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Autoimmune pancreatitis in children: The impact of immune system in a challenging disease

Autoimmune pancreatitis (AIP) is clinically characterized by obstructive jaundice with or without the presence of a pancreatic mass, defined histologically by lymphoplasmacytic infiltrate and fibrosis, but strikingly distinguished by a prompt response to corticosteroids and potential involvement of other organs [1]: AIP is rare in children and few cases have been reported in the worldwide literature [2].

Two different types of AIP have been recognized: IgG4-related AIP (also named type 1-AIP) and non-IgG4-related AIP (also named type 2-AIP). Type 1-AIP is more common in adults and linked with increased serum IgG4 and extrapancreatic involvement. Type 2-AIP is a non-alcoholic pancreatitis which is more common in children, frequently associated with inflammatory bowel disease, but to date there is poor knowledge about its specific pathogenic immunological alterations [3].

Although the increase in serum IgG4 level and tissue IgG4 plasma cells have been well established in AIP, the impact of autoantibodies is not completely understood. Several autoantibodies have been identified

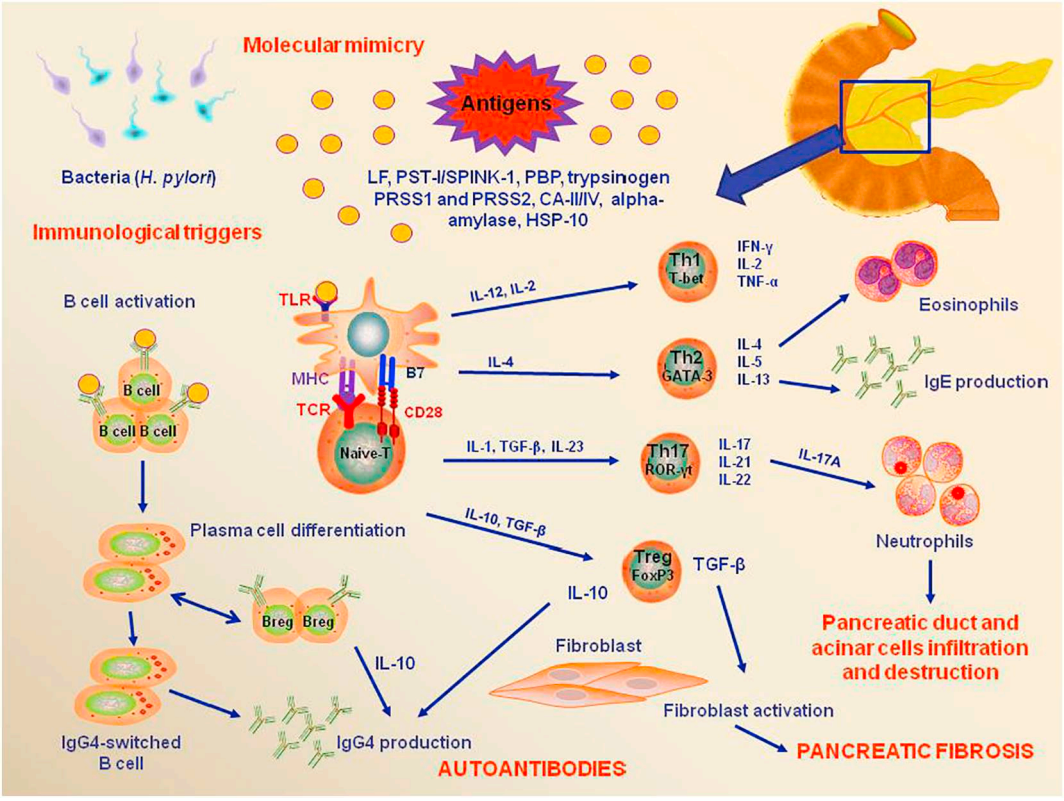

Fig. 1. The complex interplay among environmental and bacterial antigens, autoantibodies and cellular immunity in the pathogenesis of autoimmune pancreatitis. Several environmental antigens and gut bacteria can trigger an immune reaction involving many humoral and cellular mediators. The antigenic mimicry may play a specific role in activating a pancreatic autoimmune reaction, as during *H. pylori* infection. These antigens mediate the activation of naive T cells that in turn, according to the cytokine microenvironment, may differentiate in several T cell subsets, such as Tregs, Th1, Th2 and Th17 cells. Th1 cells are responsible for the production of proinflammatory cytokines, such as the cytokines of the TNF family. Th2 cells together with eosinophils favour tissue and serum IgE production. Th17 cells are characterized by the production of IL-17A, that determines neutrophil recruitment that in turn may infiltrate and destruct both pancreatic duct and acinar cells. Finally, Tregs are a subset of anti-inflammatory T cells that produce IL-10 and TGF-beta. IL-10 is able to mediate the activation and switching of IgG4-plasma blasts and the subsequent IgG4 production. TGF-beta mediates fibroblast activation and pancreatic fibrosis.

Abbreviations: *H. pylori*, Helicobacter pylori; LF, lactoferrin; PST-I/SPINK1, Pancreatic Secretory Trypsin-Inhibitor; PBP, Plasminogen Binding Protein; CA-II/IV, Carbonic Anhydrase isoforms II and IV; HSP-10, Heat shock Protein-10; TLR, Toll like Receptor; MHC, Major Histocompatibility complex; TCR, T Cell Receptor; Breg, B Regulatory cell; IFN-γ, Interferon-gamma; TNF-α, Tumor Necrosis Factor-alpha; IL, Interleukin; TGF-β, Transforming Growth Factor-beta; Th, T Helper cell; Treg, T Regulatory cell

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in AIP patients and classified as nonorgan-specific and organ-specific, i.e. antibodies against lactoferrin, carbonic anhydrase -II and -IV (CA-II/IV), pancreatic secretory trypsin inhibitor (PST-I or SPINK1), cationic trypsinogen (PRSS1), anionic trypsinogen (PRSS2), plasminogen-binding protein peptide (PBP), amylase alpha and heat shock protein 10 (HSP10) [4]. These autoantibodies recognize several antigens of pancreatic acinar cells and may interfere with cell metabolism and function, though none may be considered disease-specific.

A potential mechanism by which autoantibodies may exert pathogenetic effects is molecular mimicry. In this way, the alpha-carbonic anhydrase of *Helicobacter pylori* (*H. pylori*) present a homology with the human CA-II, and different clinical data have shown that some type 1-AIP patients might have antibodies against plasminogen-binding protein of *H. pylori* [5].

The diagnostic usefulness of autoimmune abnormalities in children with AIP is by now still undefined. Up to 40% of patients with AIP has detectable rheumatoid factor and anti-nuclear antibodies [3]. Furthermore, elevation in any among immunoglobulins is commonly seen in AIP. However, false positive elevation of each of these markers has been observed in pancreatic cancer and other inflammatory disorders. Complement C3 and C4 may be reduced in 1/3 of patients, particularly in those with high levels of circulating immune complexes [6]. Therefore, serum IgG4 antibodies and tissue IgG4 plasma cell elevation remain the best markers for diagnosis of AIP, and indeed high levels of IgG4 have been found in over 90% of patients with type 1-AIP and 25% of those with type 2-AIP [1].

On the other hand, there are also few reports regarding the role of T cell subpopulations in the pathogenesis of AIP. In this way, autoreactive lymphocytes may have a key function in mediating tissue damage in AIP patients, and both T helper (Th) 1 and Th2 cells have shown to be involved in AIP pathogenesis [7] (Fig. 1). A Th1-driven response predominates in type 1-AIP and also the number of regulatory T cells (Tregs) may be characteristically increased and related with the level of serum IgG4 in tissue-resident lymphocyte populations of these patients, though the exact role of IgG4 and its relevance in the induction of disease are still to clarify [8]. Moreover, some pro-inflammatory cytokines of the tumor necrosis factor (TNF) family appear over-expressed by acinar cells in patients with AIP [1]. Surprisingly, unlike other autoimmune diseases, circulating and tissue Tregs are increased and activated in AIP, together with an increased expression of interleukin (IL)-10 and transforming growth factor (TGF)-beta. The presence of IL-10 is strictly related to IgG4-switching, while TGF-beta has been related to the intra-pancreatic fibrotic process [8]. In this way, Tregs seem to have a pathogenetic role in mediating the production of autoantibodies and in tissue damage. This phenomenon seems to be contradictory if considering that Tregs are an anti-inflammatory subset of T cells.

On the other hand, also the pro-inflammatory Th17 cells are increased in AIP, particularly in type 2-AIP. Th17 cells are the main source of the pro-inflammatory IL-17A: this cytokine mediates the crosstalk between Th17 cells and neutrophils, and this process might be a potential mechanism of duct and acinar cell destruction via neutrophils, that is pathognomonic of type 2-AIP [9].

Different is the involvement of B cells in AIP, in particular of regulatory B cells (Bregs) and plasma blasts. While the role of Bregs remains controversial in the pathogenesis, surely a significant number of IgG4+ circulating plasma blasts has been found in AIP, and they are reduced by therapy, with a prompt rise during disease relapses. Moreover, these IgG4+ plasma blasts seem to be autoreactive in patients with IgG4-related disease [10].

A significant role in the pathogenesis of AIP is also played by innate immunity, mostly by Toll-like receptors (TLRs) [11]. In particular, basophils activated via TLR signalling play an important contribution in the pathophysiology of type 1-AIP [12], whereas the expression of TLR-7 on monocytes is significantly increased in type-1 AIP [13]. In addition, TLRs and nucleotide binding oligomerization domain-like receptors (NLRs) induce the activation of B cells, with subsequent production of IgG4. All these data demonstrating the involvement of TLRs in the pathogenesis of AIP might explain the possible interaction between immunity and gut microbiota, considering that TLRs are usually activated by bacteria [14].

In conclusion, AIP is a complex disease characterized by pathogenesis with protean faces involving several immune components and mediators of inflammation. Its management is challenging for clinicians, as several difficulties are present from the onset to its clinical staging and treatment. Children are more commonly affected by type 2-AIP, but to date the exact impact of immune system remains unraveled and no specific serum markers have been characterized for this subset of patients. Further investigation is needed to clarify the pathogenic role of different autoantibodies against many pancreatic antigens or other yet unknown molecules in order to better characterize their definite diagnostic power in pediatric patients.

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