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NK CELL RECOGNITION

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■ **Abstract** The integrated processing of signals transduced by activating and inhibitory cell surface receptors regulates NK cell effector functions. Here, I review the structure, function, and ligand specificity of the receptors responsible for NK cell recognition.

INTRODUCTION

Natural killer (NK) cells distinguish between normal healthy cells and abnormal cells by using a sophisticated repertoire of cell surface receptors that control their activation, proliferation, and effector functions.[1] Germline genes that do not require somatic recombination encode these receptors; thus, NK cells represent an arm of the innate immune system. Although they lack the ability to generate antigen-specific receptors by somatic cell genetic alterations, NK cells in many aspects are more closely related to T cells, with which they share a common bipotential progenitor, than to other populations of leukocytes of the innate immune system (reviewed in 1, 2). In particular, NK cells share a common killing mechanism with $CD8^+$ cytotoxic T lymphocytes (CTL) (i.e., using perforin and granzymes). Like CTL and $CD4^+$ Th1 cells, NK cells secrete interferon-γ (IFN-γ). Despite a similar pattern of cytokine production to CTL and $CD4^+$ Th1 cells, an important distinction is that NK cells are unable to produce IL-2. While the term "NK receptor" has been used to describe molecules that were first discovered on NK cells, the majority of these NK receptors are expressed on at least a subset of T lymphocytes, in particular on $\gamma\delta TCR^+$ T cells and on activated $CD8^+$ T cells.

Emerging evidence suggests that NK cells, previously considered an ancient immune effector cell type, have more likely coevolved with T cells, given that both of these lymphocytes are focused on recognition of conventional and nonconventional major histocompatibility complex (MHC) molecules. In this regard,

[1]See Appendix for a full list of abbreviations used.

NK cells distinguish themselves from phagocytes (macrophages and granulocytes) that rely solely on conserved pattern-recognition receptors, for example, the toll-like receptors. Functional MHC molecules are present in cartilaginous fish, but not in more primitive species. Similarly, NK cells, as they are currently defined, also have not been identified in species lower than fish. Thus, based on their lineage relationships, receptor repertoire, and effector functions, NK cells appear to be a transitional cell type bridging the innate and adaptive immune systems.

Understanding NK cell recognition is more complex than for B cells and T cells, where the antigen receptors dominate the differentiation, activation, and effector function of these lymphocytes. Rather than being regulated by any one receptor, NK cells appear to work by the integration of numerous signals from receptors that would be designated "adhesion molecules" or "costimulatory receptors" on T cells. Further, the activation of NK cells is stringently controlled by inhibitory receptors that presumably function as a fail-safe to avoid inadvertent stimulation, which may result in harm to normal healthy cells in the host.

NK cell recognition involves the initial binding to potential target cells, interactions between activating and inhibitory receptors with ligands available on the target, and the integration of signals transmitted by these receptors, which determines whether the NK cell detaches and moves on or stays and responds. NK cells respond by reorganizing and releasing cytotoxic granules and by transcribing and secreting cytokines. Recent studies have demonstrated reorientation of the relevant receptors into an "NK synapse" during NK cell encounters with potential target cells (3–7), as observed previously in the interaction between T cells and antigen-presenting cells. NK cells differ from naive T cells in that mature NK cells are poised as effector cells for an immediate response. These "ready-to-go" cells express granzymes and perforin, and their lytic response can be triggered within minutes, without requiring transcription, translation, or cell proliferation. Recent studies by Locksley and colleagues (8) have shown that NK cells constitutively express prestored transcripts for IFN-γ that are immediately available to initiate cytokine synthesis upon activation. Even at their earliest stages of development, IFN-γ transcripts are present in the NK cell progenitors in the mouse bone marrow (8). Thus, there is no equivalent in the NK cell lineage that corresponds to a "naive" T cell, which must undergo proliferation, chromatin remodeling of cytokine genes, and de novo transcription and translation of granzymes and perforin before it becomes a competent effector cell. In this regard, the phenotype of a "resting" NK cell is more similar to an effector $CD8^+$ T cell with respect to expression of cell surface receptors and effector molecules. Indeed, many NK receptors are expressed on $CD8^+$ T cells (and some $CD4^+$ T cells) only after their conversion to effector or memory cells (reviewed in 9). The ready-to-go state of NK cells and the fact that NK cell receptors are invariant and constitutively present on a large proportion of cells within the population make these cells well suited for early defense.

THE "MISSING-SELF HYPOTHESIS" REVISITED

Initially, NK cells were described as non-MHC-restricted in their recognition process because of their ability to kill target cells that either lacked MHC or expressed various allogeneic MHC molecules. However, Karre and colleagues (10) noted that rather than ignore MHC, NK cells appear to be actively inhibited from responding when they encounter certain tumor cells that express MHC class I. Subsequently, the ability of NK cells to recognize and eliminate normal host hematopoietic cells that lack MHC class I was substantiated by demonstrating NK cell–dependent rejection of bone marrow cells from β2-microglobulin-deficient syngeneic mice (11, 12). According to the "missing-self" hypothesis (13), NK cells were proposed to provide immune surveillance for cells that had downregulated MHC class I, an event that frequently accompanies cellular transformation or infection with certain viruses. Until recently, a common misconception has been that NK cells attack any cell lacking MHC molecules because the potential target cell cannot engage an inhibitory NK cell receptor for MHC class I. This notion is counterintuitive given documentation of the events involving cell-cell binding, Ca^{2+} mobilization, and synapse formation when NK cells encounter susceptible target cells that lack MHC class I. A contemporary modification of the missing-self hypothesis might state, "NK cells patrol for abnormal cells that lack MHC class I or overexpress ligands for activating NK cell receptors" (Figure 1). In essence, the inhibitory MHC class I receptors on NK cells serve as a rheostat, regulating and dampening signals transduced through activating receptors. When NK cells and potential target cells meet, the information is interpreted by an analog, not a binary process. Experimental evidence suggests that the MHC class I inhibitory receptors may serve only to dampen, rather than completely terminate, NK cell effector function and that the amount of MHC class I on the surface of the target is proportional to the degree of inhibition. In experimental models, when multiple activating NK cell receptors are engaged simultaneously (14) or when a sufficiently potent activating NK receptor is stimulated (15, 16), NK cells are capable of effectively eliminating cells even if their inhibitory receptors for MHC class I are ligated.

A corollary of the missing-self hypothesis is that failure of NK cells to respond to a potential target can be due either to active inhibition mediated by the inhibitory receptors or alternatively, to the absence of sufficient activation signals to initiate a response (Figure 1). An example of the latter situation may be represented by encounters between human erythrocytes and circulating peripheral blood NK cells. Although human red blood cells do not express MHC class I, NK cells do not attack them; therefore, erythrocytes may lack ligands capable of engaging the activating NK cell receptors. An alternative explanation for the inability of NK cells to harm normal tissues with low (e.g., neural tissues) or no (e.g., erythrocytes) MHC class I is the possibility that this target cell protection is mediated by inhibitory receptors recognizing non-MHC ligands. As precedence, macrophages express the SIRPα inhibitory receptor that inhibits their phagocytosis of erythrocytes expressing its ligand CD47 (17). Recent studies have demonstrated that an inhibitory NK receptor