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REVIEW

Natural killer cells in human autoimmune disorders

Leslie A Fogel[1], Wayne M Yokoyama[2] and Anthony R French*[1]

Abstract

Natural killer (NK) cells are innate lymphocytes that play a critical role in early host defense against viruses. Through their cytolytic capacity and generation of cytokines and chemokines, NK cells modulate the activity of other components of the innate and adaptive immune systems and have been implicated in the initiation or maintenance of autoimmune responses. This review focuses on recent research elucidating a potential immunoregulatory role for NK cells in T-cell and B-cell-mediated autoimmune disorders in humans, with a particular focus on multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematous. A better understanding of the contributions of NK cells to the development of autoimmunity may lead to novel therapeutic targets in these diseases.

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 adaptive immune responses in autoimmune diseases. A more complete characterization of the role of NK cells in human autoimmunity may lead to new therapies in these diseases.

*Correspondence: french_a@kids.wustl.edu
[1]Division of Pediatric Rheumatology, Department of Pediatrics, Washington University, Box 8208, 660 South Euclid Avenue, St Louis, MO 63110, USA
Full list of author information is available at the end of the article

NK 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]. $CD56^{dim}$ 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, $CD56^{bright}$ NK cells are more abundant than $CD56^{dim}$ NK cells in secondary lymphoid tissues such as lymph nodes and tonsils [10]. $CD56^{bright}$ NK cells express low levels of CD16, KIRs, and perforin, with higher expression levels of a number of cytokine receptors and CD94/NKG2A than $CD56^{dim}$ NK cells. The functional consequence of these differences (as well as differences in chemokine receptor expression) is that $CD56^{bright}$ NK cells in secondary lymph organs are more efficient cytokine and chemokine producers while $CD56^{dim}$ 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 upregulation 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 TNFα 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, dsyfunctional cytolysis 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 numeric 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, $CD56^{bright}$ 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, scleroderma 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, $CD95^{high}$ 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 $CD95^{high}$ phenotype during disease relapse and regain it after recovery [111].

Paired blood and cerebrospinal fluid samples from MS patients demonstrated a substantial enrichment of $CD56^{bright}$ NK cells in the cerebrospinal fluid [113]. Treatment of MS patients with daclizumab (a humanized anti IL-2Rα antibody) caused a significant expansion of $CD56^{bright}$ NK cells in the periphery as well as a decrease in circulating CD4 T cells [114,115]. The daclizumab-induced increase in $CD56^{bright}$ NK cells correlated with decreased magnetic resonance imaging contrast-enhancing CNS lesions in MS patients [114,115]. Furthermore, $CD56^{bright}$ 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 $CD56^{bright}$ NK cells in the cerebrospinal fluid, and the correlation of the expansion of $CD56^{bright}$ 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 the cerebrospinal fluid of MS patients, the majority of the NK cells in the synovial fluid of RA patients were $CD56^{bright}$ (~60% of NK cells) with elevated expression of CD94/NKG2A and decreased expression of KIRs and CD16 [69,70]. The $CD56^{bright}$ 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 $CD56^{bright}$ NK cells expressed higher levels of activation markers (CD69 and NKp44) and produced more TNFα as well as IFNγ than $CD56^{bright}$ 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 $CD56^{bright}$ NK cell activation, resulting in dysregulated production of proinflammatory cytokines rather than in immunoregulation. Taken together, these findings suggest that the enrichment of $CD56^{bright}$ 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 $CD56^{bright}$ 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 $CD56^{bright}$ 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 $CD56^{bright}$ NK cells in the synovium and/or decreased cytotoxicity by peripheral $CD56^{dim}$ 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 neurophil 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 CD56^{bright} 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 cytolysis (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 CD56^{bright} 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; STXBP2, syntaxin binding protein 2; T1DM, type I diabetes mellitus; Th, T-helper; TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

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Author details

[1]Division of Pediatric Rheumatology, Department of Pediatrics, Washington University, Box 8208, 660 South Euclid Avenue, St Louis, MO 63110, USA. [2]Howard Hughes Medical Institute, Division of Rheumatology, Department of Medicine, Washington University School of Medicine, St Louis, MO 63110, USA.

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