Reprint from The Review of DIABETIC STUDIES Vol 6 No 2 2009

The Review of DIABETIC STUDIES

SHORT REVIEW

The Role of the CXCL10/CXCR3 System in Type 1 Diabetes

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Manuscript submitted July 27, 2009; resubmitted August 3, 2009; accepted August 7, 2009

■ Abstract

Despite intervention with insulin, type 1 diabetes gradually deteriorates the patients' quality of life. The disease is characterized by an immune-mediated destruction of pancreatic beta-cells. Its etiology, however, remains controversial. Some studies argue that glutamic acid decarboxylase (GAD) antigen and GAD-reactive T cells are critical players in the development of diabetes by affecting the Th cell balance. A T-helper 1 (Th1)-dominant immune response is considered to be important in beta-cell failure in both human and animal models of type 1 diabetes. The Th1-type chemokine, CXCL10, and its receptor, CXCR3, are involved not only in the immune response, but also in the suppression of beta-cell proliferation. Thus, understanding the CXCL10/CXCR3 system may be important for finding a cure. In this short review, we discuss the role of the CXCL10/CXCR3 system in type 1 diabetes and propose relevant treatment options.

Keywords: type 1 diabetes · GAD · T cell · CD4 · CD8 · T helper cell · Th1 · beta-cell proliferation · NOD · insulitis · CD45RB · IL-10 · IL-18 · IGRP

Introduction

Type 1 diabetes is an autoimmune disease characterized by the destruction of pancreatic beta-cells. It especially affects the young and the chronic complications reduce their quality of life. To date, there has been no cure for the disease. Even with treatment by islet transplantation, survival of the transplanted islets is less than 5 years in most cases [1]. There is pressing need for a better understanding of the disease pathogenesis and a new treatment strategy based on immune intervention.

The T-helper (Th) cell system is critical for a healthy immune system that balances reactive and suppressive cell compartments. It has been argued that an imbalance in the Th cell system, caused by a predominance of the Th1 response, favors the development of autoimmune diabetes [2]. CXCL10 is an interferon-gamma inducible chemokine and reacts with its receptor, CXCR3, on Th1 cells [3]. Elevated levels of CXCL10 were detected in new onset type 1 diabetes patients and correlated with levels of GAD-reactive CD4 T cells [4]. In addition, CXCL10 is produced by beta-cells, and suppresses beta-cell proliferation [5]. Therefore, we believe that the CXCL10/CXCR3 system plays a decisive role in the pathogenesis of type 1 diabetes. In this short review article, we take a closer look at the CXCL10/CXCR3 system, and discuss its relevance in the disease process and in potential therapy approaches.

The role of the Th1 response in beta-cell failure in the NOD mouse

In the non-obese diabetic (NOD) mouse model, insulitis, with lymphocytic infiltration into the islets, is observed from 5-6 weeks of age. However, this infiltration does not result in rapid onset of diabetes. It takes 3-4 months for the NOD mouse to become diabetic. Therefore, a regulatory mechanism must be at work in this model, at least until the onset of diabetes.

During the early phase of the disease, autoreactive lymphocytes react with insulin, which is why insulin is considered to be a primary autoantigen in type 1 diabetes [6]. Reactivity against insulin results in insulitis, but the occurrence of insulitis does not necessarily mean the onset of diabetes. Diabetes onset may be regulated by a different mechanism. One of the possible mechanisms is a change in the function of regulatory CD4 T cells, (CD45RB^{low} CD4 cells) during the disease course. In the "regulatory phase", glutamic acid decarboxylase (GAD)-reactive CD45RB^{low} CD4 cells produce IL-10, which suppresses the onset of diabetes [7]. This GAD-reactive IL-10 response by CD45RB^{low} CD4 cells balances the polyclonal Th1 response by the same cell type during the disease course. However, it has been reported that the function of CD45RB^{low} CD4 T cells can change from protective to pathogenic in NOD mice [8-10]. When the Th1 response by CD45RB^{low} CD4 cells overcomes the GAD-reactive IL-10 response, then diabetes onset can occur [7].

In fact, artificial induction of GAD-reactive T cells in an adoptive transfer system results in the induction of a GAD-reactive IL-10 response and diabetes suppression [11]. This finding supports the view that GAD-reactive responses can be regulatory. On the other hand, the induction of a Th1 response by IL-18 production results in an accelerated diabetes onset [12]. Therefore, the autoimmune Th1 response plays an important role in pancreatic beta-cell failure in type 1 diabetes. However, it is assumed that islet-specific glucose 6 phosphatase catalytic subunit-related protein (IGRP)-reactive CD8 T cells are the "actual killers" of beta-cells [13]. Increased proportions of CD8 T cells in islet lesions have been observed in both animal diabetes models and humans [14, 15]. Therefore, we hypothesize that Th1 cells cooperate with CD8 T cells to destroy beta-cells (Figure 1).

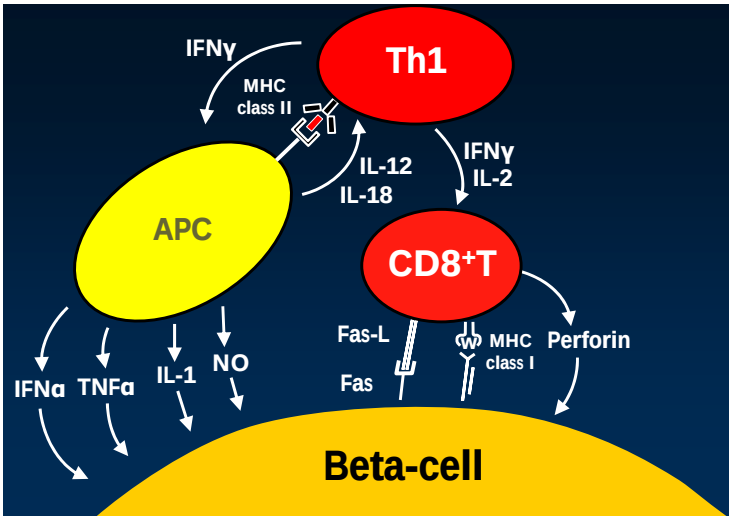

Figure 1. Hypothetical illustration of beta-cell destruction. The Th1 cell plays an important role in beta-cell destruction, although CD8 T cells are the actual killers. APC: antigen-presenting cell. IFNγ: interferon gamma. IL: interleukin. TNFα: tumor necrose factor alpha. NO: nitric oxide.

Th1 type chemokine CXCL10 in human type 1 diabetes

A Th1 type chemokine, CXCL10 (also known as IP-10), reacts with its receptor, CXCR3, which is mainly expressed on Th1 cells. These CXCR3-positive cells migrate towards regions of high CXCL10 concentration. Therefore, it has been suggested that CXCL10 could be an important chemokine in type 1 diabetes. A Japanese study [17] reported that serum CXCL10 levels in type 1 diabetes patients, including those experiencing a slow onset disease [16], were significantly higher than that measured in type 2 diabetics and healthy controls. This observation was confirmed in a study with Caucasian patients [18], indicating that this is a consistent phenomenon in type 1 diabetes irrespective of race.

Another interesting observation was that CXCL10 levels correlated with the number of islet antigen-specific CD4 T cells in type 1 diabetics [17, 19, 20]. This suggested that the level of CXCL10 may indicate anti-beta-cell immunity in type 1 diabetes. Also, the serum CXCL10 levels were negatively correlated

with disease duration and age of disease onset in type 1 diabetes, suggesting that the CXCL10 level may reflect "disease activity". Thus, serum CXCL10 appears to be a useful marker in type 1 diabetes, and its level may be used to define disease progression.

Role of the CXCL10/CXCR3 system in type 1 diabetes

As mentioned above, serum CXCL10 levels in type 1 diabetics are higher than those in healthy controls, but what does this mean in terms of pathogenesis? In the NOD model of type 1 diabetes, serum CXCL10 levels seem to correlate with high levels of CXCR3 (and high CXCL10) in pancreatic lymph nodes, where T cells are educated [4]. Moreover, longitudinal analysis of serum CXCL10 levels during the disease course indicated that the CXCL10 level seems to predict the onset of diabetes. Taken together, serum CXCL10 levels reflect an accumulation of CXCR3-positive T cells in pancreatic lymph nodes [4], a phenomenon that occurs just before the onset of diabetes.

These data provoke the following question: could the disease course be altered favorably, if the CXCL10/CXCR3 system were blocked by neutralizing CXCL10 antibodies? We tested this hypothesis and found that administration of CXCL10 monoclonal antibodies to a cyclophosphamide-induced NOD diabetes model resulted in a deceleration of diabetes onset [5]. Moreover, induction of anti-CXCL10 antibodies by a gene transfer system in young NOD mice even resulted in disease suppression [21]. These results indicate that blocking the CXCL10/CXCR3 system can be an effective intervention strategy to suppress diabetes onset both in the malignant phase [22], i.e. the active disease phase, and in the benign phase, i.e. the less active phase.

Interestingly, when both CXCL10 and CXCR3 were blocked, no difference in immunological responses, i.e. in cytokine profile, was found. Instead, a difference in pancreatic beta-cell proliferation was discovered. This means that beta-cells were significantly increased by a blockade of the CXCL10/CXCR3 system. It is of note that these interventions were performed before, rather than after, diabetes onset. We do not know, whether or not this approach is similar effective when applied in the hyperglycemic state.

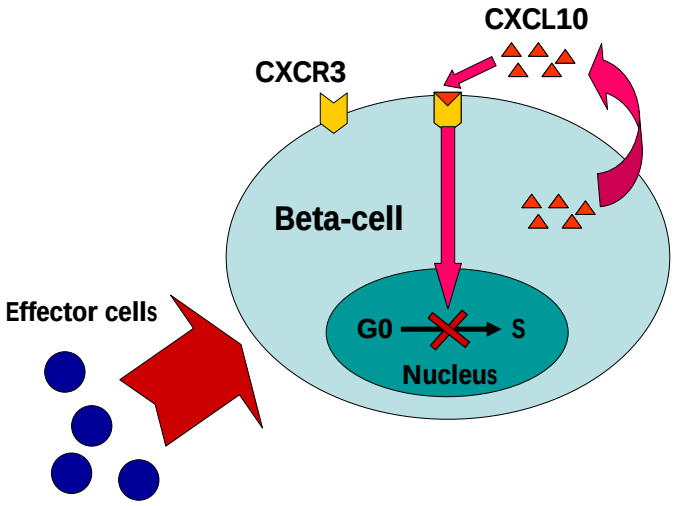

Figure 2. Suppression of beta-cell proliferation by the CXCL10/CXCR3 system. The destruction of beta-cells by effector cells results in CXCL10 production in beta-cells. CXCL10 binds to CXCR3 on beta-cells, and suppresses beta-cell proliferation in an autocrine manner. Blocking this cycle by CXCL10 neutralizing antibody results in beta-cell proliferation.

There is evidence that the effect relates to the beta-cell regeneration capacity. It has recently been shown that an interaction between CXCL10 and Toll-like receptor 4 (TLR4) can result in suppression of beta-cell proliferation [23]. As CXCL10 and CXCR3 are co-expressed in pancreatic beta-cells [5], and CXCL10 expression increases as insulitis progresses [4], we believe that, beside its role in the immune response, the CXCL10/CXCR3 system is also critical for the suppression of pancreatic beta-cell proliferation (Figure 2).

Concluding remarks

It is commonly assumed that both immune regulation and beta-cell regeneration are required to cure type 1 diabetes [24]. Some studies have suggested that the CXCL10/CXCR3 chemokine system plays a critical role in the autoimmune process and in beta-cell destruction in type 1 diabetes. Blocking the CXCL10 chemokine in new onset diabetes seems to be a possible approach for treatment. In combination with another regulatory intervention strategy, such as GAD autoantigen sensitization, this approach could contribute to a curative treatment for type 1 diabetes. We envisage that further research into the CXCL10/CXCR3 system will enable to develop a new and effective therapy.

Conflict of interest statement: Dr. Akira Shimada (M.D., Ph.D.) has research grants from Eli Lilly. All other authors declare that they have no conflict of interests.

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