diagnosed malignancies. These numbers make it be the twelfth and eleventh most common cancer in men and women, respectively. Pancreatic cancer remains a highly fatal malignancy: Worldwide, it is the seventh leading cause of cancer death in both genders, with a 5-year survival rate of 10% or less. Like most malignancies, incidence rates for pancreatic cancer are age-related: In general, it is rare before the age of 50 years. The main risk factors for pancreatic cancer are modifiable and include tobacco smoking, obesity, physical inactivity and high-calorie/fat diets; these lifestyle-related risk factors clearly contributed to the increase of the disease incidence in the last three decades, especially in developed countries, where diagnostic improvements and increased life expectancy have played a role as well[12,13].

CP (and, in detail, ordinary CP) was shown to be a clear risk factor for pancreatic cancer. In 1993 Lowenfels *et al*[14] published the results of a large multicenter and international cohort study including 2,015 patients with CP, who showed an increased risk of pancreatic cancer, independent from gender, country and type of pancreatitis. It was estimated that approximately 5% of CP patients receive a diagnosis of pancreatic cancer within 2 decades after that diagnosis[12,14].

The potential association between pancreatic cancer and AIP is currently debated. Even though AIP is a rare form of CP, this issue is raised especially in patients affected with type 1 AIP that, compared to type 2 AIP, is more common and characterized by high percentages of disease relapse after steroid therapy[15,16].

Moreover, as summarized and discussed below, all reported cases of AIP-related pancreatic cancer were described in patients affected with type 1 AIP; actually, some concerns were raised in terms of potential association with malignancies in general. Most studies on IgG4-RD and/or type 1 AIP are from Japan: Yamamoto *et al*[17] and Shiokawa *et al*[18] first reported an overall increase of malignancy incidence in their patients, even though they actually described no cases of pancreatic cancer.

A larger multi-centric and international study by Hart *et al*[15] (including 1,064 patients with AIP and, exactly, 978 with type 1 and 86 with type 2) reported 5 diagnoses of pancreatic cancer in type 1 AIP patients (no one affected with type 2 AIP developed this complication). However, as discussed by the authors themselves, even though they found a small number of pancreatic cancers (compared to the total cumulative frequency of malignancies, n = 57), the limited follow-up and lack of a control population may have limited the clinical significance of their analysis. Moreover, this study (and also another one authored by the same research group) were not focused on pancreatic cancer[15,19], as well as the following studies. Hirano *et al*[20] described their case series of 113 IgG4-RD patients (type 1 AIP: n = 95) and reported 2 patients who developed pancreatic cancer; in general, their conclusion was that the cumulative incidence of any kind of malignancies in IgG4-RD patients was similar to that observed in the general population. Shimizu *et al*[21] also made the same conclusion in their 84 type 1 AIP patients; in detail, among 9 patients diagnosed with cancer, only one developed it at the pancreas. Buijs *et al*[22] analyzed a Dutch case series of 107 patients affected with AIP (type 1: 90%, type 2: 10%), and reported no apparent difference in malignancy incidence compared to an ethnic-, age-, and sex-matched reference population (in detail, no patients developed pancreatic cancer).

However, although several clinical studies tried to address this issue, the prevalence and risk assessment of pancreatic cancer in the pathological setting of AIP have been greatly hampered by the relatively small number of participants, variable and/or

relatively short follow-up period, retrospective study design and the lack of appropriate control groups in most of these studies[23].

Therefore, some authors proposed that patients affected with AIP should be regularly monitored to reveal any potential cancerous changes and/or malignancy onset, anyway[24]. For instance, unlike the aforementioned studies, Huggett *et al*[16] reported a statistically significant odd ratio increase (odds ratio = 2.2) for all malignancy risk in type 1 AIP patients: 13 malignancy cases (out of 115 type 1 AIP and/or IgG4-RD and, 106 patients with pancreatic disease) were diagnosed, and all those tumors arose in systemic IgG4-RD patients, who represented only 56% of the whole cohort. However, only one case was affected with pancreatic adenocarcinoma.

Additional and interesting research articles, which were more focused on pancreatic complications and carcinogenesis in AIP patients, were published in the last few years. A clinical research by Gupta *et al*[25] investigated the pancreatic carcinogenesis in patients affected with AIP. These authors reviewed a case series of 84 AIP patients, and they compared the prevalence of pancreatic intraepithelial neoplasia (PanIN) in 28 cases of AIP and 30 cases of CP not otherwise specified. Overall, 82% AIP patients showed PanIN with variable histologic grade, which resulted to be more frequent than in non-autoimmune CP (63%), though such a difference was not statistically significant. Therefore, the prevalence of PanIN in AIP resulted to be comparable to ordinary CP; moreover, in the same article the authors also described their clinical experience with 84 AIP patients, and the only 2 cases of pancreatic cancer were diagnosed in the context of type 1 AIP, which was diagnosed 6 and 10 years before the detection of the malignancy, respectively. Therefore, this study raised some specific concerns as regards the risk of pancreatic malignancy in type 1 AIP patients[25]. Similarly, Ikeura *et al*[26] diagnosed 3 cases of pancreatic cancer (4.8%) in their 63 type 1 AIP patients, which was similar to what observed in the comparison group, consisting of 41 patients affected with ordinary (alcoholic and hereditary) CP, characterized by only one patient (2.1%) with a diagnosis of pancreatic malignancy.

Starting from a different perspective, Ngwa *et al*[27] described 548 patients diagnosed with pancreatic cancer and 99 different patients affected with type 1 AIP. In this study, whose main aim was to compare the IgG4 serum profiles between those two groups of patients (rather than investigating an epidemiological and/or causal link), the authors suggested no relationship between AIP and pancreatic cancer; however, a minority of histological specimens (only 30 pancreatic tissue specimens from patients with pancreatic cancer and 6 patients with "high-risk features" AIP) was reviewed. Indeed, a recent retrospective study by Xiang *et al*[28], including 74 patients with type 1 AIP, revived the debate by reporting that 5 of them (6.7%) were concomitantly diagnosed with a pancreatic tumor (pancreatic ductal adenocarcinoma, $n = 3$; solitary extramedullary plasmacytoma, $n = 1$; cholangiocarcinoma, $n = 1$). Moreover, an interesting observation was reported by Hedayat *et al*[29], who re-examined 21 pancreas specimens of previously diagnoses of intraductal papillary-mucinous neoplasm, which is a cystic and usually benign neoplasm, but with the potential for progression to pancreatic cancer. Interestingly, 4 of them (19%) showed infiltrates of IgG4-positive plasma cells, consistent with a "peri-tumoral" type 1 AIP reaction[29,30].

Conversely, two very recent retrospective studies were not supportive in this sense. Tang *et al*[31] described 17 neoplastic cases in a large cohort of 587 Chinese patients diagnosed with IgG4-RD; among those, 11 were also affected with AIP, but all developed extra-pancreatic malignancies only. The study by Ishikawa *et al*[32], including 123 type 1 AIP patients, identified only 2 patients diagnosed with pancreatic cancer (1.6%) and concluded that "AIP is unlikely to be a precancerous condition of the pancreas", but at the same time they stated that "because of the small number of cases, the characteristic findings of pancreatic cancers that develop in AIP patients are not clear".

Therefore, as summarized by these two final statements, this short and schematic overview of clinical studies provides conflicting evidence and conclusions regarding the association between AIP (and, in detail, type 1) and pancreatic cancer. Table 1 summarizes all the aforementioned clinical studies investigating the association between AIP and pancreatic cancer, by using a chronological order and focusing on the main study features and findings.

Even though one may conclude that most of the available studies do not support this association, there are some clinical and pathological observations coming from studies more focused on pancreatic cancer[25,26,28] which should keep high the attention on this issue before making final conclusions; however, this will require larger, prospective, and longer (in terms of follow-up period) studies. Unfortunately, the clinical research on this topic is undoubtedly hampered by the low prevalence and incidence of AIP, in general and in the landscape of CP, in addition to the challenges of

Table 1 Schematic overview of the clinical studies investigating the association between autoimmune pancreatitis and pancreatic cancer.

Ref.	Study population (disease)	Total patients (*n*)	AIP type 1 (*n*)	Cancer (overall) (*n*)	Pancreatic cancer (*n*)	Median follow-up (yr)	Additional specifications
Yamamoto *et al* [17] (Japan, 2012)	IgG4-RD	106	10	2	0	NA	-
Shiokawa *et al* [18] (Japan, 2013)	AIP	108	104	18	0	3.3	These 18 malignancies were diagnosed in 15 patients.
Hart *et al*[15] (International, 2013)	AIP	1064	978	57	5	NA	No patients with AIP type 2 developed any malignancies.
Gupta *et al*[25] (United States, 2013)	CP	58	11	NA	7 (PanIN)	N/A	Retrospective analysis of patients with CP. There was no statistically significant difference in the frequency of PanIN between ordinary CP and AIP: in the latter group, no difference between type 1 and type 2. In general, the only case of PanIN3 was detected in one AIP type 1 specimen.
Gupta *et al*[25] (United States, 2013)	AIP	84	NA	NA	2	4.1	These 2 cases of pancreatic cancer were diagnosed in type 1 AIP patients.
Hart *et al*[19] (United States, 2014)	AIP	116	116	23	1	3.6	-
Hirano *et al*[20] (Japan, 2014)	IgG4-RD	113	95	14	2	6	2 IgG4-RD patients diagnosed with malignancy (out of 14) were not affected with AIP.
Huggett *et al*[16] (United Kingdom, 2014)	IgG4-RD	115	106	13	3	2.7	Of these 3 cases of pancreatic malignancies, 2 were cholangiocarcinoma cases and 1 was a pancreatic adenocarcinoma.
Ikeura *et al*[26] (Japan, 2014)	AIP	63	63	NA	3	5.2	-
Shimizu *et al*[21] (Japan, 2015)	AIP	84	84	9	1	4.5	-
Buijs *et al*[22] (The Netherlands, 2015)	AIP	107	96	8	0	6.25	-
Ngwa *et al*[27] (United States, 2015)	AIP	99	99	NA	0	NA	The aim of this study was to evaluate the clinical significance of elevated sgG4 levels in patients with AIP and pancreatic cancer and potential prognostic implications of those in patients with pancreatic cancer.
Xiang *et al*[28] (China, 2019)	AIP	74	74	NA	4	NA	3 patients were diagnosed with pancreatic ductal adenocarcinoma and 1 with cholangiocarcinoma. There was also 1 case of solitary extramedullary plasmacytoma.
Tang *et al*[31] (China, 2020)	IgG4-RD	587	NA	17	0	5.1	-
Ishikawa *et al*[32] (Japan, 2020)	AIP	123	123	NA	2	4.6	-

AIP: Autoimmune pancreatitis; CP: Chronic pancreatitis; IgG4-RD: Immunoglobulin G 4-related disease; N/A: Not applicable; NA: Not available; PanIN: Pancreatic intra-epithelial neoplasia.

pancreatic diagnostics.

Nonetheless, it is established that chronic inflammatory processes represent a risk factor for pancreatic cancer and, as such, type 1 AIP, especially if relapsing and/or persistent, should be considered in the same way in principle. Moreover, concomitant immunosuppressive therapies (including steroids, rituximab, azathioprine., *etc.*) may represent additional predisposing factors to the cancer development[11]. Finally, some specific immunological aspects and considerations (also related to IgG4-RD pathogenesis) might support these concerns, as discussed in the next sections.

TYPE 1 AIP: GENERAL IMMUNOPATHOGENESIS

IgG4-RD is the clinical expression of a systemic immunological dysregulation leading to chronic inflammation and lymphocyte infiltration in several organs (including pancreas), which might have some implications in terms of pancreatic and extra-pancreatic carcinogenesis[8]. However, as discussed, the available clinical evidence does not support this hypothesis, but the small number of studies, which are also characterized by several and important limitations, likewise do not allow to rule out it either.

As said, type 1 AIP is the prevalent form of AIP and all cases of AIP-related pancreatic malignancies were described in this pathological setting. Therefore, the following immunological considerations on AIP immunologic pathogenesis and its potential role in pancreatic carcinogenesis, will refer to type 1 AIP and/or IgG4-RD specifically.

Even though the pathogenesis of IgG4-RD is complex and relies on both innate and acquired immune system mechanisms, the final result is an immunological environment characterized by a Th2 dominant immune response, which is indeed associated with increased level of serum IgG4 (systemically) and IgG4 switched lymphocytes and plasma cells (in the pancreas and other affected organs). Therefore, IgG4-RD and type 1 AIP are characterized by a cytokine profile whereby interleukin (IL)-4, IL-5, IL-13, IL-10 and transforming growth factor (TGF)-β are overexpressed [33].

Recent studies evidenced the central role that is played by the T follicular helper cells (Tfh cells), which can be found in the extra-nodal ectopic germinal centers and are involved in the generation of long-lasting humoral responses by B cells and plasma cells[9]. Increased levels of Tfh cells and, in detail, Th2-polarized cells (Tfh2 cells), have been described in IgG4-RD patients, in whom those cells correlate with serum IgG4 and IL-4 levels[34]. Moreover, Tfh2 cells, but not Tfh1 or Tfh17 cells, were demonstrated to induce the differentiation of naïve B cells into plasma blasts (with enhanced production of IgG4) and, importantly, the activation of Tfh2 cells resulted to correlate with the disease activity[35].

However, in addition to the probable intrinsic dysregulation of the adaptive immune system, the origin of these Tfh2 expansion and activation (and, more in general, Th2 predominance) must be sought in the innate immune system as well[9]. Through the use of an experimental murine model of AIP (namely, MRL/Mp mice treated with polyinosinic-polycytidylic acid), Arai *et al*[36] described the pancreatic accumulation of plasmocytoid dendritic cells (pDCs) producing IFN-α. They also showed that pDCs from human patients with type 1 AIP had an increased production of IFN-α, which was able to promote the B cells switch toward IgG4 production in a T-cell independent manner, probably by the enhanced production of BAFF (B cell-activating factor belonging to the tumor necrosis factor family). Actually, BAFF production upon Toll-like-receptor (TLR) activation was described in other innate immune cells, including basophils, through the stimulation of TLR2 and TLR4[37]. This finding is particularly interesting because the presence of basophils has been recently described in the pancreatic tissue of most patients with type 1 AIP[38].

Basophils have been demonstrated to be more than simple effector cells in several pathological contexts (including asthma and other allergic diseases) and, in detail, were proposed as one of the main sources of early IL-4, being able to drive and/or support the Th2 polarization of activated CD4+ T cells[39-41]. Overall, these observations may support the fact that basophils are activated in a IgE- (and, thus, B-cell) independent manner and, indeed, TLR-activated basophils can contribute to drive the Th2 response in type 1 AIP[38].

Interestingly, in a recent review article, Watanabe *et al*[9] highlighted several immunological similarities between IgG4-RD and Systemic Lupus Erythematosus (SLE), which is also characterized by an increased type I IFN production through pDCs, a Th2 immunological dominance and a substantial dysregulation of humoral immunity. Moreover, some human studies and murine experimental models suggested a pathogenic role for basophils in SLE, indeed[42].

However, in the landscape of all the innate immune cells implicated in the pathogenesis of type 1 AIP, the role of pDCs appears to be prominent. In addition to IFN-α, these cells resulted to be the main source of another important cytokine that has been implicated in type 1 AIP immunopathogenesis, namely IL-33. Importantly, IL-33 was also recognized to be an important inflammatory mediator in ordinary CP, whereby actually the main cell source is represented by the pancreatic acinar cells[9, 43]. IL-33 is able to activate Th2 cells and also group 2 innate lymphoid cells, which can further stimulate the production of IL-4, IL-5, and IL-13[44,45].

Finally, to complete the landscape of the innate immunity involvement in type 1 AIP, it is worth to mention M2-polarized macrophages, which were described in the pancreatic tissues of type 1 AIP patients affected with IgG4-RD[46]. Compared to classically activated or M1 macrophages (which are clearly pro-inflammatory, are polarized by lipopolysaccharide and/or Th1 cytokines, and mainly produce IL-1β, IL-6, IL-12, IL-23 and tumor necrosis factor-α), alternatively activated or M2 macrophages are polarized by Th2 cytokines and produce anti-inflammatory cytokines, such as IL-10 and TGF-β. Therefore, M2 macrophages have been implicated in angiogenesis and tissue repair, and are considered to exert an anti-inflammatory (and, for some aspects, tolerogenic effect) also in IgG4-RD and type 1 AIP[47,48].

Indeed, IL-10 and TGF-β are the main cytokines secreted by the antigen-induced or adaptive Tregs. In detail, IL-10 regulates the functions of many different immune cells, including macrophages themselves, dendritic cells, and both T and B lymphocytes. In detail, IL-10 is a potent inhibitor of antigen presentation by reducing the expression of major histocompatibility complex molecules and costimulatory molecules CD80 and CD86. Moreover, it inhibits the differentiation of dendritic cells (DCs) themselves from monocyte precursors and their further maturation. Finally, upon antigen presentation, IL-10 inhibits macrophage production of pro-inflammatory cytokines (IL-1, IL-6, IL-12, tumor necrosis factor-α), even though it does not seem to directly affect the Th1/Th2 balance[49,50].

These immune-pathogenic aspects of type 1 AIP and IgG4-RD may create a favorable immunological background in the affected pancreas for carcinogenesis promotion, as discussed in the next section.

PANCREATIC CANCER AND TYPE 1 AIP: IMMUNOLOGICAL CONSIDERATIONS

As already mentioned, the cumulative risk of pancreatic cancer in subjects with ordinary CP was reported to be 1.8% after 10 years and 4.0% after 20 years, and it is estimated to be more than 10 times higher in these patients than in healthy subjects[14,51].

Whereas carcinogenesis in the context of ordinary CP is then well established epidemiologically, this methodological approach has not clearly supported the association between AIP (in detail, type 1 AIP) and pancreatic cancer, but the numerous study limitations should prevent from ruling it out definitively, as it was previously discussed.

To start with, a few initial molecular findings should be considered. Some specific molecular alterations of pancreatic carcinogenesis may be functional to this discussion, such as K-ras mutations, which resulted to be present in > 90% of pancreatic cancers and, importantly, may occur at an early stage of this neoplastic process, namely at the PanIN stage[52]. For instance, Kamisawa *et al*[53] found that codon-12 mutation of K-ras was significantly more frequent in the pancreato-biliary regions of patients with AIP than in those affected with chronic alcoholic pancreatitis.

More recently, Kinugawa *et al*[54] also described some methylation abnormalities of tumor suppressor genes in AIP patients. Promoter region hyper-methylation with consequent gene silencing was reported for several genes in pancreatic cancer. In detail, among the 6 genes that these authors have investigated (because those were previously reported as methylated in pancreatic cancer), they found a statistically significant difference in terms of the TFPI2 (tissue factor pathway inhibitor 2) methylation ratio between specimens taken from AIP patients and those from pancreas resected for non-tumoral diseases. TFPI2 was recognized as a tumor suppressor gene, and a previous study described methylation abnormalities for this gene in 73% of pancreatic carcinomas, whereas those were completely absent in normal pancreas specimens[55].

However, further theoretical support and biological plausibility supporting a role for type 1 AIP as potential risk factors for pancreatic cancer, may derive from some immunological considerations.

Indeed, the role of the immune system and, in detail, the impairment of the immunological surveillance in the development and progression of cancer, is well supported. Both the innate and the adaptive immune system play an active role in this regard. Generally speaking, cytotoxic CD8+ T cells, Th1 cells, mature DCs, classically activated pro-inflammatory macrophages M1 and natural killer cells are variably described as the main effectors of this anti-cancer immunological surveillance[56,57]. Therefore, several aspects of the immunological environment created by and during

type 1 AIP (and, systemically, by IgG4-RD) may be favorable to cancer development in the pancreas.

First, the Th2 signature dominating these diseases, does not support cytotoxic CD8+ T cell responses[56]. Tassi *et al*[58] showed that patients affected with pancreatic cancer have a Th2 skewed immune response, which can impair the specific CD4+ T cells response against a tumor-associated antigen, namely CEA; moreover, this polarization was suggested to negatively affect the T CD8+ cell compartment as well.

Second, in type 1 AIP macrophages tend to switch to a M2 phenotype, characterized by the production of IL-10 and TGF-β, which can create a tolerogenic immunological environment in the pancreas. By the way, Th2 cells themselves produce IL-10, in addition to their hallmark cytokines, such as IL-4, IL-5 and IL-13[47]. As explained, these M2 macrophages are also characterized by poor antigen presenting ability rather than supporting lymphocyte activation, proliferation and cytotoxicity. Moreover, they are committed to promote tissue remodeling and, importantly, neo-angiogenesis. Finally, M2 macrophages also express inhibitory ligands, such as PD-L1, which is known to induce peripheral T cell tolerance. All these properties suggested an important role of M2 macrophage in reducing the anti-tumor immunity for several malignancies, including pancreatic cancer. Indeed, they represent the prevalent macrophage phenotype among so-called tumor-associated macrophages and have been thus implicated in the processes of tumoral growth and cell migration/metastasis [59-62]. Accordingly, the degree and type of M2 macrophages infiltration into the tumoral stroma resulted to be an independent prognostic factor in patients with pancreatic cancer[63].

Third, in addition to M2 macrophages, basophils were recently suggested to play a role in the pathophysiology of type 1 AIP, upon activation *via* TLR signaling[38,64]. As previously explained, these cells can strongly shift the immunological balance toward a more tumor-tolerogenic Th2-polarized tissue microenvironment. Therefore, in addition to some initial evidence that basophils may be directly implicated in type 1 AIP pathogenesis, this way basophils might indirectly promote the pancreatic tumorigenesis as well. Recently, De Monte *et al*[65] investigated the presence of basophils in in tumor-draining lymph nodes of patients affected with pancreatic cancer, which resulted to correlate with both Th2 inflammation and reduced patients' survival. In this study, the role of basophils in tumor develop-ment/progression was also supported through some observations in basophil-deficient murine experimental models. Therefore, basophils may favor the tumorigenesis and progression of pancreatic cancer by promoting both Th2 and M2 polariza-tion[66].

Interestingly, these novel findings might open to additional important associations between pancreatic cancer and autoimmune diseases other than type 1 AIP and IgG4-RD. As mentioned, Watanabe *et al*[9] provided an interesting immunopathological parallelism between IgG4-RD and SLE. Therefore, it is very interesting that a very recent meta-analysis by Seo *et al*[67] evidenced that SLE was associated with increased risk for pancreatic cancer. These authors speculated several mechanisms that may potentially explain this association (*e.g.*, chronic inflammation, excess autoantibody effect, metabolic alterations); however, based on the present discussion, basophils activation and, more in general, Th2-driven inflammation described in active SLE might be added to these speculations on the hypothetical pathophysiologic permissive mechanisms[68,69].

CONCLUSION

Currently, the association between (type 1) AIP and pancreatic cancer does not find any clear epidemiological support, even though it cannot be ruled out definitively due to the small number of participants in the available clinical studies and the numerous study limitations. Some immunological aspects characterizing type 1 AIP, such as Th2 dominance, M2 macrophage polarization and basophil implication, may lead to an immunological environment favorable to pancreatic carcinogenesis and/or tumor progression.

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