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Autoimmune pancreatitis (AIP) can present as acute pancreatitis, but is typically recognised as a distinct form of chronic pancreatitis. Key features include pancreatic lymphoplasmacytic infiltration, chronic inflammatory storiform fibrosis and hypergammaglobulinaemia [1, 2]. Heavy infiltration of the pancreas by lymphocytes targeting acinar and/or duct cells may lead to severe damage, which is to a varying extent reversible with steroid therapy. Two predominant patterns of AIP have been identified, namely, lymphoplasmacytic sclerosing pancreatitis (LPSP or type 1; see Fig. 2.1) and idiopathic duct-centric pancreatitis (IDCP or type 2; see Fig. 2.2), that both share some common histopathological features. LPSP characteristically shows the hallmark periductal lymphoplasmacytic infiltrate, high levels of serum and tissue I_gG4-positive plasma cells, storiform fibrosis and obliterative phlebitis [1A]. In contrast, IDCP is typified by intense neutrophilic infiltration in the lobule and duct, referred to as granulocyte epithelial lesions (GEL) that may lead to ductal destruction. Some use the term 'I_gG_4-related

sclerosing cholangitis (I_gG_4-SC)' in reference to the bile duct disease frequently associated with AIP [3, 4]. Little is known regarding the triggers of AIP or why the pancreatic and bile ducts become targets of immune-mediated damage. There are, however, a number of intriguing clues that provide early insight, including genetic predisposition, the number of candidate pancreatic autoantigens bearing structural similarity to microbial pathogens (attacked by molecular mimicry), animal forms of AIP that offer further insight, the roles of TGF-β and complement activation by immune complexes, as well as potential triggers for AIP including *H. pylori* [1A].

## Pancreaticobiliary Anatomy and Histological Features of AIP

Intercalated ducts are the first tier of pancreatic ducts that receive acinar secretions and gradually coalesce into larger ducts which terminate in the main pancreatic duct, contributing to and

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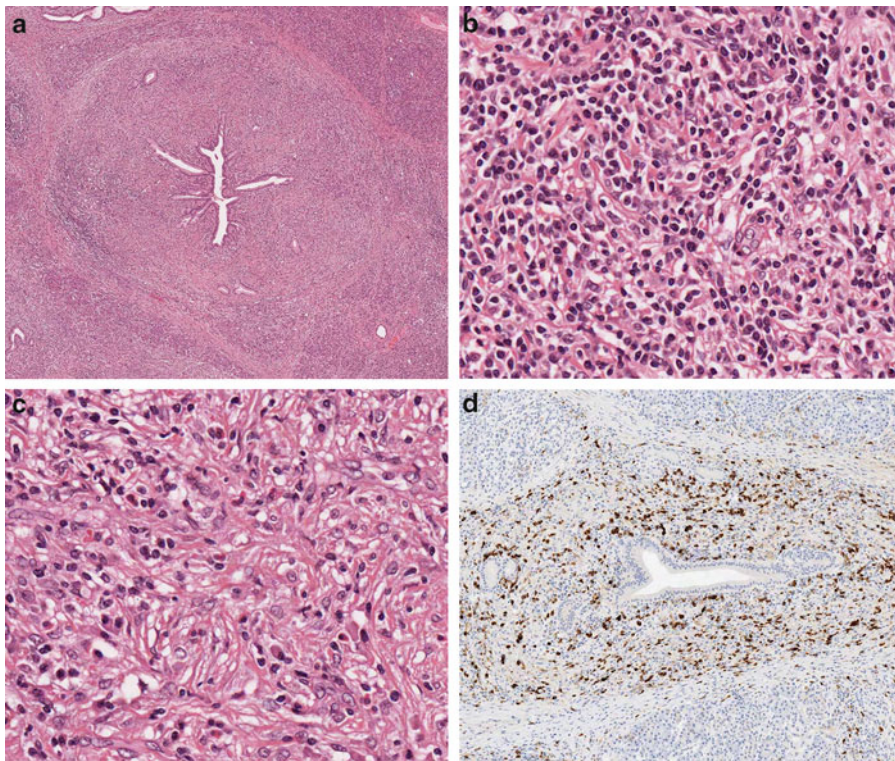
Fig. 2.1 *Lymphoplasmacytic sclerosing pancreatitis, or 'type 1 AIP'.* (**a**) Low-power view of diffuse lymphoplasmacytic infiltration with (**b**) higher-power view of storiform fibrosis with (**c**) some areas of myofibroblast predominance. Pancreatic acini are not in evidence, having been replaced by inflammation and fibrosis, although these may be preserved in other areas. The inflammation clearly surrounds the ducts but leaves the ductal epithelium and lumen largely intact (A-C, H and E). (**d**) Immunohistochemical demonstration of characteristically dense infiltration by I_gG4 plasma cells

draining exocrine secretion into the duodenum. Centroacinar cells lining the acinar lumen continue into the intercalated and intralobular ducts as cuboidal epithelium, while the epithelial lining of the larger interlobular ducts varies with their size. The biliary ducts are lined by cuboidal or columnar epithelial cells and are surrounded by capillary plexuses arising from the hepatic artery.

Pancreatic arterial supply arises from the celiac trunk and superior mesenteric artery, and venous blood drains to the portal vein. A third of lobular terminal arterioles supply islets before reaching acinar capillary beds although the functional significance is unclear [5, 6]. Abundant lymphatics around lobular blood vessels drain interstitial fluid to peripancreatic nodes and subsequently to lymph nodes draining the pancreas [7, 8].

In human AIP, pancreatic lymphoplasmacytic infiltrates co-localise with macrophages and myofibroblasts [9], likely contributing to AIP through cell-cell crosstalk. AIP distorts lobular anatomy, and secondary inflammation around the pancreatic ducts causes a severe obliterating periductal fibrosis [10–12]; small veins show obliterative phlebitis, and there is enlargement of peripancreatic and peribiliary lymph nodes [13]. Although the intrapancreatic portion of the extrahepatic bile duct is affected in AIP involving the head of the pancreas, medium- to large-sized interlobular ducts are usually targeted [10, 12, 13] and lymphoplasmacytic sclerosing cholecystitis is also reported [14]. Around the extrahepatic and intrahepatic large bile duct exist peribiliary glands which contain exocrine acini and express pancreatic exocrine enzymes and
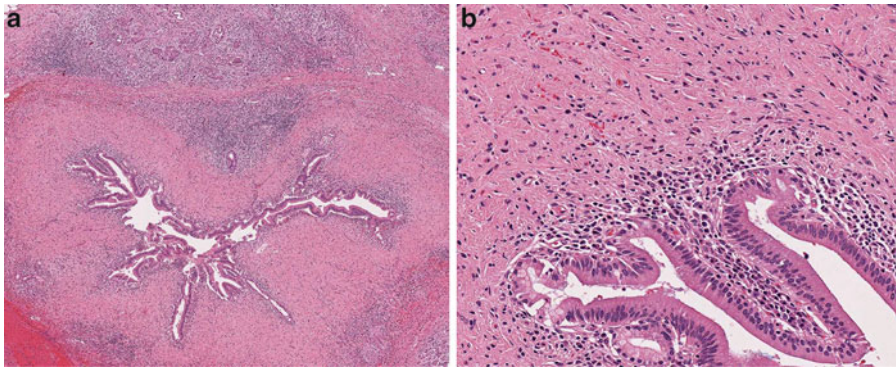
Fig. 2.2 *Idiopathic duct-centric pancreatitis, or 'type 2 AIP'*. (**a**) Low-power view showing inflammatory cell infiltrate extending to the ductal epithelium, which has been destroyed in parts. (**b**) Higher-power view of (**a**) showing infiltrate directly beneath the ductal epithelium that is damaged at one point. Beyond this, there is extensive fibrosis (H and E)

lactoferrin, a non-enzymatic secretory protein; the presence of these glands has been proposed to account for similar pathology arising from the bile duct and the pancreas [15]. These peribiliary glands are also targets of immune destruction in AIP [15]. Biliary and pancreatic ductal epithelial cells of affected ducts in AIP may be relatively spared despite being surrounded by fibrosis [15].

Although pancreatic infiltration by eosinophils was not seen in the relatively smaller number of specimens analysed by Wang et al. [16], larger studies [17, 18] showed prominent pancreatic eosinophil infiltration. Eosinophils also exist in GELs, which typify the IDCP form or AIP, although neutrophils predominate in these lesions [12]. Some studies have shown sustained reversal of peripheral eosinophilia following steroid therapy [16, 19], while others have reported variable responses [18].

Islet autoantibodies are uncommon and islets are not infiltrated by I_gG_4 cells [20, 21]. Fibrosis does occur around islets, but the total islet mass is relatively preserved in AIP [22], helped by islet differentiation from ductal precursor cells over-expressing insulin promoter factor-1 (IPF-1) [23] or by the protective effect of infiltrating macrophages [24]. Nevertheless, diabetes mellitus is observed in some cases, and epitope spreading (see next section) including to islet antigens does occur in experimental AIP [1].

A less well-studied leukocyte subset in AIP is eosinophils although peripheral eosinophilia is reported in patients with AIP [16–18].

General Overview of Immunity

A concise overview of critical components of immunity, many of which are featured in AIP, is included here to assist the general reader. Responses to invading microbes may be innate or adaptive (acquired). The innate immune response detects and alerts the host to the presence of invading pathogens and generates adaptive immune responses. The innate immune system comprises mononuclear phagocytes (monocytes, macrophages, dendritic cells), granulocytes (neutrophil, eosinophils, basophils), mast cells and natural killer (NK) cells [25].

Pathogens bear pathogen-associated molecular patterns (PAMPs) which immune cells recognise via pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) [26]. Ligation of cell-expressed TLRs leads to activation of immune cells, which secrete inflammatory cytokines via downstream signalling pathways. A well-known PRR is TLR4, which is expressed by all innate immune cells and recognises the bacterial PAMP, lipopolysaccharide (LPS). TLRs expressed by pancreatic stellate and endothelial

cells contribute to the role of these cells in immune responses.

The innate response activates the complement system to generate several immunologically active products including C3b, C3a, C4a, C5a, C5a and the membrane-attack complex, which act as opsonins, cell activators, chemoattractants and inducers of cell lysis.

Phagocytic clearance of pathogen-derived molecules by neutrophils and monocytes/macrophages causes these immune cells to become activated and secrete inflammatory cytokines, part of innate immunity driving adaptive immunity. Dendritic cells (DC) function as antigen-presenting cells (APC) which present antigen to T cells in association with major histocompatibility complex (MHC) molecules thus initiating acquired immune responses in secondary lymphoid tissues such as local draining lymph nodes [27]. The MHC genes are present in most vertebrates and code for cell-surface proteins named the human leukocyte antigens (HLA) in man. MHC molecules exist as class I via which self-peptides are presented to $CD8^+$ T cells and class II for presentation of exogenous peptides to $CD4^+$ T cells. There exists three subsets of MHC class I molecules, namely, HLA-A, HLA-B and HLA-C, and of class II molecules, namely, HLA-DP, HLA-DQ and HLA-DR. Antigen recognition is specific because the T cell receptor (TCR) is only able to recognise antigenic peptides linked with MHC molecules. A similar process occurs for B cells and is mediated by the B cell receptor (BCR). Lymphocytes only recognise small parts of antigens (epitopes), owing to the much smaller size of lymphocyte receptors relative to antigens. Haptens are antigens that are too small to elicit immune responses unless they are coupled to larger immunogenic molecules called carriers.

Effective MHC-mediated antigen presentation necessitates contact between APCs and lymphocytes and co-stimulatory activation of lymphocytes. Stable cell contact is maintained by binding of APC-expressed intercellular adhesion molecule 1 (ICAM-1) to lymphocyte-expressed lymphocyte function-associated antigen 1 (LFA-1), and co-stimulatory signals for lymphocyte activation are generated by the respective ligations of APC-expressed CD80/CD86 and CD40 by lymphocyte-expressed CD28 and CD154. Ligation of CD80/86 by lymphocyte-expressed cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) instead of CD28 downregulates lymphocyte activation and may promote tolerance [28, 29].

Autoimmunity can be initiated by unique aberrations of antigen processing, namely, epitope spreading and molecular mimicry. In epitope spreading, collateral tissue damage induced by pathogen-specific T cells causes release of self-epitopes that become targets for lymphocyte attack as a result of bearing homology to the immunodominant sequence of pathogens [30] or may occur because non-self-target antigens happen to be linked with bystander self-antigens in complexes [20]. Molecular mimicry occurs when pathogen peptides share sequence or structural similarities with self-antigens and thus trigger the production of immune cells and antibodies that cross-react with these self-proteins.

Terminally differentiated B cells called plasma cells produce immunoglobulins (I_g) which are antigen-specific antibodies. Individual B cells evolve to express only one specific antibody. Plasma-cell precursors are generated in germinal centres that arise in lymphoid tissue during the immune response [31]. Following antigen recognition, clones of B cells with high affinity and specificity for an antigen undergo proliferation and produce large quantities of antigen-specific antibody. Antibodies are composed of two identical heavy chains and two identical light chains joined by disulfide bonds. The termini of the heavy and light chains that are not involved in antigen binding form the constant region and define the class and subclass of the antibody. There exist five classes of I_g determined by the constant region of the heavy chains, namely, I_gG, I_gA, I_gM, I_gD and I_gE. I_gG is further split into four subclasses, I_gG_{1-4}.

Unlike innate responses, adaptive responses become more efficient on subsequent exposure(s) to antigens because during the primary immune response when antigen is first encountered, memory lymphocytes are generated. For instance, memory B cells produce larger amounts of

antibody with greater affinity for the antigen on subsequent exposure to antigens compared to the primary response. Functions of antibodies include classic complement pathway activation and antibody-dependent cellular cytotoxicity towards target cells.

T Cells in Inflammation

The T cell subset repertoire is ever expanding, but key subsets are CD4+, CD8+ and regulatory T cells (which can express CD4+, CD8+ and other characteristic molecules), all contributing to inflammatory responses.

CD4+ helper T cells secrete cytokines that facilitate immune responses. CD4+ T helper (T_h) cells may be T_h0, T_h1, T_h2 or T_h17 cells. T_h0 cells are uncommitted naïve cells capable of differentiating into other functional phenotypes depending on the prevailing cytokine milieu. Differentiation of T_h1 cells is stimulated by interferon gamma (IFN-γ) and interleukin-12 (IL-12), of T_h2 cells by IL-4 and of T_h17 cells by TGF-β and IL-6 or IL-23. T_h1 cells produce IFN-γ, IL-2 and IL-12; T_h2 cells produce IL-4, IL-5, IL-6 and IL-10; T_h17 cells produce IL-17A, IL-17F, IL-21 and IL-22 [32, 33]. T_h1 cytokines activate macrophages and promote T cell-mediated cytotoxicity, while T_h2 cytokines promote humoral immunity (mediated by B cell-produced antibodies). T_h17 cells have effector functions distinct from those of T_h1 and T_h2 cells, primarily clearing pathogens that are not adequately handled by T_h1 or T_h2 cells. T_h17 cells amplify immune responses at sites of inflammation and are implicated in chronic inflammation and autoimmune disease [34]. T_h17 cytokine IL-17 promotes germinal centre formation and autoantibody secretion [35], while IL-21 induces proliferation of B cells and their differentiation into I_g-producing plasma cells [36].

CD8+ cytotoxic or killer T cells eliminate virally infected cells following detection via MHC I-linked viral peptides. Cytotoxic CD8+ T cells kill target cells via the granzyme-perforin or the Fas-FasL pathways. In the granzyme-perforin pathway, granzyme serine proteinases released from activated CD8+ T cells are passed into the target cell via pores in the target-cell membrane created by perforins, also released by activated CD8+ T cells. Granzymes cleave granzyme A, granzyme B, caspases, and Bcl2-interacting domain, inducing apoptosis of the target cell. FasL-bearing CD8+ T cells can bind the Fas molecule on target cells thus activating caspases within and inducing apoptosis of target cells.

Regulatory, suppressor T cells (T_{regs}) are typically CD4+ CD25+ T cells that express the transcription factor forkhead box P3 (Foxp3). T_{regs} may occur naturally in the thymus or may be induced in peripheral lymphoid organs. T_{regs} are also identifiable by high level of expression of CD45RO, CTLA4 and glucocorticoid-induced tumour necrosis factor receptor (GITR), as well as low levels of CD127 and CD45RA. T_{regs} suppress activation, proliferation and effector functions of T cells, NK cells, B cells and a range of APCs. Suggested mechanisms by which T_{regs} induce suppressor activity include CTLA4-mediated suppression of APCs, contact-induced suppression of effector T cells and secretion of TGF-β and IL-10. The translational potential of harnessing the suppressive effect of T_{regs} is under investigation in clinical trials of autoimmune diseases [37] where impaired T_{reg} response is implicated [38]; such an approach may be applicable to AIP. T cell differentiation is tightly regulated as naïve T cells stimulated with TGF-β differentiate into T_{regs}, but into T_h17 cells in the presence of both TGF-β and IL-6 [33].

B Cells in Inflammation

B cell responses to antigenic stimulation may be T cell dependent or independent. In T cell-dependent responses, antigen taken up by B cells is processed and presented to T cells via MHC II in secondary lymphoid organs. Naïve B cells subsequently mature and undergo clonal expansion, somatic hypermutation, and class-switch recombination. Naïve B cells are of I_gM and I_gD isotypes. Class-switch recombination of I_g heavy chain permits B cells to produce

antigenic-specific antibodies of different isotypes, while somatic mutation of I_g gene rearrangements increases the antigen binding affinity of the B cell receptor (BCR). As well as maturing into I_g-secreting plasma cells, naïve antigen-specific B cells also mature into memory B cells, allowing rapid induction of high levels of high affinity I_gG, I_gA and I_gE antibodies to be generated after a secondary antigen challenge. Class-switch recombination is important for memory B cell generation and relies on interactions between T cell-expressed CD40L and B cell-expressed CD40.

T cell-independent responses are induced by polymeric antigens such as LPS which activate B cells by cross-linking surface I_g molecules [39]. Most T cell-independent antibody responses do not involve somatic mutation, resulting in weak immune memory to T cell-independent antigens. The emergence of self-reactive clones of B cells is prevented by processes such as clonal deletion, receptor editing to less self-reactive ones and clonal anergy. Autoimmune responses by self-reactive B cells can also be inhibited by macrophage-secreted IL-6 and CD40L. Failings at these checkpoints allow expansion of memory B cell pools that promote autoimmunity [40–43]. B cells promote autoimmunity by producing pathogenic autoantibodies, presenting antigen to autoreactive T cells, forming tissue-damaging immune complexes, secreting proinflammatory cytokines such as IL-2 and IFN-γ, as well as by ectopic neo-lymphogenesis [44]. Ectopic neo-lymphogenesis is de novo formation and maintenance of germinal centres in ectopic tissue sites thus amplifying local disease [45], frequently observed in AIP. B cells function as autoantigen-presenting cells in diabetic NOD mice [46]. B cell depletion by targeting the CD20 antigen, expressed by B cells at almost all stages of differentiation, is therapeutically beneficial in NOD mice with autoimmune diabetes [47] or in patients with rheumatoid arthritis [48]. B cells are also capable of inhibiting immune responses by producing IL-10 and TGF-β or promoting differentiation of T_{regs} [49].

Specific Changes of Autoimmunity in AIP

Evidence of autoimmune injury in AIP includes the presence of autoantibodies, lymphocyte infiltration, association with specific HLA haplotypes and associations with other immune inflammatory diseases. Unlike classic autoimmune diseases, AIP affects males more commonly than females, and as previously mentioned, identified autoantibodies are not completely specific for AIP. Rodent and dog models have increased our understanding of the immune process underlying AIP. Because of the clinical focus on antibodies in AIP with blood being far easier to sample than pancreatic tissue, I_gG_4 and autoantibodies are discussed first, even though it may be that T cell responses have a predominating role in the pathogenesis of AIP. A diagrammatic representation of the immune mechanisms that may contribute to AIP is given in Fig. 2.3.

I_gG4 in AIP

Serum and pancreatic tissue elevations of I_gG_4 occur in AIP [50–52]. The I_gG_4 subclass accounts for only 3–6 % of total serum I_gG in normal subjects and has significantly higher concentrations in men than women [53]. The elevation of $I_gG_4^+$ cells in AIP patients may be due to a global increase in the total number of infiltrating plasma cells (see Fig. 2.3) and not a preferential increase of $I_gG_4^+$ plasma cells alone [54].

Unlike other I_gG subclasses, I_gG_4 cannot bind C1q and is unable to activate the classic complement pathway [55]. Classic complement pathway activation, however, does occur in patients with AIP and is associated with elevated serum I_gG_1 [56]. Kawa et al. showed I_gG_4 can undergo Fc-Fc binding interactions with I_gG subtypes 1–3, which induces aggregation of I_g to form complexes; they speculated that the easier clearance of aggregate complexes terminates the inflammatory process
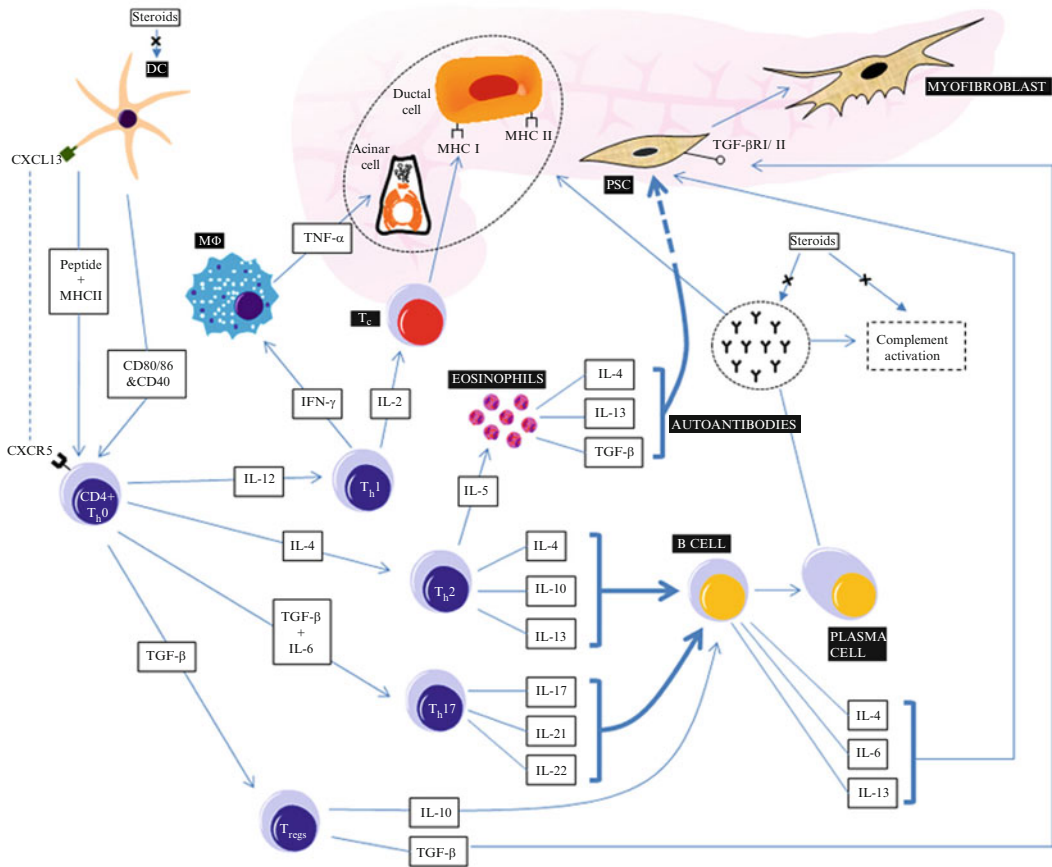
Fig. 2.3 *Schematic representation of immune events in AIP*. Autoimmune attack on pancreatic acinar and ductal cells in AIP begins with uncommitted CD4+ T helper cells (T_h0) experiencing an MHC-complexed autoantigen presented by antigen-presenting cells such as dendritic cells (*DC*) in association with appropriate co-stimulatory signals. CXCL13-expressing DC may attract and undergo cognate interactions with CXCR5-expressing lymphocytes in AIP. T_h0 cells become activated and differentiate into T_h1, T_h2, T_h17, or T_{regs} depending on the nature of the antigen and the cytokines prevalent in the pancreatic microenvironment. T_h1, T_h2, T_h17, and T_{regs} are induced by IL-12, IL-4, TGF-β and IL-6 and TGF-β alone, respectively. These T_h subsets drive immune reactions that are partly driven by the cytokines they produce. T_h2 cells drive B cell differentiation into autoantibody-producing plasma cells by producing IL-4, IL-10, and IL-13. Plasma cells produce autoantibodies directed against endocrine pancreatic antigens, thus acinar and ductal cells (*highlighted* within pancreas by *ellipse with dashed outline*).

Production of antibodies by plasma cells leads to complement activation. T_h2 cytokine IL-5 promotes recruitment of eosinophils which may themselves secrete pro-fibrotic cytokines such as IL-4, IL-13, and TGF-β. The T_h1 cytokine IFN-γ activates macrophages to secrete TNF-α which may activate acinar or endothelial cells, and IL-2 promotes differentiation of cytotoxic T cells (T_c). Aberrant MHC expression by pancreatic ductal cells renders them more susceptible to attack by T_c, particularly CD8+ T cells via granzyme-perforin or Fas-FasL pathways. T_h17 cells produce IL-17A, IL-17F, IL-21 and IL-22 which promote germinal-centre formation, autoantibody secretion, induce B cell proliferation and differentiation into I_g-producing plasma cells. T_{regs} oppose the proinflammatory actions of other T cells and promote fibrosis by activating pancreatic stellate cells (PSC) to myofibroblasts via secreted TGF-β which binds to TGF-βRI/II expressed by PSC. Steroids treat AIP by inhibiting DCs, complement activation and antigen-specific antibody production

[57]. I_gG_1 is itself elevated in AIP, even in patients with normal I_gG_4 [58]. I_gG_4 is produced by human B cells stimulated with T_h2 cytokines IL-4 [59] and IL-13 [60], as well as by the T_{reg} cytokines IL-10 and TGF-β [61, 62].

I_gG_4 is uniquely able to perform 'Fab-arm exchange' in which random swapping of heavy and light chain pairs between I_gG_4 molecules occurs leading to bi-specific antibodies (enabling cross-linking of non-identical antigens) which are anti-inflammatory [63]. I_gG_4 antibodies generated in I_gE-mediated allergic responses are usually associated with tolerance-inducing mechanisms [64]. Bi-specific antibodies formed by 'Fab-arm exchange' are functionally monovalent (cannot cross-link identical antigens) despite being structurally hetero-bivalent and are thus less likely to form large immune complexes and have a low potential for inducing inflammation. If large numbers of target and effector cells are present, binding by high levels of bi-specific antibodies can lead to immunopathology as may occur in Wegener's granulomatosis [65] and bullous pemphigoid [66]. There are no data to support a causative role for I_gG_4 in AIP, and expression of the pro-fibrotic cytokines TGF-β and PDGF-B is not affected by the I_gG_4 status of AIP patients [9]. I_gG_4 autoantibodies may simply be generated as a result of chronic autoimmune inflammation and may not actually cause injury, but based on evidence to date including work that has shown I_gG_4 in AIP can be an autoantibody [68], the possibility that I_gG_4 either exacerbates or reduces the pathology of AIP cannot be discounted.

Autoantibodies in Human AIP

The targeting of inflammatory damage to pancreaticobiliary ducts in AIP suggests antigens expressed by ductal epithelium are recognised by the immune system. Immune responses are elicited following in vivo alteration of rat pancreatic ductal antigens by ductal infusion of trinitrobenzene sulfonic acid (TNBS) which acts as a hapten [67]. The presence of organ-specific autoantibodies in the serum of AIP patients is demonstrated by increased I_gG_4 expression in normal tissue immunoreacted with sera from AIP patients, the increased I_gG_4 expression being attenuated if serum was obtained from patients treated with corticosteroids [68].

The most frequent autoantibodies detected in AIP patients are anti-lactoferrin (anti-LF) and anti-carbonic anhydrase type II and/or IV (anti-CA-II or anti-CA-IV), which detect the candidate target antigens LF and CA [69–72]. A recent series of 26 Japanese patients with AIP was reported in which 90 % of patients' sera were positive for either anti-CA-II or anti-LF and 30 % positive for both [73]. Carbonic anhydrase is also expressed by salivary glands and kidneys and lactoferrin by breast, bronchial, salivary and gastric glands. Neither is specific for AIP as either or both can be detected in Sjögren's syndrome [69], ulcerative colitis [74] and primary sclerosing cholangitis [75].

Other autoantigens implicated in AIP are α-Fodrin and serine protease inhibitor Kazal-type 1 (SPINK-1, also known as pancreatic secretory trypsin inhibitor or PSTI, mutations of which predispose to chronic pancreatitis). α-Fodrin expression is limited to AIP patients with associated Sjögren syndrome or sclerosing cholangitis [76], also an autoantigenic marker of Sjögren syndrome [77]. Autoantibodies to SPINK1 detected in patients with AIP are of I_gG1 subclass [73]. Screening of a human pancreas cDNA library with serum from a patient with AIP revealed clones identical to amylase α-2A [78] and heat shock protein 10 (HSP 10) cDNA [79]. Autoantibodies against amylase α-2A [78] and HSP 10 [79] have been detected in Japanese patients with AIP, and serum autoantibody titres were reduced by steroid therapy.

In a recently published study undertaken by Löhr et al. [80], a comprehensive genomics and proteomics approach to AIP extended our understanding through the finding that acinar cells and their protein components are targeted by the inflammatory process. The loss of acinar cells was associated with elevated autoantibody titres against cationic and anionic trypsinogens (PRSS1 and PRSS2) and SPINK-1; there was no difference in the findings between both subtypes of AIP. These autoantibodies were found to have a

Table 2.1 Autoantibodies identified in patients with AIP

Autoantibody	References
Anti-lactoferrin (anti-LF)	[69]
Anti-carbonic anhydrase II or IV anti-CA-II or anti-CA-IV)	[68–71]
Anti-α-Fodrin	[75]
Anti-amylase α -2A	[77]
Anti-heat shock protein 10 (anti-HSP 10)	[78]
Anti-cationic trypsinogen (anti-PRSS1)	[79]
Anti-anionic trypsinogen (anti-PRSS2)	[79]

predictive accuracy of 80 % for distinguishing patients with AIP from those with non-AIP chronic pancreatitis, and an accuracy of 86 % for AIP patients versus healthy controls. The detection of these antibodies by ELISA may help to distinguish AIP from other types of pancreatitis such as alcoholic pancreatitis.

All the autoantigens identified so far are expressed by pancreatic ducts and acini, in keeping with the histological injury observed in AIP. A list of the autoantibodies is given in Table 2.1. These autoantibodies may arise from cell destruction or by epitope spreading of initial autoantigens.

Cellular Responses in Human AIP

MHC class I (HLA-ABC) and II antigens (HLA-DR and HLA-DQ) are focally expressed by pancreatic ductal epithelium in AIP [81–83]. Aberrant expression of MHC I and MHC II by pancreatic ducts is seen in chronic pancreatitis [84–87]. In AIP, pancreatic duct cells may act as APC alongside dendritic cells to present MHC-complexed autoantigenic peptides to T cells. The chemokine CXCL13 and its receptor CXCR5 are expressed by cells in periductal and parenchymal areas of the pancreata of patients with AIP [54]. In tissues affected by autoimmune disease, CXCL13-expressing follicular dendritic cells and CXCR5-expressing naïve B or memory CD4$^+$ T cells are known to undergo cognate interactions crucial for maintaining lymphocytic infiltrates and supporting germinal centres of lymphoid follicles [88].

Polyclonal lymphocyte populations are detected in most patients with AIP, suggesting the immune response targets numerous antigens or numerous antigenic epitopes generated by epitope spreading [51]. Similar polyclonal B cell activation producing I$_g$M, I$_g$G$_1$, I$_g$G$_2$ and I$_g$G$_4$ plasma cells occurs in AIRE-deficient NOD mice with AIP [89].

In patients with AIP and coexistent cholangitis (autoimmune pancreato-cholangitis or AIPC), areas of pancreatitis and cholangitis are infiltrated by large numbers of CD4$^+$ CD25$^+$T$_{regs}$ [90]. The ratio of Foxp3$^+$/CD4$^+$ cells is higher in AIPC than in other autoimmune or non-autoimmune diseases, and infiltrating T$_{regs}$ may produce IL-10 and TGF-β which are highly expressed in AIPC [90]. Local IL-10 will promote B cell switching to I$_g$G$_4$-producing plasma cells, and TGF-β will activate pancreatic stellate cells (PSC) to myofibroblasts causing fibrosis. Interestingly, analysis of peripheral blood IL-10 and TGF-β in AIP patients revealed no difference from healthy controls or non-AIP chronic pancreatitis [91]. Other studies have analysed peripheral T cell counts in AIP patients and demonstrated that T$_h$1 cells predominate over T$_h$2 cells [70] with a marked increase in CD4$^+$ and CD8$^+$ T cells expressing HLA-DR$^+$ [70]; naïve T$_{regs}$ (CD4$^+$ CD25$^+$ CD45RA$^+$) are decreased while memory T$_{regs}$ (CD4$^+$ CD25$^+$ CD45RA$^-$) are elevated [91]. The increase of memory T$_{regs}$ may reflect the activation of T$_h$0 cells into effector and memory populations. However, it is difficult to reconcile the contrasting data on T$_h$1/T$_h$2 cytokine profiling in the pancreas [90] and in the peripheral blood [70] of AIP patients.

Circulating CD4$^+$ T cells expressing HLA-DR infiltrate pancreatic ductal epithelium in AIP [82, 83]. Although HLA-DR is mainly expressed by professional APCs, activated human T cells synthesise and express MHC class II molecules [92]. In vivo activated human T cells express MHC class II and co-stimulatory molecules and may be able to present peptide antigens to bystander T cells. Antigen presentation by MHC class II-expressing T cells provides downregulatory signals to antigen-responding CD4$^+$ T cells [92, 93]. This immunoregulatory role is emphasised by HLA-DR$^+$ CD4$^+$ CD25^{hi} natural T$_{regs}$, which express the highest levels of Foxp3, rapidly induce strong suppression and exhibit low in vitro expansion capabilities [94, 95].

B cells may have a pro-fibrotic role in AIP. Peripheral blood B cells are recruited and activated due to repeated injury in sites of tissue fibrosis [96]. B cells secrete IL-4, IL-6 and IL-13 which cause paracrine activation of PSC [96–98] or induce macrophages to secrete TGF-β causing paracrine activation of PSC [99, 100]. The specific role of tissue I_gG_4 in AIP is uncertain, but it certainly does reflect the large number of B cells recruited to the pancreas and to extrapancreatic sites such as the salivary glands and liver [101].

The T_h2 cytokine IL-5 is expressed in tissue affected by AIP [90] and is an important stimulus to eosinophilic infiltration and activation [102]. The exact role played by eosinophils in AIP is uncertain, but they are capable of producing cytokines including IL-2, IL-3, IL-4, IL-5, IL-7, IL-13, IL-16, TNF-α, TGF-β and RANTES, as well as cationic proteins such as eosinophil cationic protein and reactive oxygen metabolites. As in AIP, profound fibrosis also occurs in eosinophilic pancreatitis where there is heavy eosinophilic infiltration of the pancreas [17]; eosinophilic pancreatitis may be an unusual variant form of AIP [103, 104]. Eosinophil-derived mediators may activate PSC similar to their effect on fibroblasts during fibrosis elsewhere [105–107].

Rodent AIP

Spontaneous or induced rodent models of AIP have contributed to the understanding of the immune pathogenesis of AIP. Spontaneous experimental rodent models of AIP include the following (see also the complete list in Table 2.2):

(i) MRL/Mp mice spontaneously develop AIP after 22 weeks of age. Their pancreata are infiltrated by CD4+ T cells and macrophages with destruction of acini that are replaced by adipose tissue [108]. Conplastic mouse strains containing the nuclear genome of MRL/MpJ mice and the mitochondrial genome of FVB/N mice (MRL/MpJ-mt^FVB/N) mice develop a more severe parenchymal destruction inflammatory infiltrate in the pancreas by 24 weeks of age compared with MRL/MpJ controls [109].

(ii) Mice homozygous for aly (alymphoplasia) mutation lack lymph nodes and Peyer's patches, show defects in humoral and cellular immunity and spontaneously develop AIP after 14 weeks of age. Pancreatic acinar cells are destroyed by infiltrating CD4+ T cells and replaced by adipose tissue, while islet cells are completely spared [110].

(iii) Male Wistar Bonn Kobori (WBN/Kob) rats develop AIP spontaneously from 4 weeks of age marked by lymphocytic infiltration and acinar destruction. Fibrosis begins from 8 weeks of age and is accelerated with increased inflammatory cell infiltration from 12 weeks of age. The pancreas is infiltrated mainly by CD8+ T cells expressing MHC I and II, serum I_gG_{2b} levels are increased, peripheral blood T_{regs} are reduced in count and extrapancreatic lesions exist [111].

(iv) NOD mice are prone to autoimmune diseases, but they do not spontaneously develop AIP. NOD mice with knockout of CD28 gene (NOD.CD28KO mice) show defective thymic development, maintenance of peripheral T_{regs} and are predisposed to AIP. NOD.CD28KO mice transfused with islet-specific BDC2.5 T_{regs} are protected from autoimmune islet injury but develop AIP from 8 weeks of age onwards. They show increasing infiltration of the pancreas by CD4+ T cells, initially periductally then progressively spreading to result in atrophy of acinar cells and replacement by adipose tissue at 16 weeks. The inciting autoantigen was identified as α-amylase, and injecting mice with tolerance-inducing amylase-coupled splenic cells fixed with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (ECDI) has been shown to attenuate mononuclear cell infiltration and exocrine pancreatic injury [112].

(v) NOD mice lacking the tolerance-inducing autoimmune regulator (AIRE) gene show a shift in target autoantigen recognised by autoreactive T cells from islet-expressed antigen to acinar cell-expressed pancreas-

Table 2.2 Summary of available rodent models of AIP

Species	Mode	Autoantibody	Effector cell	Damage observed	Comment	Ref
AIRE KO mice	Spontaneous	Pancreas-specific protein disulfide isomerase (PDIp)	CD4+ and CD8+ T cells and B cells	Acinar destruction and fatty replacement	Polyclonal B cell activation occurs yielding I_gM, I_gG_1, I_gG_2, and I_gG_4 plasma cells	[88]
MRL/Mp mice	Spontaneous	Pancreatic secretory trypsin inhibitor (PSTI)	CD4+ and macrophages	Acinar destruction and fatty replacement	Accelerated or worsened injury if treated with poly I:C or IFN-γ, respectively	[107–110]
MRL/MpJmt$^{FVB/N}$ mice	Spontaneous	Not specified	B cells and CD8+ T cells	Acinar destruction, fibrosis, and fatty change	More severe parenchymal destruction than in MRL/MpJ controls at 24 weeks	[111]
aly/aly mice	Spontaneous	Not specified	CD4+ T cells	Acinar destruction and fatty replacement		[112]
WBN/Kob rats	Spontaneous	Not specified	CD8+ mainly but also CD4+ T cells	Acinar destruction and fibrosis	Peripheral blood Treg counts are reduced and extrapancreatic lesions exist	[113]
CD28-KO NOD mice	Spontaneous	Amylase	CD4+ T cells	Acinar atrophy and fatty replacement		[114]
HLA-DR*0405 transgenic Ab0 NOD mice	Spontaneous	Not specified	CD4+ and CD8+ T cells, B cells, and macrophages	Acinar destruction and fatty replacement	Also show acinar-to-ductal metaplasia	[115]
TGF-βR2^{fspKO} mice	Spontaneous	Not specified	Macrophages and T cells	Acinar metaplasia	No significant fibrosis	[119]
Neonatally thymectomised BALB/c mice	Immunized with CA-II or LF antigens	Carbonic anhydrase II (CA-II) or Lactoferrin (LF)	CD4+ T cells	Ductal and acinar cell apoptosis		[116]
B6 mice	Infection with MuL V	Not specified	CD4+ T cells, B cells and macrophages	Acinar destruction	? Molecular mimicry	[117]
DA(RP) or Lewis rats	Adoptive transfer of amylase-specific T cells	Amylase	CD4+ and CD8+ T cells, macrophages, and dendritic cells	Ductal inflammation, acinar destruction and fibrosis		[118]

specific protein disulfide isomerase (PDIp) which protects AIRE-deficient NOD mice from autoimmune diabetes and induces spontaneous AIP [89]. Mice show pancreatic lymphoid cell infiltration starting at 2 weeks of age progressing to intense lymphocytic infiltration of acini that are completely destroyed and replaced with adipose tissue by 8–12 weeks after birth, leaving β cell islets and pancreatic ducts relatively well preserved [89].

(vi) HLA-DR*0405 transgenic Ab0 NOD develop spontaneous AIP by 18 weeks of age or earlier with periacinar leukocytic infiltration and destruction of acini, which are replaced by adipose tissue. HLA-DR*0405 transgenic Ab0 mice have near-normal CD4$^+$ T cell count and function, unlike Ab0 mice which are severely defective. These mice additionally show acinar-to-ductal metaplasia with loss of acinar zymogen granules and formation of ductular structures, but the islet cells are preserved [113].

(vii) C57BL/6 mice with conditional knockout of TGF-β type 2 receptor (TGF-βR2) in S100A4+ cells (TGF-βR2^{fspKO} mice) show acinar metaplasia with infiltration by macrophages and T cells by 6 weeks of age, although islet cells are spared [114].

Induced models of AIP include the following:

(i) MLR/Mp mice treated with poly-inosinic:polycytidylic acid (poly I:C) develop AIP earlier at 18 weeks [115, 116], and mice treated with IFN-γ show more prominent leukocyte infiltration and worsened histological injury [117]. Of note poly I:C-treated mice show elevated anti-PSTI but not anti-CA-II or anti-LF autoantibody titres and also elevated serum I_gG_1 and I_gG_{2b} though not I_gG_4 [116].

(ii) Neonatally thymectomised BALB/c mice immunised with CA-II or LF antigens develop AIP with CD4$^+$ T cells infiltration of inflamed ductal or periductal areas and apoptotic ductal or acinar cells. Neonatally thymectomised mice lack peripheral T$_{regs}$ and are prone to autoimmunity. This was the first model to show AIP can be induced by treatment with autoantibodies and greatly strengthens their pathogenic role. Adoptive transfer of splenic T cell subsets from immunised to nude mice identified CD4$^+$ T cells as the effectors of immune damage in recipient mice. Insulitis was not induced by immunisation with CA-II or LF or by lymphocyte transfer [118].

(iii) Young B6 mice develop AIP 4 weeks after being infected with the LP-BM5 murine leukaemia retrovirus (MuLV) in addition to becoming profoundly immunodeficient, but islets are relatively preserved. Increasing leukocytic infiltration, initially seen around the pancreatic ducts with later involvement of the acini, causes acinar cell destruction peaking at 12 weeks after infection. A paucity of TUNEL-positive acinar cells suggests apoptosis is not the main mechanism of acinar cell death in this model, although lymphocytes undergo apoptosis, which may represent activation-induced cell death [119].

(iv) Adoptive transfer of amylase-specific activated CD4$^+$ T cell lines induces diffuse AIP in recipient DA(RP) rats, though less severe in Lewis rats. T cell lines specific for either CA-II or LF, however, did not induce AIP in DA(RP) rats [120].

Table 2.2 lists the various models of autoimmune pancreatitis so far described. Autoantigens thus so far identified in murine studies include pancreatic amylase [112, 120], CA-II and LF [118], PDIp [89] and PSTI [116].

Canine AIP

A naturally occurring form of autoimmune chronic pancreatitis has been described in the English cocker spaniel (ECS) which develops pancreatic duct-centric immune damage with systemic manifestations, such as by keratoconjunctivitis sicca and autoimmune polyarthritis. Histology of the pancreas in affected dogs shows duct destruction associated with periductal and perivenular infiltration by T cells and progressive interlobular fibrosis [121]. Affected dogs

often develop exocrine and endocrine insufficiency in end-stage disease, but neither serum nor tissue I_gG subsets were measured in these studies. Autoimmune disease in ECS is associated with the dog leukocyte antigen system [122], but similar canine HLA association studies in AIP are lacking. German Shepherd dogs and rough-coated Collies also develop a distinct juvenile onset autoimmune-mediated atrophic lymphocytic pancreatitis with autoantibodies directed against acini. Their pancreata are infiltrated by lymphocytes and acini are destroyed causing exocrine insufficiency, but ductal epithelial cells are not targeted. Typically CD8^{+} T cells predominate in areas of parenchymal destruction and destroyed acini of dogs are replaced by fat, but islets are relatively spared as seen in some rodent models of AIP, such as homozygous aly mice described in the preceding section [123, 124].

The burning question is to what extent these animal findings are relevant to, or can be transferred to, the human situation. There are likely to be significant insights from each species that could be applied to all. The dog has been suggested as a better model of pancreatic disease than rodents because the anatomy and function of the canine pancreas is more similar to humans [125], justifying very much further study to improve the management of AIP, not just in dogs but also in humans.

TGF-Β: Immunomodulator and Pro-fibrotic Factor in AIP

TGF-β signalling is essential for maintaining normal immune homeostasis of pancreatic acinar and ductal cells; indeed TGF-β1, TGF-β2 and TGF-β3 are highly pleiotropic cytokines that almost all cells secrete. Mice overexpressing a dominant-negative mutant form of TGF-β type 2 receptor under the influence of the pS2 promoter (which functionally inactivates TGF-β signalling selectively in pancreatic acinar and ductal cells) are more susceptible to developing autoimmune-mediated pancreatitis induced by caerulein injections [126]. Autoimmunity during pancreatitis in

these mice is suggested by serum I_gG and I_gM autoantibodies targeting pancreatic acinar cells and ductal epithelial cells [126]. These transgenic mice show markedly increased MHC class II expression in the pancreatic acinar cells that enhances APC-T cell interactions during pancreatitis [126].

Adoptive transfer of TGF-βR2-deficient dendritic cells (DC) from TGF-βR2[fspKO] mice induced AIP in syngeneic wild-type mice in vivo and caused enhanced T cell activation during in vitro assays using ovalbumin antigen, likely due to enhanced maturation of DCs in response to antigen [120].

TGF-β is crucial for transforming PSC into proliferating myofibroblasts [127, 128] and is expressed alongside its receptor in AIP tissue. In pancreatic tissue specimens from patients affected by AIP, macrophages express the TGF-β1 propeptide called latency-associated peptide (LAP) [9]; pancreatic ductal cells and infiltrating mononuclear cells express TGF-β1 itself [129], while myofibroblasts and ductal cells express TGF-βR2 [9]. TGF-β and other pro-fibrotic cytokines including PDGF-B transform PSC into myofibroblasts causing intense periductal fibrosis [9].

Potential Triggers of Disease

Effect of Immunological Genotype on AIP

The occurrence and outcome of AIP is associated with genetic factors within and outside the major histocompatibility complex (MHC). Polypeptide chains encoded by MHC I genes are HLA-A, HLA-B, HLA-C, HLA-E, HLA-G and HLA-F (all belong to human leukocyte antigen or HLA class I), and those encoded by MHC II genes are HLA-DR, HLA-DQ and HLA-DP (all HLA class II). DR and DQ subregion genes are closely linked and usually inherited together such that DR and DQ alleles form stable haplotypes in the population; α and β denote functional genes, while ψ denotes non-functional genes. A diagrammatic representation of potential triggers of AIP is given in the summary (Fig. 2.4).
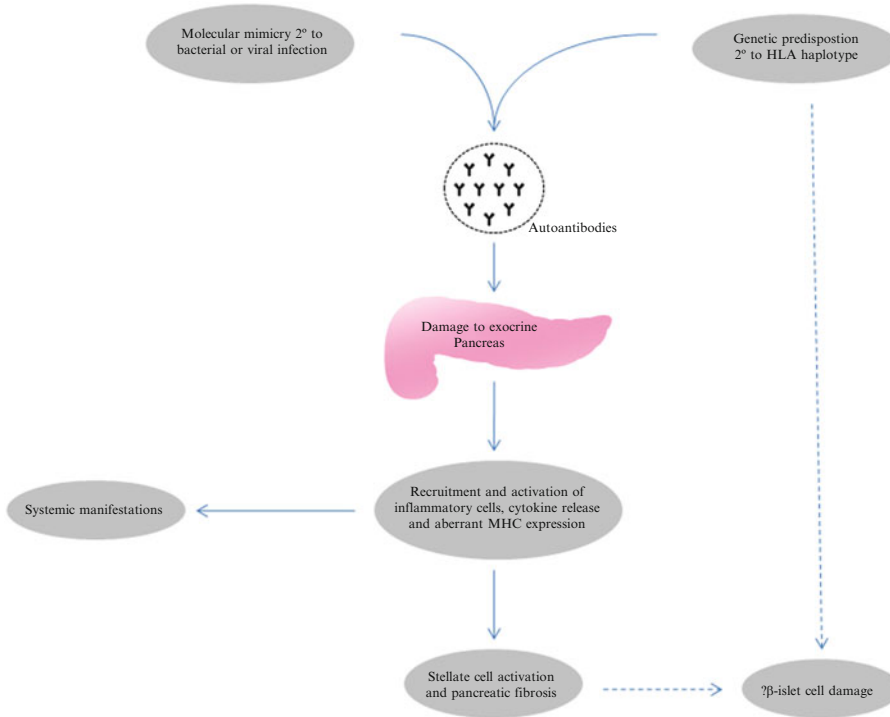
Fig. 2.4 *Overview of mechanisms leading to injury in AIP*. Triggers, such as molecular mimicry and genetic susceptibility, lead to the expression of autoantigenic epitopes and subsequently the production of autoantibodies that target the exocrine pancreas. Pancreatic injury generates a cytokine milieu that recruits inflammatory cells which become activated to secrete cytokines and cause further damage. Pro-fibrotic cytokines activate pancreatic stellate cells leading to fibrosis. Activated immune cells and cytokines entering the circulating blood may partly account for the systematic manifestations of AIP. β-islet cells may be damaged by surrounding fibrosis, but it is recognised that AIP and autoimmune diabetes share susceptibility haplotypes

Molecular genotyping of 40 Japanese patients with AIP showed that HLA haplotype DRβ1*0405-DQβ1*0401 is associated with AIP [130], and this was confirmed in a more recent study of 15 Japanese patients with AIP [78]. Another study of 43 Japanese patients with AIP showed that in addition to the haplotype HLA-DRβ1*0405-DQβ1*0401 of HLA class II, there also exists a susceptibility region that includes the C3-2-11 microsatellite located between HLA-A and HLA-E genes in the HLA class I region [131]. However, no mutual association was found between HLA-DRB1*0405-DQB1*0401 and the C3-2-11 microsatellite region suggesting these are two distinct genetic susceptibility factors for AIP. Susceptibility conferred by HLA-DR*0405 in man is reproduced in

HLA-DR*0405 transgenic Ab0 NOD mice that develop spontaneous AIP closely mimicking human disease [113]. The association of AIP and the DRB1*0405 allele may be explained by linkage disequilibrium with promoter polymorphisms in nuclear factor kappa light polypeptide gene enhancer in B cells inhibitor-like 1 (NFκBI-L1), which may represent a true susceptibility allele as it has crucial roles in inflammation and immunity [131]. The HLA-DRB1*0405-DQB1*0401 haplotype is also linked with autoimmune type 1 diabetes in Japanese patients [132].

Susceptibility MHC alleles were not found in a study of 40 Korean patients with AIP, but it was demonstrated that the HLA DQB1*0302 allele showed a significant association with the

relapse of AIP [133], and amino acid sequencing identified a single-nucleotide substitution of aspartic acid to non-aspartic acid at position 57 of the DQβ1 residue [133]. HLA susceptibility haplotypes may alter antigen presentation to T cells, enhancing responses following antigen recognition and promoting development of autoimmunity.

Polymorphisms of alleles 110G and 110A/A of Fc-receptor-like 3 (FCRL3) gene, which belongs to the Fc-receptor-like family of genes that bear homology with classical Fcγ receptor genes, have also shown association with AIP in a study of 59 Japanese patients [134]. Although independently associated with AIP, no association was found between FCRL3-110 alleles and the HLA DRB1*0405-DQB1*0401 haplotype [134]. FCRL3 gene is located on chromosome 1q21 and encodes a glycoprotein of unknown function, but is suspected to play a role in immune regulation as it contains intracellular domain tyrosine-based activation and inhibition motifs [135]. The majority of FCRL3 is expressed in germinal-centre centrocytes that are the precursors of B cells. An effect on B cell development may explain the positive correlation between the number of polymorphisms of FCRL3 susceptibility alleles and serum I_gG_4 concentrations in patients with AIP [134]. FCRL3 is expressed on B cells, and single-nucleotide polymorphisms (SNP) within the FCRL3 gene are associated with susceptibility to rheumatoid arthritis, autoimmune thyroiditis and systemic lupus erythematosus, possibly linked to altered binding affinity of the transcription factor NF-κB [136]. FCRL3 may actually be a true susceptibility gene for AIP as it causes T_{reg} dysfunction that promotes loss of self-tolerance and onset of autoimmunity [137].

Genes encoding non-MHC proteins such as cytokines may also affect susceptibility to AIP. There is a lower relative risk of disease resulting from these non-MHC genes compared with the disease-associated MHC haplotypes. CTLA-4 is a key negative regulator of the T cell immune response. The G/G genotype of a CTLA-4 SNP at position +6230 increased susceptibility to AIP (OR 2.48) in a study of 59 Japanese patients with AIP [138]. The +6230A/A genotype was found to be associated with AIP resistance (OR 0.49) but was associated with an enhanced risk of relapse, as was the +49A/A genotype (OR 5.45 and 12.66, respectively) [138]. Serum soluble CTLA-4 levels were found to be significantly higher in patients with AIP but showed no correlation with +6230 alleles [138]. CTLA-4 49A polymorphisms and the -318C/+49A/CT60G haplotype increased susceptibility to AIP in Taiwanese patients [139]. CTLA-4 polymorphisms may induce susceptibility to AIP by causing loss of self-tolerance. Adenine to guanine polymorphism at position +49 of exon 1 of CTLA-4 (CTLA4 +49A/G) is also associated with increased susceptibility to autoimmune thyroiditis and type 1 diabetes [140].

Polymorphisms of TLR4 [141] and the TNF-α promoter gene [131] were shown to have no association with susceptibility to AIP in Japanese patients. Polymorphism of the TNF-α promoter -863A, however, was found to be associated with extrapancreatic disease including nephritis, lymphadenopathy, thyroiditis and hepatitis in Taiwanese patients with AIP [139].

Molecular Mimicry

Molecular mimicry, a mechanism by which pathogens can induce autoimmune disease, is the development of cross-reactivity to a self-peptide that may arise during the immune response to a foreign peptide. An allogeneic peptide-MHC complex may resemble a self-peptide-MHC complex, which can lead to cross-reactivity by lymphocytes. Although the cross-reactivity of lymphocytes with an array of antigens allows response to diverse pathogens, cross-reactivity with self-antigens is inappropriate and breaks down immune tolerance. AIP may arise from protracted or repeated exposure to indigenous etiologic agents that can break self-tolerance, by activating CD4+ T cells because of incomplete specificity, or the regulation of specificity, of T cell antigen receptors, leading to expansion of cytotoxic T cells and antigen-sensitised plasma cells that produce autoantibodies.

Helicobacter pylori (*H. pylori*) is strongly associated with peptic ulceration and is suggested to be a pathogenic trigger of AIP [142]. Gastric peptic ulcers infiltrated by abundant I_gG_4-bearing plasma cells occur more frequently in patients with AIP compared to non-diseased controls or patients with non-autoimmune CP [143, 144], and it has recently been proposed that AIP-related gastritis is added to the list of I_gG_4-related sclerosing diseases [145]. In considering the potential role of *H. pylori* as a trigger of molecular mimicry, it must be acknowledged that AIP-related gastric ulcers also occur in the absence of *H. pylori* [144, 145].

The role of *H. pylori* in causing AIP by molecular mimicry is supported by the significant homology that exists between human carbonic anhydrase type II and an important *H. pylori* survival enzyme called α-carbonic anhydrase (α-CA), with the binding motif of the AIP susceptibility allele HLA DRB1*0405 also being present in the homologous segment [146]. This suggests that *H. pylori* may trigger AIP in genetically predisposed individuals [146]. Direct bacterial infection of the pancreas by *H. pylori* as part of molecular mimicry is unlikely because *H. pylori* DNA is not detectable in the pancreas of patients with AIP [147].

Screening of serum specimens from 35 AIP patients identified a peptide called AIP1-7 bearing sequence homology to the *H. pylori* peptide plasminogen-binding protein (PBP) and also to the pancreatic acinar enzyme ubiquitin-protein ligase E3 component n-recognin 2 (UBR2) [52]. Anti-PBP antibodies were detected in nearly all screened patients, raising the possibility that molecular mimicry due to homology of URB2 with PBP drives acinar damage [52].

Mice treated with avirulent *Escherichia coli* for 8 weeks develop delayed onset AIP with lymphoplasmacytic infiltration and anti-CA, anti-LF and antinuclear autoantibodies. The authors of the aforementioned study speculated that host self-antigen(s) may act as molecular mimics of *Escherichia coli*, stimulating host immune response in this model [148]. Gastric *Helicobacter* species (not pylori) are also detected in most dogs [149] and may drive molecular mimicry during AIP in dogs.

Action of Corticosteroids in AIP

The clinical symptoms of AIP are readily relieved by steroid therapy in the majority of patients [50]. Corticosteroids significantly lower the relapse of AIP [150], as achieved by other immunosuppressants such as azathioprine and mycophenolate [151].

Corticosteroids inhibit antigen-specific antibodies, but the relative amounts of total I_gG_4 in human peripheral blood mononuclear cells can increase after steroid therapy [152]. The differential effect of corticosteroids on circulating specific and total I_g isotype formation is due to suppression of antigen-specific lymphocyte responses that does not reduce total I_gG_4 production. The number of pancreatic $I_gG_4^+$ plasma cells, however, is reduced by corticosteroids [153]. Such therapy also significantly decreases serum immune complex concentrations in AIP patients, most likely by inhibiting the classic complement pathway, as mannose-binding lectin levels are unaffected by corticosteroid therapy [56]. Corticosteroids may also reduce antigen presentation to lymphocytes in AIP, as this therapy significantly decreases the number of peripheral myeloid and CD123$^+$ plasmacytoid DC [91].

Although corticosteroids enhance differentiation of T_{regs} [154], the number of peripheral CD4$^+$CD25^{hi} T_{regs} in AIP patients treated with corticosteroids remains unaffected, but this may be related to the dosage used [91]. In vitro assays show corticosteroids reduce expression of ICAM-1 and E-selectin on human umbilical vein endothelial cells stimulated with LPS, suggesting corticosteroids attenuate immune cell recruitment during inflammation [155].

Corticosteroids support pancreatic function by correcting CFTR localization to the apical membrane of pancreatic duct cells, restoring HCO_3^- secretion, and by promoting the regeneration of acinar cells, improving digestive enzyme secretion [153]. While the above effects of corticosteroids are advantageous, there are many well-known disadvantages, including a lack of effect on some areas of fibrotic tissue injury damage and major side effects.

The search for greater understanding of the pathogenesis of AIP will help inform the development of new therapies, which can sensibly draw upon novel approaches under development for other autoimmune diseases. To maximise the potential for progress, the pancreatic community should be ready to adopt developments from both within and outside, whether in basic or clinical research. Advances are likely to occur faster if committed centres collaborate, including with industry, to explore applications of new molecules and trial new treatments.

Learning Points

1. Autoimmune pancreatitis (AIP) is typically recognised as a distinct form of chronic pancreatitis with key features of diffuse lymphoplasmacytic infiltration and chronic inflammatory sclerosis of the pancreas associated with hypergammaglobulinaemia.

2. The two predominant patterns of AIP are lymphoplasmacytic sclerosing pancreatitis (LPSP or type 1) with elevated tissue and serum expression of I_gG4 and idiopathic duct-centric pancreatitis (IDCP or type 2) with granulocyte epithelial lesions.

3. Both acinar and ductal cells are the targets of autoantibodies in AIP; islets are most likely attacked in more advanced disease through epitope spreading. Polyclonal lymphocyte populations suggest numerous antigenic epitopes are targeted.

4. I_gG_4 may be induced by IL-4, IL-13, IL-10 or TGF-β and may serve an anti-inflammatory role because of its ability to undergo Fab-arm exchange.

5. Pancreatic stellate cells may be transformed into myofibroblasts by the important regulatory cytokine TGF-β family or by IL-4, IL-6 and IL-13 produced by T_{regs} and B cells or by mediators secreted by infiltrating eosinophils.

6. Autoantigens identified in patients with AIP include lactoferrin, carbonic anhydrase types II and IV, SPINK-1 (PSTI), α-Fodrin, amylase α-2A and anti-HSP 10; those in rodents with AIP include lactoferrin, carbonic anhydrase type II, PSTI, amylase and PDIp. Pancreatic digestive enzymes have been identified as important autoantigens that may provide the basis for more sensitive and specific diagnostic tests.

7. Fibrosis usually occurs following exocrine damage in man; however, some rodents and dogs show replacement of destroyed parenchyma with adipose tissue.

8. Individual genotypes can increase susceptibility to AIP (HLA-DRβ1*0405-DQβ1*0401, C3-2-11 microsatellite, FCRL3 and CTLA-4 gene polymorphisms), relapse of AIP (HLA DQB1*0302, CTLA-4 polymorphism) or resistance to AIP (+6230A/A genotype of CTLA4).

9. Homology between carbonic anhydrase type II and α-carbonic anhydrase as well as between URB2 and PBP of humans and *H. pylori*, respectively, implicates *H. pylori* as a pathogen that may trigger AIP through molecular mimicry.

10. Steroid therapy inhibits antigen-specific antibodies, classic complement pathway activation and dendritic cells. Increasing understanding of AIP will assist efforts to develop new and improved therapies, more likely to accelerate through collaboration between committed centres and with industry.

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