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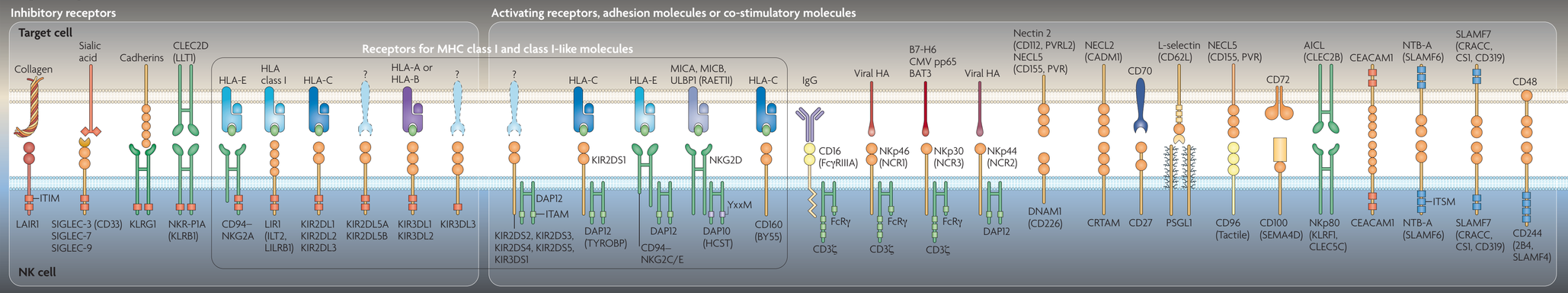
NK cells: receptors and functions

Eric Vivier and Sophie Ugolini

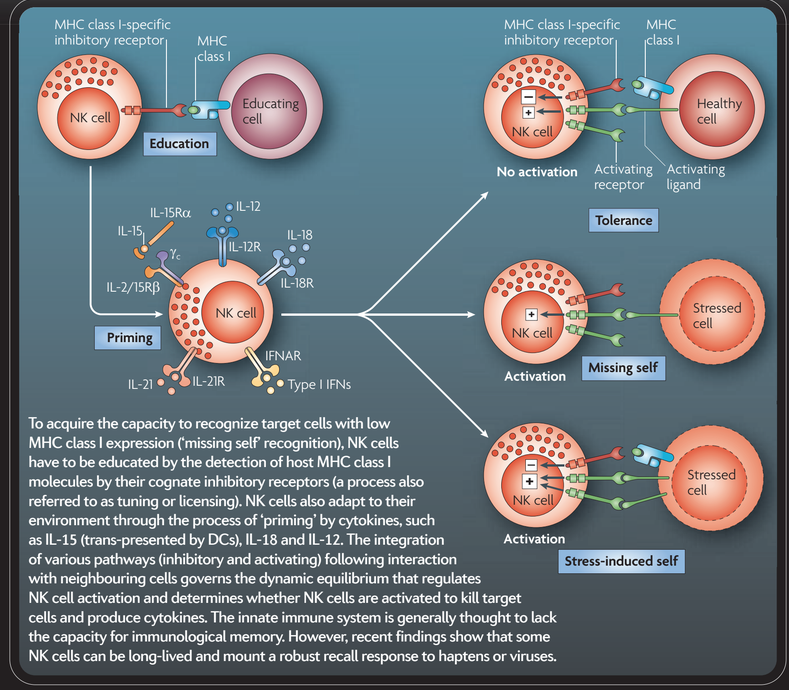
Natural killer (NK) cells were identified in 1975 as lymphocytes of the innate immune system that can kill tumour cells. Since then, NK cells have been shown to kill an array of 'stressed' cells and secrete cytokines that participate in shaping adaptive immune responses. A key feature of NK cells resides 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 MHC class I-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 absence 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 cell receptors are shown and the list is not exhaustive. 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 NKG2D), commonly used mouse strains lack orthologues of NKp30 and NKp44.

Key receptors on human NK cells



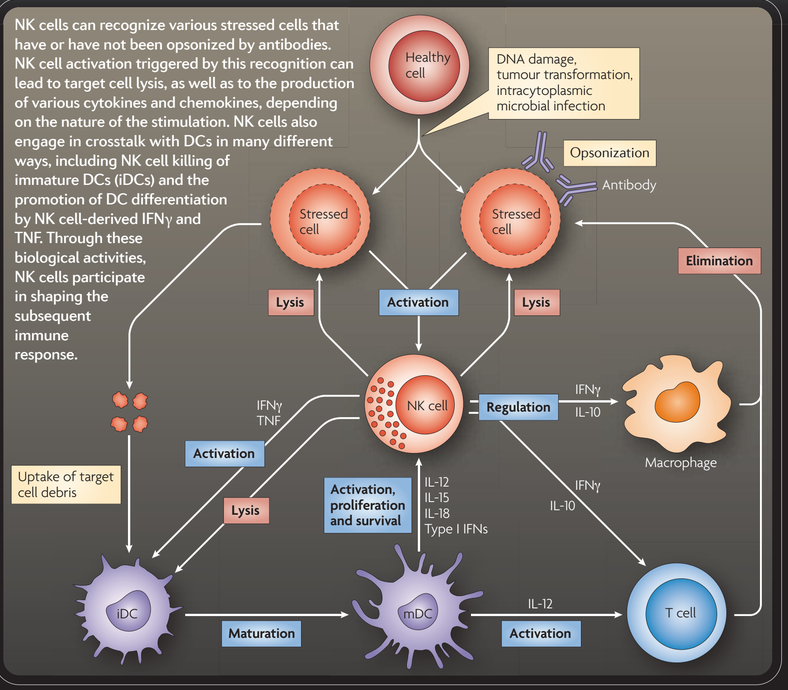
Acquisition of NK cell function



To acquire the capacity to recognize target cells with low MHC class I expression ('missing self' recognition), NK cells have to be educated by the detection of host MHC class I molecules by their cognate inhibitory receptors (a process also referred to as tuning or licensing). NK cells also adapt to their environment through the process of 'priming' by cytokines, such as IL-15 (trans-presented by DCs), IL-18 and IL-12. The integration of various pathways (inhibitory and activating) following interaction with neighbouring cells governs the dynamic equilibrium that regulates NK cell activation and determines 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 NK cells can be long-lived and mount a robust recall response to haptens or viruses.

Biological function of NK cells and cellular crosstalk

NK cells can recognize various stressed cells that have or have not been opsonized by antibodies. NK cell activation triggered 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 crosstalk with DCs in many different ways, including NK cell killing of immature DCs (iDCs) and the promotion of DC differentiation by NK cell-derived IFNγ and TNF. Through these biological activities, NK cells participate in shaping the subsequent immune response.



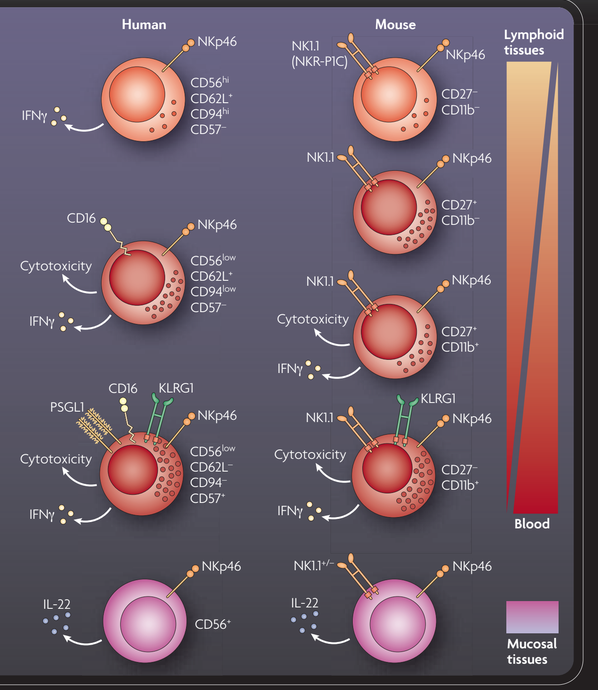
NK cell subsets and NK-like innate lymphoid cells

Various NK cell subsets can be found in many lymphoid and non-lymphoid tissues, including the liver, lungs, thymus, pancreas and uterus.

In humans, NK cells can be divided according to the density of CD56 expression. There is evidence that $CD56^{hi}$ NK cells give rise to mature cytotoxic $CD56^{low}$ NK cells, which can be further divided based on expression of PEN5, a carbohydrate epitope present on PSGL1, KLRG1, CD57, CD94 and CD62L. Uterine NK cells are $CD56^{hi}CD16^{-/low}$ and secrete a specific set of chemokines, including CXCL8, CXCL10, CXCL12 and VEGF.

In mice, four subsets of circulating NK cells can be distinguished: immature $CD27^{-}CD11b^{-}$ NK cells, intermediate $CD27^{+}CD11b^{-}$ and $CD27^{+}CD11b^{+}$ NK cell subsets, and mature $CD27^{-}CD11b^{+}$ NK cells.

Although NKp46 is a conserved marker that best defines NK cells in mammals, cells that express NCRs (NKp46 in mice, NKp46, NKp30 and NKp44 in humans) and produce IL-22 are found in mucosal tissues. These cells are not cytotoxic, do not secrete IFNγ and express the transcription factor RORγt instead of E4BP4 (also known as NFIL3), which is crucial for *bona fide* NK cells. These IL-22-producing NCR^{+} innate lymphoid cells are therefore distinct from conventional NK cell subsets.



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Species	Selection	Starting Sample	Product	Catalog #
Human	Negative	Whole Blood, Buffy Coat	RosetteSep® Human NK Cell Enrichment Cocktail	15065
		PBMC, Leukapaks	EasySep® Human NK Cell Enrichment Kit	19055
	Positive	PBMC	EasySep® Human CD56 Positive Selection Kit	18055
		Buffy Coat	EasySep® Human Buffy Coat CD56 Positive Selection Kit	18085
Mouse	Negative	Spleen or other tissues	EasySep® Mouse NK Cell Enrichment Kit	19755
	Positive		EasySep® Mouse NK Cell Positive Selection Kit	18755

Abbreviations

γc, common cytokine receptor γ-chain; AICL, activation-induced C-type lectin; BAT3, HLA-B associated transcript 3; CADM1, cell adhesion molecule 1; CD62L, CD62 ligand; CEACAM1, carcinoembryonic antigen-related cell adhesion molecule 1; CLEC, C-type lectin domain family; CMV, cytomegalovirus; CRACC, CD2-like-receptor activating cytotoxic cells; CRTAM, class I MHC-restricted T cell-associated molecule; CS1, CD2 subset 1; CXCL, CXC-chemokine ligand; DC, dendritic cell; DNAM1, DNAX accessory molecule 1; E4BP4, E4 promoter binding-protein 4; FcR, Fc receptor; HA, haemagglutinin; HCST, haematopoietic cell signal transducer; IFN, interferon; IL, interleukin; ILT, immunoglobulin-like transcript; ITAM, immunoreceptor tyrosine-based activation motif; ITIM, immunoreceptor tyrosine-based inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; KIR, killer cell immunoglobulin-like receptor; KLRG, killer cell lectin-like receptor subfamily G; LAIR1, leukocyte-associated immunoglobulin-like receptor 1; LIR1, leukocyte immunoglobulin-like receptor 1; LLT1, lectin-like transcript 1; mDC, mature DC; MIC, MHC class I polypeptide-related sequence; NCR, natural cytotoxicity receptor; NECL, nectin-like; NFIL3, nuclear factor IL-3-regulated protein; NKG2, NK group 2; NKR-P1A, NK cell receptor protein 1A; NTB-A, natural killer, T and B cell antigen; PSGL1, P-selectin glycoprotein ligand 1; PVR, poliovirus receptor; R, receptor; RAET1I, retinoic acid early transcript 1I; RORγt, retinoic acid receptor-related orphan receptor-γt; SEMA4D, semaphorin 4D; SIGLEC, sialic acid-binding immunoglobulin-like lectin; SLAM, signalling lymphocytic activation molecule family; TNF, tumour necrosis factor; TYROBP, TYRO protein tyrosine kinase-binding protein; ULBP1, UL16-binding protein 1; VEGF, vascular endothelial growth factor.

Affiliations

Eric Vivier and Sophie Ugolini are at the Centre d'Immunologie de Marseille-Luminy (CIML), INSERM-CNRS-Université de la Méditerranée, Marseille, France. E.V. is also at the Assistance Publique des Hôpitaux de Marseille, Hôpital de la Conception, Marseille, France. e-mails: vivier@ciml.univ-mrs.fr; ugolini@ciml.univ-mrs.fr

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The authors declare competing financial interests: see Web version for details.

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