Natural killer cells in human autoimmune disorders

Leslie A Fogel, Wayne M Yokoyama and Anthony R French

Introduction

Autoimmune diseases exert a large burden on humanity. In 2005, the National Institutes of Health National Institute of Allergy and Infectious Diseases estimated that autoimmune disorders affected 24 million Americans [1]. A more recent estimate by the American Autoimmune Related Diseases Association utilizing a more comprehensive list of autoimmune diseases suggested that up to 50 million Americans (nearly one in six) are afflicted by an autoimmune disorder [2]. Although these disorders are primarily mediated by T cells and B cells, natural killer (NK) cells have been implicated in the induction and/or persistence of inappropriate immune responses in autoimmune diseases. A more complete characterization of the role of NK cells in human autoimmunity may lead to novel therapeutic targets in these diseases.

Natural killer cells are granular, innate lymphocytes that do not express rearranged antigen receptors [3]. In humans, these CD3-negative lymphocytes are identified by the expression of CD16 and CD56, although recent studies have suggested that NKP46 (NCR1) may be an alternative marker [4]. NK cells comprise 5 to 15% of the peripheral blood mononuclear cells and are also found in secondary lymphoid tissues (for example, spleen, lymph nodes, and tonsils) as well as other organs such as the liver, intestine, skin, and lung [5]. In these various locations, NK cells function as innate sentinels and play a critical role in early immune responses to intracellular pathogens. In addition, NK cells are particularly abundant in the endometrium of the pregnant uterus where they influence the implantation of the embryo and the vascular function and formation of the placenta [6,7].

Human NK cells can be divided into two major subsets based on the expression of CD56 [8]. CD56dim NK cells comprise approximately 90% of circulating peripheral NK cells and express high levels of CD16, inhibitory killer immunoglobulin-like receptors (KIRs), and perforin (a pore-forming component in NK cell cytolytic granules) [9]. In contrast, CD56bright NK cells are more abundant than CD56dim NK cells in secondary lymphoid tissues such as lymph nodes and tonsils [10]. CD56bright NK cells express low levels of CD16, KIRs, and perforin, with higher expression levels of a number of cytokine receptors and CD94/NKG2A than CD56dim NK cells. The functional consequence of these differences (as well as differences in chemokine receptor expression) is that CD56bright NK cells in secondary lymph organs are more efficient cytokine and chemokine producers while CD56dim NK cells in the periphery are more potent cytolytic effectors. Furthermore, the differential expression of cytokine receptors by these two subsets allows the local microenvironment and inflammatory milieu to influence NK cell functional responses.

Regulation of natural killer cell activation and licensing

Individual NK cells express a variable number of germline encoded inhibitory and activating cell-surface receptors. The inhibitory NK cell receptors recognize either
classical or nonclassical major histocompatibility complex (MHC) class I proteins, which in humans are encoded by the human leukocyte antigen (HLA) genes. For example, KIR3DL1 binds the classical MHC class I protein HLA-Bw4 [11,12] while CD94/NKG2A binds the nonclassical MHC class I protein HLA-E [13-15]. Some activation receptors recognize the same or similar ligands as inhibitory receptors (for example, both the inhibitory CD94/NKG2A and the activating CD94/NKG2C can bind to HLA-E [13,14]), while others recognize molecules with MHC class I structural folds that are upregulated by cellular stress (for example, NKG2D binds to MHC class I polypeptide-related sequence A [16]) or proteins encoded by pathogens (for example, Nkp46 binds to influenza hemagglutinin [17]).

NK cell responses are determined by the integration of signals from these inhibitory and activating cell-surface receptors, although the activation threshold in NK cells is also influenced by cytokine stimulation [3]. NK cell responses are primarily restrained by inhibitory receptor recognition of ubiquitously expressed MHC class I ligands on host cells. However, NK cells are freed from this inhibition and have a lower activation threshold when infected or transformed cells downregulate MHC class I molecules under selective pressure to evade lysis by CD8 cytotoxic T cells (missing-self hypothesis) [18,19]. Furthermore, the upregulation of NK cell activation ligands on host cells is limited in the absence of cellular stress or infection [20,21] to minimize inadvertent NK cell activation and host damage.

Inappropriate NK cell activation is also prevented by NK cell licensing (reviewed in [22,23]). Although missing-self recognition is a well-established paradigm of NK cell activation, NK cells from MHC class I-deficient hosts are paradoxically less reactive to stimuli than cells from MHC class I-sufficient hosts [24]. Furthermore, NK cells that do not express a self-MHC-specific inhibitory receptor are hyporesponsive rather than hyperactivated [25-27]. These observations are explained by the recent concept of NK cell licensing which proposes that inhibitory NK cell receptor recognition of self-MHC class I is required for NK cells to become fully responsive to future stimulation through their activation receptors [27-29]. Although this hypothesis was initially described in murine systems [27], it has subsequently been validated in humans as well [25,30]. For example, when stimulated with MHC-deficient tumors, KIR3DL1-expressing NK cells generated substantial amounts of IFNγ if the donor was homozygous for the KIR3DL1 ligand (HLA-Bw4); however, KIR3DL1-expressing NK cells from donors that did not express HLA-Bw4 did not produce IFNγ following similar stimulation [30]. Potential autoreactivity of unlicensed NK cells is therefore prevented by their hyporesponsiveness to stimulation through activation receptors.

In summary, NK cell activation is regulated through several distinct mechanisms to prevent inappropriate responses. First, NK cells express inhibitory receptors that recognize widely expressed ligands. Second, the up-regulation of host ligands for activating receptors is regulated to prevent inadvertent damage to normal healthy tissues. Finally, full NK cell responsiveness requires licensing through inhibitory receptors, which prevents the unrestrained activation of NK cells that do not express appropriate self-MHC class I-reactive inhibitory receptors.

**Natural killer cells and immunoregulation**

The ability of NK cells to kill cells and release immunomodulatory cytokines and chemokines allows NK cells to modulate the innate immune response and mold the development of the adaptive immune response. For example, human NK cells promote dendritic cell (DC) maturation and DC production of cytokines such as TNFa and IL-12 [31-33]. Interestingly, NK cells can kill immature DCs, while mature DCs are resistant to killing as a result of their upregulation of MHC class I molecules [34,35]. Cytokine-activated human NK cells can also directly kill both activated macrophages [36] and T cells [37,38] secondary to the upregulation of NKG2D ligands on these cells. NK cells are also able to provide costimulatory signals for CD4 T cells and augment their proliferation [39]. Additionally, NK cell-derived cytokines (including IFNγ [9] and IL-10 [40-42]) influence the differentiation [43,44] and the proliferation of CD4 T cells [42].

Impaired NK cell functional responses are frequently observed in patients with autoimmune disorders (discussed below). The importance of NK cell cytolytic function in immunoregulation is highlighted in hemophagocytic lymphohistiocytosis, a life-threatening disorder with uncontrolled immune activation and excessive T-cell production of cytokines leading to unrelenting phagocyte activation. This disorder results from a failure of cytolytic lymphocytes (CD8 T cells and NK cells) to kill infected cells and/or persistently activated T cells [45,46]. Patients with hemophagocytic lymphohistiocytosis uniformly have decreased NK cell cytolytic responses. Mutations in several proteins required for cytolytic granule release or function have been identified in hemophagocytic lymphohistiocytosis, including perforin, MUNC13-4, syntaxin 11, and syntaxin binding protein 2 (STXBP2) [45,46]. Mutations in STXBP2 directly implicate defective NK cell cytolysis in this disorder since STXBP2 expression is substantially higher in NK cells than in CD8 T cells and defects in degranulation have been observed in STXBP2-deficient NK cells but not in STXBP2-deficient CD8 T cells [47]. As illustrated by hemophagocytic lymphohistiocytosis, NK cell functional
responses must be carefully regulated to prevent damage to normal tissues or dysregulation of the adaptive immune responses (for example, dysfunctional cytolyis resulting in persistent T-cell and macrophage activation or indiscriminate release of IFNγ resulting in inappropriate immune activation).

**Natural killer cell abnormalities in human autoimmune diseases**

Over the last 30 years, many studies have reported decreased NK cell numbers or impairment of NK cell cytotoxicity in the peripheral blood of patients with autoimmune diseases such as multiple sclerosis (MS), rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome, and type I diabetes mellitus (T1DM) (reviewed in [48-54]). Although some of the older reports did not distinguish between NK cells and NKT cells (T cells with NK cell markers, typically restricted by CD1), more recent studies have also clearly identified an association between *bona fide* NK cell deficits in the peripheral blood with many autoimmune disorders [55] including autoimmune thyroid disease [56,57] and psoriasis [58] as well as a number of pediatric rheumatologic diseases including juvenile dermatomyositis [59] and systemic-onset juvenile idiopathic arthritis (JIA) [60].

The significance of these correlative studies to the pathogenesis of autoimmune diseases is not clear. Although these reports raise the possibility that autoimmunity may be associated with NK cell numerical or functional deficiencies, such conclusions must be tempered by the fact that these observations have been based primarily on studies of peripheral blood samples that cannot distinguish between true deficits and sequestration of NK cells in target tissues. Furthermore, the clinical courses of rare patients with complete NK cell deficiencies are dominated by overwhelming viral infections rather than autoimmune syndromes [61-63].

In contrast to reports based solely on decreased numbers of NK cells in the peripheral blood, several studies have demonstrated accumulation of NK cells in affected tissues of autoimmune patients. For example, infiltrating NK cells have been found to accrue in the pancreatic islet of T1DM patients [64], the hair follicle of patients with alopecia areata [65], and the muscle of children with juvenile dermatomyositis [66,67]. Interestingly, CD56bright NK cells, in particular, accumulate in the skin lesions of psoriatic patients [68] and the synovium of RA patients [69,70]. These observations support the hypothesis that decreased NK cells in the peripheral blood of patients with autoimmune disorders may reflect the trafficking of NK cells to affected tissues.

Also unclear is whether the reported alterations in NK cell localization and functional responses are primary defects involved in disease pathogenesis or occur secondary to the disease and its treatments. However, NK cell defects have been identified 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 [59,71]. Furthermore, studies in T1DM have demonstrated modestly decreased NK cell numbers in the peripheral blood of patients with recent-onset T1DM but not in patients with long-standing T1DM [72]. Interestingly, NK cells were identified around the islet cells of a subset of patients with recent-onset T1DM [64] but not in postmortem pancreatic samples from T1DM patients with long-standing disease [73]. Murine models of T1DM have also demonstrated localization of NK cells near islets as well as a temporal correlation in NK cell infiltrates during the development of diabetes, with a greater influx of NK cells during the prediabetic stage compared with late diabetes [74-76]. In other disorders such as dermatomyositis–polymyositis and MS, deficits observed in NK cell cytotoxicity in patients with active disease were not seen in patients with quiescent disease [77,78]. Together, these findings suggest that NK cells may contribute to the initiation of the autoimmune process but may be less important in established disease; however, further study is needed to confirm this conclusion.

Chronic NK cell lymphocytosis, a disorder characterized by a persistent elevation of NK cells in the peripheral blood, provides some novel insights into the potential contributions of NK cells to autoimmune disorders. Studies in both humans and mice suggest that chronic NK cell lymphocytosis results from an aberrant expansion of an immature NK cell population with functional deficits [79-81]. In addition to cytopenia, chronic NK cell lymphocytosis is associated with autoimmune syndromes, including vasculitis, arthritis, and peripheral neuropathy [82-84]. This disorder provides evidence that the dysregulation of NK cell homeostasis in the context of decreased NK cell cytotoxicity may contribute to the onset of autoimmunity.

**Killer immunoglobulin-like receptor/HLA associations**

Genetic association studies in a variety of autoimmune disorders provide strong evidence that NK cells contribute to the pathogenesis of human autoimmune disorders (reviewed in [85,86]). KIRs are polymorphic, germline-encoded receptors expressed on NK cells (and a subset of T cells) that recognize HLA. The KIR locus is complex with more than 20 different haplotypes encoding various numbers of inhibitory and activating KIRs, which in the context of the individual's HLA genotype influence NK cell licensing and activation [25,30].
KIR/HLA genotype combinations that favor NK cell activation are often beneficial in protecting against infections [86]. For example, in individuals infected with HIV, the combination of KIR3DS1 and HLA-B Bw4-801 is associated with slower progression to AIDS, decreased viral loads, and fewer opportunistic infections [87,88]. However, these same activating KIR/HLA genotype combinations predispose individuals to autoimmune disorders, including Behçet’s disease, T1DM, SLE, MS, psoriasis/psoriatic arthritis, ankylosing spondylitis, and RA [89-96]. For example, spondyloarthritis is associated with the activating KIR2DS2 in the absence of its corresponding inhibitory KIR2DL2 [97]. Similarly, psoriatic arthritis is linked to the expression of KIR2DS1 and/or KIR2DS2 in the absence of the ligands for the corresponding homologous inhibitory receptors [93]. The presence of activating KIRs or KIR/HLA genotypes in the context of decreased NK cell inhibition (for example, absence of corresponding inhibitory KIRs or the HLA ligands for the inhibitory KIRs) therefore results in a lower activation threshold for NK cells (or potentially T cells) and predisposes to autoimmunity. The association of activating KIRs and KIR/HLA genotypes with autoimmune disorders provides compelling evidence implicating NK cells in human autoimmunity.

Multiple sclerosis
MS is an inflammatory disorder that affects the central nervous system (CNS). It may follow a relapsing–remitting (85 to 90%) or primary progressive course. Autoreactive CD4 T cells targeting myelin components are critical mediators of the inflammatory process, particularly in the early stages of relapsing–remitting MS. However, studies in both humans and mice have implicated NK cells in the pathogenesis of MS [98,99].

Human NK cells are postulated to play an immunoregulatory role in MS by killing activated T cells [100]; however, they can also directly lyse oligodendrocytes, astrocytes, and microglia through recognition of NKG2D ligands [101,102], raising the possibility that NK cells may exert either a beneficial or deleterious influence on the development of MS. Indeed, studies in experimental autoimmune encephalomyelitis, a rodent model of MS, underscore the potential of NK cells to either suppress or augment CD4 T-cell-mediated CNS inflammation. The majority of experimental autoimmune encephalomyelitis studies have demonstrated that depletion of NK cells [103-105] or blockade of NK cell homing to the CNS via deletion of the chemokine receptor CX3CR1 [106] resulted in severe, relapsing experimental autoimmune encephalomyelitis and increased mortality. However, other investigators have reported that NK cell depletion resulted in less severe disease [107] and that IL-18- and IL-21-mediated exacerbations of experimental autoimmune encephalomyelitis were NK cell dependent [108,109]. These results suggest that the influence of NK cells on the pathogenesis of MS is probably modulated by the inflammatory milieu, the phase of the disease, and other factors.

A temporal correlation between NK cell numbers or cytotoxicity and periods of disease progression or remission in MS supports the hypothesis that NK cells may play an immunoregulatory role in disease pathology [77,110]. For example, a study of relapsing–remitting MS patients demonstrated that depressed NK cell cytotoxicity preceded the appearance of contrast-enhancing CNS lesions on magnetic resonance imaging and the onset of clinical symptoms [77]. In addition, NK cells from MS patients in remission express high levels of CD95 (Fas, a TNF receptor superfamily member involved in inducing apoptosis) and appear to suppress autoimmune T cells [111]. Indeed, CD95\textsuperscript{high} NK cells from MS patients were able to directly inhibit T-cell IFNγ production following ex vivo stimulation with myelin-basic protein [112]. Interestingly, NK cells in the blood of MS patients lose the CD95\textsuperscript{high} phenotype during disease relapse and regain it after recovery [111].

Paired blood and cerebrospinal fluid samples from MS patients demonstrated a substantial enrichment of CD56\textsuperscript{bright} NK cells in the cerebrospinal fluid [113]. Treatment of MS patients with daclizumab (a humanized anti IL-2Rα antibody) caused a significant expansion of CD56\textsuperscript{bright} NK cells in the periphery as well as a decrease in circulating CD4 T cells [114,115]. The daclizumab-induced increase in CD56\textsuperscript{bright} NK cells correlated with decreased magnetic resonance imaging contrast-enhancing CNS lesions in MS patients [114,115]. Furthermore, CD56\textsuperscript{bright} NK cells from MS patients treated with daclizumab were able to kill autologous CD4 T cells ex vivo without IL-2 priming [114]. Taken together, the deficits in peripheral NK cell numbers in MS patients [110], the temporal correlation between NK cell cytotoxicity and disease flares, the accumulation of CD56\textsuperscript{bright} NK cells in the cerebrospinal fluid, and the correlation of the expansion of CD56\textsuperscript{bright} NK cells with decreased flares during effective immunotherapy support the hypothesis that NK cells play an immunoregulatory role in MS. However, definitive evidence of NK cell participation in the pathogenesis of MS will require further study.

Rheumatoid arthritis
RA is a chronic autoimmune disease characterized by inflammation of joints and surrounding tissues that leads to cartilage destruction and bone erosions. It is associated with elevated levels of proinflammatory cytokines (for example, TNFα, IL-1, IL-6, and IL-23) and inflammatory cell infiltrates (including T cells, B cells, and macrophages)
in the affected joints. Recent studies have implicated human NK cells in the pathogenesis of RA (reviewed in [116,117]).

NK cells comprised a significant fraction of the lymphocytes (8 to 25%) in the synovial fluid of RA patients and could be detected in the joint early during the disease course [118]. Similar to the observations in patients and could be detected in the joint early during the disease course [118]. Similar to the observations in patients and could be detected in the joint early during the disease course [118]. Similar to the observations in patients and could be detected in the joint early during the disease course [118].

Similar to the observations in patients and could be detected in the joint early during the disease course [118]. Similar to the observations in patients and could be detected in the joint early during the disease course [118].

CD56bright (60% of NK cells) with elevated expression of CD94/NKG2A and decreased expression of KIRs and CD16 [69,70]. The CD56bright subpopulation of NK cells was also found in the blood of RA patients (and normal controls) but at much lower frequencies (~10% of NK cells). The NK cells within the synovium also showed upregulated expression of several chemokine receptors and adhesion molecules that may participate in preferential recruitment into the synovium [69]. The synovial CD56bright NK cells expressed higher levels of activation markers (CD69 and NKP44) and produced more TNFα as well as IFNγ than CD56bright NK cells from the peripheral blood of the same patients [119]. Synovial NK cells could induce monocytes to differentiate into DCs [120] and have also been shown to produce IL-22, a cytokine that induces proliferation of synovial fibroblasts [121]. Aberrant expression of MHC class I polypeptide-related sequence A in the inflamed synovium [122] may augment CD56bright NK cell activation, resulting in dysregulated production of proinflammatory cytokines rather than in immunoregulation. Taken together, these findings suggest that the enrichment of CD56bright NK cells may contribute to the initiation and/or perpetuation of dysregulated production of proinflammatory cytokines in the synovium of RA patients [69,70].

In contrast to the accumulation of activated CD56bright NK cells in the synovium, patients with RA have decreased circulating NK cells in their peripheral blood [55]. In addition to the numeric deficit, peripheral blood NK cells in RA patients have decreased cytotoxicity on a per-cell basis [123]. Low numbers of peripheral blood NK cells and decreased cytotoxicity have also been identified in patients with JIA, with the most prominent deficits occurring in systemic JIA patients [60,124-126]. Furthermore, a significant subset of systemic JIA patients had almost a complete absence of circulating CD56bright NK cells [126,127]. The depressed NK cell cytotoxicity in systemic JIA patients was not solely accounted for by the reduced numeric frequency of NK cells [125,126] and was associated with low levels of perforin [124,126]. The impaired NK cell functional responses in systemic JIA patients have also been linked to defective IL-18Rβ phosphorylation [127] and heterozygous missense mutations in components of the cytolytic pathway [128-130].

These observations in conjunction with the genetic associations between inflammatory arthritis and KIR haplotypes support the hypothesis that dysregulation of cytokine production by CD56bright NK cells in the synovium and/or decreased cytotoxicity by peripheral CD56dim NK cells may contribute to pathogenesis of RA. This hypothesis is further corroborated by findings in several distinct murine models of inflammatory arthritis (for example, collagen-induced arthritis and Staphylococcus aureus-associated arthritis), which have demonstrated that NK cell depletion results in earlier onset of arthritis, more severe disease, and increased autoantibody and IL-17 production [131,132]. Interestingly, reduced peripheral NK cell numbers and decreased cytotoxicity were also observed in the collagen-induced arthritis model [131]. NK cell-generated IFNγ was shown to suppress the generation of Th17 cells (collagen-induced arthritis model [131]) as well as neutrophil recruitment to the affected joints (K/BxN model, an autoantibody model of arthritis [133]). Furthermore, activation of NK cells by blockade of the inhibitory CD94/NKG2A receptor inhibited the development of arthritis via perforin-dependent cytolysis of Th17 and T follicular helper cells in the collagen-induced arthritis model [134]. However, conclusions about the role of NK cells in regulating autoimmune arthritis in murine models must be tempered by a conflicting report that depletion of NK cells reduced the severity of arthritis and prevented bone erosions in the collagen-induced arthritis model [135].

Systemic lupus erythematosus

SLE is an immune complex-mediated disorder resulting in widespread organ dysfunction primarily in reproductive-age females. SLE is characterized by polyclonal B-cell activation and the production of a wide array of autoantibodies against nuclear proteins and DNA. Insights from murine models have implicated NK cells in the development of autoantibodies and other features of SLE [136]. For example, the development of an SLE-like disorder in C57BL/6 lpr mice (which have a defect in the Fas gene) is temporally related to an age-dependent loss of NK and NKT cells. Furthermore, NK cell depletion in these mice enhanced development of autoantibody-secreting B cells while the adoptive transfer of NK cells delayed the onset of autoantibody production [137]. Human SLE studies have also provided intriguing observations linking NK cells with the development of SLE.

Numeric deficits in peripheral NK cells have been reported in multiple cohorts of SLE patients [55,71, 138-141] and correlate with clinical manifestations of SLE, including lupus nephritis and thrombocytopenia [55], and overall disease activity [142,143]. Interestingly,
an increased proportion of CD56bright NK cells has been observed in SLE patients regardless of disease activity [144]. In addition to numeric deficits in peripheral NK cells, depressed cytotoxicity responses on a per-cell basis have been consistently documented in SLE patients [55,71,140,145] as well as in a subset of first-degree relatives [145]. An early study in pediatric SLE patients was particularly informative since it demonstrated low numbers of peripheral NK cells and defective cytolsis (on a single cell level) at diagnosis or even prior to overt progression to SLE in a subset of patients [71]. However, the majority of the human data on NK cells in SLE are correlative, and the role of NK cells in the development of SLE in humans remains less well established than NK cell contributions in RA and MS.

Conclusion
By virtue of their ability to rapidly kill abnormal cells and produce cytokines and chemokines, NK cells influence and shape adaptive immune responses and are positioned to play a role in regulating autoimmune responses. Genetic association studies implicate NK cells in the pathogenesis of human autoimmune disorders. Studies in MS, RA, and SLE, which are summarized in this review, provide tantalizing but incomplete evidence for contributions of specific subsets of NK cells (in both the periphery and affected tissues) to the onset or progression of autoimmunity. The associations found in humans and the empirical evidence from murine models demonstrate that further research into the immunomodulatory role of NK cells in autoimmunity is warranted and is likely to provide novel insights into the pathogenesis of autoimmune disorders. Furthermore, the expansion of CD56bright NK cells during effective immunotherapy and the correlation with decreased MS flares suggests that a better understanding of the role of NK cells in development of autoimmunity may lead to new therapeutic targets in these diseases.

Abbreviations
CNS, central nervous system; DC, dendritic cell; HLA, human leukocyte antigen; IFN, interferon; IL, interleukin; JIA, juvenile idiopathic arthritis; KIR, killer immunoglobulin-like receptor; MHC, major histocompatibility complex; MS, multiple sclerosis; NK, natural killer; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; STXB2, syntaxin binding protein 2; T1DM, type 1 diabetes mellitus; Th, T-helper; TNF, tumor necrosis factor.

Competing interests
The authors declare that they have no competing interests.

Acknowledgements
This work was supported by the Howard Hughes Medical Institute and National Institutes of Health R01-AI078994 (ARF), R01-AI073552 (ARF), R01-AI51345 (WMY), R01-AI33903 (WMY), and R37-A1034385 (WMY) grants.

Author details
Division of Pediatric Rheumatology, Department of Pediatrics, Washington University, Box 8208, 660 South Euclid Avenue, St Louis, MO 63110, USA.
Howard Hughes Medical Institute, Division of Rheumatology, Department of Medicine, Washington University School of Medicine, St Louis, MO 63110, USA.

References
1. Progress in Autoimmune Diseases Research [http://www.niaid.nih.gov/topics/autoimmune/documents/adccfinal.pdf]
2. The Cost Burden of Autoimmune Disease: The Latest Front in the War on Healthcare Spending [http://www.aarda.org/pdf/cbad.pdf]
3. Yokoyama WM, Kim S, French AR: The dynamic life of natural killer cells. Annu Rev Immunol 2004, 22:405-429.
4. Walzer T, Jaeger S, Chaix J, Viveri E: Natural killer cells: from CD3(-)NKP46(+) to post-genomics meta-analyses. Curr Opin Immunol 2007, 19:365-372.
5. Shi F-D, Ljunggren HG, La Cava A, Van Kaer L: Organel-specific features of natural killer cells. Nat Rev Immunol 2011, 11:658-671.
6. Hanna J, Goldman-Wohl D, Hamani Y, Avraham I, Natanson-Yaron S, Prus D, Cohen-Daniel I, Arnon TI, Manor M, Gazit R, Yutkin V, Benharroch D, Porgador A, Keshet E, Yagel S, Mandelboim O: Decidual NK cells regulate key developmental processes at the human fetal-maternal interface. Nat Med 2006, 12:1063-1074.
7. King A, Bunnell T, Verma S, Hiby S, Lake YW: Human uterine lymphocytes. Hum Reprod Update 1998, 4:480-485.
8. Cooper MA, Fehniger TA, Turner SC, Chen KS, Ghaheri BA, Gaytar T, Carson WE, Caligiuri MA: Human natural killer cells: a unique innate immunoregulatory role for the CD56(bright) subset. Blood 2001, 97:3146-3151.
9. Caligiuri MA: Human natural killer cells. Blood 2008, 112:461-469.
10. Fehniger TA, Cooper MA, Nuovo GJ, Cellia M, Facchetti F, Colonna M, Caligiuri MA: CD56bright natural killer cells are present in human lymph nodes and are activated by T cell-derived IL-2: a potential new link between adaptive and innate immunity. Blood 2003, 101:3052-3057.
11. Gumperz JE, Litvin V, Phillips JH, Lanier LL, Parham P: The Bw4 positive epitope of HLA-B molecules confers reactivity with natural killer cell clones that express NK1.1, a putative HLA receptor. J Exp Med 1995, 181:1133-1144.
12. Cellia M, Longo A, Ferrara GB, Strominger JL, Colonna M: NK3-specific natural killer cells are selectively induced by Bw4-positive HLA alleles with isolucine 80. J Exp Med 1994, 180:1235-1242.
13. Braud VM, Allen DSJ, O’Callaghan CA, Söderstrom K, D’Andrea A, Ogg GS, Lazetic S, Young NT, Bell JJ, Phillips JH, Lanier LL, McMichael AJ: HLA-E binds to natural-killer-cell receptors CD94/NKG2A, B and C. Nature 1999, 391:795-799.
14. Borrego F, Ullbrecht M, Weiss EH, Coligan JE, Brooks AG: Recognition of human histocompatibility leukocyte antigen (HLA)-E complexed with HLA class I signal sequence-derived peptides by CD94/NKG2 confers protection from natural killer cell-mediated lysis. J Exp Med 1998, 187:813-818.
15. Lee N, Llano M, Carretero M, Ishitani A, Navarro F, Lópe-Botet M, Geraghty DE: HLA-E is a major ligand for the NK inhibitory receptor CD94/NKG2A. Proc Natl Acad Sci U S A 1998, 95:5199-5204.
16. Bauer S, Groh V, Wu J, Steinele A, Phillips JH, Lanier LL, Spies T: Activation of NK cells and T cells by NKG2D, a receptor for stress-inducible MICA. Science 1999, 285:727-729.
17. Mandelboim O, Lieberman N, Lev M, Paul L, Arnon TI, Bushkin Y, Davis DM, Strominger JL, Yewdell JW, Porgador A: Recognition of haemagglutinins on virus-infected cells by NKP46 activates lysis by human NK cells. Nature 2001, 409:1055-1060.
18. Ljunggren HG, Karre K: In search of the ‘missing self’: MHC molecules and NK cell recognition. Immunol Today 1990, 11:237-244.
19. Kane K, Ljunggren HG, Pontek G, Kessling R: Selective rejection of H-2-deficient lymphoma variants suggests alternative immune defence strategy. Nature 1986, 319:675-678.
20. Gasser S, Orslic S, Brown EJ, Rauht DH: The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. Nature 2005, 436:1186-1190.
21. Strom-Gnossar N, Cur G, Biton M, Horvitz E, Elboim M, Staniuky N, Mandelboim O, Mandelboim O: Human microRNAs regulate stress-induced immune responses mediated by the receptor NKG2D. Nat Immunol 2008, 9:1065-1073.
22. Jonsson AH, Yokoyama WM: Natural killer cell tolerance licensing and other mechanisms. Adv Immunol 2009, 101:27-79.
23. Elliott JM, Yokoyama WM: Unifying concepts of MHC-dependent natural killer cell education. Trends Immunol 2011, 32:364-372.
24. Zimmer J, Donato L, Hanau D, Cazenave JP, Tongio MM, Moretta A, de la Salle F: Licensing of natural killer cells by host major histocompatibility complex class I molecules. Nature 2005, 436:709-713.

25. Yokoyama WM, Kim S: How do natural killer cells find self to achieve self-tolerance? Immunity 2006, 24:249-257.

26. Fernandez NC, Treiner E, Vance RE, Jamieson AM, Lemieux S, Raulet DH: Anfossi N, Andre P, Guia S, Falk CS, Roetynck S, Stewart CA, Breso V, Frassati C, Stewart WI, Kalinski P: Dendritic cells mediate NK cell help for Th1 and CTL responses: two-signal requirement for the induction of NK cell helper function. J Immunol 2003, 171:2366-2373.

27. Ciccone M, Braumuller H, Gumi A, Egeter O, Ziegler H, Reusch U, Bubeck A, Tung T, Reviron D, Middleton D, Sallusto F: Regulatory NK cells suppress antigen-specific T cell responses. J Immunol 2006, 177:605-609.

28. Nickoloff BJ, Sunwoo JB, Lemieux S, Hansen TH: A subset of natural killer cells achieves self-tolerance without expressing self-reactive T cells by host major histocompatibility complex class I molecules. J Immunol 2006, 177:605-609.

29. Yokoyama WM, Kim S: How do natural killer cells find self to achieve self-tolerance? Immunity 2006, 24:249-257.

30. Yokoyama WM, Kim S: How do natural killer cells find self to achieve self-tolerance? Immunity 2006, 24:249-257.

31. Yokoyama WM, Kim S: How do natural killer cells find self to achieve self-tolerance? Immunity 2006, 24:249-257.

32. Piccoli D, Sbrana S, Melandi E, Vallanite NW: Contact-dependent stimulation and inhibition of dendritic cells by natural killer cells. J Exp Med 2002, 195:335-341.

33. Moiracì R, Baumuller H, Cuny A, Egeter O, Ziegler H, Reusch U, Bubeck A, Tung T, Reviron D, Middleton D, Sallusto F: Regulatory NK cells suppress antigen-specific T cell responses. J Immunol 2006, 177:605-609.

34. Piccoli D, Sbrana S, Melandi E, Vallanite NW: Contact-dependent stimulation and inhibition of dendritic cells by natural killer cells. J Exp Med 2002, 195:335-341.

35. Moiracì R, Baumuller H, Cuny A, Egeter O, Ziegler H, Reusch U, Bubeck A, Tung T, Reviron D, Middleton D, Sallusto F: Regulatory NK cells suppress antigen-specific T cell responses. J Immunol 2006, 177:605-609.

36. Piccoli D, Sbrana S, Melandi E, Vallanite NW: Contact-dependent stimulation and inhibition of dendritic cells by natural killer cells. J Exp Med 2002, 195:335-341.

37. Moiracì R, Baumuller H, Cuny A, Egeter O, Ziegler H, Reusch U, Bubeck A, Tung T, Reviron D, Middleton D, Sallusto F: Regulatory NK cells suppress antigen-specific T cell responses. J Immunol 2006, 177:605-609.

38. Moiracì R, Baumuller H, Cuny A, Egeter O, Ziegler H, Reusch U, Bubeck A, Tung T, Reviron D, Middleton D, Sallusto F: Regulatory NK cells suppress antigen-specific T cell responses. J Immunol 2006, 177:605-609.

39. Moiracì R, Baumuller H, Cuny A, Egeter O, Ziegler H, Reusch U, Bubeck A, Tung T, Reviron D, Middleton D, Sallusto F: Regulatory NK cells suppress antigen-specific T cell responses. J Immunol 2006, 177:605-609.

40. Moiracì R, Baumuller H, Cuny A, Egeter O, Ziegler H, Reusch U, Bubeck A, Tung T, Reviron D, Middleton D, Sallusto F: Regulatory NK cells suppress antigen-specific T cell responses. J Immunol 2006, 177:605-609.

41. Moiracì R, Baumuller H, Cuny A, Egeter O, Ziegler H, Reusch U, Bubeck A, Tung T, Reviron D, Middleton D, Sallusto F: Regulatory NK cells suppress antigen-specific T cell responses. J Immunol 2006, 177:605-609.
juvenile dermatomyositis very early in their disease course: evidence of a TCRβ8 motif and increase CD56+ NK cells. *Arthritis Rheum* 1998, 41(Suppl 9):203.

68. Ottaviani C, Nasori F, Bedini C, de Pita O, Girolomoni G, Cavani A: CD56brightCD16−/− NK cells accumulate in psoriatic skin in response to CXCL10 and GCSS and exacerbate skin inflammation. *J Immunol* 2006, 36:118-128.

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

70. Pridgeon C, Lennon GP, Pazzini L, Thompson RH, Christmas SE, Moots RJ: Natural killer cells in the synovial fluid of rheumatoid arthritis patients exhibit a CD56dim, CD94++;CD158−/− phenotype. *Rheumatology (Oxford)* 2003, 42:670-675.

71. Yabuhara A, Yang FC, Nakawara T, Iwasaki Y, Moni 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.

72. Rodaki M, Sorensen B, Butty V, Besse W, Laffel L, Benoist C, Mathis D: Altered natural killer cells in type 1 diabetic patients. *Diabetes* 2007, 56:171-185.

73. Willcox A, Richardson SJ, Bone AJ, Foulis AK, Morgan NG: A long-term study of patients with chronic myeloid leukemia. *Blood* 2000, 96:2322-2327.

74. Gur C, Porgador A, Elboim M, Gazit R, Mizrahi S, Stern-Ginossar N, Achdout H, Mandelboim O: The activating receptor NKG46 is essential for the development of type 1 diabetes. *Nat Immunol* 2010, 11:121-128.

75. Poirot L, Benoist C, Mathis D. Natural killer cells distinguish innocuous and destructive forms of pancreatic islet autoimmunity. *Proc Natl Acad Sci U S A* 2004, 101:8102-8107.

76. Brauner H, Ellemans M, Lemos S, Brocker B, Holmberg D, Flosstrom T, Tullberg M, Karre K, Hoglund P: Distinct phenotype and function of NK cells in the pancreas of nonobese diabetic mice. *J Immunol* 2010, 184:2272-2280.

77. Pastores GL, Burgart LJ, Shuster JJ, Case CL, Pack S, McKee AD, King MR: Anti-CD56 mAb therapy augments T-cell function in patients with type 1 diabetes. *J Clin Invest* 1998, 55:109-117.

78. Gonzalez-Amaro R, Alcoler-Varela J, Alarcón-Segovia D: Natural killer cell activity in dermatomyositis–polymyositis. *J Rheumatol* 1987, 14:307-310.

79. Lima M, Almeida J, Montero AG, Texeira MDós A, Queiroz ML, Santos AH: Balanazanque A, Estevinho A, Alguero M, Barreira F, Fonseca S, Amorim ML, Cabeda JM, Pinho L, Gonzalez M, San Miguel J, Justo B, Orfão A: Clinicobiological, immunophenotypic, and molecular characteristics of monoclonal CD56− NK chronic natural killer cell large granular lymphocytosis. *Am J Pathol* 2004, 165:1117-1127.

80. Orange JS, Chehim J, Ghavimi D, Campbell D, Sullivan KE: Decreased natural killer (NK) cell function in chronic NK cell lymphocytosis associated with decreased surface expression of CD11b. *Clin Immunol* 2001, 99:53-64.

81. French AR, Kim S, Fehniger TA, Pratt JR, Yang L, Song YJ, Caligiuri MA, Lifson JD, Allen TM, Carrington M, Altfeld M: Changes in the immune composition in HIV-infected subjects on highly active antiretroviral therapy. *J Exp Med* 2001, 193:159-168.

82. Martin MP, Nelson G, Lee-J H, Pellet F, Gao X, Wade J, Wilson MJ, Trowsdale J, Gladman D, Carrington M: Cutting edge: susceptibility to psoriatic arthritis: influence of activating killer Ig-like receptor genes in the absence of specific HLA-C alleles. *J Immunol* 2002, 169:2818-2822.

83. van der Slik AR, Koelman BPC, Verduijn W, Bruining 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.

84. Rabbani GR, Phyliky RL, Tefferi A: Association of killer cell immunoglobulin-like receptors with scleroderma. *Arthritis Rheum* 2005, 52:3586-3595.

85. Fusco C, Guerini FR, Nocera G, Ventura G, Caputo D, Valentino MA, Agliardi C, Gallotti L, Morra VB, Florio C, Clerici M, Lombardi ML: KIRs and their HLA ligands in remitting-relapsing multiple sclerosis. *J Neuroimmunol* 2010, 229:232-237.

86. Pellett F, Siannis F, Vukin L, Lee K, Urowitz MB, Gladman DD: KIRs and autoimmunity: studies in systemic lupus erythematosus and scleroderma. *Tissue Antigens* 2007, 69(Suppl 1):106-108.

87. Momot T, Koch S, Hunzelmann N, Krieg T, Ulbricht K, Schmidt RE, Witte T: Association of killer cell immunoglobulin-like receptors with sclerosis. *Arthritis Rheum* 2004, 50:1561-1565.

88. Morandi B, Bramanti P, Bonaccorsi I, Montalto E, Oliveri D, Pezzino G, Navarra M, Ferrazzo G: Role of natural killer cells in the pathogenesis and progression of multiple sclerosis. *Pharmacol Res* 2008, 57:1-5.

89. Gandhi R, Laros A, Weiner HL: Role of the innate immune system in the pathogenesis of multiple sclerosis. *J Neuroimmunol* 2010, 221:7-14.

90. Jiang W, Chai NR, Maric D, Bielekova B: Unexpected role for granzyme K in CD56− NK cell-mediated immunoregulation of multiple sclerosis. *J Exp Med* 2008, 205:1127-1139.

91. Moro RS, Ségurin R, McCrea EL, Antel JP: NK cell-mediated lysis of autologous human oligodendrocytes. *J Neuroimmunol* 2001, 116:107-115.

92. Saikali R, Antel JP, Newcombe J, Chen Z, Freedman M, Blain M, Rayl PR, Hart JA, Arbour N: NKG2D-mediated cytotoxicity toward oligodendrocytes suggests a mechanism for tissue injury in multiple sclerosis. *J Neurosci* 2007, 27:1220-1228.

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

94. Matsumoto Y, Koyama K, Akawa Y, Shin T, Kawaize 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.

95. Xu W, Fazekas G, Hara H, Tabira T: Mechanism of natural killer (NK) cell regulatory role in experimental autoimmune encephalomyelitis. *J Neuroimmunol* 2005, 163:24-30.

96. Huang D, Shi F-D, Jung S, Pien GC, Wang J, Salsasar-Mather TP, He TT, Weaver JT, Ljunggren HG, Biron CA, Littman DR, Ranishoff RM: The neuronal chemokine CX3CL1/fractalkine selectively recruits NK cells that modify experimental autoimmune encephalomyelitis within the central nervous system. *FASEB J* 2006, 20:986-995.

97. Winkler-Pickett R, Young HA, Cherry JM, Dehl J, Wine J, Back T, Berre WE, Mason AT, Ortaldo JR: In vivo regulation of experimental autoimmune encephalomyelitis by NK cells: alteration of primary adaptive responses. *J Immunol* 2008, 180:4495-4506.

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

99. Vollmer TL, Liu R, Price M, Rhodes S, La Cava A, Shi F-D: Differential effects of IL-21 during initiation and progression of autoimmunity against neuroantigen. *J Immunol* 2005, 174:2969-2971.

100. Munschauer FE, Hartrich LA, Stewart CC, Jacobs L: Circulating natural killer cells but not cytotoxic T lymphocytes are reduced in patients with active disease risk genes in rheumatoid arthritis. *J Exp Med* 2001, 193:159-168.

101. Martin MP, Nelson G, Lee-J H, Pellet F, Gao X, Wade J, Wilson MJ, Trowsdale J, Gladman D, Carrington M: Cutting edge: susceptibility to psoriatic arthritis: influence of activating killer Ig-like receptor genes in the absence of specific HLA-C alleles. *J Immunol* 2002, 169:2818-2822.
relapsing multiple sclerosis and little clinical disability as compared to controls. J Neuromuc 1995, 62:177-181.

Takahashi K, Miyake S, Kondo T, Terao K, Hatakenaka M, Hashimoto S, Yamamura T: Natural killer type 2 bias in remission of multiple sclerosis. J Clin Invest 2001, 107:R23-R29.

Takahashi K, Aranami T, Endoh M, Miyake S, Yamamura T: The regulatory role of natural killer cells in multiple sclerosis. Brain 2004, 127(Pt 9):1917-1927.

Hamann I, Dorr J, Gumm R, Chanvilard C, Jansen A, Millward JM, Paul F, Ranosoff RM, Infante-Duarte C: Characterization of natural killer cells in paired CSF and blood samples during neuroinflammation. J Neuromuc 2012, 254:165-169.

Bielekova B, Catalfamo M, Reichert-Scrivner S, Cerma M, Waldmann TA, McFarland H, Henkarta P, Martin R: Regulatory CD56(bright) natural killer cells mediate immunomodulatory effects of IL-2Ralpha-targeted therapy (dazalcumab) in multiple sclerosis. Proc Natl Acad Sci U S A 2006, 103:5941-5946.

Bielekova B, Howard T, Packen A, Richert N, Blevins G, Ohayon J, Waldmann TA, McFarland HF, Martin R: Effect of anti-CD25 antibody dazalcumab in the inhibition of inflammation and stabilization of disease progression in multiple sclerosis. Arch Neurol 2009, 66:483-489.

Ahem DJ, Brennan FM: The role of natural killer cells in the pathogenesis of rheumatoid arthritis: major contributors or essential homeostatic modulators? Immun Lett 2011, 136:115-121.

Cingolani P, Scivo R, Valesin G, Pecastere R: Emerging role for NK cells in the pathogenesis of inflammatory arthropathies. Autoimmun Rev 2011, 10:S77-S84.

Tak PP, Kummer JA, Hack CE, Daha MR, Smeets TJ, Erkelens GW, Meinders AE, Groh V, Bruhl A, El-Gabalawy H, Nelson JL, Spies T: Aramaki T, Ida H, Izumi Y, Fujikawa K, Huang M, Arima K, Tamai M, Machii M, de Matos CT, Berg L, Michaelsson J, Fellander-Tsai L, Karre K, Soderstrom K: Defective phosphorylation of interleukin-18 receptor beta causes natural killer cell dysfunction in patients with systemic-onset juvenile rheumatoid arthritis and macrophage activation syndrome. Arthritis Res Ther 2009, 12:R30-R37.

de Jager W, Vastert BJ, Beeckman JM, Wulfraat NM, Kuis W, Cofer PI, Prakken BJ: Defective phosphorylation of interleukin-18 receptor beta causes impaired natural killer cell function in systemic-onset juvenile idiopathic arthritis. Arthritis Rheum 2009, 60:2782-2793.

Vastert SJ, van Wijk R, Dilapous-Urban LE, de Voogt KMK, de Jager W, Ravelli A, Magni-Manzano S, Insalaco A, Coutes E, van Solinge WW, Prakken BJ: Wulfraat NM, de Benedetti F, Kuis W: Mutations in the perforin gene can be linked to macrophage activation syndrome in patients with systemic onset juvenile idiopathic arthritis. Rheumatology (Oxford) 2010, 49:441-449.

Hazen MM, Woodward AL, Hofman I, Degar BA, Grom A, Filipovich AH, Binstadt BA: Mutations of the hemophagocytic lymphohistiocytosis-associated gene UNC13D in a patient with systemic juvenile idiopathic arthritis. Arthritis Rheum 2008, 58:367-370.

Zhang K, Broschak J, Glass D, Thompson SD, Finkel T, Passo MH, Binstadt BA, Filipovich A, Grom A: Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis is associated with MUNC13-4 polymorphisms. Arthritis Rheum 2008, 58:2892-2896.

Lo CK, Lam QLK, Sun L, Wang S, Ko KH, Xu H, Wu CY, Zheng B-J, Lu L: Natural killer cell degeneration exacerbates experimental arthritis in mice via enhanced interleukin-17 production. Arthritis Rheum 2008, 58:2700-2711.

Nilsson N, Bremell T, Tarkowski A, Carlsten H: Protective role of NK1.1+ cells in experimental Staphylococcus aureus arthritis. Clin Exp Immunol 1999, 117:63-69.

Wu H-J, Sawaya H, Binstadt B, Brickelmaier M, Blasis A, Gorelik L, Mahmood U, Weisleder R, Carulli J, Benesl C, Mathis D: Inflammatory arthritis can be reined in by CpG-induced DC–NK cell cross talk. J Exp Med 2007, 204:1911-1922.

Leavenworth JW, Wang X, Westender CS, Spee P, Cantor H: Mobilization of natural killer cells inhibits development of collagen-induced arthritis. Proc Natl Acad Sci U S A 2011, 108:15458-15459.

Soderstrom K, Steen E, Colmenero P, Purath U, Muller-Ladner U, de Matos CT, Tamer H, Robinson WH, Englemann EG: Natural killer cells trigger osteoclastogenesis and bone destruction in arthritis. Proc Natl Acad Sci U S A 2010, 107:13026-13031.

Yuan D, Thet S, Zhou X, Wakeland EK, Dang T: The role of NK cells in the development of autoantibodies. Autoimmunity 2011, 44:641-651.

Takeda K, Dennett 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, 177:155-164.

Huang Z, Fu B, Zheng SG, Li X, Sun R, Tian Z, Wei H: Involvement of CD226+ NK cells in immunopathogenesis of systemic lupus erythematosus. J Immunol 2011, 186:3421-3431.

Schleinitz N, Chiche L, Guia S, Bouvier G, Vermer J, Monroe A, Houssaint E, Harlé J-P, Kaplanski G, Montero-Jukan FA, Vély F: Pattern of DAP12 expression in leukocytes from both healthy and systemic lupus erythematosus patients. PLoS ONE 2009, 4:e6264.

Hervier B, Beziat V, Haroche J, Mathian A, Lebon P, Ghillani-Dalbin P, Musset L, Debré P, Amourat Z, Viellard V: Phenotype and function of natural killer cells in systemic lupus erythematosus: excess interferon-γ production in patients with active disease. Arthritis Rheum 2011, 63:1698-1706.

Puxeddu I, Bongiorni F, Chimenti D, Bombardieri S, Moretta A, Bottino C, Migliorini P: Cell surface expression of activating receptors and co-receptors on peripheral blood NK cells in systemic autoimmune diseases. Scand J Rheumatol 2012, 41:298-304.

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

Riccieri V, Spadaro A, Parisi G, Taccani E, Moretti T, Bernardini G, Favaroni M, Strom R: Down-regulation of natural killer cells and of gamma/delta T cells in systemic lupus erythematosus. Does it correlate to autoimmunity and to laboratory indices of disease activity? Lupus 2000, 9:333-337.

Schepis D, Gunarsson I, Eloranta M-L, Lampa J, Jacobson SH, Karre K, Berg L: Increased proportion of CD56(bright) natural killer cells in active and inactive systemic lupus erythematosus patients. Clin Exp Immunol 2005, 141:165-173.

Cite this article as: Fogel LA, et al. Natural killer cells in human autoimmune disorders. Arthritis Research & Therapy 2013, 15:216.

doi:10.1186/ar4323

Page 9 of 9