The Application and Prospects of Protein Therapy in the Treatment of T1DM

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Abstract:

Type 1 diabetes (T1DM) is an autoimmune disease with complex causes. The current treatment methods are mostly exogenous insulin injections, which are costly and have limited therapeutic effects, placing a heavy burden on patients. Existing research shows that targeted therapy has huge application potential in the treatment of T1DM. Therefore, this study explores protein therapies targeting immune regulation, enhancing β-cell function and reducing complications based on important targets in the pathogenesis of T1DM. In addition, this article provides a comprehensive analysis and comparison of recent clinical trials. Although there are currently protein therapies entering the clinical trial stage, research gaps still exist in understanding the exact mechanisms and long-term efficacy of these treatments. This article analyzes the research results of monoclonal antibodies (mAbs), growth factors, immune regulatory cytokines and signaling molecules in T1DM disease management. By elucidating gaps in therapeutic potential and current understanding, this study provides valuable insights for future research to guide more effective and comprehensive treatments for T1DM.

Keywords: Protein therapy; T1DM; monoclonal antibodies.

1. Introduction

Type 1 diabetes (T1DM) represents chronic autoimmune disorder that disruptures the intricate balance of blood sugar regulation within the human body. The fundamental pathology of this condition lies in the immune system's erroneous identification and subsequent destruction of the pancreatic β cells, the essential producers of insulin. This intricate interplay of genetic and environmental factors results in a pronounced insulin shortage, a hormone crucial for facilitating cells in utilizing glucose for energy. The consequence is elevated blood sugar levels, eventually leading to the manifestation of diabetes. Unlike type 2 diabetes, where the primary issue is insulin resistance, individuals with T1DM grapple with the inability to produce insulin. Patients suffering from T1DM are usually diagnosed in infancy or adolescence and have to rely on exogenous insulin to survive[1].

Managing T1DM imposes a complex set of challenges on patients. They must meticulously calculate precise insulin dosages, engage in real-time monitoring of their blood sugar levels, and bear the significant financial burden associated with drugs and therapies. T1DM is also a quite complicated issue in contemporary healthcare systems since it raises the risk of several complications in addition to the everyday struggles that patients face. Including but not limited to diabetic retinopathy, neuropathy, etc.

Since the creation of recombinant human insulin in 1982, the field of protein therapy has shown tremendous promise. The development of Fc fusion proteins, best demonstrated by the success of Etanercept, which represents a major advance in the field. These fusion proteins cleverly combine the properties of several proteins and increase the serum half-life of the peptide or protein, thereby increasing their potential applications in medicine [2]. Antibodies are the largest and fastest growing class of protein therapeutics, demonstrating the effectiveness of protein therapy.

The field of protein therapeutics is evolving with increasing goals to enhance efficacy, improve safety, and deliver efficiency. This integrated field brings together clinical, scientific and commercial considerations to promote the development of innovative technologies by establishing needs. For example, optimized Fc fusion proteins and engineered protein scaffolds stand out as groundbreaking advances that offer promising avenues for different medical fields, including the treatment of T1DM.

2. Protein Therapy in T1DM

Traditionally, the medical approach to T1DM has revolved

around insulin supplementation. However, the evolving therapeutic landscape explores protein function-based interventions, ushering in a new era of possibilities in immunosuppression and regulation. Protein therapies for T1DM aim to confront the underlying autoimmune responses and β cell dysfunction, prompting into strategies to modulate the immune system, enhance β cell function, and mitigate associated complications [3].

One pivotal avenue of exploration involves immunomodulation to regulate the immune system's assault on pancreatic β cells. Researchers are investigating novel protein therapeutics that could suppress autoimmune responses, potentially preserving β cell function and slowing disease progression. These approaches offer a glimpse into a future where the destructive cascade of T1DM could be tempered through precise immunological interventions.

Protein therapy for T1DM centers on enhancing β cell function and mitigating complications. These interventions restore or protect remaining functional β cells, thereby prolonging insulin independence and improving glycemic control. They address the underlying causes of β cell dysfunction and provide treatment options beyond symptom control. In addition, protein therapies show promise in treating other complications such as cardiovascular and renal. By targeting the effects of the disease on multiple fronts, these therapies improve patients' overall quality of life. In conclusion, protein therapeutics offer a promising approach to T1DM management, providing new avenues for effective and personalized treatment strategies.

2.1 Special Proteins in T1DM Therapy

T1DM is characterized by a complicated interaction between insulin insufficiency, pancreatic β cell death, and autoimmune dysregulation. Although insulin replacement therapy has been the mainstay of traditional treatment, recent research indicates that certain proteins may also be able to control the progression of the disease and enhance clinical results in the control of T1DM. Several important proteins that have demonstrated promise in T1DM treatment are discussed in detail below.

2.2 mAbs Targeting Immune Cells

mAbs, capable of targeting immune cells responsible for the destruction of pancreatic β cells, represent a breakthrough approach in the treatment of T1DM. Anti-CD3 antibodies such as Teplizumab and Otelixizumab can inhibit T cell-mediated β cell destruction by regulating T cell function and promoting immune tolerance. Clinical trials have demonstrated the potential of anti-CD3 mAbs to protect β cell function, delay T1DM progression, and improve long-term glycemic control in newly diagnosed individuals [4].

2.3 Growth Factors and B-Cell Survival Proteins

Some growth factors and proteins involved in β cell survival and regeneration, which can preserve and restore pancreatic β cells in T1DM. It provides additional ideas for the treatment of T1DM. For example, glucagon-like peptide 1 (GLP-1) analogues have received widespread attention for their ability to stimulate β cell proliferation, inhibit apoptosis, and enhance insulin secretion [5]. In addition, growth differentiation factor 15 (GDF15) has emerged as a potential therapeutic target, with clinical studies demonstrating its ability to enhance β cell tolerance to cytokine-induced apoptosis, thereby protecting patients' remaining viable β cells [6].

## 2.4 Immunomodulatory Cytokines and Signaling Molecules

In T1DM, immunological tolerance and immune response regulation are critically dependent on immunomodulatory cytokines and signaling molecules.

A promising therapeutic target for reestablishing immunological balance and tolerance in T1DM patients is interleukin-2 (IL-2), a crucial cytokine implicated in T-cell homeostasis and regulatory T-cell (Treg) function [7]. Low-dose IL-2 therapy has been the subject of clinical trials that have demonstrated encouraging outcomes in terms of increasing Treg populations, reducing autoreactive T-cell responses, and maintaining β cell function in patients with recent onset T1DM.
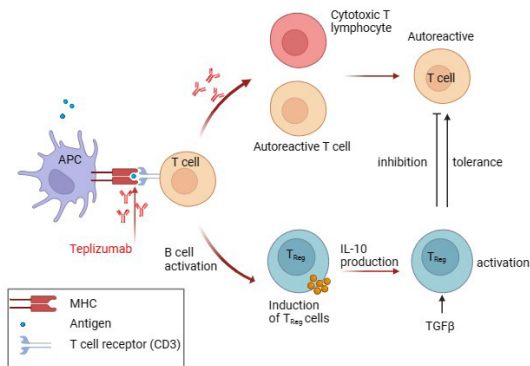
3. Mechanism

3.1 mAb Therapy

T1DM is caused by a complex interplay between genetic predispositions, environmental triggers, and dysregulated immune responses, singularly leading to the autoimmune destruction of pancreatic β cells. Understanding the underlying mechanisms of T1DM is critical to developing targeted therapeutic interventions.
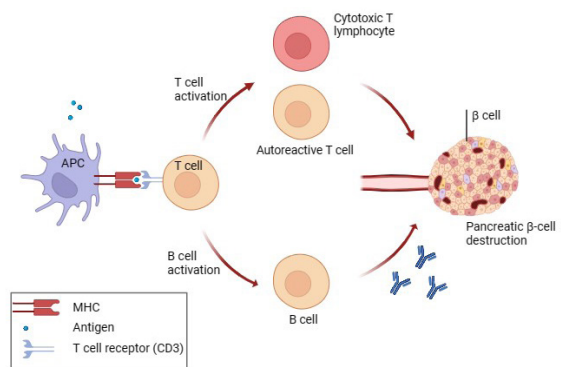
Fig. 1 The pathogenic mechanism of T1DM.

According to the pathogenesis of T1DM shown in Figure 1, pancreatic autoantigens are processed by resident antigen-presenting cells (APCs), which then migrate to pancreatic lymph nodes. Here, they activate autoreactive CD4+ T cells, causing them to proliferate. These activated CD4+ T cells target pancreatic β cells, inducing insulitis, which is characterized by attracting cytotoxic T cells and other inflammatory cells. The production of pro-inflammatory cytokines will further exacerbate the T lymphocyte response. B lymphocytes may act as APCs early in the disease, producing antibodies against antigens. The core focus is on the dysregulated immune response against pancreatic β cells. On this basis, T1DM therapeutic drugs can be designed to intervene in the autoimmune process. For the mAb therapy, its targets are shown in Figure 2.

Fig. 2 Schematic diagram of the action targets of Teplizumab and Otelixizumab

Teplizumab and otelixizumab are two non-Fc receptor-binding CD3-specific humanized mAbs. These antibodies exhibit a biphasic mechanism of action, providing a dual approach to mitigate the underlying autoimmune response in T1DM. As shown in Figure 2, these antibodies block the activation of pathogenic T cells to a certain extent, thereby temporarily reducing the immune attack on pancreatic β cells. The second phase is the induction of Treg, which plays a crucial role in immune regulation and tolerance maintenance. Specifically, it produces IL-10 as well as FOXP3 CD4 and CD8 [8].

The CD4 Treg cell population exerts its regulatory functions primarily through the production of transforming growth factor-β (TGFβ) and IL-10. These immunoregulatory cytokines help suppress the activity of autoreactive T cells, thereby restoring immune tolerance and preventing further β cell destruction [9]. Briefly, teplizumab and otelixizumab can suppress immune responses, enhance self-tolerance, and prevent autoimmune-mediated pancreatic β cell damage by promoting the expansion of Treg cells.

Notably, this induced Treg population cooperates with other immune regulatory mechanisms, including those mediated by APCs and major histocompatibility complex (MHC) molecules, can orchestrate immune homeostasis and prevent abnormal autoimmune responses in T1DM [10].

3.2 GDF15

GDF15 can act through multiple mechanisms and have varying effects on cellular processes relevant to the pathophysiology of various diseases, including T1DM. Understanding the mechanism of GDF15 can provide insights into its therapeutic potential for T1DM. GDF15 has emerged as a key regulator of β cell survival and regeneration [11]. Preclinical studies have demonstrated its ability to protect pancreatic β cells from cytokine-induced apoptosis, a process associated with autoimmune destruction of β cells in T1DM [12]. Additionally, GDF15 promotes β cell proliferation and regeneration, helping to maintain and restore β cell mass in the pancreas.

GDF15 is a protein that plays critical roles in various physiological processes, including metabolism, inflammation, and tissue repair. The mechanism of GDF15 involves its interaction with specific receptors and downstream signaling pathways. GDF15 works by binding to specific receptors on target cells. The primary receptor for GDF15 has been identified as GDNF family receptor alpha-like (GFRAL) [13]. GFRAL requires the coreceptor RET to initiate intracellular signaling. Therefore, GFRAL is critical for mediating the anti-obesity effects of GDF15. After GDF15 binds to its receptor complex, it activates intracellular signaling pathways that regulate various cellular responses. For example, GDF15 has been shown to induce anti-apoptotic effects in cardiomyocytes. In addition, the response of endothelial cells to high glucose stimulation can be attenuated [14]. In terms of inflammation, GDF15 has been shown to play a role in regulating immune responses and promoting tissue tolerance. It can induce immune tolerance in acute infections and sepsis by mobilizing triacylglycerols in the liver, thereby reducing systemic inflammation [15].

3.3 IL-2

Treg have been shown to induce tolerance in T1DM [16]. IL-2 is a key cytokine that affects Treg. Therefore, under-

standing the mechanism of Treg function in the context of T1DM can better understand the role of IL-2.
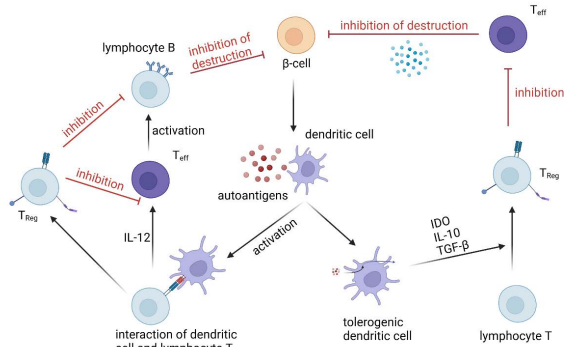
Fig. 3 Mechanism of the suppressive action of Treg lymphocytes in T1DM

As shown in Figure 3, Treg can inhibit the activation and function of effector T cells, which are responsible for co-ordinating immune responses and pro- moting inflammation. This means that inhibiting the activity of Teff helps attenuate the autoimmune attack on pancreatic β cells, thereby slowing the progression of T1DM. IL-2 is crucial for the survival and proliferation of Treg cells, and its IL-2 receptor (CD25) is highly sensitive to IL-2 signaling. By providing exogenous IL-2 cytokines, it induces immune tolerance, increases the number of Treg cells, and enhances the regulatory ability of the immune system, thereby protecting the function of the remaining pancreatic islet β cells [17]. This provides inspiration for long-term treatment of T1DM.

4. Clinical Outcomes

Clinical trials of teplizumab have shown promising results in delaying the onset of clinical T1DM and preserving β cell function. In a phase 2 trial involving high-risk relatives of patients with T1DM, teplizumab significantly prolonged the meantime to diagnosis of T1DM compared with placebo (48.4 months vs. 24.4 months), with annualized diagnosis rates of 43% and 72%, with a hazard ratio of 0.41 (p= 0.006) [4]. Adverse events included rash and transient lymphopenia, and no significant long-term side effects were observed. In contrast, studies with another monoclonal antibody, octelizumab, showed different results. The 9 mg dose was shown to preserve β cell function for up to 18 months, but higher doses (>18 mg) were associated with an increased risk of adverse effects related to cytokine release [18]. These findings highlight the potential of teplizumab in delaying the onset of T1DM and preserving β cell function, and also support the superior safety profile of teplizumab compared with otelizumab. Comprehensive clinical data on GDF15 are currently lacking as the specific function of GDF15 has not yet been elucidated, but research into its therapeutic potential has yielded important conclusions. In experiments on NOD mice [6], administration of recombinant GDF15 significantly reduced insulin inflammation, simultaneously leading to a decrease in markers of oxidative stress and lipid peroxidation, supported by a decrease in 4-hydroxynonenal (4HNE) immunostaining. Additionally, mice treated with rGDF15 had a 53% reduction in the incidence of diabetes compared with controls, and ongoing monitoring showed that treated mice had a lower incidence of diabetes. Immunostaining analysis of pancreatic sections provided by diabetic patients revealed that GDF15 abundance was significantly reduced in islets from patients with T1DM compared with non-diabetic patients, supporting a potential therapeutic role of GDF15 in T1DM. Overall, these findings highlight the protective role of GDF15 on islets and its potential as a promising target for treatments aimed at preventing or delaying the onset of T1DM.

The therapeutic potential of IL-2 for T1DM was demonstrated in a Phase I study conducted at Yale University and UCSF using a comprehensive approach involving nine eligible T1D patients [19]. The treatment regimen consisted of a single infusion of autologous polyclonal Tregs, followed by one to two 5-day courses of recombinant human low-dose IL-2. Results showed a significant increase in both infused and endogenous Tregs, with concomitant effects on various immune cell subsets, including activated NK cells, mucosal-associated invariant T cells, and clonal CD8+ T cells. This combination of agents is designed to enhance Treg survival and function, potentially halting the progression of T1DM.

5. Conclusion

In conclusion, research into protein therapies for T1DM has demonstrated great potential. These studies of mAbs targeting immune cells, growth factors, immunoregulatory cytokines, and signaling molecules respectively provide different options for potential therapeutic strategies. This article illustrates the importance of continued research in this area by highlighting the understanding of the mechanisms of T1DM and the impact of protein therapies on immune regulation and β cell function..

Research still has limitations, and many studies are still in preclinical or early clinical stages, especially those related to GDF15. Further research is needed to understand its specific function before it can be safely promoted. Furthermore, although protein therapies show promise in attenuating autoimmune responses and preserving β cell function, they still cannot fundamentally address T1DM, such as preventing disease onset or long-term complications. For patients, there is hope that they can escape the

burden of insulin injections and significantly delay the course of T1DM.

Going forward, future research should focus on addressing these limitations and exploring new therapeutic approaches. This includes studying combination therapies that simultaneously target multiple aspects of T1DM pathophysiology and developing personalized treatment strategies based on individual patient characteristics. Additionally, ongoing research should continue to focus on the underlying mechanisms of protein therapeutics and their long-term effects on immune regulation and β cell function.

In conclusion, although protein therapy represents a promising approach to the management of T1DM, further research is needed to optimize its efficacy, safety, and long-term outcomes. By addressing current limitations and exploring new avenues for intervention, future research has the potential to change the landscape of T1DM treatment and ultimately significantly improve the lives of patients with T1DM.

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