

Investigating the Role of Immune System in Type 1 Diabetes

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Abstract. Type 1 diabetes (T1D) refers to the immune system's eradication of the cells that produce insulin in the patients' islets. Dendritic cells (DCs), macrophages, and lymphocytes are some of the immune cells attended in the relevant immune responses and have been connected to the pathogenesis of T1D. In addition, it is also highlighted that cytokines also activate regulatory processes, like tumor necrosis factor α (TNF- α), interleukin 6 (IL-6) and interleukin 7 (IL-7). It is possible to develop clinical trials for T1D that combine selective cytokine blocking as a component of preventive or interventional immunotherapy. In this project, the current knowledge on the relationship between inflammation and T1D is summarized. Non-specific immune system and specific immune system are highly involved in the complex mechanism and have specific responsibilities respectively. In addition, the roles of different types of cytokines in T1D and cytokine-related potential treatment options are also be discussed in this article.

Keywords: Type 1 Diabetes, Inflammation, Cytokines.

1. Introduction

Within two to three decades, a comprehensive understanding of the molecular pathways behind cell toxicity has been amassed. Except in the case of islet transplantation, the effectiveness of specific proinflammatory cytokine inhibition in animal models of T1D has been erratic and typically limited. As a chronic autoimmune disorder, T1D is characterized by the slow and sneaky elimination of beta cells [1]. The destruction of pancreatic cells and overt hyperglycemia in this state are caused by immune system malfunction, which is primarily mediated by islet activation, T helper 1 (Th1) cells, and immune cell infiltration [2]. It is believed that islet damage or physiological cell death results in T1D by homing macrophages and DCs, which subsequently trigger an inflammatory response. Pro-inflammatory cytokines and others that attract macrophages, T lymphocytes, and DCs speed up inflammation in patients' systems. Besides, some non-specific immune cells including macrophages and DCs can present the specific antigen to active lymphocytes to attend the responses [3].

Exogenous insulin replacement is the mainstay of current T1D treatment, underscoring the need for immunotherapies to slow the progression of the disorders and enhance therapeutic results. During the early stage of this biphasic autoimmune disease, known as insulinitis, a variety of leukocytes enter the islets. The bulk of the cells eventually die when the islet infiltration changes from a mostly benign interlude to a pathological lesion. The consequent loss of glucose homeostasis results in a series of incapacitating disorders known as diabetes. The destroy of insulin-producing beta cells in pancreatic islet cause T1D. In this project the different regulating roles of specific and non-specific immune system will be illustrated.

Targeting proinflammatory cytokines for treatment is clinically useful in a number of autoimmune disorders. The functions of several typical cytokines and related therapies for T1D will be discussed in the following sections as well. It is possible to develop clinical trials for T1D that combine selective cytokine blocking as a component of preventive or interventional immunotherapy since some of these cytokines are directly implicated in the pathophysiology of the disease. Interventional strategies that aim to preserve the largest number of endogenous cells while treating the underlying autoimmune illness.

2. Innate immune system

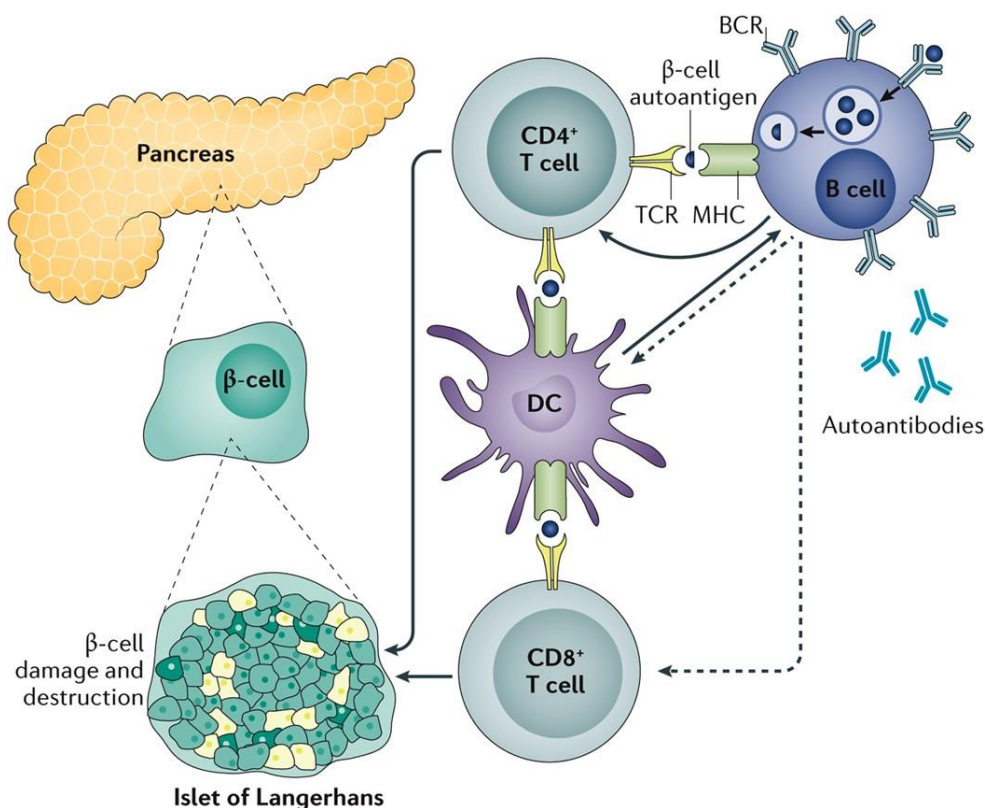
2.1. DCs and macrophage

Antigen-presenting cells (APCs) are critical for the causes and control of inflammation, including innate and adaptive, effector, and tolerance responses. Due to their distribution in peripheral tissues and their capacity to react to pathogens by recognizing the special pathogens through toll-like receptors (TLR), they form a dense network serve as immune system sentinels [4].

The behavior of the immune response is heavily influenced by DCs and macrophages [4]. On the one hand, they help people develop and maintain self-protection, while on the other hand, they help individuals lose the tolerance and develop disease.

As APCs, DCs and macrophages have the ability to phagocytose pathogens and damaged cells to form specific antigens and then present to lymphocytes. As seen in Figure 1, DCs develop and change from a tolerogenic to an immunogenic phenotype by upregulating major histocompatibility complex (MHC) and costimulatory molecules. Furthermore, they are responsible for the secretion of cytokines which relevant to inflammation as well, therefore evoking a robust immune response in the presence of proinflammatory signals and pathogen-derived products. Naïve T cells are normally activated by APCs in peripheral lymphoid organs during immunological responses [5]. The tissue-derived antigens that circulating naïve T cells detect must be delivered to T cell zones of neighboring lymphoid organs and converted into MHC-peptide complexes since they typically cannot access peripheral nonlymphoid tissues. The T cells multiply and differentiate into effector cells upon antigen recognition and activation, which circulate through nonlymphoid tissues and are retained where they recognize cognate antigen.

Recent research suggests that by enhancing culture conditions, actively suppressing genes, or encouraging their overexpression, DCs gain tolerogenic features during in vitro manipulations, with therapeutic promise in the prevention and treatment of autoimmune diabetes.



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Figure 1. Schematic of DCs involving in the pathogenesis of T1D [6]. Activated DCs can present antigens to T cells to accelerate the immune responses in T1D.

2.2. Neutrophil

DCs and macrophages can become active and mature by responding to signals from neutrophil activation. Neutrophils also regulate T-cell immunity to a range of pathogens and tumor antigens [7]. Some research on neutrophils has revealed that they are the genuine masters of regeneration and resolution, not just plain suicidal killers. Evidence of both ongoing neutrophil recruitment to the site and prevention of neutrophils' normal spontaneous apoptosis during the resolution of inflammation, which lengthens and intensifies the inflammatory response, support the persistence of neutrophil stay in the wound site [7]. Previous studies demonstrate that natural killer cells play a critical role in associating with other leukocytes directly and indirectly. For instance, interleukin 17 (IL-17) secreted by type 17 helper T (Th17) cells could improve neutrophil proliferation and recruitment to the pancreas. Damage and death of β -cells could occur as a result of local infiltrating neutrophils.

3. Adaptive immune system

The adaptive immune system is relied upon to cooperate in reaction if the non-specific immune system is unable to eradicate the pathogen on its own. The particular bacterial or viral strain that is causing the illness is the focus of the lymphocytes. The adaptive immune system is more focused than the innate immune system, yet it takes longer to react to an infection. Ability of remembering is beneficial as well, which enables the specific immune system to react more swiftly when it detects a recognized germ. Some illnesses are only communicable once in a lifetime due to this memory since the body then develops "immunity." When a pathogen is discovered for the first time, the adaptive immune system could take a few days to react, but the body can react right away the next time. The second infection sometimes does not even get unnoticed since it is so light.

3.1. T cells

T lymphocytes, commonly referred to as T cells, are primarily produced in the bone marrow before traveling via the bloodstream to the thymus, where they develop and differentiate. "T" in their name's is derived from the word "thymus". The autoimmune destruction of insulin-producing cells in the endocrine pancreas is caused by $CD4^+$ and $CD8^+$ T lymphocytes, as well as macrophages which invaded the islets, results in T1D, a multifactorial, organ and cell-specific disease.

During the asymptomatic period and early period of T1D, at-risk patients' autoantibodies and T cell responses to autoantigens can be identified. Autoantibodies are the reliable diagnostic and prognostic hallmarks, and autoreactive T cells are considered as the primary target of T1D immunotherapy. In human T1D, cell-mediated immunity to insulin was first observed in 1975 [8]. The rapid cloning of human insulin-specific T cells was made possible as a direct consequence of recent developments in T cell cloning as well as the discovery of the genes encoding for T cell receptors. This gave rise to the idea that T1D may be treated without harming the entire T cell repertoire by depleting specific T cells (and thus inducing global immunosuppression). However, the research done by Culina S have shown the fail in removing or deactivating insulin-specific T lymphocytes to halt T1D [8].

The hypothesis that $CD4^+$ and cytotoxic T lymphocytes are essential in the demise of insulin producing cells is supported by analysis of pancreatic slices obtained from T1D patients, which showed fulminant immune infiltration inside individual islets. Recent studies on non-obese diabetic animal model illustrated that islet-reactive T lymphocytes which express CD4 are the main reason cause the inflammation and are responsible for the producing of certain cytokines like interferon gamma (IFN). There is evidence that in human T1D, beta cell death is predominantly mediated by cytotoxic T lymphocytes when the other subset of T lymphocytes can indirectly attend this process through transferring the phenotype of macrophages. It's intriguing to consider that regulatory T cells (Tregs) could provide a method for achieving islet-specific tolerance in autoimmune disorders. Therefore, in both transplantation models and autoimmune models, it is particularly desirable to use immunotherapies that develop an expansion of Tregs.

3.2. B cells

Regulatory B cells (Bregs) could intervene the immune response earlier than Tregs and also critical in the development of autoimmune and allergy disorders. In addition to antibodies production ability, B cells also can serve as antigen presenters. Previous research has shed light on the antibodies producing cells' function in the generation of cytokines and autoantibodies in response to islet antigens. Uncertainty exists about the precise pathogenic mechanism of B cells in T1D. Research on T1D mice has shown that islet-reactive B lymphocytes provide a developing risk in the etiology of T1D, most likely by transferring the autoantigens to the inflammation relevant T cells. [9]. Lack of antigen presentation due to loss of B cell anergy may be brought on by inherited or environmental factors. T1D is most likely caused by T cells being excessively activated and proliferating as a consequence of pancreatic cells being killed as a result of B cells presenting an antigen. One of the greatest markers of T1D pathophysiology islet autoantibodies. People who have high-affinity anti-insulin antibodies or antibodies to more than one islet antigen might practically acquire T1D throughout their lifetime. The presence of autoantibodies suggests that B cells are one of the pathogenic factors in T1D and are a sign of the onset of the disease. However, the pathogenicity of these antibodies is unclear. Multiple studies suggest that the production of autoantibodies is an epiphenomenon that results from anergic B cell activation. Previous study demonstrated that the mutation is essential for the upregulation of antigen-specific T lymphocytes in the peripheral via downregulating T cell tolerance to insulin in the thymus. More immune cells may get implicated in the disorder as a result of increased the certain subpopulation of T cells activating the inflammation attended B lymphocytes.

4. T1D related cytokines

Numerous cytokines are identified as the possible position to develop the immunotherapeutic strategies for T1D. It is believed that cytokines, which may activate regulatory mechanisms like interleukin 10 and transforming growth factors, restore immunological tolerance and guard against cell apoptosis. On the other hand, cytokines that improve the transform and activity of specific immune cells that cause diabetes are thought to be responsible for the onset and progression of T1D.

4.1. IL-6

By successfully treating a portion of autoimmune illnesses by focusing on the IL-6 receptor (IL-6R) and relevant proteins, it has been illustrated that this cytokine has pathogenic importance. Autoimmune disorders develop and advance via the action of IL-6 [10]. The efficiency of therapeutic IL-6 inhibition in sustaining cell function in T1D with sudden onset is being studied in current clinical research.

Macrophages, B cells, and T cells were shown to be infiltrated along with a pronounced insulinitis when IL-6 was overexpressed in the local pancreatic cells. In T1D, IL-6 may mediate effector T cell migration and inflammatory reactions. IL-6 also can stimulate CD4⁺ T cells possessed a unique transcriptome and genes that are overexpressed involved in T-cell migration and activity, according to whole-transcriptome analysis. These findings show that IL-6 is context-dependent and that it has several degrees of action.

4.2. TNF- α

TNF- α is an important cytokine that regulates the formation of DCs and is associated with the activation of islet-specific T lymphocytes in pancreatic lymph nodes. The first studies to record the existence of TNF- α generating macrophages and DCs found in invades of islet cells demonstrated that these cells were the main and earliest makers of TNF- α . Furthermore, these cells were found in infiltrates of pancreatic islets. TNF- α has been shown to upregulate MHC-I molecules, which increases cell death. Thus, through a CD40/ CD154-independent mechanism, islet-infiltrating dc and macrophages cross-present exogenous islet antigens to CD8⁺ T cells. According to other studies, TNF

increased the maturation of DCs, possibly recruiting diabetogenic T lymphocytes to the tissue. These results suggest that TNF- α is essential for the onset of T1D. Anti-TNF therapy eliminates the resistance of insulin in newly diagnosed T1D mice, according to research. Self-tolerance, normal insulin activation, and stable glucose regulation are all restored by interim anti-TNF monotherapy.

When considered collectively, the findings of previous research confirm that this kind of cytokine have a diabetogenic function in the development of T1D and enhance the case for TNF- α targeting as a novel treatment approach.

4.3. IL-7

A pro-inflammatory cytokine called IL-7 affects the continuation and growth of immature T lymphocytes. Additionally, inhibiting IL-7 receptor (IL-7R) can increase Tregs without changing their suppressive function. Through its interaction with the IL-7 receptor, IL-7 is necessary for the growth and homeostasis of T lymphocytes. IFN-producing cells can differentiate when the naive T cells are exposed to IL-7. Furthermore, it has been shown that the inhibitory programmed death-1 (PD-1) receptor is expressed less when IL-7 is present in diabetogenic T cells. These studies' results imply that IL-7 has a pathogenic role in T1D. Additionally, IL-7 is essential for the immunoregulatory function that DCs play in delaying the development of T1D. These findings demonstrate the importance of IL-7 signaling in maintaining the equilibrium between immunosuppressive cells and diabetogenic T cells in T1D. IL-7R suppression reduces the number of IFN-secreting T lymphocytes while raising the quantity of Tregs, according to research on NOD mice. Together, these results suggest the feasibility of blocking the IL-7 and IL-7R crosstalk in T1D to preserve immunological homeostasis and cell function, although the clinical effectiveness of this strategy has not been shown.

5. Conclusion

As outlined above, the staging of inflammation throughout both the start and destruction phases of T1D is largely regulated by cytokine networks. This insight into the pathophysiology of the disease and prospective treatment options has been truly astonishing. Clinical trials are presently evaluating methods to target certain cytokines. The function of cytokines may be influenced by immune cell plasticity, which might alter their regulatory or pathogenic effects in the diverse T1D microenvironments.

The most important questions are not which cytokine is at the root of the disease, but how immune cell function changes as the disease progresses, which tissue microenvironments contribute to the development of the disease, and the significance of cytokine networks implicated in the development of T1D. DC's maturational stage and the surrounding microenvironment are key determinants of how it behaves.

Over the course of T1D pathogenesis, inflammatory cytokines sensitize cells to cell death in many ways, which have been the subject of substantial recent fundamental biomedical study. Numerous molecular players in these stressors have been discovered. Particularly, the pro-inflammatory factors have been recognized as significant contributors to β -cell stress and mortality in T1D. To significantly facilitate islet transplantation, modern gene transfer techniques that help reduce the exposure of transplanted islets to cellular and autoimmune-mediated stress can be used. The idea that the islets and the immune system interact is demonstrated by the cytokine-induced synthesis, and that it is this interaction that triggers Insulinitis that is an important cause of diabetes. Proinflammatory cytokines have a noticeable effect on T cell regulation, induction of tolerance, and adaptive and innate immunity, according to a wealth of in vitro data. Contrastingly, individual proinflammatory cytokine blockade has been inconsistent and generally ineffective in treating T1D in animal models, with the exception of islet transplantation. This suggests that combination therapy may be necessary or that timing of the cytokine blockade relative to anti-cell immune activation is crucial.

In general, targeting proinflammatory factors are a feasible treatment for T1D, and more research and experiments are needed in the future to develop related therapies.

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