NK cells: receptors and functions

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Natural killer (NK) cells were identified in 1975 as lymphocytes of the innate immune system that can kill tumour cells. Since then, NK cells have been shown to kill an array of ‘stressed’ cells and secrete cytokines that participate in shaping adaptive immune responses. A key feature of NK cells resides in their capacity to distinguish stressed cells (such as tumour cells, infected cells and damaged cells) from normal cells. Although NK cells are generally considered to be components of early innate immune defence, many processes that were originally restricted to adaptive immunity, such as priming, education and memory, are now known to occur in NK cells. Indeed, NK cells undergo sophisticated processes of adaptation that allow them to be tuned to their environment. There is also a growing interest in manipulating NK cells in innovative therapeutic settings. For example, the understanding of NK cell inhibition by key NK cell-specific receptors has prompted the design of innovative anticancer therapies.

The NK cell detection system includes numerous receptors, the engagement of which dictates the quality and intensity of the NK cell response. NK cells use inhibitory receptors to gauge the abundance of constitutively expressed self molecules on susceptible target cells. As a consequence, NK cells can recognize ‘missing self’ on haematopoietic cells. By interacting with MHC class I molecules that are constitutively expressed by most healthy cells under steady-state conditions but that may be lost under conditions of stress, MHC class I-specific inhibitory receptors provide a way for NK cells to remain tolerant to healthy self cells while being toxic towards stressed cells. By contrast, NK cell activating receptors detect self molecules that are expressed under conditions of cell stress. Only human NK cells have receptors that are not self-expressed.

There are several differences in NK cell receptors between mice and humans. In mice, inhibitory MHC class I-specific receptors are lectin-like dimers of the Ly49 family. Although several activating NK cell receptors are present in humans and mice (such as CD16, NKp46, DNAM1 and NG2D), commonly used mouse strain lack orthologues of NKp30 and NKp44.

Key receptors on human NK cells

Inhibitory receptors

- CD94/NKG2A
- KIR2DS2
- KIR3DL1
- CD94/NKG2B
- CD94/NKG2C
- CD94/NKG2D
- KIR2DS4
- KIR2DS5
- KIR3DL2

Activating receptors

- NKG2D
- NKp46
- NKp44
- CD16
- CD56

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- NKp44
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Biological function of NK cells and cellular crosstalk

NK cells can recognize various stressed cells that have or have not been killed by other immune cells, and in response to killing by other immune cells, and in response NK cell activation (trigged by this recognition can lead to target cell lysis, as well as to the production of various cytokines and chemokines, depending on the nature of the stimulation. NK cells also engage in education with other cells, and educate their cells to sequences of pathways (inhibitory and activating) following interaction with either immune or non-immune cells. They regulate NK cell activation and determine whether NK cells are activated to kill target cells and produce cytokines. The innate immune system is generally thought to lack the capacity for immunological memory. However, recent findings show that some immune system can be functionally memory. In these settings, they have been shown to be capable of long-lived memory responses to haptens or viruses.

Abbreviations

- CD, cluster of differentiation
- MHC, major histocompatibility complex
- NK, natural killer
- TCR, T cell receptor
- CD56, cell surface glycoprotein
- ITAM, immunoreceptor tyrosine-based activation motif
- ITIM, immunoreceptor tyrosine-based inhibition motif
- IFN, interferon
- IL, interleukin
- TNF, tumour necrosis factor
- LFA-1, lymphocyte function-associated antigen 1
- MAC-1, macrophage 1
- ICAM-1, intercellular adhesion molecule 1
- NKT, natural killer T cells
- PBMC, peripheral blood mononuclear cells
- PBMCs, peripheral blood mononuclear cells
- T h1, Th1 helper cell
- T h2, Th2 helper cell
- NK I-A, natural killer I-A
- NK I-E, natural killer I-E
- IFN, interferon
- IL, interleukin
- TNF, tumour necrosis factor
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Acquisition of NK cell function

To acquire the capacity to recognize target cells with low MHC class I expression (missing self recognition), NK cells are capable of being educated by the detection of host MHC class I molecules by their inhibitory receptors. Inhibitory receptors recognize MHC class I molecules on target cells and inhibit cell lysis. On the other hand, activating receptors provide a way for NK cells to be activated by the recognition of MHC class I molecules that are constitutively expressed by most healthy cells under steady-state conditions but that may be lost under conditions of stress. MHC class I-specific inhibitory receptors provide a way for NK cells to remain tolerant to healthy self cells while being toxic towards stressed cells. By contrast, NK cell activating receptors detect self molecules that are expressed under conditions of cell stress. Only human NK cells have receptors that are not self-expressed.

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