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Progress and Prospects of Immunotherapies and Vaccines for Type 1 Diabetes

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Abstract: Type 1 diabetes (T1D) is an autoimmune disease known as the destruction of pancreatic β cells, which results in the patient being permanently dependent on insulin. While conventional insulin therapy remains the primary treatment, it does not address the underlying autoimmune mechanisms driving the disease. Novel immunotherapy and vaccination offer promising methods for modifying immune responses and preserving β cell function. Antigen-specific immunotherapy (ASI) can induce immune tolerance by targeting key autoantigens and showing efficacy in delaying disease progression. Immune-modulating therapies also shown potential in delaying disease onset by modulating T-cell activity. Additionally, emerging platforms, such as mRNA vaccines and nanoparticle-based delivery systems, offer new opportunities for targeted immune modulation. Despite these advancements, challenges remain, including patient heterogeneity, variability in immune responses, and safety concerns. Moreover, the long-term efficacy of these interventions is not yet fully understood. Personalised treatment, improved biomarkers for early detection, and combination therapies may enhance treatment efficacy. This review explores the progress and translational potential of immunotherapies and vaccines for T1D, highlighting key developments and ongoing challenges.

Keywords: type 1 diabetes, immunotherapy, vaccine, autoantibody, autoimmune disease

1. Introduction

Type 1 diabetes (T1D) mellitus is an autoimmune disease in which patients experience the destruction of β cells (insulin-producing cells) by the acquired immune system. This is caused by T and B cells attacking β cells in the pancreas, macrophages infiltrating the islets of Langerhans, and environmental infectious or inflammations [1]. T1D is considered as the "juvenile diabetes" as it predominantly occurs in children and is less common in adults [2]. T1D accounts for about 9.5% of the world population worldwide, and its incidence continues to increase gradually due to gene-environment interaction [1]. Although the exact reason causing T1D remains unknown, several studies demonstrated that genetic, environmental, immunological and lifestyle factors all contributed to the aetiology of T1D [2,3].

Patients with T1D require lifelong exogenous insulin administration and long-term pharmacological management to prevent hyperglycemia, diabetic ketoacidosis and other life-threatening complications [2]. Additionally, patients require disease-specific education, as well as personalized dietary and lifestyle modifications for better glycemic control. Oral medications, including GLP-1 analogues and metformin, are also essential to mitigate the risk of complications

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associated with T1D. However, both adjunctive treatments and insulin injections can lead to adverse effects, such as diarrhoea, skin issues, or hepatotoxicity, which may result in patients' poor adherence to their treatment. It is important to note that despite the recent advancements in insulin and medication delivery, such as pre-mixed insulin formulations and shorter needles, approximately 40% of patients still fail to adhere to their prescribed medication regimens [4].

Therefore, there is a growing need for ways to prevent T1D in its early stages. Recent developments in immunotherapy and vaccination have created novel treatment options for T1D, with an emphasis on modifying the immune response to maintain β cell function and delay the onset of the disease. This conference aims to summarise the development of advanced immunotherapy and vaccination strategies for early T1D management.

2. The pathophysiology of T1D

Although the exact cause of T1D is unknown, it is widely accepted that numerous gene mutations contribute to the disease. Surprisingly overt T1D is present in less than 5% of children with 90–95% risk-associated haplotypes [5]. Around 60 genes are linked to the development of T1D, and 40–50% of the genetic susceptibility is caused by the human leucocyte antigen (HLA) class II alleles. More than 90% of T1D patients have DR3-DQ2 and DR4-DQ8, which are two alleles of the HLA class II that are found on chromosome 6p21 [3,5]. In the DR3-DQ2 and DR4-DQ8, the aspartic acid at position 57 is replaced by a neutral or positively charged amino acid, which stimulates autoreactive T cell activation [3]. Although having a lesser impact than HLA genes, other non-HLA loci, such as INS, PTPN22, IL2RA, and CTLA4, also play a role in the development of T1D [5].

Despite genetic factors, environmental factors need to be involved in the development of T1D. The occurrence of T1D is influenced by several environmental factors, including diet, gut microbiota, ethnicity, and viruses [3,5]. There has long been research on the link between viral infection and T1D. Enteroviruses such as coxsackieviruses (CVB) have been considered as a trigger of T1D, as positive CVB IgM serology is found in around 60% of children who are diagnosed with T1D [5]. Although the precise mechanism by which the virus induces islet immunity is still unknown, exosomes containing autoantigens can be released by β-cells due to virus-induced inflammation and endoplasmic reticulum stress, and these exosomes can be taken up by antigen-presenting cells (APCs) and activate the adaptive system for additional β-cell damage [5].

The progression of T1D can be classified into three stages, and each stage is defined by the screening of key autoantigen and the presence of dysglycemia. Stage 1 is described as subjects with a normal blood glucose level but has more than two T1D-associated autoantibodies. This stage takes place long before any clinical symptom appears. Stage 2 is characterised by the progressive loss of β cell mass and function, which raises blood glucose levels. Stage 3 is equivalent to preclinical T1D in which clinical symptoms (including polyuria, polydipsia, weight loss, etc) occur but still have insulin secretion [1,3]. Since most patients who are suspected of T1D will experience these stages, interrupting any three phases can halt the progression of autoimmunity in the early stage.

3. Antigen-specific immunotherapy

Antigen-specific immunotherapy (ASI) represents a safe way to delay the onset of T1D. ASI aims to retrain the immune system to become tolerant to specific T1D self-antigens that are recognised by autoreactive T cells, including insulin, glutamic acid decarboxylase 65 (GAD65), insulinoma-associated antigen-2 (IA-2), and zinc transporter 8 (ZnT8), thereby preventing autoimmune destruction of pancreatic β-cell [3]. Oral insulin has been introduced into clinical trials to induce immune tolerance by triggering the gut-associated lymphoid tissue (GALT). The mechanism is to

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be precisely involved within the gastrointestinal tract and release insulin into the gastric lining without causing perforation [3]. One of the main autoantigens in T1D is IA-2, a tyrosine phosphatase-like protein in pancreatic β cells that can be used as a biomarker for T1D prediction [4]. Early research has demonstrated that IA-2 vaccination can help delay the onset of T1D either alone or in conjugation with plasmid IL-4/MCP-1. In animal studies, the new peptide vaccination, IA-2-P2, can also lower blood glucose levels [4].

Compared to other autoantigens, the GAD65 antibody is studied more frequently as a susceptibility marker detected in T1D. Animal studies have demonstrated that the injection of GAD65 can prevent autoimmune damage to pancreatic β-cells, encouraging researchers to use this autoantigen in human treatments [6]. Around a decade ago, aluminium hydroxide was used as the adjuvant for the GAD65 antibody to enhance the immune response more significantly [4]. However, the GAD-alum vaccine (Diamyd) failed in phase II trials, as the HbA1c and injected insulin levels did not improve with Diamyd treatment [7]. Nevertheless, combining CTB-insulin and CTB-GAD with IL-10, along with the use of GAD65 antibodies that target glial fibrillary acidic protein (GFAP), has also been shown to reduce β-cell autoimmunity and improve C-peptide secretion in T1DM [4]. More recently, the administration of GAD-alum into lymph nodes, alongside vitamin D supplementation, has the potential to preserve C-peptide in newly diagnosed T1D patients who carry HLA DR3-DQ2 [8]. It is worth mentioning that to enhance the tolerance of the immune system to self-antigens, new delivery platforms, including fabricated microparticle (MP) vaccines and microsphere vaccines, are designed [4].

Despite the IA-2 and GAD65 vaccines, other autoantibodies show promise for T1D treatment. For instance, ZnT8 is a zinc transporter protein encoded by the SLC30A8 gene located on chromosome 8, is specifically expressed in pancreatic tissues and plays a key role in zinc homeostasis, which results in regulating insulin secretion [9]. In addition, the ZnT8 antibody (ZnT8A) is a newly identified biomarker for screening T1D, as it is detected in 60-80% of newly diagnosed T1D patients, with 26% detected with no other diabetogenic autoantibodies. Notably, ZnT8A-positive individuals have a higher risk of developing T1D than those without it [9]. Although further experiments are required, ZnT8 is now being investigated as a potential vaccine target.

4. Immune-modulated therapy

Immune-modulated therapy aims to modify the autoimmune response in T1D by maintaining β-cell function and delaying disease progression. Numerous systemic immunological treatments, including monoclonal antibodies, have already been investigated.

Teplizumab, an Fc-receptor (FcR) non-binding anti-CD3 monoclonal antibody (mAb), is the first immunotherapy that has been approved by the Food and Drug Administration (FDA) to delay the onset of stage 3 T1D in patients 8 years of age or older with stage 2 T1D [10]. FcR non-binding mAb Teplizumab protects β-cell by binding to CD3 and producing a partial T cell receptor (TCR) signal that functionally inactivates autoreactive T-cells. Also, Teplizumab induces a temporary decline in circulating lymphocytes, indicating that T-cells can migrate to other organs, particularly the GALT, where $CD4^+$ T cells produce TGF-β and IL-10, and result in immune suppression [3]. Moreover, Treg cells are selectively preserved by FcR non-binding CD3-targeted mAbs [3]. Teplizumab has been proven in clinical trials, including the AbATE and Protégé study, to not only retard the onset of T1D in high-risk individuals but also to improve C-peptide responses even over a year after treatment without causing severe cytokine release syndrome [3]. According to some clinical trials, some patients who receive Teplizumab treatment experience prolonged protection against the progression of T1D. This may be because Teplizumab increases the expression of the

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programmed cell death protein 1 (PD-1) on anergic and central memory CD8+ T cells, which leads to long-term immune tolerance [3].

Rituximab, a CD20-targeted monoclonal antibody that targets B cells, is essential for maintaining β-cell activity and slowing the progression of the disease in patients newly diagnosed with T1D [3]. CD20-targeted mAb is initially used in the treatment of rheumatism and tumours [1]. Interestingly, the TrialNet trial demonstrated that Rituximab can delay the rate of C-peptide decline in individuals with stage 3 T1D who had more than one detectable diabetic autoantibodies [1]. However, the benefit is not long-lasting. The initial benefit of Rituximab is brought on by the decrease of B cells, which disrupts their association with T cells and temporally lowers autoreactive immunological activity. However, the autoimmune response gradually resumes due to the return of autoreactive B cells and continuing T cell activity [3]. Since the benefit of Rituximab is temporary, it may be necessary to employ alternative approaches that target both innate and adaptive immunological components to establish prolonged β-cell protection.

Abatacept, a CTLA-4 Ig fusion protein, has been used in many other autoimmune diseases, like psoriasis and rheumatoid arthritis. Abatacept inhibits T-cell activation and cytokine production by binding to CD80 and CD86 on APCs and preventing CD28 from interacting with effector T-cells [1]. Although one study from TrialNet showed that Abatacept can slow down the decline of β-cell function in stage 3 T1D patients, it is insufficient to completely stop the disease from progression [1].

5. Cell-based immunotherapy

Regulatory T cells (Tregs) are key immune modulators as they negatively modulate other immune cells, including dendritic and cytotoxic T cells. In diabetic patients, the unstable expression of forkhead box P3 (Foxp3) or abnormal synthesis of the proinflammatory cytokine by autoreactive T-cells can cause Tregs to become dysfunctional [11]. The disruption of many metabolic pathways, such as the TCR activation and IL-2 signalling pathways, is linked to the loss of Treg function in T1D patients [12]. Additionally, research has shown that Foxp3-expressing CD4+ Tregs play a crucial role in the pathogenesis of T1D [13]. Because Treg impairment is a contributing factor in T1D, it has been suggested that Treg therapy may restore immunological homeostasis and prevent β cells from being destroyed by dysregulated immune responses. According to a phase I clinical trial, isolated and expanded polyclonal $Foxp3^{+}CD4^{+}CD25^{hi}CD127^{lo}$ Tregs from T1D patients did not exhibit any high-grade side effects related to cell therapy. Additionally, the C-peptide levels from the subject remained elevated for over two years following the transfer, indicating that β cells are being protected. Notably, the trial used deuterium-labelled infused Tregs to track the Treg stability in peripheral blood and found no decrease in FOXP3 expression [14].

However, the quantity of Treg that was cultivated in vitro and subsequently introduced into the human body gradually decreased with time, suggesting that other methods for maintaining Treg are required. A solution is to use umbilical cord Treg, which is a better option for preserving lineage stability [12]. A different strategy for activating Tregs for β cell protection relies on the low dosages of IL-2 to stimulate CD4+ and CD8+ Foxp3+ Tregs. Treg survival depends on IL-2, and exogenous IL-2 has been thoroughly described as a treatment method for patients with T1D autoimmune response suppression [12]. Furthermore, effector T-cells could also be inhibited by a low dosage of IL-2 [14]. Despite these encouraging results, Treg infusion can only temporarily slow the development of T1D. The effectiveness of Treg immunotherapy is challenged by several factors. First, Treg therapy is more effective when given at the early stage of the disease to protect a higher number of β-cells from autoimmune attack [13]. Furthermore, T1D-induced autoimmune inflammation may change Treg stability, turning them into pro-inflammatory cells rather than

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autoimmunity-suppressive cells [13]. In addition, large-scale production of autoantigen-specific Tregs is challenging [13].

Chimeric Antigen Receptor (CAR)-Tregs therapy is a more advanced technique compared to conventional Treg therapy. The theory of employing CAR-Treg to modulate the immune system involves genetically modifying the Tregs that are extracted from the human body to express CAR, a synthetic receptor that selectively recognises antigens expressed by pancreatic β cells. The genetically engineered CAR-T cells are reintroduced back into the human body to attach to CD8+ cytotoxic T-cells and induce apoptosis by expressing FasL and inhibitory molecules like CTLA4 [14,15]. Additionally, CAR-Tregs secrete anti-inflammatory cytokines such as TGF-β, IL-10, and IL-35, to reduce undesired immune responses [14]. Compared to Treg immunotherapy, CAR-Treg therapy has several advantages. One of the main benefits of CAR-Treg therapy is its ability to provide targeted immunomodulation. Autoantigen-specific CAR-Tregs can suppress pathogenic T cells at the particular autoimmune cells, which greatly reduces the risk of widespread immunosuppression. Furthermore, research indicates that by establishing immunological tolerance, CAR-Tregs can help T1D patients experience long-lasting remission. Notably, CAR-Treg therapy requires personalisation to customed different individuals, which improves its efficacy [15]. There are also several obstacles to overcome with CAR-Treg treatment. First, the development of CAR-Treg therapy needs to find pancreatic β cell-specific cell surface molecules in order to ensure Treg cell activity and function. Research has been done in generating CAR-Treg cells to recognise insulin and HPi2. Both insulin-specific and HPi2-specific CAR Tregs failed eventually. Insulin-specific CAR Tregs were ineffective as this therapy can only recognise specific forms of insulin, while tonic CAR signalling hindered the HPi2-specific ability of CAR Treg to expand and function [14]. Additionally, the accessibility may also be restricted by the complexity and cost of developing and administering CAR-Tregs [15].

6. Conclusion

Targeting crucial autoantigens like insulin, GAD65, IA-2, and ZnT8, antigen-specific immunotherapy is designed to retrain the immune system and minimise β-cell autoimmunity. Although some clinical trials, like the development of GAD-alum, have produced inconsistent outcomes, novel delivery systems and combinatory medicines can increase their therapeutic potential. Additionally, by specifically altering T-cell responses, immune modulatory treatments, such as mAb, have shown promise in delaying the disease. Despite these developments, there are still issues, such as the variability in patient response, adverse effects, and the requirement for accurate biomarker-based stratification for personalised treatments. Future research ought to focus on refining existing treatments, incorporating nanoparticle-based antigen delivery systems, and investing in combination strategies to enhance efficacy while minimizing hazards. Finally, the development of immunotherapies and vaccination represents a great shift in T1D management. Translating these discoveries into therapeutic applications will require more clinical trials and research on immune mechanisms. By solving current obstacles, the goal of delaying T1D onset may become a reality in the future.

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