

Natural killer cells in human autoimmunity

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Natural killer (NK) cells are innate immune cells. Although NK cells are best characterized for their ability to control tumors and infections, recent data have indicated that they also are important regulatory cells by virtue of interactions with many types of immune and nonimmune cells. Thereby, they can affect the outcome of adaptive immune responses and maintain immune homeostasis. Thus, NK cells can either exacerbate or limit immune responses, including those to autoantigens. Here, we discuss current insights into the role of NK cells in human autoimmunity.

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Introduction

Human natural killer (NK) cells were described more than 30 years ago as large granular lymphocytes exhibiting ‘natural cytotoxicity’ against several types of cells [1]. Significant progress has been made since then in the dissection of mechanisms whereby NK cells discriminate potential target cells from healthy cells [2]. The target cell ‘detection system’ includes a variety of cell surface activating and inhibitory receptors, engagement of which regulates NK cell activities (Table 1). Activating NK cell receptors can detect the presence of ligands on cells in ‘distress’, such as stress-induced self-ligands (e.g. ULBP and MIC molecules in humans) recognized by the activating-receptor NKG2D [3]. In parallel, NK cells use inhibitory receptors to monitor the absence of constitutively expressed self-molecules on potential target cells, a recognition strategy originally referred to as ‘missing-self’ detection [4]. The most prominent inhibitory receptors

are the killer cell immunoglobulin-like inhibitory receptors (KIR) that bind some classical MHC class I molecules (in particular certain HLA-B and HLA-C molecules), and CD94/NKG2A receptors that bind the nonclassical MHC class I molecule HLA-E [5].

NK cells are also critical components of the innate immune response because of their ability to produce a variety of cytokines and chemokines [6,7]. Thus, NK cells may drive, shape, and regulate the activities of other immune cells and affect adaptive immune responses. NK cells respond to initial cues from myeloid cells including myeloid-derived dendritic cells (DC), macrophages, and plasmacytoid DC. This response is possible because NK cells express receptors for several myeloid-derived cytokines, for example, interleukin (IL)-1, IL-10, IL-12, IL-15, and IL-18 [7,8]. Thus, secondary to triggering of myeloid cells by pattern recognition receptors, NK cells can relay and amplify cytokine signals. The most prominent cytokine produced by NK cells is interferon (IFN)- γ . However, NK cells can also secrete a number of other factors, including tumor necrosis factor (TNF)- α and immunoregulatory cytokines such as IL-5, IL-10, IL-13, the growth factor GM-CSF, and chemokines MIP-1 α , MIP-1 β , IL-8, and RANTES. The ability to respond to a variety of cytokines suggests that the local microenvironment in which NK cells exist may shape and modulate their function [6–8].

Consistent with their functions as innate sentinels, NK cells are spread throughout lymphoid and non-lymphoid tissues. In many tissues, they represent a minor fraction of total lymphocytes. However, in other tissues like the liver and pregnant uterus, as well as in several secondary lymphoid organs, they are abundant. Human NK cells are typically defined as CD3[−]CD56⁺ cells. In the analysis of NK cells, distinct subsets have been defined based on discrete phenotypic, functional and anatomical features [9]. Human NK cells can be subdivided into two major subsets, CD56^{dim} and CD56^{bright} cells. Typically, CD56^{dim} NK cells constitute the majority (90%) of NK cells in blood, whereas CD56^{bright} NK cells are more abundant in secondary lymphoid tissues, in particular in lymph nodes and tonsils [7,8]. Underlying the differential distribution of these two subsets, CCR7 expressed on CD56^{bright} NK cells is likely to regulate their homing to lymph nodes, while CXCR1 expressed on CD56^{dim} NK cells can mediate recruitment to peripheral inflammatory sites. CD56^{dim} NK cells express high levels of CD16, multiple types of inhibitory receptors for MHC

Table 1**Specificity and signaling of human NK cell receptors**

Receptor	Signaling	Cellular ligand	Function
FcγRIIIa (CD16)	Activation	IgG	Elimination of antibody coated cells (ADCC)
NKp30 (CD337)	Coactivation	B7-H6	NK cell — myeloid cell cross-talk, tumor recognition
NKp44 (CD336)	Activation	?	?
NKp46 (CD335)	Coactivation	?	Surveillance of mitotic cells
KIR (CD158a, b, and others)	Activation	HLA class I	?
CD94/NKG2C (CD159c)	Activation	HLA-E	?
NKG2D (CD314)	Coactivation	ULBP, MICA, MICB	Surveillance of tumor cells and genotoxic stress
NKp80	?	AICL	NK cell — myeloid cell cross-talk
DNAM-1 (CD226)	Coactivation	CD112, CD155	Surveillance of tissue integrity
2B4 (CD244)	Coactivation	CD48	Interaction with hematopoietic cells
CRACC (CD319)	?	CRACC (CD319)	Interaction with hematopoietic cells
CD2	Coactivation	CD58	Interaction with hematopoietic and endothelial cells
KIR2DL4 (CD158d)	?	HLA-G (soluble)	Trophoblast-induced vascular remodeling?
LFA-1 (CD11a/CD18)	Granule polarization	ICAM	Recruitment and activation during inflammation, efficient cytotoxicity
KIR (CD158)	Inhibition	HLA class I alleles	Assess loss of MHC class I alleles
LIR1, LILR1 (CD85j)	Inhibition	HLA class I	Assess loss of MHC class I expression
CD94/NKG2A (CD159a)	Inhibition	HLA-E	Gauge MHC class I expression
KLRG1	Inhibition	E-cadherin	Assess loss of tissue integrity
NKR-P1 (CD161)	Inhibition	LLT1	?
LAIR-1 (CD305)	Inhibition	Collagen	Control activation in extracellular matrix
Siglec-7 (CD328)	Inhibition	Sialic acid	?
Siglec-9 (CD329)	Inhibition	Sialic acid	?
IRp60 (CD300a)	Inhibition	?	?

class I, and high levels of perforin. In contrast, CD56^{bright} NK cells express low levels of CD16, exclusively the inhibitory receptor CD94/NKG2A that binds the non-classical MHC class I molecule HLA-E, and 10-fold less perforin than CD56^{dim} NK cells. CD56^{bright} NK cells also express higher levels of cytokine receptors than CD56^{dim} NK cells. Because of these and other findings, CD56^{dim} NK cells are often regarded as being specialized in cytotoxicity acting in the periphery, while CD56^{bright} NK cells are considered specialized in the secretion of cytokines and chemokines acting in secondary lymphoid organs and at sites of inflammation [6–9].

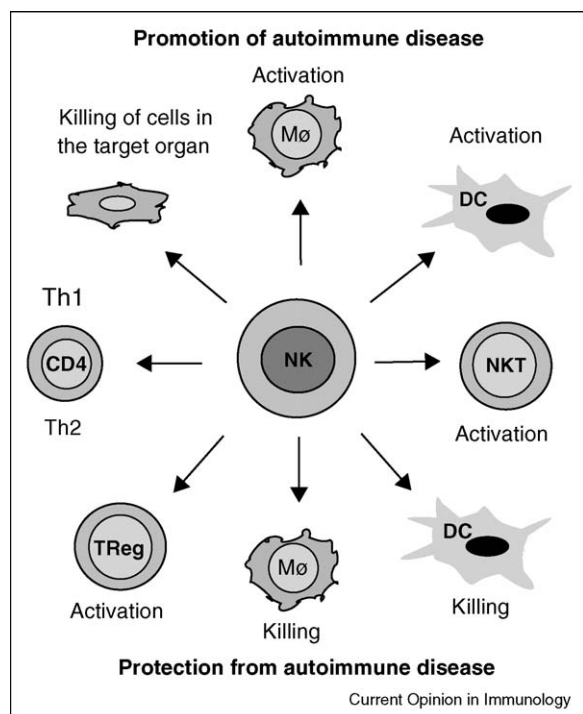
NK cells and human autoimmunity

Classically, autoimmune diseases typify syndromes caused by inappropriate activation of cells of the adaptive immune response, that is, T cells and B cells, resulting in cell-specific, organ-specific or systemic tissue damage. Examples of such diseases include multiple sclerosis (MS), rheumatoid arthritis (RA), and insulin-dependent diabetes mellitus (type 1 diabetes, T1D). Autoimmune diseases are initiated in steps, including release of self-antigens from the target organ, a priming step in secondary lymphoid organs, and finally immune cell homing to the target organ/tissue and subsequent tissue destruction [10]. NK cells can act at all these steps, that is, as mediators of initial target damage leading to release of self-antigens, at the level of T-cell priming in secondary lymphoid organs, and at the level of the target organ as immunomodulatory or effector cells [11,12*,13*,14–16] (Figure 1).

Most research results pointing toward a role for NK cells in human autoimmune diseases are, obviously, correlative. Associations between NK cell activity and autoimmune conditions have been made in several reports, including studies finding altered numbers, phenotypes, and functions of NK cells [11,12*,13*,14–16]. Some older studies are, however, difficult to interpret since they fail to distinguish NK cells from regulatory NKT cells or T cells expressing NK cell-associated receptors. An additional problem is determining if abnormalities in NK cell populations are a cause and/or an effect of a given disease state. Finally, most studies rely on assessment of NK cells from peripheral blood, not from appropriate secondary lymphoid organs or affected tissue. Despite these shortcomings, a substantial amount of evidence supports a direct involvement of NK cells in human autoimmunity.

The impaired NK cell cytotoxic function frequently observed in some humans with autoimmune diseases and/or other inflammatory conditions highlight the role of NK cells in controlling other cells, for example, macrophages. Macrophage activation syndrome (MAS) is associated with several rheumatic diseases, most commonly with systemic juvenile idiopathic arthritis (sJIA) [17*,18]. Clinically, this syndrome closely resembles familial hemophagocytic lymphohistiocytosis (FHL), a life-threatening genetic disorder in which NK cell function is absent or depressed [19,20]. As in FHL, patients with macrophage activating syndrome have profoundly decreased NK cell cytotoxic activity. Therefore, impaired

Figure 1



NK cells may affect autoimmune diseases in many different ways, either by promoting or preventing functions of other cells. NK cells have also been able to promote organ-specific autoimmunity by direct killing of specific cells, for example, insulin-producing β cells in the pancreas. The figure illustrates possible cellular interactions involving NK cells and other cells as well as their outcomes. Depending on which interaction will dominate, the autoimmune response will be promoted or prevented.

NK cell cytotoxicity might be, at least in part, causative of MAS. Supporting this notion, a sJIA patient with low NK cell cytotoxic function was found to harbor compound heterozygous splice site and missense mutations in *UNC13D*, a gene associated with FHL [21^{••}]. Another link between NK cells and macrophages comes from studies showing that CD56^{bright} NK cells accumulate in certain inflammatory lesions and, in the appropriate cytokine environment, can engage with monocytes in a reciprocal activation fashion, thereby amplifying the inflammatory response. Moreover, CD56^{bright} NK cells can trigger differentiation of monocytes into DCs [22]. Such positive feedback loops can well promote the pathogenesis of chronic inflammatory conditions such as RA [23[•]]. Moreover, naturally occurring mutations in genes that cause a defect in NK cells are found in patients with abnormalities in TAP-peptide transporters, who typically suffer from chronic infections in childhood and autoimmune manifestations later in life [24^{••}]. Notably, while interactions with macrophages are of particular interest to organ-specific autoimmunity, NK cells are also able to modulate innate and adaptive immunity by interactions with many other cell types, for example, several other

lymphocytes including NKT cells as well as effector and regulatory T cells [25–30].

Genetic association studies

Linkage analysis in several autoimmune disease conditions has implicated various NK cell receptors in pathogenesis [31]. Recent data have demonstrated that certain KIR receptor genes, the products of which are expressed on NK cells and some T cell subsets, are associated with the development of autoimmune diseases. KIR genes are polymorphic and the KIR gene complex is polygenic encoding varying numbers of inhibitory and activating receptors. Interactions of the independently segregating KIR and HLA loci are important for NK cell 'licensing' and target cell recognition [32]. The existence of KIR–HLA genotypes that tune NK cells toward activation are favorable in some infectious diseases, but might also predispose to autoimmunity [31]. A number of associations predisposing to autoimmune diseases have been identified where activating KIR or KIR/HLA genotypes are accompanied by lack of inhibition. For example, scleroderma, a disease of tissue fibrosis, inflammation, and vascular injury, has been linked to the presence of activating *KIR2DS2*, in the absence of a corresponding inhibitory *KIR2DL2* [33[•]]. Likewise, the risk of psoriatic arthritis is enhanced in patients carrying *KIR2DS1* and/or *KIR2DS2*, and this effect is augmented in the absence of ligands for the inhibitory *KIR2DL1* and *KIR2DL2/3*, respectively [34[•]]. Similarly, for RA increased risk is associated with the presence of the *KIR2DS2* gene [35[•]]. In T1D, disease is associated with an expression of KIR2DS2/HLA ligand-pairs in an environment of weak inhibitory interactions [36[•],37[•]]. Ankylosing spondylitis shows a strong relationship with *HLA-B27*, a ligand for KIR3DL2, and NK cells from patients with this disease have elevated KIR3DL2 expression and show an activated phenotype as measured by CD38 expression [38[•]]. Thus, the interplay between human NK cell inhibitory and activating-receptor MHC class I ligand pairs has provided significant evidence with respect to the involvement of NK cells in human autoimmunity. Noteworthy, however, the function of KIR may in some instances also be exerted at the level of autoimmune T cells, for example, through augmentation of low affinity activation signals.

In addition to receptors that bind MHC class I molecules, NK cell specificity is dictated by a number of other receptors that bind stress-induced ligands or regulate interaction with other immune cells. Inappropriate expression of activating-receptor NKG2D ligands can lead to detrimental NK cell activation, which in turn may trigger or exacerbate autoimmunity. The best-characterized NKG2D ligands are the MICA/B cellular stress-induced molecules that act as danger signals to alert NK cells and CD8 T lymphocytes [39]. Acquisition of MICA/B ligands on the surfaces of potential target cells

may lead to the breakdown of tolerance. MIC molecules, when inappropriately expressed, may thus trigger or worsen an autoimmune response. The involvement of NKG2D and its ligands in autoimmunity was first revealed in patients with RA [40]. More recently, it has been demonstrated that MIC molecules are over expressed on gut epithelium during active celiac disease [41[•]]. In situations of MICA/B over expression, these molecules may be targets not only for NK cells but also for T cells, as demonstrated in several studies [42]. Polymorphisms of human *MICA* have been associated with a variety of autoimmune disorders. The functional implications of such polymorphism are, however, far from clear, and *MICA* associations frequently reflect a linkage disequilibrium with *HLA-B* alleles [43]. It remains to be established whether mutations in the NKG2D gene (*KLRK1*) might be associated with autoimmune diseases. Recently, however, a single nucleotide polymorphism (SNP) in *CD226*, conferring an amino acid substitution in the DNAM-1 receptor, has been associated with the development of MS, RA, and T1D, and autoimmune thyroid disease [44[•]]. In addition, two intronic SNPs in *CD244*, that likely increase 2B4 receptor surface expression, have been associated with the development of RA in a Japanese cohort [45]. Together, these data implicate activating NK cell receptors in autoimmune disease susceptibility. It should be noted, however, that despite the often-used term 'NK cell receptors' these receptors are expressed also on other lymphocyte populations and it remains to be established to what degree genetic associations are conferred by alterations in NK cell function.

NK cells in MS, T1D, and RA

As evident from the discussion above, numerous studies have established links between NK cells and the development or maintenance of autoimmune diseases. Below, we discuss briefly some additional studies performed on three prototypic human autoimmune diseases, MS, T1D, and RA.

Multiple sclerosis is an inflammatory disease that affects the central nervous system (CNS). Autoimmune T cells target myelin components and play a crucial role in mediating the inflammatory response that results. Most patients with MS have clinically stable periods of variable duration (remission), interrupted by unpredictable relapses [46]. Protective roles for NK cells in patients with MS have been suggested, since patients in remission from MS disease manifest unusually high frequencies of CD95 (Fas)-positive NK cells in their peripheral blood. These NK cells have been classified as 'NK2' cells, distinguished by the secretion of Th2 cytokines, such as IL-5 and IL-13. Such NK cells may actively suppress potentially pathogenic autoimmune T cells that can mediate inflammatory responses in the CNS. Interestingly, these cells are lost when a relapse of MS occurs but are regained after recovery. This sequence of events has

thus led to the suggestion that NK cells play an active role in maintaining the remission of MS [47^{••}, 48^{••}, 49]. In a phase II clinical trial with a humanized monoclonal antibody against the IL-2 receptor α chain in MS, an expansion of CD56^{bright} NK cells was observed [50[•]]. The relative and absolute expansion of this NK cell subset, and their increased perforin expression, correlated with the reduction of inflammatory activity. These findings mirror the dual beneficial and deleterious roles of NK cells during the progression of MS.

Type 1 diabetes results from a destructive immune reaction against pancreatic insulin-producing β cells [51]. The disease is believed to be T-cell-mediated, but other immune cells such as B cells, macrophages, and NK cells may also be involved. Data on NK cells in human T1D are scarce. Early studies reported a numeric reduction or functional defects of NK cells in the peripheral blood of some T1D patients [12[•]]. A more recent study revealed a reduced frequency of NK cells in peripheral blood in recent-onset patients, but not in patients with long-standing T1D [52[•]]. NK cell defects, as reflected by lowered production of IFN- γ as well as decreased expression of NKp46 and NKp30, were evident in long-standing T1D and most prominent in patients with high levels of glycosylated hemoglobin. Thus, peripheral NK cell numbers may be altered at T1D onset, but changes in NK functions are most likely secondary to the metabolic disturbances associated with the disease. Further, T1D patients, irrespective of disease duration, harbored NK cells expressing reduced levels of NKG2D [52[•]]. A recent study has demonstrated the presence of NK cells in pancreas specimens from recently diagnosed T1D patients [53[•]]. NK cells, visualized as CD94⁺CD45RO⁻ cells, were found around the pancreatic islets from three of six patients. The islets were also positively stained by an antibody that detects the VP1 protein of Coxsackieviruses, a family of viruses associated with the onset of T1D [54]. The islet remnants in the three patients with no detectable NK cells were negative for VP1. However, in a larger collection of pancreas samples removed post-mortem from 29 T1D patients, Willcox *et al.* failed to detect pancreas-infiltrating NK cells [55[•]]. An important note is that these studies were conducted on pancreatic material from patients who were already diagnosed with the disease, and that no investigations have been done during the pre-diabetic phase when β cells are actively being destroyed. Further investigations on the pancreas and its draining lymph nodes before and at disease onset, as well as studies on the molecular mechanisms behind the NK cell abnormalities observed in T1D patients, should substantiate whether or not NK cells are involved in β cell autoimmunity.

RA is a systemic autoimmune disease characterized by joint inflammation and cartilage destruction. Several cell types are known culprits in different stages of RA

pathogenesis, such as T helper cells, B cells, and macrophages [56]. NK cells are less well studied in RA, but have been retrieved in substantial numbers from the inflamed joints of RA patients [57,58]. Indicative of a disease-promoting role, joint-derived NK cells express higher levels of activation markers and produce more IFN- γ upon cytokine stimulation compared to NK cells from the peripheral blood of the same patients. However, NK cells from peripheral blood of RA patients show a much reduced activity on a per-cell basis compared to healthy donors [59]; therefore, it is difficult to determine whether the difference between the blood and the joint results from an NK cell enhancing environment in the joint or an NK cell depressing environment in the blood. Interestingly, NK cells from the joints are phenotypically unique compared to those from peripheral blood NK cells. The former are almost exclusively CD56^{bright} [16,48]. The presence of these cells could result from selective recruitment of a small population of blood NK cells into the joint or from local differentiation from stem cells [9]. The presence of activated NK cells in arthritic joints suggests a possible influence of NK cells on other cells, for example, macrophages, as discussed above.

Conclusion

With the exception of genetic linkage analysis, relatively few studies have been undertaken to explore the role of NK cells in human autoimmunity. Much knowledge on the role of NK cells in autoimmunity still comes from studies in experimental animal models, and caution must be taken before translating those results directly to human conditions. The emerging view, however, is that NK cells may function as important regulatory cells during the priming phase of adaptive immune responses and as regulatory and effector cells at the sites of target organ during inflammation. We speculate that NK cell control of macrophage activation may be one important checkpoint at the level of the target organ in the development of autoimmunity. The ability of NK cells to influence adaptive immune responses and to control immune cell homeostasis in humans deserves further attention. Improved comprehension of how NK cells affect different autoimmune conditions may pave the way for new immunotherapeutic approaches toward alleviating or preventing such diseases.

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