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NK T cells in rheumatoid arthritis

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Keywords

CD161, natural killer T cell, NKR-P1, rheumatoid arthrtitis, Th1/Th2 imbalance

Context

In rheumatoid arthritis (RA), T helper (Th)1 cells, which secrete interferon (IFN)-?, predominate over Th2 cells, which secrete interleukin (IL)-4, IL-5, IL-10 and IL-13. To date, neither the nature of the Th1 predominance nor the relevance to pathogenesis or disease course has been fully understood. Natural killer (NK) T cells have been suggested as a potential source of IL-4 for Th2 differentiation. NK T cells express unique NK cell markers in addition to T cell receptor (TCR)a?. In mice, NK T cells comprise 0.4% of a?-thymocytes but 5% of splenic T cells and 40% of bone marrow T cells. A large fraction of peripheral NK T cells is characterized by expression of the invariant Va14Ja281 TCRa in mice and Va24JaQ in humans (90% homology at the amino acid level in the CDR3 region) and both have restricted TCR V? expression, suggesting the recognition of similar antigens. NK T cells recognize the MHC class I-like CD1d protein. The independent capacity of NK cells to secrete IL-4, in addition to IFN-?, has implicated them in the differentiation of naive T cells into Th2 cells. Interestingly, a more general role for NK T cells in autoimmune disease has been suggested since selective reduction of $Va14^{+}$ NK T cells has been associated with disease development in several autoimmunity-prone mice such as C57BL/6 lpr/lpr, C3H gld/gld or non-obese diabetic mice. Furthermore, in humans, a selective reduction of $Va24JaQ^{+}$ NK T cells, which usually comprise 20-100% of $CD4^{-}CD8^{-}$ T cells in healthy people, has been reported in patients with systemic sclerosis and diabetes mellitus type I. To assess the number of NK T cells in patients with RA compared to healthy controls, and any relation between number of NK T cells and activity or severity of the disease.

Significant findings

In patients with RA the number of NK T cells (25 ? 20/?l) and the number of $CD56^{+}CD3^{+}$ cells (60 ? 46/?l) was significantly reduced compared to healthy controls (143 ? 53/?l, $p < 0.0001$, and 116 ? 54/?l, $p < 0.0001$, respectively). In contrast, there was no difference in the number of conventional NK cells ($CD56^{+}CD3^{-}$) between RA patients and controls. Also, the ratio of NK T cells/NK cells ($NKR\text{-}P1A^{+}CD3^{+}/CD56^{+}CD3^{-}$) was significantly reduced in RA patients versus healthy controls. A weak

correlation was found between the number of NK T cells and serum ?-globulin. No relevant influence of the various disease-modifying anti-rheumatic drugs on the number of NK T cells could be found.

Comments

The authors confirm previous data showing that conventional NK cells are not different in RA patients and controls (Taylor et al, Scand J Rheumatol 1993, ***22*** *:280-283 [* Abstract *]; Thoen et al, Clin Rheumatol 1987,* ***6*** *:215-225). However, the finding of decreased NK T cells in RA is new and this merits further attention. Recent data suggests a differential regulation of cytokines by NK T cells in mice. When stimulated in vitro with anti-CD3, murine NK1.1$^+$CD4$^+$ T cells produce large amounts of IL-4 and IFN-?. In contrast, upon stimulation via CD1 substantial amounts of IL-4 but little IFN-? are produced and NK1.1 may serve as a receptor leading to IFN-? production but not causing IL-4 production (Chen et al , J Immunol 1997,* ***159*** *:2240-2249). Therefore, a complex role in regulating immune responses has been suggested for NK T cells. The fact that in several autoimmunity-prone mice levels of Va14$^+$ cells are reduced during or shortly before disease onset (see above) is particularly intriguing. Along this line, the reduction of Va24JaQ$^+$ cells in systemic sclerosis (Sumida et al, J Exp Med 1995,* ***182*** *:1163-1168) and in diabetes type I (Wilson et al, Nature 1998,* ***391*** *:177-181) suggests a more general role of NK T cells in autoimmunity. Although we do not know with certainty that the NKR-P1A$^+$ cells investigated in the present study are also Va24JaQ$^+$ this is likely to be the case. RA appears to be another autoimmune disease related to a change in this particular NK T cell subset.*

Methods

Peripheral blood cells from 60 patients with RA and 36 healthy controls were immunostained using monoclonal antibodies directed against NKR-P1A (DX1), CD56 (Leu-19) and CD3 (Leu-4) and subsequently analysed by three-colour flow cytometry. The NK T cell population was defined as NKR-P1A$^+$CD3$^+$, and was distinguishable from conventional T cells (CD3$^+$CD56$^-$NKR-P1A$^-$), NK cells (CD56$^+$CD3$^-$ or NKR-P1A$^+$CD3$^-$) and CD56$^+$CD3$^+$ cells (T cells with the NK marker).

References

1. Yanagihara Y, Shiozawa K, Takai M, Kyogoku M, Shiozawa S: Natural killer (NK) T cells are significantly decreased in the peripheral blood of patients with rheumatoid arthritis (RA). Clin Exp Immunol . 2000, 118: 131-136.