REVIEW ARTICLE

Type 1 diabetes: immune pathology and novel therapeutic approaches

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Abstract

Type 1 diabetes (T1D) is characterized by the progressive destruction of insulin-producing beta cells in the pancreas. Despite improvements in insulin monitoring techniques, there remains no cure for T1D. Individuals with T1D require lifelong insulin therapy and some develop life-threatening complications. T1D is a complex, multifactorial, autoimmune condition. Understanding why people get T1D and how it progresses has advanced our knowledge of the disease and led to the discovery of specific targets that can be therapeutically manipulated to halt or reverse the course of T1D. Scientists investigating the potential of immunotherapy treatment for the treatment have recently had some encouraging results. Teplizumab, an anti-CD3 monoclonal antibody that has been approved by the FDA, delays the onset of clinical T1D in patients ≥ 8 years of age with preclinical T1D and improves beta cell function. Therapies targeting beta cell health, vitality, and function are now thought to be an essential component of successful combination therapy for T1D. The idea that the beta cells themselves may influence their own destruction during the development of T1D is a notion that has recently been gaining acceptance in the field. Researchers have recently made remarkable strides in beta cell replacement therapy and beta cell regeneration techniques. This review offers a detailed exploration of the pathophysiological mechanisms of T1D. It discusses the intricate interplay of factors leading to T1D development and the innovative approaches being explored to discover new treatments and a cure for the millions of people living with T1D worldwide.

Keywords Type 1 diabetes · Autoimmunity · Beta cells · Immunopathology

Physiological function of the pancreas

The pancreas is the organ which produces insulin, one of the main hormones that helps to regulate blood glucose levels. The pancreas is located behind the lower part of the stomach, in front of the spine. It measures about 15 cm in length and is divided into the head, body, and tail, with the head adjacent to the duodenum and the tail near to the spleen. It is vascularized by branches of the celiac and superior mesenteric arteries, with a microvasculature that supports and regulates beta cell functions, including insulin production [4]. Additionally, it is richly innervated by sympathetic and parasympathetic nerves [6]. The pancreas plays a part in both the endocrine system and the exocrine system. The endocrine system includes organs which produce hormones, which are delivered via the blood to help regulate our mood, growth, metabolism, and reproduction. In the pancreas, the endocrine component is organized into the Islets of Langerhans, and includes various hormone-producing cells such as alpha cells (production of glucagon), beta cells (insulin), delta cells (somatostatin), pancreatic polypeptide cells (pancreatic polypeptide), and epsilon cells (ghrelin), which are essential for blood glucose regulation and metabolic balance [7]. The exocrine system is comprised of glands which release substances such as sweat (to the skin), saliva (in the mouth) or, in the case of the pancreas, digestive enzymes such as amylase, lipase, and proteases which assist with carbohydrate, fat, and protein digestion.

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Susceptibility to T1D

A combination of genetic predisposition and environmental triggers determines an individual's susceptibility to develop T1D [8]. Specific genes, notably those in the human leukocyte antigen (HLA) complex class II, are strongly associated with the risk of developing T1D. In addition, overexpression of HLA class I is thought to predispose islet cells for recognition by immune cells such as CD8^{+} T cells. The occurrence of increased HLA class I expression on insulin-positive beta cells is a characteristic feature of both T1D and its pre-diabetic stages [9]. The upregulation of HLA class I in patients with T1D occurs prior to immune cell infiltration and the cause, although as yet unknown, is thought to be due to environmental factors [10]. There is a striking correlation between the levels of STAT1 measured in the beta cells of patients with T1D and HLA class I hyperexpression. STAT1 is elevated in beta cells soon after T1D diagnosis but its expression declines with disease duration, thereby correlating with a similar decline in HLA class I. It is possible that the two may be coordinately regulated or that increased production of HLA class I in beta cells occurs as a consequence of enhanced STAT1 expression. STAT1 is a critical protein involved in mediating antiviral responses to interferons, and its early upregulation in the progression of T1D would be expected to place beta cells in a heightened state of responsiveness to these cytokines [10]. The upregulation of HLA class I affects the immune system's ability to distinguish self from non-self, making individuals more prone to autoimmune reactions against their own beta cells. Epigenetic modifications (such as changes in DNA methylation and histone modifications) [11–13] can also be influenced by both genetic and environmental factors and may further contribute to the pathogenesis of T1D. Defects in antigen presentation by thymic cells contribute to the escape of autoreactive T cells from negative selection [14]. Regulatory T cells, which are crucial for maintaining self-tolerance and suppressing autoimmune responses, may also be deficient or defective in individuals with T1D. Genetic and cellular studies in patients with T1D point to an imbalance between effector T cells and regulatory T cells as a potential driver of the disease [15–20]. However, the exact role of regulatory T cells in the progression of T1D remains uncertain [21, 22].

It is believed that environmental factors can also exacerbate the susceptibility to T1D. Epidemiological studies showing variations in the incidence of T1D both seasonally and geographically, support this hypothesis [23]. Viral triggers, for example, are known to cause the immune system to become overactive or misdirected, leading to an autoimmune attack on the beta cells [24–27]. Viral infections can also disrupt the thymic selection process. Other environmental factors, such as diet, early childhood nutrition, and exposure to toxins, can also influence the course of T1D. Diet and exposure to environmental toxins and pollutants may also contribute to the disruption of immune tolerance, further amplifying the autoimmune response.

The combination of genetic susceptibility, immune system dysregulation, and environmental triggers, results in a breakdown in self-tolerance, allowing autoreactive T cells to evade elimination. The resulting autoimmune destruction of pancreatic beta cells, is a defining characteristic of T1D.

The initiation of T1D

T1D is thought to start in a few isolated islets within the pancreas. Insulitis is the process of inflammation in which cells of the immune system invade the pancreas and accumulate in proximity to, and within, pancreatic islets [28]. In rodents, this process occurs intensively as the disease progresses until most islets display extensive infiltration. However, this feature of intense insulitis is largely absent in the human pancreas. Studies from pre-diabetic pancreata have shown that the damage is initially self-limiting and progresses in a relapsing/remitting pattern within a marginal number of islets, and therefore, does not initially affect glycemic control. However, the autoimmune response progresses swiftly within a given islet and the eventual destruction of beta cells (following the initial targeting of self-antigens), leads to the release of danger signals that amplify the immune response. A critical point is reached at an as yet unpredictable point of time, when the situation becomes uncontrollable and the majority of islets are affected, leading to clinical manifestation of the disease.

In T1D, the antigens which are targeted by the patient's own immune system include proteins expressed by beta cells, including insulin, glutamic acid decarboxylase (GAD), islet-specific glucose 6 phosphatase catalytic subunit-related protein (IGRP), and insulinoma-associated protein 2 (IA-2). It is possible that the autoimmune response may be initiated by molecular mimicry, where external pathogens display antigens that closely resemble self-antigens, causing cross-reactivity. The immune system may react to these pathogen-derived antigens and inadvertently attack beta-cell antigens, which sets off an autoimmune inflammatory cascade [29]. Ordinarily, autoreactive cells are either eradicated or strictly regulated to prevent the development of autoimmunity. However, a failure in regulatory mechanisms occurs during T1D development, which leads to the activation of autoreactive T cells that mistakenly target beta-cell antigens [30]. The immune system then initiates insulitis, the immune

system's way of trying to eliminate the perceived threat. However, this process inadvertently causes collateral damage to healthy tissues within the pancreas. Autoreactive T cells (the majority of these being CD8^{+}) recognize and attack beta cells in the pancreas leading to their destruction and subsequent insulin deficiency.

Immunopathology at different stages of T1D development

Overt hyperglycemia, metabolic imbalance, and clinical symptomatology form the basis of the T1D diagnosis. However, the critical immunological events leading to islet cell damage occur prior to diagnosis, which is one of the many difficulties of studying T1D pathology in humans. In addition, access to human pancreatic samples (especially samples pre-diagnosis) is difficult and researchers often have to study the immunopathology of human T1D using cells from peripheral blood rather than from within the pancreas. Sharing of postmortem pancreatic material from patients with recent-onset disease has given researchers a chance to increase our knowledge about the pathology of T1D in humans.

Earlier diagnosis of T1D in first- or second-degree relatives of individuals with T1D has also enabled further research into the underlying mechanisms of T1D pathology and led to the design of T1D prevention clinical trials, with enrollment criteria and end points based on specific disease stages [31–33]. Recent multinational studies have included both people at high risk of developing T1D and those with recent onset disease.

The results of these studies have shown that T1D progresses sequentially in a variable but predictable manner through distinct identifiable stages prior to the onset of symptoms (Table 1) [34]. The rate of progression from onset of beta cell autoimmunity to glucose intolerance and then to symptomatic disease can last from months to decades (Fig. 1) [35].

Immunopathology during Stage 1 of T1D development (prediabetes)

Proteins and peptides such as insulin, proinsulin, GAD65, IA-2, and ZnT8 have been identified as target antigens in T1D and autoantibodies secreted by autoreactive B cells which are specific for these islet antigens can be detected in the serum of peripheral blood [36]. Children who develop ≥ 2 of these autoantibodies have an increased likelihood of developing clinical T1D later in life, compared with children who have fewer autoantibodies [37–39]. In this stage of T1D development, ≥ 2 autoantibodies directed towards these peptides can be detected but the beta cells are still able to produce insulin and control blood sugar levels.

Why do some people produce the autoantibodies that precede the development of T1D? It is very difficult to determine which of the factors that are present in this early stage of T1D are triggers or accelerators of the autoimmune process, and which factors are caused by the disease process itself. There is some evidence to suggest that abnormal lipid metabolism may precede seroconversion to autoantibody positivity [40, 41]. Furthermore, in the TRIGR study, Ludvigsson et al. showed that increased glucose concentration in peripheral blood was related to the initial production of islet cell autoantibody. This beta cell stress hypothesis [42] suggests that an increased amount of sugar in peripheral circulation will place a high demand on insulin secretion, leading to beta cell stress that contributes to a rapid progression to symptomatic T1D [43–45]. The progression rate of T1D at this very early stage of disease can be influenced by age at the time of seroconversion and high titers of insulin autoantibodies [46].

Table 1 The stages of T1D development

	Stage 1	Stage 2	Stage 3
Immunopathology	• Autoantibodies • No evidence for beta cell loss	• Autoantibodies • CD4^{+} and CD8^{+} T cells contribute to autoimmunity • Some islets are lost	• A loss of beta cells, and acinar cells • Immune cell infiltration • Substantial damage to islets
Clinical relevance	• Normoglycemia • No clinical symptoms • Circulating autoantibodies indicate an increased likelihood of developing clinical T1D • This stage can last from weeks to decades	• Dysglycemia • No clinical symptoms • Biomarkers, including autoantibodies, which predict transition to Stage 3	• Dysglycemia • Clinically symptomatic disease
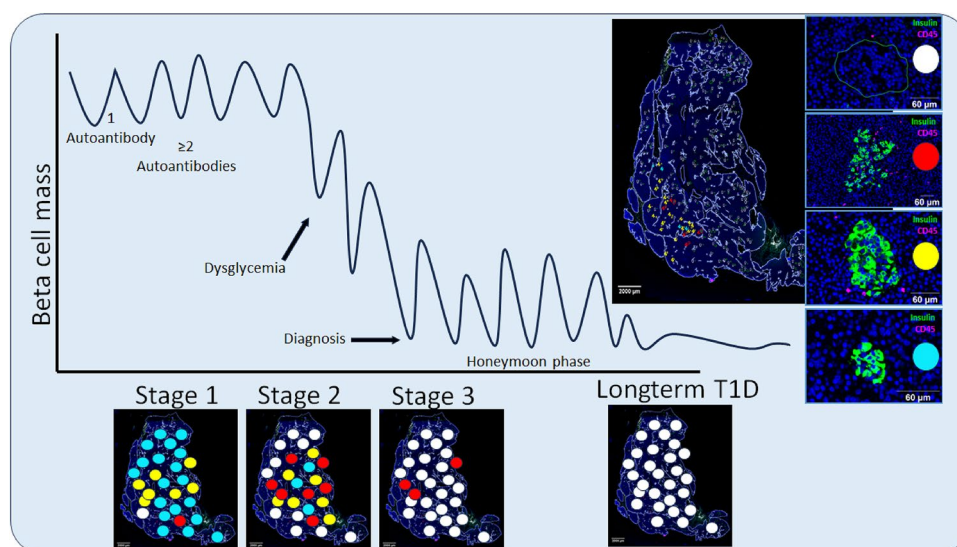
Fig. 1 Inflammation in the pancreas at different stages of T1D. This human, formalin-fixed, paraffin-embedded section from a donor with T1D (#6247) from the Network for Pancreatic Organ Donors with Diabetes (nPOD) was stained with whole-slide immunofluorescence for insulin (green), CD45 (magenta) and Hoechst as the nuclei stain (blue). Insulin-deficient islets (IDI) were identified in a consecutive slide stained for glucagon, and a pixel classifier was trained to identify IDI based on the glucagon signal. The map with IDI was cre-ated and then transferred to the insulin-stained slide showed in the picture. Insulin-containing islets (ICI) were manually added based on the insulin signal. ICI were classified depending on the amount of CD45+ cell infiltration into: ≤ 3 cells (no infiltration, blue), > 3 but < 15 cells (low infiltration, yellow), ≥ 15 cells (high infiltration, red), and IDI (white). The images at the bottom of the Figure are a visual representation of the process of beta cell destruction at different stages of T1D development

Pancreas volume declines early in the course of T1D progression [47–55]. The reason for the smaller pancreas is not known but it is thought that changes in the exocrine pancreas may be important in T1D pathogenesis and both reduced acinar cell number and evidence of fibrosis have been reported [55–57]. Although the mechanism is not known, it is possible that the process affecting the exocrine compartment ultimately leads to beta cell loss [58, 59]. Indeed, reduced pancreatic function (fecal elastase) and pancreatic exocrine insufficiency have been reported in some individuals with T1D [56, 60].

Immunopathology during Stage 2 of T1D development (prediabetes)

During this stage of T1D development some initial islet destruction is present along with signs of beta cell autoimmunity and some associated dysglycemia, but there are no other clinical symptoms of T1D.

The nonpathogenic autoantibodies are viewed as biomarkers of the autoimmune process, with the presence of multiple autoantibodies being predictive of the transition from Stage 2 to Stage 3 disease [37, 61, 62]. CD4+ and CD8+ T cells can be detected and isolated from islets and pancreatic lymph nodes of patients with T1D and these cells and their associated cloned cell lines have been shown

to react to a range of islet antigens and post-translationally modified peptides or neoantigens [63–65].

Studies from autopsy pancreas samples, from patients who died soon after the diagnosis of T1D, have revealed that the principal cells involved in the destructive process in the islets are likely to be CD8+ cytotoxic T cells [66–69]. However, other immune cells such as macrophages and CD20+ B cells are also found to infiltrate the islets. At this stage the progression of T1D occurs in a lobular manner across the pancreas, which is indicative of a process that includes local as well as systemic drivers (Fig. 2) [70–73].

Immunopathology during Stage 3 of T1D development

By Stage 3, when T1D is often clinically diagnosed, autoimmune damage has occurred throughout the pancreas. Signs and symptoms of T1D, which can range from diabetic ketoacidosis to modest hyperglycemia, are usually present, and insulin therapy can be initiated. Although there will have been a loss of both beta cells and acinar cells, some beta cells are still present and functional. Beta cells from many patients with longstanding T1D still secrete small amounts of insulin [55]. However, by the time of clinical presentation most of the remaining islets are insulin-negative with only occasional rare islets present which contain functional beta

Fig. 2 T1D occurs in a lobular manner. This image shows a whole pancreatic tissue section from a donor with T1D. There are some remaining insulin-producing cells (green) and many alpha cells (red). The progression of T1D occurs in a lobular manner across the pancreas
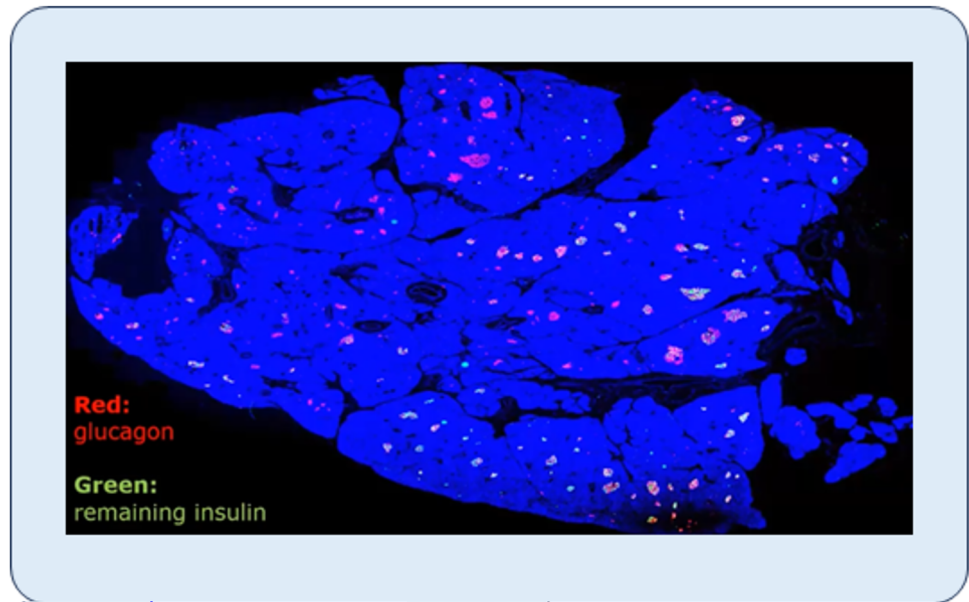
cells. It is estimated that~60–90% of beta cell mass has been lost by this time [74]. Immune cell infiltration can be seen both in the islets and the exocrine pancreas [69].

A "honeymoon phase" often occurs soon after diagnosis, during which patients with T1D experience a period of partial remission in which they have reduced insulin requirements [75–80]. A longer remission period is associated with better residual beta cell function and a reduced risk of acute and long-term T1D complications [75–78, 81] It is possible that novel treatments could be utilized to promote, extend and enhance the remission period by targeting the subset of immune cells which facilitate a naturally occurring mechanism of protection during this time [82]. Treatment during this therapeutic window may further protect the remaining beta cells and reduce long-term complications.

Factors involved in the progression of T1D

The conditions that drive the progression of T1D from autoantibody positivity to islet cell destruction are unclear but are likely to be multifactorial in nature. Metabolomics studies suggest that metabolic dysregulation precedes the clinical presentation of T1D [83–85]. In particular, specific sugar derivatives and microbial metabolites differ between rapid and slow progressors to T1D at this stage in disease development [44]. The Finnish T1D Prediction and Prevention study (DIPP) has given an insight into the mechanisms that may underlie progression to clinical disease. In this study, the participants, who had increased HLA susceptibility to T1D, were prospectively observed for various islet cell antibodies from the age of 3 months to 15 years of age or to the diagnosis of T1D [44, 86]. Increasing levels of

sugar derivatives in the peripheral circulation were found to contribute to accelerated progression to T1D [44].

Studies have also shown that dysregulated microbial metabolites in the gut microbiota are associated with the development of T1D [87–92]. Microbiota-derived indole metabolites promote intestinal homeostasis and are known for their immunomodulatory signaling activity [88, 93, 94]. Microbiota-derived metabolite 3-indole-acetic acid was found to be upregulated in children who rapidly progressed to T1D following the appearance of autoantibodies [44]. An increase in such tryptophan catabolites suggests a shift from saccharolytic to proteolytic fermentation in the gut [44, 89]. This shift in microbial fermentation could dysregulate microbial tryptophan catabolism and exacerbate the development of T1D.

The growing prevalence of overweight and obese children with T1D has led to much interest in the coexistence of these conditions. Higher body mass index (BMI) in children is associated with preserved C-peptide at T1D onset [95–97], however, it does not protect from a rapid decrease in beta cell function in these patients. Among a pooled European cohort of teens with T1D over 1 year of follow-up [98], higher BMI at diagnosis was associated with a greater rate of fasting C-peptide decrease, thus more rapid disease progression. The significant decrease in residual beta cell function in children with the highest BMI may be the result of a negative impact of elevated levels of inflammatory cytokines on pancreatic beta cells in the course of obesity [95–97].

Persistent infection by pathogens that can evade or suppress the immune system and establish a long-term infection may also drive the progression of autoimmunity in T1D [99]. In addition to molecular mimicry, persistent infections can induce polyclonal B cell activation, leading to the production

of autoantibodies [100]. Furthermore, persistent infections can lead to the activation of toll-like receptors which can trigger the production of pro-inflammatory cytokines and chemokines, leading to chronic inflammation and tissue damage [101].

Heterogeneity of autoimmunity in T1D and T2D

The extent and timing of beta cell loss varies significantly with age. Individuals in whom T1D develops early in life (before the age of 7 years) lose beta cells more quickly/more extensively than those who receive a diagnosis after the age of 7 years of age [69, 102, 103]. The existence of distinct profiles of insulitis, which are associated with very different rates of beta cell loss [68, 69], or intrinsic age-related differences in the function of the immune system may contribute to these age-related differences.

The American Diabetes Association classification of type 2 diabetes (T2D) is "a non-autoimmune progressive loss of adequate beta cell insulin secretion, frequently on the background of insulin resistance and metabolic syndrome" [104]. However, many patients who are initially diagnosed with T2D, may also have undiagnosed beta cell autoimmunity. The prevalence of T2D is increasing and if 10% of these patients are positive for islet autoantibodies then testing for them during the diagnostic assessment will be of benefit to many patients [105]. Such assessments may reveal patients who are likely to have a higher rate of progression to insulin requirement and, may therefore, help to personalize treatment plans for these patients [106].

Individuals with T1D are prone to develop diabetic ketoacidosis (DKA) which is a serious metabolic complication [107]. Certain individuals with T2D also develop DKA without precipitating factors, (referred to as ketosis-prone T2D [KPD]). Because KPD often presents with acute hyperglycemia and DKA, just like acute-onset T1D, it is very important to differentiate between these two types of diabetes at the onset. Unprovoked KPD is characterized by male predominance, onset at a young age, obesity, sudden onset of DKA without precipitating factors, and a transient decrease in insulin secretion capacity, which can be recovered with temporary intensive insulin therapy. It is possible that the mechanism of transiently impaired insulin secretion in these cases is associated with glucotoxicity or lipotoxicity.

The diagnostic criteria for slowly progressive T1D (slowly progressive insulin dependent diabetes mellitus; SPIDDM) have recently been revised by the Committee on T1D of the Japan Diabetes Society [108]. All of the following three criteria must be met: (1) presence of anti-islet autoantibodies at some point in time during the disease course; (2) absence of ketosis or ketoacidosis at diagnosis with no immediate

requirement for insulin treatment; and (3) gradual decrease of insulin secretion over time. The phenotype of progressive beta cell dysfunction in patients with SPIDDM which occurs at > 30 years of age is similar to that of latent autoimmune diabetes of the adult (LADA), which is generally defined by diagnosis at > 30 years of age, presence of circulating islet autoantibodies, and lack of insulin requirement for 6 months after diagnosis. However LADA is a concept that includes both insulin-dependent and non-insulin-dependent states with anti-islet autoantibody positivity [109].

Patients with LADA need insulin earlier during disease progression and are likely to respond poorly to oral anti-diabetic mediation. However, these patients could respond favorably to immunomodulator therapy. Anti-inflammatory and immunomodulatory therapies have also proven effective in improving the metabolic profile of many patients with T2D, by disrupting autoimmune processes and inhibiting the decline of beta cell function [105, 110]. The presence of self-reactive T cells in autoantibody-negative patients with T2D also identifies an autoimmune process that is associated with metabolic dysregulation [111]. Further research is needed to understand the complex immune interactions relevant to T2D and specific immunomodulation strategies to treat these patients. However, in the meantime it is important to remember that lifestyle changes also repress inflammation and autoimmune reactions, and are therefore, a major tool to help decrease beta cell stress.

Another subset of T1D, fulminant T1D (FT1D), is characterized by extremely rapid pancreatic beta cell destruction with rapid progression of hyperglycemia and ketoacidosis. It was initially classified as idiopathic T1D due to the absence of autoimmune markers. However, subsequent studies showed evidence for the involvement of autoimmunity in the rapid beta cell loss in FT1D pathogenesis [112]. Since the introduction of immune checkpoint inhibitors for the treatment of cancer, several cases of FT1D have been reported. However, it is unclear if FT1D and immune checkpoint inhibitor-induced diabetes share the same pathology. In FT1D, beta cells are destroyed very rapidly and are almost absent at diagnosis, compared to the relatively slow destruction that takes place in conventional acute-onset T1D, which can occur over several months/years. The speed of disease development in patients with immune checkpoint inhibitor-related FT1D is placed between conventional acute-onset T1D and FT1D in terms of timing of beta cell destruction, with destruction happening within the first few weeks. Regarding the trigger for disease initiation, in immune checkpoint inhibitor-related FT1D blocking of the PD-1/PD-1 ligand pathway is the known trigger. In contrast, viral infection has been suggested as a potential trigger in patients with FT1D, with common cold-like symptoms frequently observed prior to symptom-onset and IGRP-specific CD8 + T cells are thought to significantly contribute to the

pathogenesis [113]. It is currently unknown whether immune checkpoint inhibitor molecules are involved in the destruction of beta cells in other subsets of T1D [114, 115].

While the fundamental pathophysiological process remains consistent across different populations, there are notable variations in clinical presentation and genetic predisposition between Eastern and Western countries. Understanding these differences is crucial for tailoring effective management strategies and advancing our global approach to the treatment of T1D. The frequency of T1D in Japan and most East Asian countries is very low and typically less than one-tenth that seen in white populations of European descent. In contrast, most people with FT1D are from East Asian countries and only a limited number of cases have been reported in white European populations. [116–120]

Western populations: in Western populations, extensive research has established a strong association between T1D and specific HLA class II alleles. Notably, HLA-DR3-DQ2 and HLA-DR4-DQ8 haplotypes are critical risk factors. These alleles play a central role in immune recognition and activation, contributing to the autoimmune attack on pancreatic beta cells.

Eastern populations: contrastingly, Eastern populations exhibit distinct genetic profiles. A recent genome-wide association study conducted by the Japan Diabetes Society focused on Japanese patients with FT1D. The study not only confirmed the strong association with Class II HLA genes but also revealed a novel genetic locus: the CSAD/lnc-ITGB7-1 region on chromosome 12. Interestingly, these SNPs did not show any linkage to autoimmune T1D, suggesting a distinct pathogenesis in FT1D.

Despite genetic and environmental differences, the core pathophysiological process—autoimmune destruction of beta cells—remains consistent. Autoreactive T cells play a central role in both Eastern and Western T1D. Collaborative efforts between Eastern and Western researchers can enhance our understanding of T1D. Comparative studies may reveal additional genetic loci and provide insights into shared mechanisms.

Do beta cells play an active role in the development of T1D?

It had previously been thought that during the development of T1D, the beta cell was an "innocent victim" of an unprovoked "attack" by an overactive or under-regulated immune system. However, the idea that the beta cells themselves may influence their own destruction during the development of

T1D is a notion that has recently been gaining acceptance in the field [121].

Beta cells are certainly the primary targets of the immune system in the context of T1D. However, the extent to which they contribute to their own targeting, either by facilitating or resisting it, is not fully understood. Pre-diabetes typically lasts several years before clinical manifestation and during this time, beta cells often display signs of stress and malfunction even before they become the direct targets of the immune response [122, 123]. It is now hypothesized that the progression towards T1D is partly due to the highly secretory nature of the beta cells and a well-vascularized environment, which make them more susceptible to changes in the cellular environment [70, 124–126]. Paradigm-shifting research has suggested that beta cells may actively "reveal" themselves by presenting their own antigens when they experience cellular stress [121]. There are likely multiple mechanisms at play including beta cell dysfunction; altered interactions between beta cells and immune cells; and increased immunogenicity. These mechanisms may also be amplified by internal factors such as endoplasmic reticulum stress or external stress from viral infections and inflammatory cytokines.

Heightened expression of HLA class I molecules on the surface of beta cells is largely attributed to inflammatory stress within the cellular environment [127, 128]. The consequence of this hyperexpression is believed to be an enhanced visibility of these beta cells to CD8^{+} T cells infiltrating the islets. These T cells identify and destroy beta cells that display surface class I molecules presenting autoantigenic epitopes [129] essentially "revealing" themselves as targets for the immune system. Islets from different regions of the pancreas are differentially affected, creating a multifocal pattern [71]. The cause of this lobularity remains unclear, although viral infections, the inflammatory milieu in the pancreas, innervation, and the intrinsic etiology are all thought to play a role.

In situations where the stress on beta cells is heightened and the demand for insulin throughout the body surpasses the ability of the cells to secrete it, the system responsible for processing proinsulin (an inactive precursor of insulin) can become overloaded. An increase in the expression of proinsulin relative to insulin has been observed in beta cells in the islets of donors with T1D (both early in the development of T1D and in long-standing T1D) [130, 131]. The accumulation of proinsulin within beta cells may be due to various factors, including endoplasmic reticulum stress and impaired processing.

These new insights into T1D pathology underscore the intricate relationship between beta cell dysfunction, immune inflammation, and the role of beta cells themselves in triggering the autoimmune response. The limited long-term efficacy of immune intervention therapies and the continued presence of beta cells even after diagnosis and progression

of T1D, suggests that both beta cells and the immune system, play an active role in the development of T1D and that both will need to be targeted to provide an effective therapy. Therapeutic strategies that aim to prevent or treat T1D at its earliest stages by preserving beta cell function, are therefore, currently undergoing rigorous assessment.

Novel therapeutic approaches for the treatment of T1D

By the time that we detect T1D, it is normally too late to prevent it, so we need to learn to identify which individuals are at risk, watch out for very early signals, and treat the underlying immunological mechanisms. The complexity of the pathways that lead to inflammation in T1D and the number of mechanisms that are involved means that it has been difficult to find a suitable method to treat all individuals. Currently available therapies include daily insulin injections to maintain blood glucose levels, suppressive immunotherapy to decrease the symptoms associated with autoimmunity, and islet transplantation to replace destroyed beta cells and restore insulin production. Lifestyle modifications are also recommended to increase sensitivity to insulin, control blood sugar levels and lower the risk of heart disease and nerve damage. An immune-targeted therapy that has recently been shown to have efficacy for the treatment of T1D is the T cell-specific anti-CD3 antibody teplizumab, which delayed disease onset in participants at high risk for T1D in the TrialNet 10 study [5, 132, 133]. The mechanisms of action of other T1D therapies that are being studied in clinical trials are discussed in Table 2.

Several therapies currently in development aim to boost the regulatory T cell population in patients with T1D [145] and other potential future therapies include anti-IL21, conversion of alpha cells to beta cells, GLP-1 receptor agonists, calcium channel blockers, such as verapamil and low-dose anti-thymocyte globulin (ATG). The treatment strategy will differ depending on the stage/severity of disease and can include treatment before the development of autoimmunity to islet autoantigens (primary prevention); after the development of humoral or metabolic markers of high risk of progression to diabetes (secondary prevention); maintenance of residual beta-cell function after the onset of diabetes (tertiary prevention), and/or islet cell transplantation (Table 3).

Primary prevention

Asymptomatic children and adolescents at high risk for T1D according to genetic predisposition (a positive family history or by the occurrence of known genes associated to T1D) can receive primary prevention strategies.

Such measures can include changes to diet or the addition of physical exercise to prevent childhood obesity and vaccination of children against infectious diseases [2].

The US FDA has also recently approved the use of teplizumab for the treatment of T1D. In a clinical trial, teplizumab delayed T1D by an average of three years in people who were at high risk of developing the condition [5]. In the United States, teplizumab can now be prescribed to people who are at high risk of developing T1D. There have also been encouraging results with the use of Vitamin D in primary prevention studies of T1D. However, such data have not been confirmed in larger trials. Studies are also currently underway with (amongst others) oral insulin, GAD, GAD plus vitamin D3, or drugs that regulate T cells (e.g. abatacept [CTLA-4 Ig]).

Secondary and tertiary prevention

Most prevention studies are tertiary in nature (conducted in children, adolescents and adults with newly diagnosed T1D) with the aim of prolonging the remission phase. Tertiary prevention studies can also provide important information on the pathophysiology of T1D.

Studies investigating treatment with autoantigens (alone or in combination) or with monoclonal antibodies (teplizumab, otelixizumab, rituximab, abatacept) have shown good clinical results including transient preservation of C-peptide and brief metabolic improvement. However, beta cell activity tends to decline after the initial phase of treatment and patients often become dependent on exogenous insulin administration [2].

Cardiovascular disease, is an established cause of premature death among patients with T1D and insulin use is associated with increased risk of weight gain, which is a known risk factor for cardiovascular disease. Medications that can improve glycemic control while reducing insulin requirements and weight gain may therefore be promising adjunctive treatments for T1D. While glucagon-like peptide 1 (GLP-1) receptor agonists are not approved for the treatment of T1D, long-acting GLP-1 medications are commonly prescribed off label in clinical practice. For example, liraglutide has been used as an add-on therapy to insulin and despite the limited number of patients and varying study durations in the clinical trials, results are relatively consistent across studies [3].

Advances in islet cell transplantation

Whole pancreas transplants can be successfully performed with relatively high graft survival rates. Islet cell transplantation is therefore a potential long-term therapy for patients with T1D. However, there are limited

Table 2 Mechanisms of action for different approaches for the treatment of T1D

Treatment		Aim of treatment	Mechanism of action
Insulin [134]	The main treatment for T1D. Given in daily injections or via an insulin pump	• Replaces insulin	• Direct replacement of insulin to reduce blood glucose levels
Lifestyle modifications [135]	Suggested lifestyle modifications include eating a healthy balanced diet, keeping active and maintaining a healthy weight	• Increases sensitivity to insulin • Controls blood sugar levels • Lowers the risk of heart disease and nerve damage	• Adipose tissue increases production of TNF-α which contributes to insulin resistance in some patients with T1D, so reducing the amount of adipose tissue through diet and exercise helps to increase sensitivity to insulin • Regular exercise increases the secretion of anti-inflammatory cytokines and reduces the production of leptin which is associated with CRP • Physical activity improves endothelial function
Islet cell transplant [136]	Extraction of islet cells from the pancreas of a deceased donor and implantation in the liver of someone with T1D. This treatment is for people with T1D who have experienced ≥ 2 severe hypos within the last 2 years, and have impaired awareness of hypoglycemia. Islet transplants involve a small but increased risk of certain cancers, severe infections and other side effects related to the immunosuppressive medication that will need to be taken to prevent graft rejection	• Replaces the lost beta cell mass and restores insulin secretion capacity	• Once implanted, the beta cells begin to make and release insulin, this reduces blood glucose levels
Teplizumab [5, 132, 133]	A humanized monoclonal antibody to CD3 on T cells approved as a treatment to delay the onset of clinical T1D (Stage 3) in patients ≥ 8 years with preclinical (Stage 2) disease	• Preserves endogenous insulin secretion	• Preservation of beta cells • Inhibits T cell activation through steric inhibition of antigen recognition • It may act as a partial agonist at the TCR, increasing the number of exhausted T cells. These exhausted T cells are unable to contribute to further beta cell destruction • The regulatory T cell population may be expanded leading to the re-establishment of immune tolerance
Golimumab [137]	A humanized monoclonal antibody, specific for TNF alpha. Currently in clinical trials	• Preserves endogenous insulin secretion	• Preservation of beta cells • The inflammatory process, initiated and mediated by TNF alpha is inhibited
Baricitinib [138]	A tyrosine kinase inhibitor. Currently in clinical trials	• Preserves endogenous insulin secretion	• Preservation of beta cells • Inhibits the effect of pro-inflammatory cytokines • Reduces immune-mediated pancreatic beta cell destruction

Table 2 (continued)

Treatment	Aim of treatment	Mechanism of action
Frexalimab [139]	• Preserves endogenous insulin secretion	• Preservation of beta cells • Communication between T cells and B cells is disrupted • Reduces both the cellular and the humoral immune response • Reduces immune-mediated pancreatic beta cell destruction
Anti-IL21 [140]	• Preserves endogenous insulin secretion	• Preservation of beta cells • Blocks IL–21 from promoting trafficking of CD8 + T cells from lymph nodes and the exocrine pancreas to the pancreatic islets
Alpha-to-beta cell trans-differentiation [141]	• Replaces the lost beta cell mass and restores insulin secretion capacity	• It is hoped that viral gene therapy can be used to drive the expression of pdx1 and MafA in alpha cells, to transform them into functional beta cells
GLP-1 receptor agonists (liraglutide) [140, 142]	• Preserves endogenous insulin secretion	• Preservation of beta cells • Potential immune-modulatory and anti-inflammatory effects
Verapamil [143]	• Preserves endogenous insulin secretion	• Preservation of beta cells • Reduces pancreatic beta cell apoptosis during glucotoxicity-induced beta cell death
Low-dose anti-thymocyte globulin (ATG) [144]	• Preserves endogenous insulin secretion	• Preservation of beta cells • Possible mechanisms include T-cell clearance from the circulation, a modulation of T-cell activation, and an increase in the number/activity of regulatory T cells

Treatment column descriptions:

Frexalimab [139]: A monoclonal antibody against the CD40-Ligand on the surface of activated T-cells. Currently in clinical trials

Anti-IL21 [140]: A promising candidate for immunotherapy in T1D. Currently in clinical trials

Alpha-to-beta cell trans-differentiation [141]: Several attempts have been made to reprogram alpha cells into insulin-producing beta cells ex vivo and in vivo. Translation of this therapeutic gene strategy to treat T1D in humans may be possible via the noninvasive procedure endoscopic retrograde cholangiopancreatography (ERCP)

GLP-1 receptor agonists (liraglutide) [140, 142]: Initially developed for treating T2D. They could also be used as a novel intervention to modify the disease course and delay the onset of T1D. Currently in clinical trials

Verapamil [143]: A calcium channel blocker used in hypertension therapy. Currently in clinical trials

Low-dose anti-thymocyte globulin (ATG) [144]: A long-approved immunosuppressive product, containing cytotoxic antibodies against a large variety of antigens, which are predominantly expressed on human T cells. Currently in clinical trials

Table 3 Novel therapeutic approaches for the treatment of T1D

	Population	Potential strategies
Primary prevention	Asymptomatic children and adolescents at high risk for T1D according to genetic predisposition: Positive family history or occurrence of known genes associated with T1D	• Changes to diet or the addition of physical exercise to prevent childhood obesity • Vaccination against infectious diseases • Vitamin D3, oral insulin, GAD, GAD plus vitamin D3, or drugs that regulate T cells (e.g. abatacept [CTLA-4 Ig]) • GLP-1 receptor agonists
Secondary and tertiary prevention	Children, adolescents and adults with newly diagnosed T1D	• Autoantigens (alone or in combination) or with monoclonal antibodies (teplizumab, otelixizumab, rituximab, abatacept) • GLP-1 receptor agonists • Teplizumab treatment
Islet cell transplantation	Adults (> 18 years) who have had T1D for ≥ 5 years and who continue to have hypoglycemic unawareness despite optimal insulin therapy	• Whole pancreas transplants • Stem cell-derived beta cell transplants • Engineered devices containing islets/islet cells plus molecules/gels to support their function • Minimal long-term treatment with immunosuppressants

numbers of eligible donors [1] and long-term treatment with immunosuppressants, (to protect the graft from host rejection) can lead to severe side effects.

The use of stem cell-derived beta cell transplantation has recently received considerable focus. However, the ischemic conditions of the transplant site and immune rejection, (which destroys approximately half of the islets one-week post-transplantation) are still problems that need to be overcome. Advances in biomedical engineering have led to the development of novel devices which can be used to encapsulate and protect islets and islet cells [1]. These devices can also contain molecules/gels to support the function of the islet following transplantation. In addition, devices have also been developed to enhance the vascularization of the implant as well as to protect islets from the host's immune system. The current goal of islet replacement therapy is to find a regimen that reduces the treatment burden of immune modulation while maximizing the efficacy of islet replacement therapy. Finding the ideal strategy will require a delicate balancing act and it is unlikely that a single solution alone will protect the transplanted cells and enhance their functionality. Scientists will also need to further identify the developmental pathways that drive the differentiation of stem cells into insulin-producing cells, thus providing an endless source of cells.

Conclusion

Understanding why people get T1D and how it progresses has advanced our knowledge of the disease and led to the discovery of specific targets that can be manipulated to change the lives of the millions of people who are living with T1D worldwide. Recent advances in the treatment of T1D include immunotherapies targeting T cells and the development of innovative technologies to enable islet cell transfer to be an effective and well-tolerated treatment. Hopefully, future research will lead to strategies to not only treat T1D, but also to prevent and reverse it.

Declarations

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