Role of Immune Responses in the Onset and Progression of Type 1 Diabetes: Mechanisms, Mediators, and Therapeutic Prospects

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ABSTRACT

Type 1 diabetes (T1D) is a chronic autoimmune disorder that involves autoreactive T cells, which target and destroy the insulin-producing beta cells of the pancreas. Even though there are advancements in insulin therapy and glucose monitoring, there is no particular cure for T1D, and it continues to be a potential public health problem globally. The onset of the disease is caused by genetic factors like human leukocyte antigen class II polymorphisms and environmental factors like viral infections, childhood microbiome disruption, and gut permeability. The immune response includes innate and adaptive in T1D with crucial contributors like dendritic cells, macrophages, natural killer cells, inflammatory cytokines, CD4+ and CD8+ T cells, and autoantibody-producing B cells. Chronic islet inflammation, known as insulitis, plays a significant role in disease progression. Autoantibodies are identified as the critical biomarkers for early detection of disease. Even though potential therapies like antigen-specific tolerance approaches, immune checkpoint agonists, and monoclonal antibodies like teplizumab have shown positive results, the long-term benefit remains limited. Stem-cell-based and immune cell therapies aim to restore beta cell functioning and immune tolerance but come with challenges like graft rejection and immature beta cell differentiation. Mixed strategies like stem cell therapies, immunosuppressive drugs, and gene editing should be used in treating T1D. However, a significant part of the focus should be on addressing the underlying causes of this autoimmune disorder to achieve a positive result.

Keywords: Type 1 diabetes, Autoimmune disorder, Insulitis, Immune modulation, Beta cell destruction

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Introduction

Type 1 diabetes (T1D) is an autoimmune condition that occurs when the T cells of the immune system attack and destroy the beta cells of the pancreas. Even though there is progress seen in the development of insulin analogs and continuous monitoring of glucose, which improve diabetes management, there is no known cure for T1D, and many individuals experience serious complications.[1] According to a 2021 report, 8.4 million individuals were affected with T1D, of which around 1.5 million individuals (18%) were under 20 years, 5.4 million individuals (64%) were of the age group 20–59 years, and 1.6 million individuals (19%) were aged 60 years and older. Approximately one-fifth of the T1D incidence was in low-income and middle-income countries.[2] Despite the significant advancements in the technologies for maintaining glycemic targets, around 73% of individuals with T1D fail to meet the recommended glycemic targets.[3–5]

T1D affects both large blood vessels and small blood vessels. It is associated with acute complications like diabetic ketoacidosis and severe hypoglycemia, as well as chronic complications like retinopathy, nephropathy, and neuropathy.[6] These complications will have a significant impact on the life expectancy of individuals with T1D, with a global average of 24 years less than those without the condition. According to epidemiological projections, the prevalence of T1D is expected to increase by 60–107% by 2040, and the most anticipated increase can be observed in low-income and lower-middle-income countries, highlighting the global disparities.[2] These projections indicate that there is an urgent need to understand the pathophysiology of T1D in individuals, with the growing evidence pointing toward the gut microbiome as a crucial area for understanding the pathophysiology as well as developing new therapeutic techniques that are designed to target specific functions of the gut microbiota. The T cell tolerance toward the autoantigens, which are derived from the beta cells of the pancreas, is significantly impaired in type 1 diabetic individuals.[7] The results of both murine and human studies show the crucial role of autoreactive T cells in the destruction of beta cells and the progression of T1D. Specifically, autoreactive cytotoxic CD8+ T cells were notably observed, which were targeting and destroying the insulin-producing beta cells of the pancreas.[8,9] Genetic factors also play a significant role in the susceptibility of T1D, which was highlighted by the familial linkage analyses and genome-wide association studies, which identified more than 50 key genetic factors contributing to the disease progression.[10] One of the main genes responsible for T1D is determined to be polymorphisms in human leukocyte antigen (HLA) class II genes, with variations like HLA-DR3-DQ2 and HLA-DR4-DQ8 accounting for around 40–50% of inherited T1D.[11,12] However, genetic factors alone are not sufficient to account for the upsurge in the incidence of T1D.[13]

Overview of Immune System Involvement in T1D

Genetic Susceptibility and Autoimmunity

The gut barrier comprises multiple key protective components, such as a mucus layer, antimicrobial peptides rich in immunoregulatory molecules, and an intestinal epithelial layer held tightly by forming a junction with transmembrane and scaffolding proteins.[14] The intestinal barrier integrity was disrupted in the studies of T1D in prediabetic and diabetic stages.[14,15] In several preclinical studies, interventions that accelerate the initiation of diabetes are often due to the increase in intestinal permeability.[16] Hyperpermeability, commonly known as "leaky gut," is observed when there is a space between the intestinal epithelial cells. This happens when the zonulin (a natural regulator of tight junctions in the intestine) levels are elevated, and the

junction proteins are reduced.[17,18] Low-grade intestinal inflammation, which is characterized by the lowered mucosal output of IL-17A, IL-22, and IL-23A—cytokines that play a vital role in maintaining gut barrier integrity and mucosal immunity—is also observed.[19] Loose gut barrier integrity allows the bacterial byproducts and diabetogenic antigens to activate the mucosal immune cells and enter the bloodstream. In nonobese diabetic (NOD) mice, low-dose dextran-sulfate-sodium-induced disruption in the intestine triggers the activation of the islet-reactive T cells in mesenteric lymph nodes, which relocate to the pancreas and contributes to the destruction of pancreatic beta cells and the onset of T1D.[14]

Environmental Triggers

Environmental triggers are external factors apart from a person's genetic factors that can be responsible for developing T1D. These environmental factors include infections, vaccinations, birth weight, infant growth, childhood obesity, the gut microbiome, and diet. Viruses are considered a potential environmental factor contributing to T1D. Acute fulminant diabetes, a specific type of T1D, has been observed in individuals following infections like mumps, Coxsackie B3, B4, rubella, and influenza. One of the significant characteristics of this condition is an immediate onset of hyperglycemic ketosis. The symptoms of such conditions typically appear within a week. In these conditions, islet autoantibodies will be absent, and C-peptide levels will be lower, which indicates a total loss of beta cell function in the pancreas. This complete loss of beta cell functioning may result from the direct lytic effect of viral infection, which destroys beta cells and causes insulin deficiency. There is no such evidence pointing to any childhood vaccination programs that can cause T1D. Other contributing factors are high birth weight and rapid infant growth. A systematic review and meta-analysis showed that higher birth weight, greater than 4 kg, was linked with a 17% increase in T1D risk. Early-life gut microbiota influences immune system development. In the case of T1D, beneficial bacteria like *Bacteroides*, *Prevotella*, *Bifidobacteria*, and *Lactobacillus*, which produce beneficial short-chain fatty acids, are reduced on digestion. These changes can cause beta cell autoimmunity and increase gut inflammation, gut permeability, and gut exposure to dietary antigens.[13]

Innate Immune Response in T1D Onset

Role of Dendritic Cells and Macrophages

Specialized immune cells, such as myeloid cells, reside in the islets of the pancreas, keeping them healthy and protected. In T1D conditions, more macrophages enter the islets of the pancreas and cause inflammation. When activated, another group of immune cells known as dendritic cells moves to pancreatic draining lymph nodes, activating T cells, which then move into islets. CD4+ T cells recognize autoantigens and harmful signals presented by the immune cells, like macrophages and dendritic cells, whereas CD8+ T cells attack and destroy the insulin-producing beta cells of the pancreas. However, whether the dendritic cells remain in the islets and, if so, in what numbers and forms they remain is still not clear.[20]

Inflammatory Cytokines

Cytokines are the chemical messengers produced by the immune cells and pancreatic cells, which play a vital role in the development and progression of T1D. Some specific cytokines, namely IL-10, TGF-β, IL-5, IL-4, IL-2, IL-15, IL-33, and IL-35, help regulate the immune system by activating cells that release anti-inflammatory signals, such as IL-10, to reduce inflammation. For instance, IL-7 produced by the regulatory dendritic cells helps regulatory T cells (Tregs) survive. These T cells are vital for managing the immune system attacks in the case of T1D because they have the IL-7Rα receptor, which responds to IL-7 signals efficiently. Some proinflammatory cytokines like IL-6, TNF-α, IFN-α, IL-17, and IL-21 cause inflammation by activating the immune cells, which attack and damage the insulin-producing beta cells. Some cytokines like IL-2 and IL-15 have double roles in activating both harmful and protective cells. Beta cells with cytokine receptors are susceptible to these signals and can cause cell death or repair. Therefore, the role of cytokines in T1D largely depends on the balance between inflammatory and regulatory signals.[21]

Pattern Recognition Receptors (PRRs)

The innate immune system utilizes PRRs, such as toll-like receptors, NOD-like receptors, and RIG-I-like helicases, to identify pathogens through PAMPs. These PAMPs bind to PRRs and trigger immune responses by releasing cytokines and chemokines, which fuel inflammation and help protect and heal tissues. However, abnormal and excessive inflammation causes autoimmune diseases like T1D.[22]

Adaptive Immune Response: Key Effector Mechanisms

CD4+ and CD8+ T Cells

In T1D, insulitis infiltrates mainly consist of CD4+ and CD8+ lymphocytes with a significant predominance of cytotoxic T cells. The elevated proportion of cytotoxic T lymphocytes highlights their role in destroying insulin-producing beta cells in the pancreas. Notably, higher glucose levels accelerate beta cell destruction, possibly by enhancing the insulin peptide fragments, which may boost killer T cells. Even though T lymphocytes take up a major part of the infiltrate, other immune cells like B cells and macrophages are also present. Remarkably, the constituents and the composition of these infiltrating cells are linked with the level of destruction and vary with the age of T1D onset in an individual.[23]

B Cells and Autoantibodies

Islet autoantibodies are the major predictors of T1D incidence, which are predominantly produced in childhood

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and observed as early as six months of life. Five primary autoantibodies that are observed in T1D are insulin autoantibodies (IAA), GAD Antibodies (GADA), insulinoma-associated protein 2 (IA-2A), ZnT8A, and tetraspanin-7 (Tspan7A). Of these five autoantibodies, IAA appear first, followed by others that target most pancreatic islet cell antigens. Several studies on T1D patients have highlighted that islet autoantibodies produced by B lymphocytes are regarded as the primary markers of the disease rather than direct factors in its pathogenesis.[24]

Tregs

Early research studies suggest a lower frequency of FOXP3+ Tregs in individuals with T1D, but more recent studies using specific markers such as low CD127 and FOXP3 expression indicated that their overall frequency remains unchanged. However, these markers are not always reliable, as FOXP3 can also appear in other T cells temporarily, potentially causing a mix-up of regulatory and nonregulatory cells.[25]

Figure 1 shows the immunopathogenic cascade underlying the development of T1D. The autoimmune process is initiated by a breakdown in self-tolerance, leading to the activation of antigen-presenting cells (APCs). These APCs orchestrate downstream immune responses by releasing proinflammatory cytokines (TNF-α, IL-6, IFN-γ), promoting β-cell cytotoxicity, and triggering the production of islet-specific autoantibodies such as IAA, GAD65, IA-2A, and zinc transporter 8 (ZnT8A). The combined effect of cytokine-mediated inflammation, autoreactive cytotoxic T cell infiltration, and humoral autoimmunity culminates in the targeted destruction of pancreatic β-cells. This progressive β-cell loss ultimately manifests as symptomatic T1D.

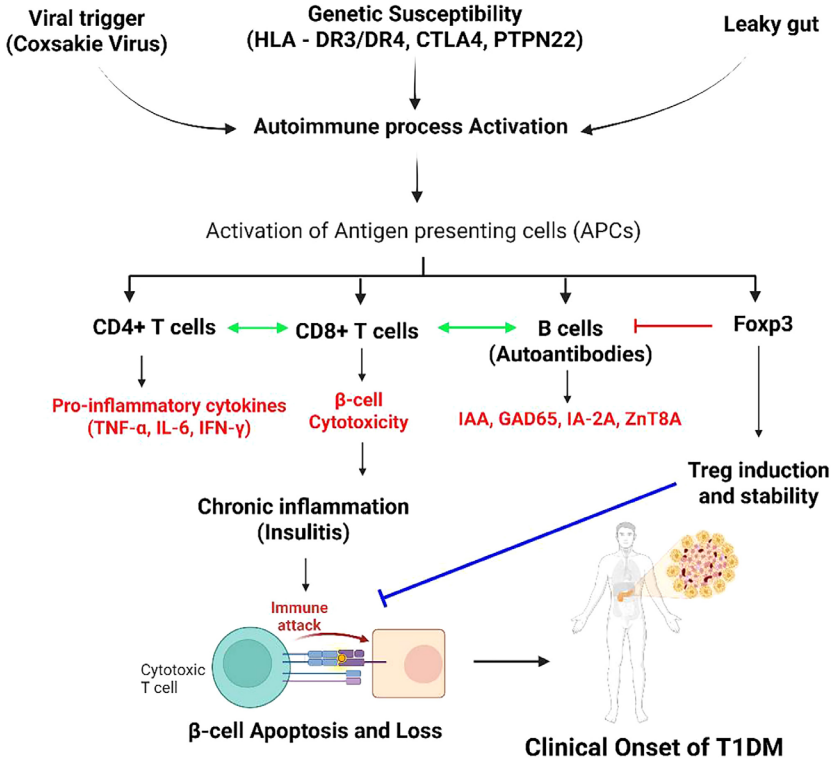

Fig 1 | Key therapeutic targets across the immunopathogenic axis of T1D

Chronic Inflammation and Islet Destruction

Figure 2 shows the different mechanisms underlying pancreatic islet destruction in diabetes. T1D is an autoimmune disorder mediated by T cells. One of the significant attributes of this condition is insulitis—an inflammatory lesion observed in the islets of the pancreas. This insulitis is characterized by the autoimmune attack on beta cells and immune cell infiltration within and around the islets of the pancreas. It is defined by six or more CD3+ cells within and around the islets, with three or more islets per pancreas section. Standard features of insulitis include: (i) dominant lymphocyte infiltration in the islets of Langerhans, (ii) detection of at least 15 CD45+ cells per islet, and (iii) lesions present in at least three islets. Insulitis can occur either at the periphery of the islet (peri-insulitis), where inflammatory cells form a cluster at one particular side in connection with the islet periphery, or inside the islet itself (intra-insulitis). According to several studies, peri-insulitis in humans is the most commonly observed form of insulitis.[26]

Chronic inflammation and the destruction and dysfunction of the beta cells in islets play a vital role in the initiation of T1D, further contributing to symptoms such as severe hyperglycemia. Many studies indicate that beta cell destruction is a slow, steady, and heterogeneous process that continues for many years after an individual is diagnosed with T1D. Several other studies have shown the presence of insulin-producing beta cells decades after the diagnosis, where the glucose transporters continued to be expressed. In some patients with long-term disease duration, beta cells also expressed survivin—a molecule that persistently supports the beta cell's attributes. In such patients, low levels of beta cell apoptosis were also observed, indicating some potential beta cell turnover.[27–29]

Biomarkers and Diagnostic Relevance

Despite T1D being a heterogeneous condition, present consensus points out its progression in three distinct stages. Stages 1 and 2 are considered presymptomatic. Stage 1 is marked by the presence of multiple islet autoantibodies in the bloodstream without any symptoms of dysglycemia. In stage 2, dysglycemia develops along with the presence of multiple islet autoantibodies. Stage 3 is considered the symptomatic, transition stage of the disease.[29]

Immediately following the discovery of islet autoantibodies, when the actual history of T1D was extensively studied through three birth cohorts, it revealed that the children who developed two or more islet autoantibodies on or before the age of five have around 80% greater risk of progressing to T1D by the age of 20. Islet autoantibodies, also called islet cell antibodies, which could predict T1D even before the symptoms appear, were first discovered in the 1970s. However, initial test methods that included incubating the serum

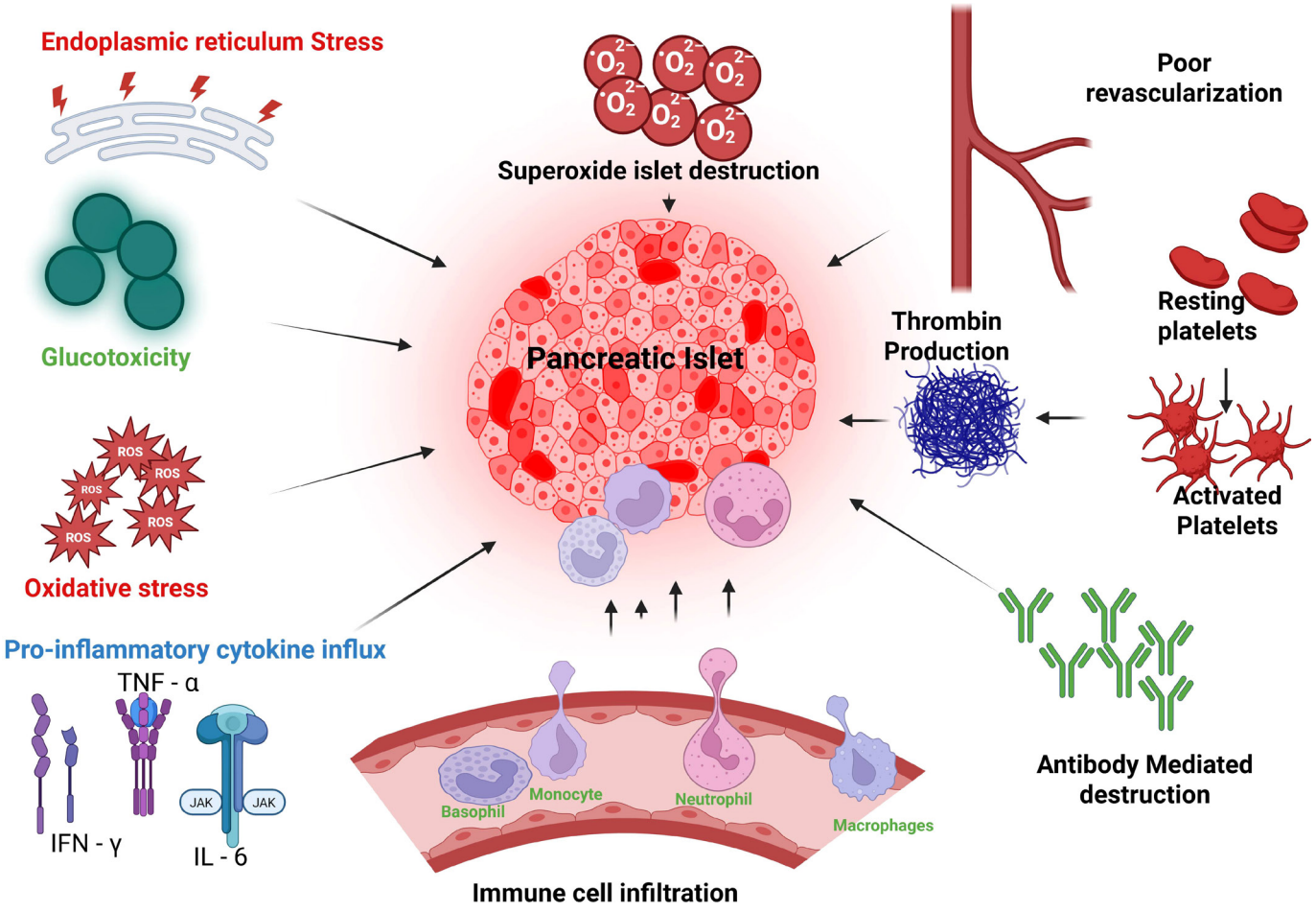

Fig 2 | Mechanisms underlying pancreatic islet destruction in diabetes. Pancreatic islet β-cell destruction results from multiple mechanisms, including glucotoxicity, oxidative and ER stress, and superoxide-induced damage. Proinflammatory cytokines (IFN-γ, TNF-α, IL-6) drive immune cell infiltration, while autoantibodies, thrombin generation, and platelet activation exacerbate inflammation and impair islet revascularization. Collectively, these processes contribute to β-cell dysfunction and loss

on pancreatic tissue were very complicated and were not accurate as they highly relied on the individual performing the test. While this test is still widely used, it has been largely superseded by more accurate assays that target the four primary T1D autoantigens: insulin (IAA), glutamic acid decarboxylase (GADA), IA-2A, and ZnT8A. Recent studies show that Tspan7A has been used as a T1D autoantigen, but its role in predicting the risk of developing T1D remains poorly defined.[29]

Radio-binding assays are one of the gold standards for detecting islet autoantibodies. It is widely used in studies such as TEDDY and TrialNet because of its high sensitivity. However, due to safety concerns and cost issues, they are being replaced by alternative methods, such as bridging enzyme-linked immunosorbent assay, luciferase immunoprecipitation systems, electrochemiluminescence, and antibody detection by agglutination PCR. These methods are being evaluated through standardized tests in workshops like the islet autoantibody standardization performance. For more precise and wider screening and clinical trials, there is an increasing need for more cost-effective, high-throughput tests and much simpler sample collection techniques.[29]

Immunomodulatory Approaches and Therapies

Figure 3 shows the emerging immunomodulatory approaches for preserving β-cell function in T1D. The main aim of experimental immunotherapies for many autoimmune diseases and transplant rejection cases is to suppress the harmful immune responses without harming the protective immune system. One pivotal challenge is the absence of targeted immune signaling, which reduces effectiveness and can lead to unwanted suppression. So, to address this key challenge, intralymph node injection of degradable microparticles, which carry self-antigens and rapamycin, is being extensively studied to improve targeted immune system modulation. Antigen-specific tolerance is systemic but avoids nonspecific immune suppression in the case of T1D. Microparticle treatment stimulates tolerogenic microdomains in lymph nodes, which enhances memory markers in antigen-specific Tregs and causes long-lasting immune tolerance.[30]

Recent research studies on immune checkpoint-based therapies highlight the action of inhibitory receptors (IRs) in stimulating peripheral tolerance in autoimmune diseases. Several studies on animals

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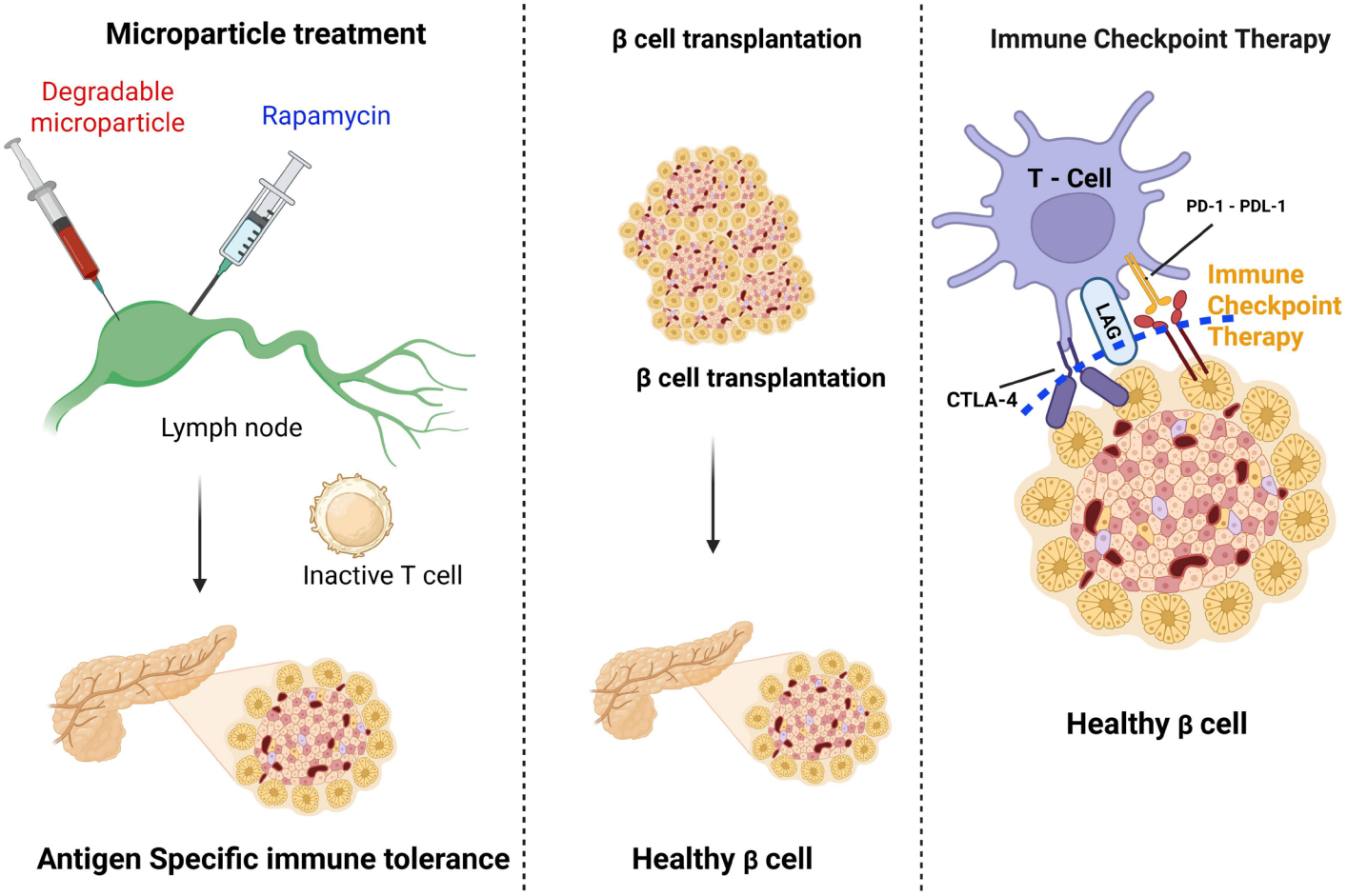

Fig 3 | Emerging immunomodulatory approaches for preserving β-cell function in T1D. This figure highlights three complementary therapeutic approaches to halting autoimmune-mediated β-cell destruction and promoting β-cell survival in T1D. Left panel: Microparticle therapy involves intra-lymph node injection of degradable microparticles encapsulating self-antigens and immunosuppressive agents like rapamycin. This strategy promotes antigen-specific immune tolerance by inducing tolerogenic microenvironments and converting autoreactive T cells into inactive or regulatory phenotypes, thereby protecting β cells from immune attack. Middle panel: β-cell transplantation restores endogenous insulin production by replacing destroyed islet cells. However, successful engraftment and long-term function require concurrent immunosuppression or immune modulation to prevent rejection and recurrence of autoimmunity. Right panel: Immune checkpoint therapy reinforces peripheral tolerance by activating inhibitory signaling through checkpoint molecules such as PD-1, CTLA-4, and LAG-3 on autoreactive T cells. Engagement of these pathways limits T cell effector function and preserves pancreatic β-cell mass. Collectively, these interventions represent promising avenues for durable disease-modifying therapy in T1D

and humans have shown promising results by improving IR signaling through targets such as CTLA-4, PD-1, TIM-3, LAG-3, and TIGIT, which can potentially treat autoimmune diseases beyond cancer treatment. In the case of autoimmune T1D, immune cell therapy mainly aims to suppress the mistaken immune attack on insulin-producing beta cells. This holds a key role as a potential cure in the initial stages. Insulin production can be normalized when beta cells are restored. However, this comes with several challenges, such as immune system rejection and very few HLA-matched donors, which have obstructed the transplantation success rates.[31]

Future Perspectives and Research Gaps

Over the years, multiple studies have identified new treatments for T1D, which shifted the focus from controlling insulitis to recovering the destructed tissues. However, limited success was observed with these treatment methods. Recent studies explore nonantigenic (NAg) drugs, targeted therapies, and antigen-specific agents. Although several drugs such as cyclosporine, azathioprine, ketotifen, and ATG have shown promising benefits of restoring the beta cell function for the short term, none of these have prevented the onset of T1D or demonstrated long-term efficiency.[26]

One of the targeted therapies that was developed for T1D included the human anti-CD3 monoclonal antibodies (mAbs), which showed promising results in reducing islet immunogenicity, but they do not have an impact on early autoimmunity. Some trials of second-generation mAb otelixizumab have highlighted the reduced insulin necessity in those who are newly diagnosed with T1D. Another promising result was observed with teplizumab, which helps preserve the C-peptide levels in patients with low HbA1c. However, the efficiency of this method was not seen in phase III trials.[26]

Most of the NAg immunomodulators in T1D patients mainly aimed to slow the disease progression but did not address beta cell destruction or insulin insufficiency.

Insulin is considered a vital autoantigen in T1D patients according to several preclinical trials; however, those trials using subcutaneous insulin failed due to the risk of hypoglycemia. Later, oral insulin was shown to be a potential treatment approach for delaying the onset of T1D in patients with high anti-IAA levels. Some of the safer antigens, such as DiaPep277, which are derived from the heat shock protein 60, are explored, and promising results have been shown in animal models in phase III trials for protective effects against T1D.[26]

Another potential treatment approach that emerged recently is stem cell grafting. Several clinical trials showed potential benefits in reducing the progression, with no significant side effects observed. Several approaches that use mesenchymal stem cells, human embryonic stem cells, and bone marrow hematopoietic stem cells aim at restoring immune tolerance and protecting beta cell functioning, but the results remain uncertain so far. To address these issues, a combination of different strategies is suggested for treating T1D. These strategies include using safe stem cell therapies with islet transplantation, immunosuppressive drugs, bioengineering techniques, and gene therapies, which positively result in effective treatment for T1D.[26]

Cell therapy is also extensively explored for preventing and reversing T1D due to limited success rates observed with the stem cell grafting method. However, some of the pivotal challenges include the generation of mature and functional beta cells, which improves differentiation and helps protect the cells against immune attack and achieve insulin independence. Thus, protective encapsulation and gene editing are necessary to improve this approach, reduce reliance on antirejection drugs, and address the root cause of the disease.[26]

A novel technology used in treating T1D involves combining anti-IL-21 and liraglutide to delay autoimmune destruction and sustain the β-cell functioning. IL-21 triggers CD8+ cells to attack the pancreatic islet cells and makes it a primary target in slowing down the disease progression. Liraglutide is a GLP-1 analog, which is used in treating type 2 diabetes mellitus, helps in the survival of the β-cells and improves glucose-dependent insulin secretion. This shows a promising use in treating T1D when paired with mild immunomodulation.[32]

Another new treatment strategy focuses on antiapoptotic and pro-proliferative agents specifically targeting the PAX4 gene, which supports the islet cell growth. According to a study, one of the most common genes linked to reduced gene function in T1D (about 75%) is the PAX4 C/C genotype when compared to the control group (33%). Notably, around 11% of individuals with islet autoimmunity who were not diagnosed with T1D had the C/C genotype, which highlighted the protective action of functional PAX4 variant against disease progression.[33]

Conclusion

The etiology of T1D is complex, involving a multifaceted interplay between genetic, environmental, and immunological factors. While current strategies and therapies manage the disease, they are insufficient in halting or reversing beta cell destruction. Several advancements and breakthroughs were seen in immunotherapy, stem cell transplantation, and targeted drug delivery. However, they come with challenges like immune rejection, improper maturation of beta cells, and insufficient sustainable outcomes. The crucial treatment approach lies in achieving immune tolerance without harming the protective immunity. Future advancements should focus on precision approaches that include immunomodulatory approaches, regenerative medicines, and biomarker-guided interventions. Also, innovations like antigen-specific therapies, encapsulation techniques, and gene editing should address safety concerns and cost issues. Conclusively, a comprehensive understanding of immune response in the case of T1D is crucial in formulating curative therapies and strategies that can go beyond glucose control to address the root cause of the autoimmune disorder.

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