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REVIEW

Plasmacytoid dendritic cells in autoimmune diabetes – Potential tools for immunotherapy

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Abstract

Type 1 diabetes (T1D) is an autoimmune disease in which a T-cell-mediated attack destroys the insulin-producing cells of the pancreatic islets. Despite insulin supplementation severe complications ask for novel treatments that aim at cure or delay of the onset of the disease.

In spontaneous animal models for diabetes like the nonobese diabetic (NOD) mouse, distinct steps in the pathogenesis of the disease can be distinguished. In the past 10 years it became evident that DC and macrophages play an important role in all three phases of the pathogenesis of T1D. In phase 1, dendritic cells (DC) and macrophages accumulate at the islet edges. In phase 2, DC and macrophages are involved in the activation of autoreactive T cells that accumulate in the pancreas. In the third phase the islets are invaded by macrophages, DC and NK cells followed by the destruction of the beta-cells. Recent data suggest a role for a new member of the DC family: the plasmacytoid DC (pDC). pDC have been found to induce tolerance in experimental models of asthma. Several studies in humans and the NOD mouse support a similar role for pDC in diabetes. Mechanisms found to be involved in tolerance induction by pDC are inhibition of effector T cells, induction of regulatory T cells, production of cytokines and indoleamine 2,3-dioxygenase (IDO). The exact mechanism of tolerance induction by pDC in diabetes remains to be established but the intrinsic tolerogenic properties of pDC provide a promising, yet underestimated target for therapeutic intervention.

Keywords: Autoimmunity; Dendritic cells; DC; Immunotherapy; Plasmacytoid DC; PDC; Type 1 diabetes

Contents

Abbreviations: DC, dendritic cells; pDC, plasmacytoid dendritic cells; cDC, conventional dendritic cells; T1D, type 1 diabetes; NOD, nonobese diabetic; IDO, indoleamine 2,3-dioxygenase; DP, diabetes prone; BB, biobreeding rat; APC, antigen-presenting cells; M-CSF, monocytes/macrophage colony-stimulating factor; NK, natural killer; IFN, interferon; TLR, toll-like receptor; TGF, transforming growth factor.

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Introduction

Autoimmune destruction of insulin-producing β-cells in the pancreas causes type 1 diabetes (T1D), an organ-specific autoimmune disease that is clinically detected by hyperglycemia due to insulin insufficiency. To prevent the rise of blood glucose to pathological levels, T1D-patients have to receive a life-long treatment with exogenous insulin. T1D is predominantly diagnosed in children and young adults and forms a major health concern in developed countries. The World Health Organization (WHO) estimates that more than 180 million people worldwide have diabetes. This number is likely to more than double by 2030. Of them, about 10% have T1D and studies suggest that the onset of the disease is shifting further to a younger age (Gardner et al. 1997; Diamonds Project Group, 2006). Despite insulin supplementation, variably elevated glucose levels in T1D patients increase the risk for severe complications such as cardiovascular disease, nephropathy, neuropathy and retinopathy. This notion reinforces the need for novel treatments that, ideally, cure the disease, but at least delay or prevent the onset. Such treatments require delicate manipulations of the immune response. In this review, we outline the evidence that a subtype of dendritic cells (DC), the plasmacytoid DC (pDC), May provide a promising, yet underestimated target for such therapeutic tuning of the immune system.

The etiology and pathogenesis leading to T1D in humans are largely unknown. For obvious ethical but also practical reasons, the study of the autoimmune disease pathogenesis in humans is restricted to autopsy material. However, the onset of the disease and clinical/diagnostic signs are preceded by a long non-clinical phase during which an aggressive autoimmune reaction might be taking place. To overcome this problem, various animal models of spontaneously occurring or experimentally induced variants of the human autoimmune diseases have been developed. In general, these have shown that both genetic and environmental factors essentially determine the susceptibility to develop the disease but neither of them individually leads to the full-blown disease. The interplay of environmental factors with an autoimmune-prone genetic background is required for the initiation and progression of the inflammatory process that destroys the β-cells. The most extensively investigated spontaneous animal models of T1D are the nonobese diabetic (NOD) mouse and the diabetes-prone (DP) biobreeding (BB) rat. Studies in these animal models have enabled the description of the early processes in the pancreas, long before the symptoms and diagnostic signs of diabetes are detectable.

Pathogenesis of the autoimmune destruction in the pancreas in both models can be divided into distinct steps: Phase 1, accumulation of antigen-presenting cells (APC), particularly DC and subclasses of macrophages in the pancreas prior to clear signs of inflammation. It is not clear yet why at this point and from where these cells accumulate or what their precise function in the pancreas should be. Investigation by our group shows that macrophage and DC precursors in the pancreas seeded in the fetal life are a probable source of the early accumulating cells, rather than that they infiltrate from the circulation (Geutskens et al. 2005 and unpublished results). F4/80+ macrophages and macrophage precursors have been found in the pancreas before the formation of the functional blood vessels. We consider that macrophages (and possibly DC) play a role in the homeostasis of the developing pancreas, since they are located in the close proximity of the developing insulin-producing β-cells and stimulation of macrophage development by M-CSF in the explant-cultures of the pancreas buds significantly increased β-cell generation. Phase 2 of the autoimmune destruction is the period of activation and expansion of autoreactive T cells, which initially takes place in the pancreas-draining lymph nodes and subsequently in the pancreas itself. APC play a crucial role in this process at both locations (Marleau et al. 2008; Yadav et al. 2004). At this point, lymphocytic infiltrates are evident in the pancreas as determined by histological analysis. Infiltrates contain both T and B cells as well as macrophages, DC and NK cells. In the 3rd phase, CD8+ T cells and inflammatory scavenger macrophages invade the islets of Langerhans and employ immune-mediated effector mechanisms to cause the final β-cell destruction in the pancreas. This leads to the clinical manifestation of diabetes.

Taken together, the pathogenic process in the NOD mouse (in particular) has been thoroughly described, mainly using histological analysis. However, the variables involved in each step are numerous and the exact role of the different cell types in this process is not clear yet.

The role of dendritic cells in different steps of diabetes pathogenesis

APC control tissue homeostasis, initiate T cell-mediated immunity and control the maintenance of