

New Approaches to the Immunotherapy of Type 1 Diabetes Mellitus Using Interleukin-27

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Abstract

Type 1 diabetes (T1D) is a pancreatic beta cell specific autoimmune disease. One of the most significant current discussions in T1D studies is therapy. Since the conventional therapy, islet transplantation and external insulin, e.g., cannot prevent the destructive autoimmune process against original beta cells and persistent hyperglycemia remains, so recent developments in the field of T1D therapy paved the way to a renewed interest in immunotherapy based on the disease process, especially monoclonal antibody therapy. Due to encouraging laboratory results, cytokine antibody-based drugs could be effective in the clinical direction of the T1D disease process. Hence, implementation of this approach can be useful to improve clinical and laboratory manifestations of T1D.

Introduction

Type 1 diabetes initiates with an autoimmune process, results from self-reactive CD4⁺ and CD8⁺ T cells, that is followed by massive immune-mediated destruction of pancreatic β cells of langerhans islets. T1D has been reported worldwide. Nonetheless, it has an unusual geographic distribution with highest incidence in the Nordic countries.^{1,2} Typical symptoms (urination, excessive thirst and hunger) as the clinical signs result from the underlying hyperglycemia that is in turn caused by inadequate amounts of insulin.^{1,3} Destruction course of insulin-producing β cells is caused by infiltration of dendritic cells, macrophages and T lymphocytes.⁴ There are three conventional therapeutic options used for treating T1D, which are currently available: insulin therapy, transplantation and immunotherapy. In spite of the success of insulin therapy, it is now obvious that even discrete control of blood glucose via receiving exogenous insulin only delays, but does not prevent the development of diabetic complications. Also replacement of β cells could be accomplished by transplantation of islets or stem cells or through islet regeneration. Meanwhile, lack of abundant source of donors for islet transplantation and the active destructive autoimmune process against the original β cells limit the application of these methods.⁵ T1D has an autoimmune and subsequent occurrence some stages in insulinitis and invading immune cells produce cytokines such as IFN- γ , TNF- α , IL-6 and IL-1 β , cytotoxic to pancreatic β cells.^{6,7} Correlation studies between local cytokines expressed in the islets and autoimmune diabetes have shown that β cells destructive insulinitis is associated with increased

expression of pro-inflammatory cytokines (TNF α , IFN γ and IL-1) and other type 1 cytokines such as IFN γ , TNF β , IL-2, IL-6 and IL-12.⁶ It is plausible that cytokines (IL-1, TNF α , TNF β and IFN γ) exert direct cytotoxic effects on β cells. As well, cytokines may sensitize β cells to T-cell-mediated cytotoxicity by up-regulating MHC class I expression (action of IFN- γ) and inducing Fas expression on β cells (via IL-1, and possibly TNF- α and IFN- γ).⁸

Therefore, therapeutics that modify the immune response and restore normal immune function is indispensable to improve the outcomes of T1D patients. Over the last 90 years, a minute altered has been achieved in the primary treatment of T1D, but immunotherapy techniques hold the promise of finding a factual treatment. A variety of therapeutic strategies have been developed to tolerize autoreactive T cells and prevents autoimmune pathology. Cytokines are critical mediators in autoimmunity. As many human autoimmunity is caused by an imbalance of cytokine production profiles of Th cells.⁹ So, future cytokine-based therapies may offer decreased toxicity and greater specificity in the treatment of autoimmune diseases such as type 1 diabetes by novel cytokine targets.¹⁰

In this context, Baslund et al. have experimented that neutralization or blockade of IL-15 is an attractive strategy for treatment of rheumatoid arthritis.^{11,12} Subsequently, IL-10 and TGF- β , has been reported as a novel therapy for T1D and inflammatory bowel disease (IBD) in animal models.^{13,14} In addition to preventive performance in systemic lupus erythematosus, G-CSF

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has been utilized effectively to prevent the diabetes onset in NOD mice, presently via Th2 polarization in both models.¹⁵ The previous study reported that an antagonistic form of IL-15 is one of few short-term therapies that enduringly restores islet self-tolerance in new onset diabetic NOD mice.¹⁶ Additionally, the IL-2 and IL-15 Ig molecule known as an effective therapy prevents type 1 diabetes in the NOD mice.¹¹

Evidence suggests that IL-12 is an incredibly attractive target for immune intervention in several autoimmune disorders.^{9,13,17,18} The pro-diabetic effect of IL-12 and other members of this family, IL-23 and IL-27, appears to be controversial. In this respect, despite the association between polymorphism of the IL-12B gene, which encodes the p40 subunits of IL-23, with a late onset of type-1 diabetes in humans, Mensah-Brown *et al.* observed that animals treated with IL-23 had significant hyperglycemia and enhanced diabetogenesis.¹⁵

Interleukin 27 (IL-27), a recently identified cytokine, is a heterodimeric molecule of IL-6/IL-12 family members. It is composed of two subunits: Epstein-Barr virus induced gene-3 protein and IL-27 p28.¹⁹ EB13 was first recognized from the screen of genes expressed in Epstein-Barr virus transformed B cell lines. The following recognition that IL-27p28 is a partner for EB13 was a result of a computational approach, using the genomic databases that appeared in the late 1990s, to identify novel α -helical cytokines of the IL-6/IL-12 family.²⁰

IL-27 receptor consists of a signaling chain gp130, a shared subunit of the IL-6R family, and the WSX-1 subunit (TCCR) homologous to IL-12R.²¹ Initial studies have recommended that IL-27 can promote inflammation by inducing T helper type 1 (Th1) differentiation in the early hours during immune responses.^{19,20} However, current data have suggested that IL-27 regulates pro-inflammatory responses as well as anti-inflammatory responses.²⁰ It promotes rapid clonally development and differentiation of naive CD4⁺ T cells, stimulate the activation of mast cells and NK cells, manage B cell immunoglobulin class switching. So, plays an essential role in the link between innate and adaptive immunities. IL-27 is an impressive cytokine while it could exert two distinct roles: one as an initiator and the other as an attenuator of immune responses (Figure 1).²²

The main quandary to be clarified before the IL-27 signal as a promising target of immune therapy is the obvious dissection of the pro- and anti-inflammatory signal pathways downstream of the IL-27R.²³⁻²⁵ IL-27 is highly expressed in IBD and EAE.^{26,27} Therefore, management of IL-27 for these patients may become a novel therapeutic approach.²⁸ Also, studies reported an important implication of multiple sclerosis patients' response to IFN- β therapy. Furthermore, IL-27 can exert a suppressive effect on inflammation and can attenuate collagen-induced arthritis when administered at the onset of the disease.²⁹

To discern the role of IL-27 in T1D, Y. Li *et al.* used diabetes-transfer model and it was concluded that

blockade of IL-27 can reduce the incidence of diabetes, while IL-27-treated diabetic splenocytes from 12-week-old NOD mice can promote diabetes onset or occurrence.³⁰ Also according to corroborant data, it is suggested that IL-27 is the most essential key for diabetes-onset in NOD mice.^{31,32}

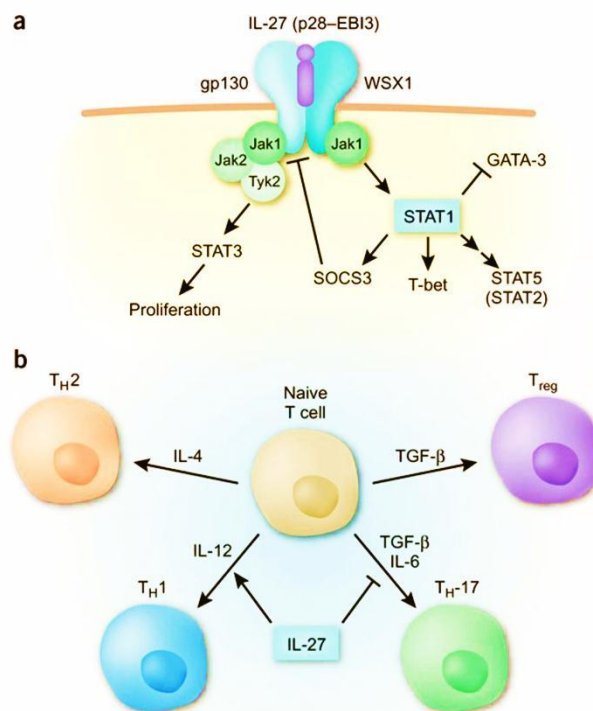


Figure 1. Regulation of CD4⁺ T cell differentiation by IL-27. (a) Components of IL-27 and its receptor. Engagement of the IL-27 receptor recruits Jak kinases. Substrates for the Jak proteins include the STAT transcription factors, which enter the nucleus and modulate target gene expression after being phosphorylated. Tyk2, tyrosine kinase 2. (b) CD4⁺ T cell differentiation, emphasizing the involvement of IL-27 and other IL-12 family members (IL-12 and IL-23). TGF- β , transforming growth factor- β ; Treg, regulatory T cell.⁴⁴

Previous studies showed that recombinant IL-27 could induce enhancement and secretion of IFN- γ by naïve CD4⁺ T cells.³³ This proposed that IL-27 plays a potential role in T1D. Moreover, it is found that T CD4⁺ cells are crucial case for splenocyte-transferred diabetes. Furthermore, IL-27 promote diabetes by affecting T CD4⁺ cells.³⁰ Conventional therapeutic approaches suppress the activity of the leukocytes (anti-inflammatory) and lymphocytes (immunosuppressive) in T-cell-mediated diseases. Extension or blocking of IL-27 signaling have been demonstrated widely in various disease models.^{34,35} In addition, IL-27 treatment suppressed inflammation in the joints, and production of IL-17, IFN- γ , and IL-6.²⁹ In the course, by the advent of monoclonal antibodies (mAb) directed against any antigens of significance, drug immunoconjugates, recombinant mAb-cytokine fusion proteins, immunotherapy based on mAb-therapy of human autoimmune disease has been presented for the first time.³⁶ Throughout the last ten-year period, Infliximab (chimeric

anti-TNF- α monoclonal antibody), Teplizumab (anti – CD3 monoclonal antibody (humanize) hOKT3 γ 1 (Ala-Ala)) used for diabetic patients. Laboratory observations and gene genomic researchers suggested that IL-27 involve in the pathogenesis of T1D.^{15,30} The further characterization of inflammatory features of T1D disease may eventually lead to the development of better treatment modalities.^{37,38}

Clinical and laboratory observations proposed a central role of IL-2, IL-12 family and Th1cells- mediated process in the pathogenesis of T1D.⁸ IL-27p28 might be a capable therapeutic agent that limits inflammation and following disease by inhibition of gp130 signaling.

In support of a role for IL-27 in intensification inflammation in human disease, It is assumed that increased susceptibility to chronic hepatitis B virus infection is associated with IL-27 gene expression. Furthermore, serum levels of IL-27 have been significantly higher in patients with ischemic heart disease compared with the healthy control group.^{24,35,39}

In a monozygotic quadruplet case study, IL-27 signaling, have been reported as one of the most differently managed immune signaling cascade between the diabetic and the non-diabetic quadruplets ($p=0.0034$). The gene expression arrays data showed IL-27 signaling pathway contributed to the onset of T1D in two of the quadruplets.⁴⁰

IL-27p28 gene expression is mediated through MyD88–NF- κ B Signaling pathway is regulated by factors such as IFN- γ .⁴¹ Beside it has been suggested that activation of TLR-2 and TLR-4 leads to the downstream cytokine and NF- κ B production. Again, TLR-2 identifies the β -cell death as a mediator of inflammation. TLR-2 particularly is involved in the inflammation process through the MyD88-dependent pathway. So the TLR pathway (MyD88-dependent) inhibition can be an option to control the complications of diabetes.^{42,43}

Considering the fact that if in new studies, researchers focus on this perspective, it could possibly be found a better aspect in T1D disease therapy based on its immunopathogenesis. On account of encouraging clinical results; antibody-based drugs against IL-27 (In order to block or neutralization IL-27p28) could be effective for the clinical management of T1D disease.

In this case, confirmation of the inhibitory function of IL-27 can be helpful for development of new therapeutic agent objecting T1D. Although the role of IL-27 in human immune system is so composite, further research is required. In conclusion, this arrangement is regarded as one suggest to alternative therapy by neutralization of IL-27p28 or its signaling network as an acceptable immunological intervention target.

Ethical Issues

Not applicable.

Conflict of Interest

The authors report no conflicts of interest.

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