Current Trends in Immunology
Vol. 22, 2021

Mini-Review

The immune microenvironment of pancreatic islet

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ABSTRACT

Pancreatic islets are critical micro-organs responsible for the material metabolism, especially glucose homeostasis. The majority of islet cells are endocrine cells, while immune cells play important roles in the islet function. The change of immune microenvironment in islets may lead to inappropriate hormone secretion, leading to various clinical symptoms, such as diabetes. Type I diabetes is due to absolutely insufficient secretion of insulin by pancreatic beta cells, which are functionally injured by immune cells in the islet microenvironment. Though type II diabetes is due to insulin resistance, the changes in islet immune microenvironment accompany the relative insulin deficiency. Here, we review the infiltration of different types of immune cells and the functions of the immune cytokines in islet immune microenvironment, so as to facilitate a better understanding of diabetes from an immunological aspect.

KEYWORDS: immune microenvironment, pancreatic islet, beta cell, diabetes.

1. Introduction

Islets are endocrine cell clusters scattered in the pancreatic acinar tissue, and the endocrine cells are capable of sensing blood levels of nutrients (e.g., glucose) and respond accordingly by secreting hormones. At least five types of endocrine cell are found in islets including insulin-secreting β cells, glucagon-secreting α cells, ghrelin-secreting δ cells, ghrelin-secreting ε cells, and pancreatic polypeptide producing PP cells. β cells are gathered in the core of islets and make up 60-80% of islet cells with other endocrine cells surrounding them [1]. Insulin secreted by β cells is the only hormone capable of reducing blood glucose levels in the body. Therefore, β cells and insulin play crucial roles in the glucose homeostasis.

Besides endocrine cells, the infiltration of immune cells into the islets also has an important role in the functions of islets especially under pathological state. The islets are highly vascularized: islet mass accounts for only 1-2% of the pancreas mass, but blood flow in islets account for 6-20% of that in total pancreas [2]. The rich vascular environment not only ensures the transport of hormones, but also facilitates the effects of immune cells and cytokines on islet cells.

Variation of the islet immune microenvironment may trigger disturbances of hormonal regulation, leading to various clinical symptoms, such as diabetes. Diabetes is a chronic metabolic disorder with high blood glucose levels and usually classified into Type I and Type II diabetes. Type I diabetes is due to absolutely insufficient insulin secretion by β cells, which are damaged by autoimmune process [3]. Type II diabetes is characterized by insulin resistance in the responsive tissues and relative insulin deficiency. In recent years, with the increasing prevalence and incidence of diabetes, many efficient therapeutic strategies for diabetes are developing [4]. Immunotherapy has received a lot of attention and exhibits advantages in many advanced cancers [5]. Therefore, it is essential to better understand the normal condition and changes of islet immune microenvironment in diabetes.

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2. Immune cells and cytokines in normal islets

2.1. Macrophages

Under normal conditions, very few macrophages are infiltrated into islets. However, the proliferation of β cells requires functional macrophages in the islets [6]. β cells highly express IL-1 type I receptor and show high sensitivity to IL-1β [7], which could be produced by macrophages. IL-1β could promote the biosynthesis and release of insulin and the proliferation of β cells in short term [8]. However, long-term IL-1β action will exert excessive insulin synthesis pressure on β cells, leading to β cell failure and apoptosis, finally decreasing the total secretion of insulin [9].

2.2. T cells

T cells (also called T lymphocytes) together with B cells are two primary types of lymphocytes, which mediate the adaptive immunity. While T cells carried out cell-mediated immune response, activated B cells produce antibodies and control the humoral immune response. According to the functions and surface markers, T cells could be divided into different sub-populations including cytotoxic T cells (Tc), helper T cells (Th) and regulatory T cells (Treg). Moreover, multiple CD4 Th subsets have been identified including Th1, Th2, Th17 and Tfh (follicular T helper) cells [10]. Previous studies have revealed that the balance of IFNγ producing Th1 cells and IL-4 producing Th2 cells is essential to maintain the stability of the islet immune microenvironment [11]. More recently, Th17 cells secreting IL-17A and IL-17F have been found to play critical pro-inflammatory role in autoimmunity [12], which adds new immune reactions to the Th1/Th2 cell responses. Similar to the Th1/Th2 balance, balance between Th17 and Treg cells were also found in the islets [13]. Treg cells produce anti-inflammatory cytokines such as IL-10, which maintain immune tolerance and suppress inflammatory immune responses [14].

3. Immune cells and cytokines in islets of type 1 diabetes

Type 1 diabetes is an autoimmune disease and the infiltration of immune cells into islets is initiated by the release of auto-antigens after β cells apoptosis. β cell apoptosis could be divided into physiological apoptosis and stress-induced apoptosis. Physiological apoptosis of β cells has been observed in young rodents (rats), both in normal and diabetes-prone strains [15]. The process of phagocytosis and clearance after apoptosis of β cells may produce signals to activate antigen-presenting cells (APCs). Stress-induced apoptosis may increase endoplasmic reticulum pressure and activate IL-1β-induced NFκB and Fas signaling pathways in β cells, thereby stimulating β cell apoptosis [16, 17].

3.1. Macrophages

Though the priming factors leading to the pro-inflammatory islet microenvironment remain to be clarified, macrophages derived from circulating monocytes are the first immune cells to sense the pro-inflammatory microenvironment in pancreatic islets and promote the death of β cells by producing pro-inflammatory factors [18]. Pro-inflammatory macrophages phagocytose damaged β cells and recruit T-cells *via* antigen presentation. Therefore, macrophages play a central role in β cell destruction and the initiation of autoimmune insulitis in type 1 diabetes [16].

Macrophages produce IL-1β, which activates NFκB-mediated apoptosis pathway by upregulating the expression of inducible Nitric oxide (NO) synthase (iNOS) gene in β cells [19]. NO-mediated cytotoxicity is important in the destruction process of β cells. Notably, although α cells could be affected by NO, they are not induced to produce iNOS [20], which partly explains why β cells, rather than α cells, are the main targets in the progression of type 1 diabetes. Moreover, IL-1β could induce other cytokines and chemokines, such as IL-6, IL-8, IL-33, TNF, CCl2, etc., which could attract more macrophages into the islet inflammatory microenvironment and produce more IL-1β, forming a positive feedback loop.

Macrophages produce TNFα, which promotes the apoptosis of β cells and enhances the invasion of APCs such as macrophages and dendritic cells [21, 22]. These cells present the antigen to $CD8^+$ T cells. Moreover, TNFα promotes the maturation of DC cells, thereby enhancing their ability to activate islet-specific T cells in islet lymph nodes [23]. The role of TNFα in the progression of type 1 diabetes mellitus has been demonstrated by the study of TNFα blocking [24], suggesting that

TNFα plays an important role in the progression of type 1 diabetes.

3.2. T cells

In the histological observation of pancreatic islets, auto-reactive T cells account for the largest proportion of the immune infiltrates [17, 25]. It is reported that thymectomized NOD mice did not develop diabetes, but they developed diabetes after T cells were transplanted [15]. Circulating T cells meet APCs (mainly DC cells) carrying β cell antigens in islet lymph nodes and activated T cells migrate into islets. They are reactivated in the islets and remain in the islets enhancing islet inflammation. In the early stage of diabetes, $CD8^+$ T cells are the main infiltrating immune cells [16, 17]. $CD8^+$ T cells differentiated into cytotoxic T lymphocyte (CTL). CTL cells directly recognize β cell MHC-I molecules and induce the expression of Fas in islet cells by secreting certain cytokines, such as IL-1, IFNγ and TNFα [26, 27]. It has been found that activated T cells express FasL and could induce the apoptosis of β cells through the Fas pathway [18]. Fas-deficient NOD mice did not develop diabetes [28, 29]. In addition to the Fas pathway, CTL could induce cell apoptosis through the perforin/granulase pathway [30].

$CD4^+$ T cells recognize β cell antigens through indirect presentation of MHC-II molecules in APCs and activated $CD4^+$ T cells could secret varied cytokines in different subtypes. Th1 cells could recruit islet-specific $CD4^+$ T cells to islets and thus promote the transition from islet inflammation to diabetes mellitus, while Th2 cells could reduce the apoptosis of β cells and maintains the state of islet inflammation [31].

Th17 cells secrete IL-17A and IL-17F, which could recruit inflammatory cells (such as neutrophils) to the islets [32]. However, because of the plasticity of Th17 cells, the precise initiation site of Th17 response at T1D onset is still unclear [33]. At the same time, the role of IL-17A is much clearer. IL-17A expression levels in the islets were correlated with insulitis of NOD mice [34] and IL-17A knockout mice showed resistance to Streptozotocin (STZ)-induced diabetes [35]. IL-17A could induce iNOS production and NO-dependent toxicity in mouse pancreatic islets [36]. IL-17A synergistic with IFNγ and IL-1β increases the pancreatic islet inflammation [37]. Therefore, IL-17A may be an effective target in the treatment of T1DM [38].

Treg cells could inhibit the autoimmune reaction mainly through inhibiting the secretion of certain cytokines such as IFNγ, TNFα, IL-17A from T effective cells (Teff) [39-41]. If Treg cells were ablated, Teff cells were rapidly activated and the levels of IFNγ were increased, which showed pro-diabetic effects [41, 42]. In reverse, the activated Teff cells may be responsible for the suppression of Treg cells. Activated Teff cells could secrete some inhibitory cytokines or synthesis less IL-2, so as to lower the number or the regulatory activity of Treg cells [43-45].

Besides, IL-6 receptor was highly expressed on the surface of both $CD8^+$ T and $CD4^+$ T cells. Overexpression of IL-6 on β cells could enhance the migration of Teff and promote the inflammatory response of Teff [46]. B cells are less important in the islet microenvironment than T cells. B cells have been shown to present self-antigen to $CD4^+$ T cells during diabetes development [47].

3.3. NK cells

NK cells, as a bridge between innate and adaptive immunity, are a kind of cytotoxic lymphocytes, which play an important role in the development of T1D. NK cells could interfere the priming of autoimmune responses by inhibiting the antigen presentation of DCs at the initial stage. NK cells could even influence the downstream response by promoting excessive auto-reactive T lymphocytes through IFN γ secretion [48]. Changes of NK cell function and number were found in the peripheral blood of Type I diabetic patients [49]. At the same time, the infiltration of NK cells into pancreatic islets were observed in Coxsackie B4 virus-infected diabetic patients [50]. NK cells gradually infiltrate into islets as the insulitis progressed to type 1 diabetes, and NKp46 is essential for the development of type 1 diabetes [51].

4. Immune cells and cytokines in islets of type 2 diabetes

Type II diabetes is linked to both innate and adaptive immune factors during the development of insulin resistance. Obesity is a major risk for type 2 diabetes, and adipose tissue inflammation closely correlate with insulin resistance. In the

adipose tissues, CD45+ T cell number was increased, while suppressive Treg cells and protective NK cell number were decreased, and leukocytes polarized to pro-inflammatory phenotype in both obesity and type 2 diabetes [52]. Besides adipose, the liver, muscle and peripheral blood also exhibit changed immune cells and cytokines in type 2 diabetes [53].

In the islets of type 2 diabetes, increased macrophage infiltration was observed together with increased levels of islet-derived inflammatory factors including IL-6, IL-8, chemokine KC, granulocyte colony-stimulating factor (G-CSF), and macrophage inflammatory protein 1alpha (MIP-1α) [54]. β cells try to compensate the insulin resistance by releasing more insulin. Macrophages could sense the changes in β cell function and could polarize into different subtypes [55]. Macrophages have high heterogeneity under varied conditions. M1 macrophages are pro-inflammatory and related to host defense response. M2 macrophages are anti-inflammatory and related to immune regulation and repair functions. Blocking the M1 polarization or promoting M2 function could probably be a promising strategy for diabetes therapy. IL-1β blockade could improve β cell function in type 2 diabetic mice models [56]. Moreover, human umbilical cord-derived MSCs (hUC-MSCs) infusion exerted anti-diabetic effects and significantly promoted islet recovery in T2D mice with decreased M1 and increased M2 macrophages in islets [57].

5. Conclusion

Changes in beta cells could induce different phenotypes of immune cells in the islet, while changes of immune cells and cytokines could reversely affect the function of beta cells. The crosstalk between endocrine cells and immune cells in islets makes a mini-world, which could alter the nutrition metabolism of the whole body. Understanding the balance of endocrine cells and immune cells within pancreatic islets could help to clarify the underline mechanism of diabetes and develop immune-based therapy strategies.

CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

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