**Natural killer cells and autoimmunity**

Anthony R French and Wayne M Yokoyama

1Division of Pediatric Rheumatology, Department of Pediatrics, Washington University School of Medicine, St Louis, MO, USA
2Howard Hughes Medical Institute, Division of Rheumatology, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA

Corresponding author: Wayne M Yokoyama (e-mail: yokoyama@im.wustl.edu)

Received: 5 Nov 2003 Accepted: 24 Nov 2003 Published: 9 Dec 2003

**Abstract**

Autoimmune diseases are often characterized as clinical syndromes caused by the inappropriate activation of T or B cells resulting in systemic or organ-specific damage. However, studies support a role for the innate immune system, and in particular natural killer (NK) cells, in stimulating or suppressing autoimmunity. This review focuses on recent research elucidating a potential immunoregulatory role for NK cells in modulating T and B cell-mediated autoimmunity.

**Keywords:** autoimmunity, immunoregulation, natural killer cells

**Natural killer cells**

Natural killer (NK) cells are large, granular, bone marrow-derived lymphocytes that do not express T or B cell receptors [1]. In humans, these CD3-negative cells are identified by the surface markers CD16 and CD56 and comprise 5–15% of the peripheral blood mononuclear cells in normal individuals [2]. Although they were initially identified by their ability to lyse tumor cells without prior sensitization, more recent work has demonstrated that they have a crucial role in the initial defense against pathogens and are particularly important in responding to viral infections (reviewed in [3,4]).

NK cell responses result from the integration of signals from both cytokine receptors and germline-encoded NK cell inhibitory and activation receptors. NK cell receptors include the murine C-type lectin-like receptors in the Ly49 family, the C-type lectin-like receptors shared by mouse and human (for example NKR-P1, NKG2D and CD94/NKG2A), the human immunoglobulin-like receptors in the killer immunoglobulin-like receptor (KIR) family, and the immunoglobulin-like receptors shared by both mouse and human (for example 2B4) including the natural cytotoxicity receptor family (Nkp30, Nkp44 and Nkp46; reviewed in [1,10–13]).

Although NK cells are prepared to kill abnormal cells and rapidly release cytokines, they are normally restrained by inhibitory receptors that recognize target-cell-expressed MHC class I molecules and allow NK cells to survey tissues for normal MHC class I expression (Fig. 1). When MHC class I molecules are downregulated or absent, NK cells are released from the inhibitory influence of these receptors and kill target cells more efficiently (‘missing self’ hypothesis) [14]. It has been proposed that NK cells all express at least one inhibitory receptor that recognizes...
self MHC to provide NK cell tolerance and to prevent inappropriate NK cell responses directed at self [15,16]. However, release from inhibitory receptor effects does not automatically lead to NK cell activation against cellular targets. NK cells also express different combinations of various activation receptors, allowing them to respond to ligands on potential target cells [17–20]. The ligands for activation receptors are often closely related to the ligands for inhibitory receptors. In other cases, the activation receptor ligands may be upregulated in response to stress or infection, as illustrated by the upregulation of the NKG2D ligand MHC class I-related chain A (MICA) during infection [21–23].

NK cells can also respond directly to cytokines such as interleukin (IL)-12 and IL-18 that stimulate their production of other cytokines, including IFN-γ (not shown in Fig. 1). Such cytokine-mediated responses are generally not regulated by MHC class I expression, although MHC class I expression does regulate target-cell-stimulated cytokine release (Fig. 1).

**Observations of NK cell abnormalities in human autoimmune diseases**

Since the early 1980s, many studies have documented decreased NK cell numbers and impairment of NK cell function in the peripheral blood of patients with autoimmune diseases such as multiple sclerosis (MS), systemic lupus erythematosus (SLE), Sjögren’s syndrome, rheumatoid arthritis (RA), and type I diabetes (reviewed in [24–26]). However, some of the older reports did not distinguish between NK cells and NKT cells, a potential immunoregulatory subpopulation of T cells that are also able to rapidly release large amounts of cytokines. Better discrimination between these two populations has shown that in addition to the decreased NK cell numbers found in many autoimmune diseases, NKT cells are decreased in RA and psoriasis [27,28], but this topic is beyond the scope of this review.

More recent reports have also shown an association between NK cell deficits and autoimmune thyroid disease [29,30] and psoriasis [31] as well as several pediatric rheumatologic diseases including juvenile dermatomyositis [32] or SLE [33]. Low NK cell numbers have also been found in patients with systemic-onset juvenile rheumatoid arthritis (JRA) [34], and decreased NK cell function has been documented in systemic-onset JRA patients with macrophage activation syndrome or hemophagocytic lymphohistiocytosis [35–37].

Although there is substantial evidence correlating decreased NK cell numbers and function with autoimmune diseases, it is not clear whether the reported NK cell alterations occur secondarily to the disease and its treatments or are primary defects involved in the disease pathogenesis. However, recent studies have documented NK cell defects in treatment-naïve patients before overt progression to disease or at the time of diagnosis, demonstrating that the defects are not solely treatment-related or the result of chronic inflammation from long-standing disease [32,33]. In addition, a temporal correlation has been identified between NK cell numbers or activity and periods of disease progression or remission in MS and SLE, suggesting that NK cells may play an immunoregulatory role in disease pathology [38–43].

The correlation of decreased NK cell numbers and/or function with autoimmune diseases raises the possibility that autoimmunity may arise from NK cell deficiencies. However, such conclusions must be tempered by the fact that reports of NK cell defects in patients with autoimmune diseases have been based almost exclusively on studies of peripheral blood samples, which would not dis-
It is proposed that the unusual enrichment of NK cells in target tissues. In addition, the clinical course of patients with selective, complete NK cell deficiencies has been dominated by overwhelming infections, often from herpesviruses, and not by autoimmune syndromes [44–46]. In contrast, NK cell lymphocytosis and leukemia are associated with autoimmune syndromes, such as vasculitis and RA [47–49], suggesting that peripheral-blood NK cell defects in systemic autoimmune syndromes may be due to the sequestration of NK cells in target tissues.

Alterations in KIR expression on NK cells (and/or on T cells) have also been associated with autoimmune diseases such as Behcet's disease, type I diabetes, and psoriasis [50–52]. In addition, aberrant expression of NK cell receptors on subpopulations of CD4+ T cells has been observed in patients with RA [53–56]. Skewed KIR receptor repertoires may potentially lower the threshold for NK cell or T cell activation when activating forms of the immunoglobulin-like receptors (KARs) are present either in the absence of their corresponding inhibitory KIRs or in the absence of the HLA ligands for the inhibitory KIRs [50–53,55].

Abnormal expression of another NK cell activation receptor, NKG2D, has also been observed on a fraction of CD4+ T cells in patients with RA [57]. Furthermore, expression of MICA, an inducible ligand for the NKG2D [58], has also been identified in the synovium of patients with RA, suggesting that the abnormal expression of MICA in the context of upregulation of NKG2D on CD4+ T cells in patients with RA may result in this subpopulation of CD4+ T cells receiving persistent co-stimulation [57]. In addition to potentially prolonging T-cell activation, the aberrant expression of MICA may also be involved in modulating the responses of NK cells in the inflamed synovium.

Indeed, NK cells comprise a significant fraction of the lymphocytes found in the synovial fluid of patients with RA (8–16% of lymphocytes) and can be detected in the joint at an early stage in the disease course [59]. Interestingly, most of the NK cells in the synovial fluid of patients with established RA are CD56bright, with elevated expression of both CD94 and NKG2A and decreased expression of KIRs and CD16 [60,61]. The CD56bright subpopulation of NK cells is also found in the blood of patients with RA and normal controls but at much lower frequencies (typically 10% of NK cells). Although originally thought to be immature NK cells, evidence now supports the hypothesis that CD56bright NK cells are a separate subpopulation that produce high levels of cytokines and may potentially play a role in immunoregulation [62,63]. The NK cells within the synovium also have an upregulated expression of several chemokine receptors and adhesion molecules that may participate in preferential recruitment into the synovium [60]. It is proposed that the unusual enrichment of CD56bright NK cells may have a role in the initiation and/or perpetuation of dysregulated production of proinflammatory cytokines in the synovium of patients with RA [60,61]. It is also possible that aberrant expression of MICA in the inflamed synovium [57] is involved in modulating the responses of this subset of NK cells, resulting in the dysregulated production of proinflammatory cytokines rather than in immunoregulation.

Most of the evidence from human autoimmune diseases suggests that NK cells may be involved in immunoregulation and/or autoimmune disease pathogenesis. However, because it is difficult to determine potential mechanistic roles of NK cells in these diseases and to rule out epiphenomena in humans, we will now shift our focus to mouse models of autoimmunity.

**Insight into the role of NK cells in autoimmunity from mouse models of autoimmune diseases**

The role of NK cells in autoimmune responses has been examined in several murine models of autoimmune diseases (reviewed in [25,26]). The evidence from these studies (discussed below) suggests that NK cells can affect the development of autoimmunity through several mechanisms, including suppressing viral infections and potential subsequent autoimmune responses, modulating autoreactive responses of other immune cells, or, as effector cells, directly mediating tissue damage (Fig.2). Different NK cell responses in these models presumably result from alterations in the balance between inhibitory and stimulatory signals mediated through the interactions of NK cell receptors and their ligands. The expression levels of ligands for both inhibitory and activation NK cell receptors in target tissues as well as the immediate cytokine milieu modulate the NK cell activation threshold, allowing different NK cell responses that could potentially suppress or augment autoimmunity.

Viral infections have been implicated in the pathogenesis of several autoimmune diseases due to molecular mimicry or polyclonal immune activation [64]. It is well established that NK cells have a crucial role in the initial defense against viral infections [3,4]. It is therefore not surprising that several investigators have attributed the impact of relative deficiencies of NK cell numbers or function seen in many autoimmune diseases to a decreased ability to respond to viral infections.

Results from mouse models show a role for NK cells in suppressing autoimmune responses after viral infections (Fig.2a). For example, NK cells are important in preventing encephalitis in a murine model of MS induced by Theiler’s murine encephalitis virus [65]. Depletion of NK cells in resistant mice resulted in the development of diffuse encephalitis and meningitis early in the post-infection period [65]. NK cells are also thought to prevent coxsack-
Murine models show that natural killer (NK) cells affect autoimmunity through several potential mechanisms. (a) NK cells limit viral-induced tissue damage by directly killing virally infected cells or by releasing cytokines that can suppress viral propagation either directly or indirectly by activating other cells such as macrophages. Defective NK cell responses to viral infections may result in autoimmunity in genetically predisposed strains of mice as a result of uncontrolled infection leading to increased tissue destruction, with accompanying exposure of self antigens. (b) NK cells participate in the immunoregulation of other immune cells. Control of autoreactive T and B cells by NK cells may be mediated directly through the release of cytokines and chemokines or indirectly through bidirectional interactions with other components of the innate immune system such as dendritic cells (DCs). In addition, it is possible that NK cells may kill autoreactive lymphocytes or inappropriately activated immature DCs. (c) NK cells could potentially mediate an autoimmune response by inappropriately killing normal tissues.

Less information is available on how NK cells perform this potential immunoregulatory role. It is possible that this role is mediated directly by the release of immunomodulatory cytokines and chemokines involved in lymphocyte recruitment, activation, and suppression, such as IFN-γ and transforming growth factor-β. However, NK cell-derived cytokines and chemokines may act indirectly by inducing cytokine production in other cells, activating macrophages, or supporting the maturation of dendritic cells (DCs). Indeed, bidirectional interactions between NK cells and other components of the innate immune system such as DCs and NKT cells have been reported ([73–75]; reviewed in [9,76]). It is also possible that the immunoregulatory role of NK cells is mediated by the killing of autoreactive lymphocytes or immature DCs by NK cells. The immunoregulatory role of NK cells in suppressing colitis in a murine CD4+ T cell transfer model was found to be dependent on perforin, suggesting that the NK cells were directly killing autoreactive T cells or some other intermediate effector cells such as DCs [69]. In addition, several studies have shown that NK cells are potentially able to influence the subsequent adaptive immune response by lysing immature DCs [74,75] or developing T cells [77]. Therefore, it appears that NK cells may employ several different mechanisms to regulate the responses of other immune cells and thereby affect the development of autoimmunity.

Murine models of other autoimmune diseases suggest that NK cells may also participate in the initiation of temporally related to an age-dependent loss of NK and NKT cells. Furthermore, antibody-mediated NK cell depletion in these mice enhanced the development of autoantibody-secreting B cells, whereas the adoptive transfer of NK cells delayed the onset of autoantibody production [67]. Studies in vitro have shown that rat NK cells can inhibit autoreactive T cell cytokine production and proliferation [68]. Indeed, depletion of NK cells worsened colitis in a CD4+ T cell transfer model in mice, demonstrating an immunoregulatory role for NK cells [69]. Several investigators have reported similar findings in experimental autoimmune encephalomyelitis (EAE), a Th1-mediated mouse model of MS [70,71]. Depletion of NK cells before immunization of sensitive mice with myelin oligodendrocyte glycoprotein (MOG35–55) peptide resulted in clinically more severe, relapsing EAE [70]. Depletion of NK cells also resulted in more severe disease after passive transfer of an EAE-inducing CD4+ T cell line, showing that NK cells are not only involved in the initiation of EAE but can inhibit effector T cells [70]. NK cell depletion in rats before immunization with myelin basic protein also exacerbated the clinical features of EAE and increased mortality [71]. However, these results conflict with a third study, which reported that NK cell depletion resulted in less severe clinical scores [72]. Overall, NK cells appear to participate in regulating T and B cell-mediated autoimmune responses.

Evidence from murine models also supports an immunoregulatory role for NK cells in modulating other immune cell responses (Fig.2b). The development of autoimmune in C57BL/6Jpr mice, which have a defect in Fas, a gene encoding a tumor necrosis factor receptor superfamily member involved in inducing apoptosis, is...
autoimmunity through interactions with autoreactive T and B cells. Experimental autoimmune myasthenia gravis (EAMG) is an antibody-mediated autoimmune disease in which autoantibodies against the acetylcholine receptor (AchR) in neuromuscular junctions are stimulated in susceptible mice by repeated immunizations with Torpedo AChR in adjuvant. Depletion of NK cells before immunization resulted in significantly delayed onset and decreased severity of EAMG with decreased anti-AChR antibody production [78]. Interestingly, NK cell depletion after the initial immunization had no impact on the development of EAMG. In a mouse model of asthma, initial immunization with ovalbumin in adjuvant followed by repeated daily exposure to aerosolized ovalbumin resulted in CD4+ T cell-dependent pulmonary eosinophilic inflammation and systemic IgE production, consistent with a Th2 immune response [79]. Depletion of NK cells before the initial immunization but not later during the challenge period resulted in a diminished infiltration of pulmonary eosinophils and CD3+ T cells as well as a decreased systemic production of IgE, suggesting a role for NK cells in promoting allergen-induced airway inflammation [79]. Interestingly, the temporal impact of NK depletion observed in these models has also been reported in an EAE model in which the depletion of NK cells after the primary immunization did not impact development of EAE [72]. These results suggest that NK cells may be most influential at the initiation of the autoimmune response.

In addition to potential immunoregulatory roles for NK cells in autoimmunity, NK cell-mediated cytotoxicity may result directly in significant organ-specific damage (Fig.2c). Several groups have shown that activated NK cells can lyse autologous neurons in vitro, suggesting that NK cell cytotoxicity may have a role in EAE [80,81]. NK cells have also been implicated in the selective neuronal death in the superior cervical ganglia of rats treated with guanethidine [82]. Recent experiments have shown that NK cells can kill syngeneic dorsal root ganglia neurons by a perforin-dependent mechanism [83]. Interestingly, it was shown that this response was mediated by NKG2D recognition of a ligand on dorsal root ganglia neurons that was not expressed on resistant central nervous system-derived neurons [83]. NK cell-mediated killing of syngeneic neurons expressing an NK cell activation receptor ligand supports the hypothesis that inappropriate killing of self tissues by NK cells may reflect a loss of NK cell ‘tolerance’ occurring in tissues that have inappropriately downregulated MHC class I ligands for NK cell inhibitory receptors or that have aberrant expression of ligands for NK cell activation receptors or expression of these ligands in tissues that are normally isolated from NK cells.

NK cells appear to participate in mediating organ-specific damage in several murine models of autoimmunity. Experimental autoimmune uveoretinitis (EAU) is induced by immunizing sensitive strains of mice with ocular autoantigens. Depletion of NK cells before immunization resulted in significantly less severe EAU, demonstrating that NK cells participate in the development of EAU, either by directly mediating cellular damage or by supporting rather than suppressing autoreactive T cells [84]. A murine model of autoimmune-mediated diabetes after viral infection with CVB4 provides another example of organ-specific, NK cell-mediated damage [85]. In this model, mice whose pancreatic beta cells express a transgene for the suppressor of cytokine signaling (SOCS-1), an inhibitor of interferon signaling, develop diabetes soon after CVB4 infection. However, depletion of NK cells before infection with CVB4 prevented the development of diabetes, implying that NK cells contributed to the destruction of the infected pancreatic beta cells, although no direct evidence was presented to show the involvement of NK cell-mediated cytotoxicity [85]. Therefore, in spite of in vitro data suggesting that NK cell-mediated cytotoxicity may result in organ-specific autoimmunity, more direct in vivo experimental evidence in murine models is needed to support this hypothesis.

Conclusions
There is strong evidence that the innate immune system, and in particular NK cells, influence subsequent adaptive immune responses. By virtue of their ability to rapidly kill abnormal cells and produce cytokines and chemokines, NK cells are positioned for a key role in regulating autoimmune responses. The results summarized in this review demonstrate that NK cells are involved in modulating responses to self antigens and that in some circumstances NK cells can either suppress or augment autoimmunity, directly or indirectly. The associations found in humans and the empirical evidence from murine models suggest that further research into the immunomodulatory role of NK cells in autoimmunity is warranted and is likely to provide new insights into the pathogenesis of autoimmune disorders.

Competing interests
None declared.

References
1. Yokoyama WM: Natural killer cell receptors. Curr Opin Immunol 1996, 10:298-305.
2. Seaman WE: Natural killer cells and natural killer T cells. Arthritis Rheum 2000, 43:1204-1217.
3. Biron CA, Nguyen KB, Pine GC, Cousens LP, Salazar-Mather TP: Natural killer cells in antiviral defense: function and regulation by innate cytokines. Annu Rev Immunol 1999, 17:189-220.
4. French AR, Yokoyama WM: Natural killer cells and viral infections. Curr Opin Immunol 2003, 15:45-51.
5. Horwitz DA, Gray JD, Ohutsuka K, Hirokawa M, Takahashi T: The immunoregulatory effects of NK cells – the role of TGF-β and implications for autoimmunity. Immunol Today 1997, 18:538-542.
6. Fearon DT, Locksley RM: The instructive role of innate immunity in the acquired immune response. Science 1996, 272:50-53.
uncovered patients with juvenile dermatomyositis (JDM) are associated with disease activity scores (DAS). Arthritis Rheum 2002, 46(suppl 9):S490.

33. Yabuhara A, Yang FC, Nakazawa T, Iwasaki Y, Mori T, Koike K, Kawai H, Komiyama A: A killing defect of natural killer cells as an underlying immunologic abnormality in childhood systemic lupus erythematosus. J Rheumatol 1996, 23:171-177.

34. Wouters CH, Ceuppens JL, Stevens EA: Different circulating lymphocyte profiles in patients with different subtypes of juvenile idiopathic arthritis. Clin Exp Rheumatol 2002, 20:239-248.

35. Wulfraat NM, Rijkers GT, Elssasser AL, Kuis W: Reduced perforin expression in systemic juvenile idiopathic arthritis is restored by autologous hematopoietic stem-cell transplantation. Rheumatology (Oxford) 2003, 42:375-379.

36. Imashuku S, Hyakuna K, Funabiki T, Ikuta K, Sako M, Iwai A, Fukushima T, Kataoka S, Yabe M, Muramatsu K, Kohdera U, Naka- date H, Kitazawa K, Toyoda Y, Ishi E: Low natural killer activity and central nervous system involvement in patients with systemic lupus erythematosus. Neurol Res 2002, 24:303-308.

37. Grom AA, Villanueva J, Lee S, Goldmontz EA, Passo MH, Filipovich A: Natural killer cell dysfunction in patients with systemic-onset juvenile idiopathic arthritis and macrophage activation syndrome. J Pediatr 2003, 142:292-296.

38. Erkeller-Yusel F, Hulstaart F, Hennet I, Isenberg D, Lydyard P: Lymphocyte subsets in a large cohort of patients with systemic lupus erythematosus. Lupus 1993, 2:29-31.

39. Erkeller-Yusel FM, Lydyard PM, Isenberg DA: Lack of NK cells in lupus patients with renal involvement. Lupus 1997, 6:708-712.

40. Munschauer FE, Hartwich JA, Stwart CC, Jacobs L: Circulating natural killer cells but not cytotoxic T lymphocytes are reduced in patients with active relapsing multiple sclerosis and little clinical disability as compared to controls. J Neuromuscul Dis 1995, 2:177-181.

41. Kastrukoff LF, Morgan NG, Zecchini D, White R, Petkau AJ, Satoh J, Boyd DW: A role for natural killer cells in the immunopathogenesis of multiple sclerosis. J Neuromuscul Dis 1998, 8:123-133.

42. Ricciere V, Spadaro A, Parisi G, Taccari E, Moretti T, Bernardini G, Favaron M, Strom R: Down-regulation of natural killer cells and of gamma/delta T cells in juvenile dermatomyositis. Does it correlate to autoimmunity and to laboratory indices of disease activity? Lupus 2000, 9:333-337.

43. Takahashi K, Miyake S, Kondo T, Terao K, Hatakenaka M, Takahata N, Yamamoto S, Yamamura T: Natural killer type 2 bias in remission of multiple sclerosis. J Clin Invest 2001, 107:123-130.

44. Biron CA, Byron KS, Sullivan JL: Severe herpesvirus infections in an adolescent without natural killer cells. N Engl J Med 1989, 320:1731-1735.

45. Jawahar S, Moody C, Chan M, Finberg R, Geha R, Chalita T: Natural Killer (NK) cell deficiency associated with an epilidemic- gene deficient Fc receptor type III (CD16-II). Clin Exp Immunol 1996, 103:408-413.

46. Orange JS: Human natural killer cell deficiencies and susceptibility to infection. Microbes Infect 2002, 4:1545-1568.

47. Lamy T, Loughran TP Jr: Clinical features of large granular lymphocytic leukemia. Semin Hematol 2003, 40:185-195.

48. Telfer A, Li CY, Witzig TE, Dhodapkar MV, Okuno SH, Phyllyki RL: Chronic natural killer cell lymphocytosis: a descriptive clinical study. Blood 1994, 84:2721-2729.

49. Rabinovici GR, Phyllyki RL, Telfer A: A long-term study of patients with chronic natural killer cell lymphocytosis. Br J Haematol 1999, 106:960-966.

50. Martin MP, Nelson G, Lee JH, Pellet F, Gao X, Wade J, Wilson MJ, Trowsdale J, GlaxoSmithKline. Evaluation of susceptibility to parasitic arthritis: influence of activating killer-like receptor genes in the absence of specific HLA-C alleles. J Immunol 2002, 169:2818-2822.

51. van der Slak AR, Koelman BP, Verduijn W, Bruning GJ, Roep BO, Giphart MJ: KIR in type 1 diabetes: disparate distribution of activating and inhibitory natural killer cell receptors in patients versus HLA-matched control subjects. Diabetes 2003, 52:2639-2642.

52. Takeno M, Shimoyama Y, Kashiwakura J, Nagaiuchi H, Sakane T, Suzuki N: Abnormal killer inhibitory receptor expression on...
natural killer cells in patients with Behcet’s disease. Rheuma- tol Int 2003 [epub ahead of print].

53. Namekawa T, Snyder MR, Yen JH, Goehringer BE, Leibson PJ, Weyand CM, Goronzy JJ: Killer cell activating receptors function as costimulatory molecules on CD4+CD8-Null T cells clonally expanded in rheumatoid arthritis. J Immunol 2000, 165:1138-1145.

54. Warrington KJ, Takemura S, Goronzy JJ, Weyand CM: CD8a+CD28- T cells in rheumatoid arthritis patients combine features of the innate and adaptive immune systems. Arthritis Rheum 2001, 44:13-20.

55. Yen JH, Moore BE, Nakajima T, Scholl D, Schaid DJ, Weyand CM, Goronzy JJ: Major histocompatibility complex class I-recogniz- ing Th1/Th2 cytokine profiles and disease risk genes in rheumatoid arthritis. J Exp Med 2001, 193:1159-1168.

56. Snyder MR, Lucas M, Vivier E, Weyand CM, Goronzy JJ: Selective activation of the c-Jun NH2-terminal protein kinase signaling pathway by stimulatory KIR in the absence of KARAP/ Clin1/12 in CD4+ T cells. J Exp Med 2003, 197:437-449.

57. Groh V, Bruhl A, El-Gabalawy H, Nelson JL, Spies T: Stimulation of T cell autoreactivity by anomalous expression of NKGD2 and its MiC ligands in rheumatoid arthritis. Proc Natl Acad Sci USA 2003, 100:9492-9497.

58. Bauer S, Groh V, Wu J, Steinle A, Phillips JH, Lanier LL, Spies T: Activation of NK cells and T cells by NKGD2, a receptor for stress-inducible MiCA. Science 1999, 285:727-729.

59. Tak PP, Kummer JA, Hack CE, Dara MA, Smeets TJ, Erkelens GW, Meinders AE, Klun PM, Breedveld FC: Granzyme-positive cytotoxic T cells are specifically increased in early rheumatoid synovial tissue. Arthritis Rheum 1994, 37:1735-1743.

60. Dalbeth N, Callan MF: A subset of natural killer cells is greatly expanded within inflamed joints. Arthritis Rheum 2002, 46: 1763-1772.

61. Pridgeon C, Lennon GP, Pazmany L, Thompson RN, Christmas SE, Moots RJ: Natural killer cells in the synovial fluid of rheumatoid arthritis patients exhibit a CD56brightCD94brightCD158negative phenotype. Rheumatology (Oxford) 2003, 42:870-878.

62. Groh V, Fehniger TA, Turner SC, Chen KS, Ghahei BA, Ghayur T, Carson WE, Caligiuri MA: Human natural killer cells: a unique innate immunoregulatory role for the CD56bright subset. Blood 2001, 97:3146-3151.

63. Farag SS, Vandeusen JB, Fehniger TA, Caligiuri MA: Biology and clinical impact of human natural killer cells. Int J Hematol 2003, 78:7-17.

64. Fujimori RS: Can virus infections trigger autoimmune disease? J Autoimmun 2001, 16:229-234.

65. Paya CV, Patick AK, Leibson PJ, Rodriguez M: Role of natural killer cells as immune effectors in encephalitis and demyeli- nation induced by Thelier’s virus. J Immunol 1989, 143:95-102.

66. Fairweather D, Kaya Z, Shellam GR, Lawson CM, Rose NR: From infection to autoimmunity. J Autoimmun 2001, 16:175-188.

67. Takeda K, Dennert G: The development of autoimmunity in C57BL/6 lpr mice correlates with the disappearance of natural killer type 1-positive cells: evidence for their suppressive action on bone marrow stem cell proliferation, B cell immunoglobulin secretion, and autoimmune symptoms. J Exp Med 1993, 177:115-184.

68. Smetz RB, Wolf NA, Swanborg RH: Inhibition of autoimmune T cell responses in the DA rat by bone marrow-derived NK cells in vitro: implications for autoimmunity. J Immunol 1999, 163: 1390-1397.

69. Fort MM, Leach MW, Rennick DM: A role for NK cells as regulators of CD4+ T cells in a transfer model of colitis. J Immunol 1998, 161:3256-3261.

70. Zhang B, Yamamura T, Kondo T, Fujiwara M, Tabira T: Regulation of experimental autoimmune encephalomyelitis by natural killer (NK) cells. J Exp Med 1997, 186:1677-1687.

71. Marumo Y, Koyama K, Akawa Y, Shin T, Kawazoe Y, Suzuki Y, Tanuma N: Role of natural killer cells and TCR gamma delta T cells in acute autoimmune encephalomyelitis. Eur J Immunol 1998, 28:1681-1688.

72. Shi FD, Takeda K, Akira S, Sarvetnick N, Ljunggren HG: IL-18 directs autoreactive T cells and promotes autodestruction in the central nervous system via induction of IFN-gamma by NK cells. J Immunol 2000, 165:3099-3104.

73. Carnaud C, Lee D, Donnars O, Park SH, Beavis A, Kozuza Y, Bendelac A: Cutting edge: cross-talk between cells of the innate immune system: NKT cells rapidly activate NK cells. J Immunol 1999, 163:4647-4650.

74. Gerosa F, Baldani-Guerra B, Nissi C, Marchesini V, Carra G, Trinchieri G: Reciprocal activating interaction between natural killer and dendritic cells. J Exp Med 2002, 195:327-333.

75. Piccoli D, Sbrana S, Melandri E, Valiante NM: Contact-depen- dent stimulation and inhibition of dendritic cells by natural killer cells. J Exp Med 2002, 195:335-341.

76. Moretta A: Natural killer cells and dendritic cells: rendezvous in abused tissues. Nat Rev Immunol 2002, 2:957-964.

77. Schott E, Bonasio R, Ploegh HL: Elimination in vivo of develop- ing T cells by natural killer cells. J Exp Med 2003, 198:1213-1224.

78. Shi FD, Wang HB, Li H, Hong S, Taniguchi M, Link H, Van Kaer L, Ljunggren HG: Natural killer cells determine the outcome of B cell-mediated autoimmunity. Nat Immunol 2000, 1:245-251.

79. Korsgren M, Persson CG, Sundler F, Bjerke T, Hansson T, Chambers BJ, Hong S, Van Kaer L, Ljunggren HG, Korsgren O: Natural killer cells determine the development of allergen-induced eosinophilic airway inflammation in mice. J Exp Med 1999, 189:553-562.

80. Backstrom E, Chambers BJ, Kristenson K, Ljunggren HG: Direct NK cell-mediated lysis of syngenic dorsal root ganglia neurons in vitro. J Immunol 2000, 165:4895-4900.

81. Morse RH, Seguin R, McCrea EL, Antel JP: NK cell-mediated lysis of autologous human oligodendrocytes. J Neuroimmunol 2001, 116:107-115.

82. Hickey WP, Ueno K, Hiserodt JC, Schmidt RE: Exogenously- activated dendritic cell-mediated neuronal killing: a novel pathogenetic mechanism. J Exp Med 1992, 176:811-817.

83. Backstrom E, Chambers BJ, Ho EL, Naidenko OV, Mariotti R, Fremont DH, Yokoyama WM, Kratennon K, Ljunggren HG: Natural killer cell-mediated lysis of dorsal root ganglia neurons via RAEl/NKGD2 interactions. Eur J Immunol 2003, 33:92-100.

84. Kitaichi N, Kotsake S, Morohashi T, Onoe K, Ohno S, Taylor AW: Diminution of experimental autoimmune uveoretinitis (EAU) in mice depleted of NK cells. J Leukoc Biol 2002, 72:1117- 1121.

85. Flodstrom M, Maday A, Balakrishna D, Cleary MM, Yoshimura A, Sarvetnick N: Target cell defense prevents the development of diabetes after viral infection. Nat Immunol 2002, 3:373-382.

Correspondence
Wayne M Yokoyama, Howard Hughes Medical Institute, Box 8045, Division of Rheumatology, Washington University, 660 South Euclid Avenue, St Louis, Missouri 63110, USA. Tel: +1 314 362 9075; fax: +1 314 362 9297; e-mail: yokoyama@im.wustl.edu