nature REVIEWS

IMMUNOLOGY

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

Acquisition of NK cell function



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.

How to Obtain High Yields of NK cells with STEMCELL **Technologies**

The isolation and culture of highly purified, functional NK cells are critical for successful NK cell research. STEMCELL Technologies offers products for fast and easy cell isolation, as well as serum-free culture media for the generation, differentiation, and expansion of NK cells.

Achieve efficient cell isolation with our immunomagnetic and immunodensity cell separation systems, EasySep™ and RosetteSep™. For full automation of EasySep™ NK cell isolations, RoboSep™ instruments can simultaneously process up to sixteen samples with minimal sample handling and no cross-contamination. Expand your purified NK cells with ImmunoCult™ NK Cell

Expansion Kit, or obtain high yields of NK cells from hematopoietic stem and progenitor cells (HSPCs) or human pluripotent stem cells (hPSCs) using StemSpan[™] NK Cell Generation Kit or STEMdiff[™] NK Cell Kit, respectively.

NK cell isolation kits and culture media from STEMCELL have supported cutting-edge research, including genetically engineering NK cells for immunotherapy¹ analyzing NK cell function^{2,3}, and studying the role of NK cells in HIV pathogenesis⁴ and immunology⁵.

Learn more about our specialized products for NK cell research or request a sample at www.stemcell.com/nkcells 1. Pomerov et al. (2020) Mol Ther 28(1): 52–63.

- 2. Zhu S et al. (2014) Blood 123(3): 403–411.
- 3. Briercheck EL et al. (2015) J Immunol 194(4): 1832-1840. 4. Norman JN et al. (2011) Nat Immunol 12(10): 975–983.
- 5. Huang Q-Q et al. (2015) Nat Commun 6: 7086.

Document # 10000010956 Version 01 For Internal Use Only Material # 28771

Species Selection Starting Sample Product EasySep™ Human NK Cell 17955 Isolation Kit Negative PBM EasySep™ Direct Human 19665 NK Cell Isolation Kit Whole Blood RosetteSep™ Human NK Cell Enrichment Cocktail EasySep™ Release Human 17755 CD56 Positive Selection Kit EasySep™ Human CD56 17855 Positive Selection Kit II EasySep™Human BuffyCoat | 18085 CD56 Positive Selection Kit | Buffy Coat EasySep™ Mouse NK Cell 19855 Isolation Kit Negative Spleen or othe EasySep™ Mouse CD49b 18755 e Selection Kit

Biological function of NK cells and cellular crosstalk

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 IFN γ and TNF. Through these biological activities, NK cells participate Activation Lysis iDC



NK cells: receptors and functions

Eric Vivier and Sophie Ugolini



Abbreviations

Catalog #

15025

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 factor; TYROBP, TYRO protein tyrosine kinase-binding protein; ULBP1, inhibitory motif; ITSM, immunoreceptor tyrosine-based switch motif; UL16-binding protein 1; VEGF, vascular endothelial growth factor.

NK cell subsets and NK-like innate lymphoid cells

Various NK cell subsets can be found in Human many lymphoid and non-lymphoid **0** NKp46 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, CD16 o NKp46 KLRG1, CD57, CD94 and CD62L. Uterine NK cells are CD56^{hi}CD16^{-/low} and secrete Cytotoxicity specific set of chemokines, includin 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⁺ CD16 KLRG1 NK cell subsets, and mature PSGL1, CD27⁻CD11b⁺ NK cells. PNKp46 Although NKp46 is a conserved marker that best defines NK cells in mammals. CD56^{lo} Cytotoxicit cells that express NCRs (NKp46 in mice, CD62L-CD94-NKp46, NKp30 and NKp44 in humans) CD57* and produce IL-22 are found in mucosal tissues. These cells are not cytotoxic, do not secrete IFN γ and express the transcription factor RORyt 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.

Affiliations

KIR, killer cell immunoglobulin-like receptor; KLRG, killer cell lectin-like $\gamma_{,}$ common cytokine receptor γ -chain; AICL, activation-induced C-type 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; ROR γ t, 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



Edited by Lucy Bird; copyedited by Isabel Woodman; designed by Simon Bradbrook. © 2010 Nature Publishing Group. <u>http://www.nature.com/nri/posters/nkcells</u>

$\sum_{T \in C} \sum_{H \in V} \sum_{D \in U} \sum_{G \in V} \sum_{T \in V} \sum_{T$

Scientists Helping Scientists[™] | WWW.STEMCELL.COM



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

Acknowledgements E.V. and S.U. are supported by grants from the European Research Council, Agence Nationale de la Recherche, Ligue Nationale contre le Cancer (Equipe labellisée 'La Ligue')

and institutional grants from INSERM, CNRS and Université de la Méditerranée to the CIML. The authors declare competing financial interests: see <u>Web version</u> for details.