



Review on The Role of Natural Killer T Cells in Regulation of Autoimmune Disease

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Abstract

Natural Killer T (NKT) cells, a specialized subset of lymphocytes exhibiting characteristics of both T cells and natural killer (NK) cells, play a critical role in the regulation of immune responses. Unlike conventional T cells, NKT cells recognize lipid antigens presented by CD1d molecules, making them key players in both innate and adaptive immunity. In autoimmune diseases, characterized by the immune system's attack on self-tissues, NKT cells exhibit a dual nature—acting as either protectors by promoting immune tolerance or as contributors to disease progression through inflammatory responses. Subsets of NKT cells, including invariant NKT (iNKT) cells, have been implicated in both the suppression of autoimmunity via anti-inflammatory cytokines like interleukin-4 (IL-4) and in the exacerbation of disease through pro-inflammatory cytokines such as interferon-gamma (IFN- γ). These functions are particularly evident in diseases like multiple sclerosis, type 1 diabetes, and systemic lupus erythematosus. This review explores the diverse roles of NKT cells in autoimmune diseases, emphasizing their potential as therapeutic targets for modulating immune function and improving disease outcomes.

Keywords: Natural Killer T cells, immune regulation, CD1d, iNKT cells, multiple sclerosis, type 1 diabetes, systemic lupus erythematosus.

Introduction

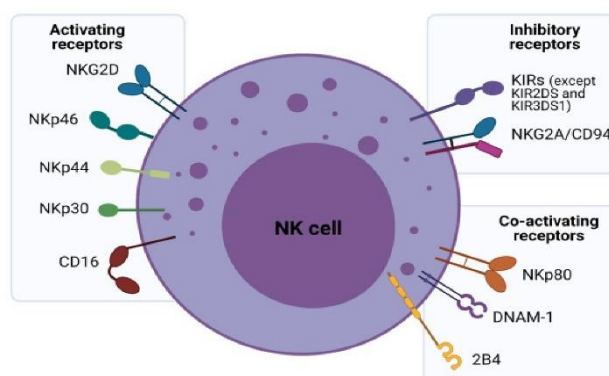
Natural Killer T (NKT) cells are a unique subset of lymphocytes that straddle both the innate and adaptive immune systems. They are distinguished by their ability to recognize lipid antigens presented by CD1d molecules, unlike conventional T cells, which recognize peptide antigens presented by MHC molecules. This lipid antigen recognition allows NKT cells to respond rapidly to a variety of microbial, tumor, and self-antigens, making them key regulators of immune responses [1]. A hallmark of NKT cells is their ability to produce large amounts of cytokines within hours of activation, thereby influencing the function of various immune cells, including dendritic cells, macrophages, and conventional T cells [2].

In the context of autoimmune diseases, where the immune system erroneously targets self-antigens, NKT cells have been found to play a paradoxical role—both protective and pathogenic. Autoimmune diseases such as multiple sclerosis (MS), type 1 diabetes (T1D), and systemic lupus erythematosus (SLE) are characterized by an imbalance in immune regulation, often resulting in chronic inflammation and tissue damage [3]. NKT cells are involved in both promoting and regulating this dysregulated immune response. For example, in T1D, a reduction in the number and function of invariant NKT (iNKT) cells has been associated with disease progression, suggesting a protective role for these cells in maintaining immune tolerance [4]. Similarly, in MS, NKT cells have been shown to suppress disease severity through the production of anti-inflammatory cytokines such as interleukin-4 (IL-4) [5]. However, in other contexts, such as SLE, NKT cells can contribute to the pathogenesis by secreting pro-inflammatory cytokines, including interferon-gamma (IFN- γ), which exacerbates tissue damage [6].

The dual nature of NKT cells in autoimmune diseases is largely dependent on their functional plasticity and the cytokines they produce. iNKT cells, which express a semi-invariant T cell receptor (TCR), are the best-studied subset and are known for their ability to rapidly produce both pro-inflammatory cytokines (IFN- γ , TNF- α) and anti-inflammatory cytokines (IL-4, IL-10). This cytokine production allows iNKT cells to either enhance or suppress immune responses depending on the disease context [7]. Additionally, the interaction between NKT cells and other immune cells, such as regulatory T cells (Tregs) and dendritic cells, further influences the outcome of autoimmune diseases [3].

Recent studies have suggested that modulating NKT cell activity may hold therapeutic potential for autoimmune diseases. For example, therapies aimed at enhancing NKT cell numbers or function have been explored in T1D, with promising results in preclinical models [3]. Conversely, targeting NKT cell-mediated inflammatory pathways may offer new strategies for diseases where these cells contribute to disease exacerbation, such as SLE [6]. As researchers continue to uncover the complex roles of NKT cells in autoimmunity, these cells emerge as both biomarkers for disease progression and potential targets for immunotherapy.

Figure 1 : Natural killer t cell



(Islam, R., Pupovac, A., Evtimov, V., Boyd, N., Shu, R., Boyd, R., & Trounson, A. (2021). Enhancing a natural killer: Modification of NK cells for cancer immunotherapy. *Cells*, 10(5), 1058. <https://doi.org/10.3390/cells10051058>)

Role of NKT Cells in Autoimmune Diseases

1) Type 1 Diabetes (T1D):

Type 1 diabetes (T1D), also known as insulin-dependent diabetes mellitus or juvenile diabetes, is brought on by T lymphocytes destroying the pancreatic cells that produce insulin. T lymphocytes, both CD8⁺ and CD4⁺, have been linked to the pathophysiology of type 1 diabetes. In T1D patients, the condition of NKT cells is extremely contentious.[8,9]. According to reports, the frequency of NKT cells in the peripheral blood of T1D patients can either rise [10] fall [11,12] or stay the same [13,14] when compared to normal control participants.

Several study teams have looked into how NKT cell activation can affect diabetes in NOD mice.[8,15,16].Results from repeated α -GalCer injections have consistently demonstrated protection against the onset of diabetes on its own [17,18,19,20].According to Falcone et al. (2004), upregulating CD1d expression prevented autoimmune diabetes and restored the immunoregulatory function of NKT cells[21]. A Th2 shift within the pancreatic islets was linked to the protection provided by NKT cells, and IL-4 has been identified as a crucial immunoregulation mediator [22,23].

2) Experimental autoimmune encephalomyelitis and multiple Sclerosis :

NOD mice were protected against experimental autoimmune encephalomyelitis, which is thought to be a useful model for human multiple sclerosis, by transgenic overexpression of the invariant NKT TCR. Although it was not dependent on IL-4, this was linked to a notable suppression of antigen-specific IFN γ production [24]. Moreover, research employing α GalCer-induced NKT cell stimulation verified that NKT cells can influence the illness by generating Th2 cytokine profiles [25,26]. Some, however, claimed that the protective effect was linked to increased IFN γ production by NKT cells that were limited to the liver [27].

MS is a long-term inflammatory condition that affects the human central nervous system. Myelin antigens in the central nervous system are the target of this Th1-mediated autoimmune condition [28]. It has been shown that MS patients have lower levels of Va24 mRNA in their peripheral blood [29]. Furthermore, DN NKT cells secreted less IL-4 [30].However, as compared to patients in relapse, CD4⁺ NKT cell lines taken from remission patients displayed a significant Th2 bias [31]. These findings lend credence to NKT cells' immunoregulatory role in MS [32].

3) Systemic Lupus Erythematosus (SLE):

NKT cells are decreased in lupus-prone animals and systemic lupus erythematosus patients, which may indicate that these cells prevent the development of lupus [33,34].However, studies showing that administration of α GalCer worsened the condition have highlighted a potential harmful involvement of NKT cells [35]. In juvenile lupus-prone mice, the transfer of activated NKT cells caused an autoimmune-like inflammation [36], while anti-CD1d blocking antibody treatment improved the condition [35].According to Yang et al. (2003), NKT cells might be involved in the regulation of lupus dermatitis development.[37].They postulated that treatments targeted at the in vivo activation of NKT cells might aid in the management of dermatitis because lupus disease activity appears to inversely correlate with circulating NKT cell numbers, and humans with lupus and other systemic autoimmune diseases have lower numbers of NKT cells [38]. Furthermore, their discovery that NKT cells can proliferate upon repeated in vivo activation may have consequences for the development of NKT cell-based treatments for long-term immunological disorders [37].

4) Rheumatoid Arthritis (RA):

It has recently been discovered that RA and a wide spectrum of other disorders marked by autoreactive tissue damage have decreased NKT cells [39]. Additionally, the rheumatoid synovium had less invariant TCR transcripts [40]. According to reports, some RA patients' NKT cells did not proliferate when stimulated with GalCer and

displayed a Th1 bias in their blood .It is noteworthy that NKT cells in the synovial fluid of every patient showed a Th0 cytokine profile and reacted to stimulation . also found that soluble CD1d expression levels were decreased in RA patients

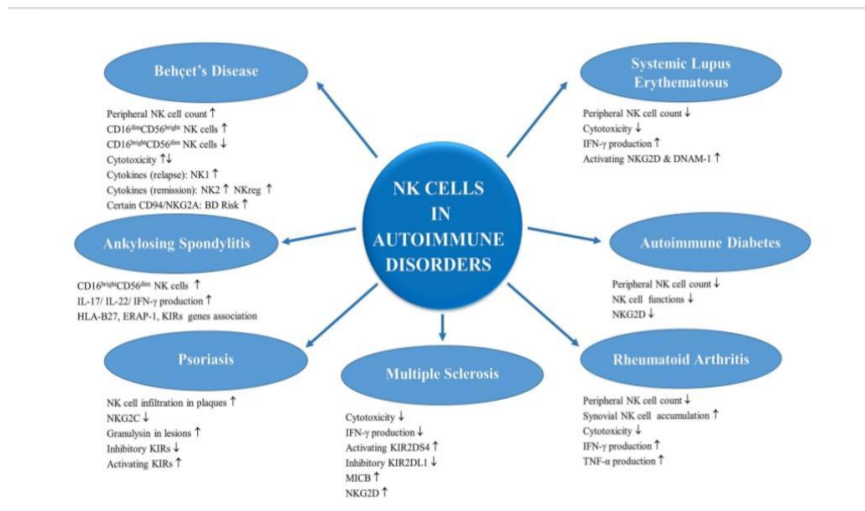


Figure 2: Roles of Natural killer t cells

(Kucuksezer, U. C., Aktas Cetin, E., Esen, F., Tahrali, I., Akdeniz, N., Gelmez, M. Y., & Deniz, G. (2021). The role of natural killer cells in autoimmune diseases. *Frontiers in Immunology*, 12. <https://doi.org/10.3389/fimmu.2021.622306>)

Mechanisms of Action

Natural killer T (NKT) cells are a distinct subset of lymphocytes that express characteristics of both T cells and natural killer (NK) cells. They play a critical role in modulating immune responses, particularly in the context of autoimmune diseases. The mechanism by which NKT cells contribute to autoimmunity is multifaceted, involving antigen recognition, cytokine production, and interactions with other immune cell.

1. Antigen Recognition:

NKT cells are activated by glycolipid antigens presented on the CD1d molecule of antigen-presenting cells (APCs). This is distinct from conventional T cells, which recognize peptide antigens. In autoimmune diseases, aberrant lipid presentation can activate NKT cells, contributing to immune dysregulation. In diseases like systemic lupus erythematosus (SLE), NKT cells may recognize self-lipids, leading to autoimmunity [3].

2. Cytokine Production:

Upon activation, NKT cells rapidly secrete large quantities of cytokines, including interferon-gamma (IFN-γ), interleukin-4 (IL-4), and tumor necrosis factor-alpha (TNF-α). These cytokines can either promote or suppress immune responses:

2.1) Pro-inflammatory role:

As seen in Type 1 Diabetes (T1D) and Multiple Sclerosis (MS), NKT cells have the ability to produce IFN-γ and TNF-α, which increase inflammation and autoreactive T cell activation [42].

2.2) Regulatory role: NKT cells, on the other hand, have the ability to release IL-4 and IL-10, which regulate the immune system and aid to reduce autoimmunity by reducing overreactions [2].

3. Immune Cell Interactions:

NKT cells interact with various immune cells, such as dendritic cells (DCs), macrophages, and B cells, influencing the overall immune response:

3.1)With Dendritic Cells (DCs):

NKT cells can regulate DC function, which is crucial for the activation of conventional T cells. Dysregulated NKT-DC interactions can lead to exacerbation of autoimmunity [37].

3.2)With Macrophages:

NKT cells have the ability to activate macrophages, which can exacerbate tissue damage and increase the production of pro-inflammatory cytokines, especially in conditions like rheumatoid arthritis (RA) [43].

3.3)With B Cells:

NKT cells have the ability to affect B cells' generation of antibodies, which is especially important in conditions like SLE that are marked by autoantibodies [44].

4.Impaired Tolerance and Autoimmunity:

Preventing autoreactive immune cell activation is one of NKT cells' vital roles in preserving immunological tolerance. Tolerance breakdown results from this regulating function being compromised in autoimmune disorders. Wilson et al. (2010) state that in T1D, for instance, NKT cells are unable to stop the death of pancreatic β -cells, which results in insulin insufficiency and hyperglycemia. [45].

5.Th1/Th2 Balance:

The immune response can be shifted by NKT cells in either a Th1 or Th2 direction. NKT cells frequently favour a Th1-type inflammatory response in autoimmune disorders such as MS, which intensifies disease pathology by encouraging autoreactive T cells [46].

Conclusion

A special subpopulation of immune cells known as natural killer T (NKT) cells possesses both innate and adaptive immunological traits. Their function is complicated in autoimmune illnesses since they can either increase inflammation or support immunological control. By generating cytokines like IL-4 and IFN- γ , NKT cells control immunological responses. These cytokines can support tolerance and inhibit negative immune responses. Nonetheless, NKT cells may become dysregulated in a number of autoimmune conditions, including multiple sclerosis, systemic lupus erythematosus, and type 1 diabetes, which can accelerate tissue damage and inflammation.

NKT cells are a viable target for therapeutic intervention because of their capacity to affect the immune system. Restoring the equilibrium between detrimental autoimmune reactions and protective immune control may be possible by altering their activity. New therapies that target either improving NKT cells' regulatory role or reducing their harmful effects in autoimmune diseases may result from this. To completely comprehend how NKT cells might be altered to effectively treat autoimmune illnesses, more research is necessary.

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