

Deep Learning the Crosstalk between Follicular Helper T cells and Type 1 Diabetes

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Abstract. Damaged beta cells can lead to type 1 diabetes (T1D), which influences people worldwide. Individuals with T1D have higher risk of developing other cardiovascular disease although life-insulin injection is taken. However, the specific reasons which trigger the destruction of beta cells are still not fully understood. Researchers demonstrated the importance of follicular helper T (Tfh) cells in T1D development. Tfh cells refer to a specific subpopulation of CD4⁺ T cells which normally express an upregulated C-X-C chemokine receptor type 5 (CXCR5). The dysregulated Tfh cells can be widely found in T1D individuals, which could be caused by excessive antigen presenting process. Mutation of several gene are also shown to be associated with the abnormal Tfh cells. Furthermore, increasing Tfh cells can secret more interleukin-21 (IL-21) to recruit CD8⁺ lymphocyte to damage beta cells. Besides, antibodies producing function of B cells could also be enhanced by Tfh cells to accelerate T1D. In this project, the mechanism of Tfh involving in T1D will be explained in detail.

Keywords: Follicular Helper T Cells, Inflammation, Type 1 Diabetes.

1. Introduction

T1D is thought to be caused by autoimmune responses that target the beta cells in the pancreas. Originally, these beta cells are responsible to produce insulin which is a regulator for coordinating the blood glucose level. As a result, dysfunction of beta cells and insufficient insulin cause hyperglycemia, which further leading to the endothelium dysfunction. As a prevalent disease, the number of patients with T1D has increased to 8.4 million all over the world [1]. One-fifth of them were from low-income and lower-middle-income countries [1]. In addition, researchers predicted that the number of cases of T1D would reach 13.5-17.4 million by 2040. Then these predictions and appalling numbers give the governments a warning to increase spending on research for the treatment. For example, the UK government spent 1.9 billion pounds from 2010 to 2011 on direct costs and indirect costs of T1D. Nevertheless, studies make a prognosis that the government spending on T1D will increase to 4.2 billion pounds by June 2035 [1].

However, the pathology of T1D is still need to be studied. One thing that people have already found is that T1D is an autoimmune disease, and it provides a hint for researchers to study the immune responses for the development of T1D treatment. The specific islet antigens in the human pancreas can trigger inflammation and are the indicator of the occurrence of T1D. T lymphocytes are central in the pathogenesis of T1D. Among them, cytotoxic T lymphocytes can kill the damaged beta cells to accelerate T1D when the main function of CD4⁺ T cells is to regulate other immune cells through secreting cytokines. In addition, B cells can produce specific antibodies to neutralize the antigens and regulate inflammation. Recent studies showed that a specific subpopulations of T cells may be mainly responsible for the progress of T1D. This specific Tfh cells are considered as the significant participant in stimulating corresponding B cells by secreting chemokines and cytokines, including IL-21. Also, they can improve the maturation of B cells in the secondary lymphoid tissues. Research has already shown that the level of Tfh cells substantially raises within T1D patients. In this project, the function of Tfh cells in T1D will be explained in detail.

2. Overview of T1D pathogenesis

T1D refers to an autoimmune disease that influences a wide range all over the world since they have to take lifelong insulin injections and expensive costs. In addition, T1D can increase the potential risk of other serious cardiovascular diseases such as cardiovascular disease [2]. This complex situation rises the burden on healthcare systems and societies. Currently, progress on the research of pathology of T1D has already been made. Evidence shows that there are some environmental factors that lead to increased incidence of T1D, including public hygiene and UV light. Simultaneously, it has been demonstrated that T1D is mainly caused by the damaged beta cells which are attacked by multiple immune cells and responses and then lose the insulin producing function. The healthy beta cells are responsible for the blood glucose balance [3]. People will lose control of blood glucose if the β -cells are destroyed.

As T1D develops substantially, islet-specific T cells are highly involved in the overactivated immune responses. Some non-specific immune cells including macrophages are the first team to migrate into the pancreas [4]. Then, it is possible to detect T cells surround the pancreas and these T cells are regarded as the original causes of T1D. It is because that these innate immune cells as the main antigen presenting cells (APCs) could transfer the antigen to the autoreactive T cells and activate them in lymph nodes. The recited $CD8^+$ could mediate the death of β cells. Furthermore, cytokines and chemokines would be secreted by both $CD8^+$ and $CD4^+$ T cell to prompt the auto-immune response. Besides, the attacked islet also can in contrast accelerate the inflammation [4]. At this time, genetic factors also contribute to the process that T cells attack self-beta cells. It can be discovered the spontaneous mutation of autoimmune regulator (AIRE) gene that regulates level of the islet relevant antigens. Additionally, insulin is an AIRE-regulated islet protein that plays a necessary role in epithelial cells [4].

While genetics contribute to T1D susceptibility, other factors, such as infection with the coxsackievirus, can also play a significant role. When rat pancreatic α and β cells are exposed to coxsackievirus, α cells boost gene expression for virus clearance to a greater extent than β cells. Induction of these cytokines regulated genes mounts an effective defense against the infecting virus. As initial infection isn't resolved in β cells, a persistent low-level infection can cause chronic inflammation and recruitment of immune cells [3]. It is believed that this differential ability to clear viral infections is a cause of selective β cell loss in T1D.

The complex situation of T1D is metabolic dysregulation which leads to elevation of blood glucose concentration. In healthy human body, blood glucose could increase after meal because it is absorbed through the gastrointestinal tract [1]. This increase in concentration of blood glucose could be detected by β cells in islet of Langerhans. After that, β cells do have the responsibility to secrete insulins to regulate the abnormal level of glucose. However, there are other products during the process of manufacturing insulin, such as C-peptide. Both C-peptide and insulin are processed from same precursor protein, and they are produced in equal level. So, the concentration of C-peptide is an important standard to find out whether patients have T1D. Insulin can also migrate to muscle cells, brain cells and other locations by blood circulation to decrease the blood glucose level. This mechanism involves glucose transporter (GLUT) to increase the permeability of cell surface membrane towards glucose. In contrast, the destruction of beta cell can cause the dysregulated metabolism [2].

3. Dysregulated Tfh cells in T1D

As the content mentioned the T1D is an autoimmune disease, and it is highly associated with Tfh cells. Evidence demonstrates that the number of Tfh cells elevated in the T1D patients' bodies. Investigators typically measure the level of Tfh through the universal markers CD4 and CXCR5, and other biomarkers can be applied in the research of Tfh cells.[4] However the involvement of Tfh in T1D pathogenesis is still unclear. Primarily, researchers tried to investigate the relationships between T1D and Tfh cells from their function. Researchers use non-obese diabetic (NOD) mice as their model

because they share similar pathophysiology of T1D with humans. As seen in Figure 1, complex mechanism and signal pathways are associated with the dysregulated Tfh in T1D. The sustained antigen presenting process target the T cell receptor (TCR) and encourage the proliferation of Tfh. Furthermore, the increasing self-reactive T cells further deteriorate the T1D. In addition, cytokines are also critical to regulate Tfh in T1D. Interleukin-2 (IL-2) are responsible to help the differentiation of Th1 cells. The upregulation of IL-2 is demonstrated to be associated with the decrease of Tfh by activate signal transducer and activator of transcription 5 (STAT5) to mediate the translation of B lymphocyte-induced maturation protein-1 (Blimp-1).

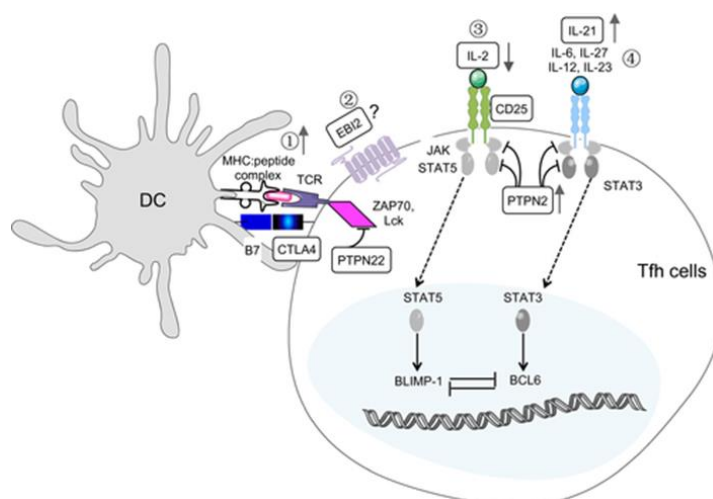


Figure 1. The schematic of potential single pathways involved in the dysregulated Tfh cells in T1D [5].

B In contrast, a group of Chinese researchers focuses on susceptible genes, and they have already discovered more than 50 types of relevant genes by connection analysis and data through genome-wide association studies [6]. Various kinds of genes play a central role to mediate Tfh cells relevant activities, such as cytotoxic T lymphocyte antigen (CTLA)-4, tyrosine phosphatase and non-receptor type (PTPN) 2 [7]. CTLA-4 is regarded as a significant suppressor for T cells activation, and massively present in Tfh cells [8].

As seen in Figure 2, Tfh cells is highly associated with pathogenesis of T1D through several different aspects. IL-21 that is an important cytokine secreted by Tfh cells is highlighted in T1D and IL-21 receptor (IL-21R)-deficient NOD mice have a lower rate of having T1D [9]. Meanwhile the upregulation of IL-21 can lead to the deterioration of autoimmune diabetes through recruiting more CD8⁺ T cells. Some other pro-inflammatory cytokines are also produced by Tfh cells to attend the inflammation in T1D. Besides, Tfh has the ability to recruit specific reactive B lymphocytes to attend the development of this disease. Furthermore, the recruited B cells could produce more specific antibodies to accelerate the immune responses.

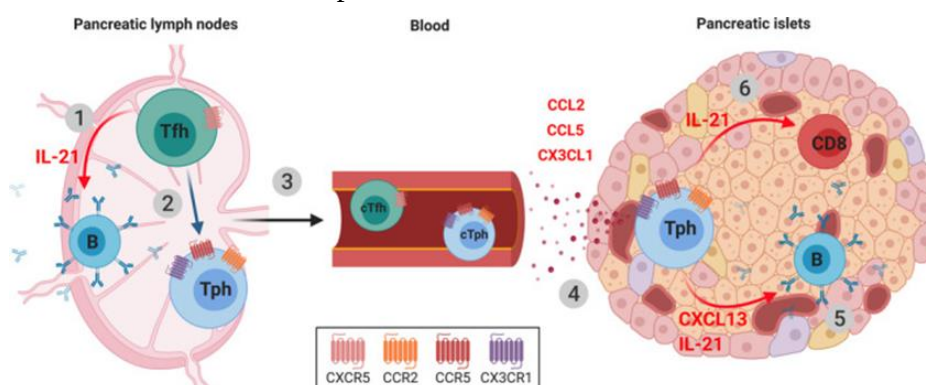


Figure 2. The schematic of potential mechanism that the Tfh cells cause T1D [10]. Tph is a subpopulation of Tfh with higher level of other 2 type of receptors.

4. Conclusions

The possible mechanism of Tfh cells' affection for the progress of T1D can be divided into two aspects. The first one is that biological markers or cytokines produced by Tfh cells stimulate corresponding CD8⁺ T lymphocytes and B cells to attend to the pathogenesis of T1D. This can be demonstrated by the ascending level of this kind of helper T cells and B lymphocytes around the pancreas in T1D patients. Specific cytokines target the position and activates enzyme-controlling reactions which lead to the immune response associated with furthering damage of the beta cells in the pancreas. The second one is that relevant genes in Tfh cells are involved in the activities and proliferation of Tfh cells. The mutation of these genes is the main reason for the abnormal proliferation of Tfh cells, which could prompt T1D progress. Also, there are several types of gene that affect T1D indirectly.

Given the understanding of the immune mechanism of T1D, several potential treatments are widely studied. Some researchers start figuring out the pancreatic β cells getting from stem cells which have made some progress in diabetes mice. This method can help T1D patients to get rid of the heavy burden of high costs and insulin life-long injections. However there still some limitations and problems about this cure such as production and its effectiveness in human body. Some other researchers focus on genetic engineering such as gene editing methods. Virus and non-virus vector delivery approaches are included in it. In 2013, it was first reported that a group transfer a short slice of DNA into T1D mice model to induce healthy beta cells. Recently, the gene therapy has been learned a lot and achieved huge progress. However, the most research on gene therapy for T1D are still in animal models. It is still difficult to transfer the results from animal experiment to clinical treatments. After all, it is expected that there will be more and more possible treatment for T1D that will be evaluated and applied all over the world.

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