Viewpoint

Natural killer T cells and rheumatoid arthritis: friend or foe?

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Published: 14 February 2005

Arthritis Res Ther 2005, **7**:88-89 (DOI 10.1186/ar1714)

Natural Killer T (NKT) cells have been described as T lymphocytes expressing NK receptors such as NK1.1. This lymphocyte subset consists of several subpopulations, each with distinct characteristics [1, 2]. Unlike conventional T cells, the vast majority of mouse NKT cells recognize glycolipid antigens including α-galactosylceramide (α-GalCer), a glycosphingolipid originally isolated from marine sponges that can not be found in mammalian cells [3]. α-GalCer is presented by an MHC class I like antigen presenting molecule, CD1d. Several studies have highlighted the unique features of NKT cells, because their T cell receptor (TCR) repertoire is highly skewed with an invariant TCR-α rearrangement, Vα14-Jα18. In humans, a similar NKT cell subset with an invariant TCR-α chain, Vα24, exists. Therefore, these cells are often referred to as Vα*i* NKT cells.

A characteristic feature of Vα*i* NKT cells is their rapid production of large quantities of both Th1 and Th2 cytokines upon stimulation. These cells, therefore, may profoundly regulate the immune system: they may either enhance or suppress immune responses [4]. Several groups have investigated whether Vα*i* NKT cells are relevant for the pathogenesis of autoimmune diseases. There is evidence suggesting that Vα*i* NKT cells naturally influence autoimmunity and from other experiments it appeared that a vigorous but unnatural activation of Vα*i* NKT cells by α-GalCer is required to elicit their regulatory function. For example, in type 1 diabetes Vα*i* NKT cells are considered to be protective [5], although some conflicting reports exist [6, 7]. Vα*i* NKT cells are also considered to be of relevance in the pathogenesis of other autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus and experimental colitis although their precise role in these diseases remains unclear at present [4]. Few data exist on the putative role of Vα*i* NKT cells in the pathogenesis of rheumatoid arthritis (RA). It has been reported that RA patients have abnormalities in the number and function of Vα*i* NKT cells that are $CD4^{-}CD8^{-}$ in peripheral blood lymphocytes compared to healthy individuals, suggesting a protective role for these cells in RA [8], although indirect effects induced by for example therapy have not been ruled out.

Due to their immunomodulatory properties, manipulation of Vα*i* NKT cell mediated responses is an attractive potential therapeutic strategy for the treatment of autoimmune diseases [4]. This is illustrated by the beneficial effects of α-GalCer treatment in experimental models of autoimmune diseases. Interestingly, the CD1d system is highly conserved throughout mammalian evolution, which is illustrated by the ability of CD1d glycolipid antigens such as α-GalCer to stimulate both mouse and human Vα*i* NKT cells [9]. In addition, all human individuals have these cells with identical specificity, and α-GalCer specifically targets them with little toxicity in humans [10]. Nevertheless, administration of α-GalCer also has some disadvantages such as the simultaneous stimulation of both Th1 and Th2 cytokines. This problem could be circumvented by designing analogues of α-GalCer that are still able to stimulate Vα*i* NKT cells but give rise to an altered immune response compared to that induced by α-GalCer. An analogue of α-GalCer with a truncated sphingosine tail, OCH, was reported to preferentially promote IL-4 secretion and to be more potent than α-GalCer in preventing autoimmune encephalomyelitis [11]. Likewise, repeated administration of OCH, compared to α-GalCer, resulted in a substantial improvement of joint swelling and inflammation in collagen induced arthritis [12]. Therefore, inducing a polarization in the cytokine response induced by Vα*i* NKT cells by altered glycolipid CD1d antigens has sparked the interest of many researchers as a therapeutic strategy to treat autoimmune diseases.

Until now it was generally believed that Vα*i* NKT cells had a protective role in RA. However, a recent paper by Kim *et al*., challenged this concept by examining the role of Vα*i*

α-GalCer = α-galactosylceramide, MHC = major histocompatibility complex, NKT = natural killer T cell, RA = rheumatoid arthritis, TCR = T cell receptor, Th = T helper.

NKT cells in antibody-induced arthritis in the K/BxN serum transfer model [13]. Transfer of serum or immunoglobulins from K/BxN mice to healthy mice causes inflammatory arthritis by deposition of autoantibody in joint spaces, inducing an inflammatory cascade with activation of complement and Fcγ receptor pathways [14]. This model is considered to be reminiscent of the terminal effector mechanisms of RA. The development of antibody-induced arthritis was first examined in Jα18$^{-/-}$ and CD1d$^{-/-}$ mice and was found to be less severe compared to wild-type controls. In addition, adoptive transfer of NKT cells from C57BL/6 mice into CD1d$^{-/-}$ mice reversed the observed reduction in inflammatory arthritis, illustrating the disease perpetuating role of Vαi NKT cells in this model. Conversely, stimulation by repeated *in vivo* administration of α-GalCer resulted in a moderate increase in clinical paw swelling although no histological analysis was performed. The dual functionality of Vαi NKT cells observed in the K/BxN serum transfer model versus collagen-induced arthritis may reflect a distinct role for these cells in different phases of RA, with a suppressive role in the induction phase and a provocative role in antibody-induced joint inflammation.

A particularly fascinating and novel aspect of the current report is the notion that Vαi NKT cells may actively contribute to synovial inflammation by residing in a niche where they are usually absent. Hence, Vαi NKT cells were reported to appear within the synovium of wild-type mice as early as three days after serum transfer. Their appearance results in important alterations in cytokine balances within the joints. In CD1d$^{-/-}$ mice a marked increase in transcripts of transforming growth factor-beta 1 (TGF-β1) was observed, contrary to C57BL/6 mice in which the levels were found to be reduced. By contrast, IL-4 and to a lesser extent IFN-γ transcripts were found to be reduced in CD1d$^{-/-}$ mice versus controls. However, no differences in transcript levels of either TGF-β1, IFN-γ or IL-4 were apparent in the spleen. The crucial role of TGF-β1 in mediating the observed effect in NKT cell deficient animals was shown by *in vivo* neutralization studies in which anti-TGF-β1 treatment was shown to abrogate the protective effect of Vαi NKT cells in CD1d$^{-/-}$ mice, while not affecting joint inflammation in wild-type animals. Although several studies have highlighted important immunoregulatory properties for TGF-β1 in experimental arthritis, the cellular communication network that results in TGF-β1 secretion is only partially understood. Kim *et al.*, propose that Vαi NKT cells suppress the production of TGF-β1 by synovial cells through the production of IFN-γ or IL-4. Whereas IFN-γ has been known to be a negative regulator for TGF-β1 for many years, the role of IL-4 reported by Kim *et al.* is unexpected and warrants further investigation [15]. Likewise, the precise mechanism(s) by which Vαi NKT cells are attracted to synovial tissue and the reason(s) why they get activated locally in the K/BXN serum transfer model to induce TGF-β1 have yet to be elucidated.

Taken together, the data illustrate the multifaceted roles of Vαi NKT cells in autoimmune diseases, particularly RA, and underline the important and non redundant role of these innate-like lymphocytes in immune regulation.

Competing interests

The author(s) declare that they have no competing interests.

Acknowledgements

DE is supported by the Fund for Scientific Research-Flanders, the Research-Fund of Ghent University and the Marató Foundation. We thank Dr. Hilde De Winter for critical reading of this manuscript.

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