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# Regulatory role of natural killer T cells in diabetes

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ABSTRACT

Type 1 and type 2 diabetes are growing public health problems. Despite having different pathophysiologies, both diseases are associated with defects in immune regulation. Invariant natural killer T (iNKT) cells are innate-like T cells that recognize glycolipids presented by CD1d. These cells not only play a key role in the defense against pathogens, but also exert potent immunoregulatory functions. The regulatory role of iNKT cells in the prevention of type 1 diabetes has been demonstrated in murine models and analyzed in diabetic patients. The decreased frequency of iNKT cells in non-obese diabetic mice initially suggested the regulatory role of this cell subset. Increasing the frequency or the activation of iNKT cells with agonists protects non-obese diabetic mice from the development of diabetes. Several mechanisms mediate iNKT regulatory functions. They can rapidly produce immunoregulatory cytokines, interleukin (IL)-4 and IL-10. They induce tolerogenic dendritic cells, thereby inducing the anergy of autoreactive anti-islet T cells and increasing the frequency of T regulatory cells (Treg cells). Synthetic agonists are able to activate iNKT cells and represent potential therapeutic treatment in order to prevent type 1 diabetes. Growing evidence points to a role of immune system in glucose intolerance and type 2 diabetes. iNKT cells are resident cells of adipose tissue and their local and systemic frequencies are reduced in obese patients, suggesting their involvement in local and systemic inflammation during obesity. With the discovery of potential continuity between type 1 and type 2 diabetes in some patients, the role of iNKT cells in these diseases deserves further investigation.

Type 1 diabetes (T1D) is an autoimmune disease characterized by the selective destruction of pancreatic islet β-cells, in the context of an underlying multigenetic inheritance [1]. When 80% of the β-cells are destroyed, the consecutive lack of insulin results in hyperglycemia and requires a life-long insulin replacement therapy. The physiopathology of T1D is complex

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and still not entirely understood. It involves both innate and adaptive immune systems; both are inappropriately activated by a triggering event, initiating an immune cascade that results in loss of self-tolerance and islet destruction [2,3]. T1D is a typical Th1 cell-mediated autoimmune disease characterized by the presence of autoreactive anti-islet T cells, which play a prominent role in the development of the disease [4]. Autoreactive B cells produce autoantibodies targeting β-cell antigens, and could act as antigen-presenting cells (APCs), but have a limited role in the pathophysiology. The emergence of diabetogenic T cells appears to be associated with defective immunoregulation [5]. Numerical and functional deficiencies of $CD4^+$ $FoxP3^+$ T regulatory (Treg) cells have been demonstrated in T1D [6,7]. However, Treg cells do not account for the entire regulatory functions; another regulatory T cell subset, invariant natural killer T (iNKT) cells, has also been demonstrated to be involved in the pathophysiology of the disease.

Type 2 diabetes (T2D) accounts for over 90% of the diagnosed cases of diabetes. It is a heterogeneous disorder characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production, and β-cell dysfunction. T2D is frequently associated with obesity or overweight, and insulin resistance could be mostly secondary to the coexistence of this increased adiposity [8,9]. If insulin resistance is present, the β-cells increase insulin output in order to maintain glucose homeostasis. When the β-cells cannot release sufficient insulin, blood glucose concentration rises, leading to glucose intolerance and T2D. As in T1D, genetic factors and environment interact in the development of the disease. In contrast to T1D, genome-wide association studies found that most of the genes implicated in T2D are linked to β-cell function, whereas genes associated with an increased risk of T1D mostly involve the immune system. A link between obesity, systemic inflammation, and metabolic complications has been proposed for decades [9]. Recent studies demonstrated that metabolism and the immune system are strongly associated in the development of obesity-dependent insulin resistance, where both innate and adaptive immune systems play a role.

In this review, we will discuss the role of NKT cells in the pathophysiology of T1D and T2D: protective, pathologic, and still partially mysterious.

## iNKT cells

NKT cells are a non-conventional subtype of αβ T lymphocytes. Contrary to conventional αβ T cells that recognize peptides presented by major histocompatibility complex (MHC) molecules, NKT cells recognize lipids presented by CD1d molecules. CD1d is a non-polymorphic MHC class I-like molecule that is mainly expressed by dendritic cells (DCs) and other APCs. The name NKT reflects one of their phenotypical characteristics, as they express cell surface markers associated with the natural killer (NK) cell lineage, and particularly CD161 in humans or NK1.1 in mice [10]. NKT cells are remarkably conserved among mammals, suggesting a crucial role in immunity [11]. Classically, NKT lymphocytes are divided into three groups: iNKT, type II NKT, and NKT-like lymphocytes, according to their antigenic specificity and the expression of their T cell receptor (TCR) [12].

iNKT cells represent the majority of NKT cells. They express a semi-invariant TCR α-chain, Vα24Jα18 in humans and Vα14Jα18 in mice, associated to a restricted set of β-chains, usually Vβ11 in humans and Vβ8, Vβ7, or Vβ2 in mice. They recognize glycosphingolipids that are presented by CD1d, such as glycosylceramides. A glycolipid isolated from a marine sponge, α-galactosylceramide (α-GalCer), has been shown to be a potent activator of iNKT lymphocytes in both mice and humans. iNKT cells are either $CD4^+$ or $CD4^-CD8^-$ double-negative (DN). iNKT lymphocytes are considered as innate-like T lymphocytes as they harbor an activated/memory phenotype ($CD69^+$, $CD44^{hi}$, $CD62L^-$), and are rapidly able to produce large amounts of cytokines after the stimulation of their TCR [13]. They can rapidly produce interleukin (IL)-4 and interferon (IFN)-γ, but also have cytotoxic effects. After activation, they interact with both innate and adaptive immune systems, such as NK cells, DCs, T and B cells, through the rapid production of Th1 and Th2 cytokines and the expression of cell surface markers.

Type II NKT lymphocytes display both variable TCR-α and -β chains. These cells do not recognize α-GalCer, but recognize other antigens such as sulfatides and lysophosphatidylcholine and are also restricted by CD1d [14,15]. NKT-like lymphocytes represent a more heterogeneous population, with variant and invariant TCRs that express NK markers. Among NKT-like is the recently described mucosal associated invariant T (MAIT) cell, which TCR has the invariant Vα7.2-Jα33 chain in humans and Vα19-Jα33 in mice. The ligands of MAIT cells are metabolites from riboflavin synthesis by bacteria, modified by small molecules such as methylglyoxal [16].

iNKT cells are a relatively rare lymphocyte population in humans, as they represent less than 0.1% of peripheral white blood cells. However, the development of Vα14-Jα18 transgenic mice and the improvement of the specific detection of iNKT cells with CD1d–α-GalCer tetramers and 6B11 antibodies have permitted a thorough study of these cells. iNKT cells exert various functions in immunity. They play a key role in the defense against pathogens such as bacteria, viruses, and parasites [11,17–19]. They are also involved in defense against tumors and metastases. Although iNKT cells have cytotoxic properties, they are also major players in immune regulation.

Among other immune alterations, a defect of iNKT cells has been observed and correlated with susceptibility to various autoimmune diseases in mice and humans. In *lpr* C57BL/6 mice, an animal model of systemic lupus erythematosus, the development of autoimmunity is correlated with a decrease of iNKT cell frequency [20,21]. A defect of frequency and function of iNKT cells was observed in non-obese diabetic (NOD) mice, as discussed below [22,23]. Similar iNKT cell abnormalities were also described in patients with autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and T1D [24–28].

## iNKT cells in T1D

The role of iNKT cells in the physiopathology of T1D has been evidenced in animal models and suggested in humans [12].