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Function of natural killer cells in immune defence against human leukaemia

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Summary

Although progress has been made in the management of acute leukaemias, most patients who fail to respond to front-line therapies with cytostatic agents and stem cell transplantation, or who relapse after an initial response die from progressive disease. Novel treatment modalities exploiting donor-derived natural killer (NK) cells generate an alloreactive graft-versus-leukaemia response and eliminate the residual malignant clones in transplanted patients. NK cells are components of the innate immunity playing an important role in the surveillance of human tumours. Recognition of malignant cells depends on a dynamic balance between antagonistic functions of an array of NK activating and inhibitory receptors. The natural cytotoxicity receptors (NCRs) are NK cell-specific and together with the NKG2D receptor are responsible for NK cell activation and tumour cell killing. The killer immunoglobulin-like receptors (KIRs) recruit phosphatases and can antagonise the activating signals and prevent the cytolytic NK cell programme. Understanding of the integration of these multiple signals at the molecular level is central for exploring the cytolytic function of NK cells. This review describes molecular mechanisms of NK receptor-ligand interactions controlling target cell recognition and addresses the potential of NK cells for the specific elimination of leukaemic clones with the goal of advancing immunotherapy of leukaemia.

Key words: NK cells; human leukaemia; NK cell receptors; signalling pathways; stem cell transplantation; immunotherapy

Introduction

Natural killer (NK) cells are potent effectors of the peripheral immune system. This lymphocyte subset, phenotypically defined as $CD56^{+}CD3^{-}$, has developed as part of protective responses against microbial pathogens and, according to recent studies, plays an important role in the surveillance and eradication of malignant cells [1, 2]. Upon recognition of tumour- or virus-transformed cells, peripheral NK cells are capable of an immediate release of the content of cytotoxic granules and production of inflammatory cytokines, such as tumour necrosis factor-α (TNF-α) and interferon-γ (IFN-γ). This illustrates how NK cells link the innate and adaptive arms of the immune system [3]. Unlike T lymphocytes, NK cells lack the ability to recognise antigens in the context of classical human lymphocyte antigen (HLA) molecules. Instead, NK cell function is regulated by signals delivered by an array of cell surface receptors that recognise different cellular ligands and can discriminate between target and non-target cells [4, 5]. Engagement of the activating receptors triggers the cytolytic programmes whereas inhibitory receptors antagonise the activating pathways. This equilibrium between the opposing signals defines the NK cells effector function. Recent progress in understanding this unique mechanism of receptor-dependent NK cell activity has revitalised interest in the potential immunotherapeutic value of these cells [6, 7]. Below, the molecular basis of NK cell function and current knowledge on the role of NK cells in immune responses against leukaemia are reviewed.

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NK cell receptors and signalling pathways

NK cell receptors are encoded in the genome, rather than being generated by somatic recombination like the antigen-specific components of the T cell receptor. In contrast to T lymphocytes, NK cells use the diverse receptor repertoire to screen potential targets for the presence of specific cell

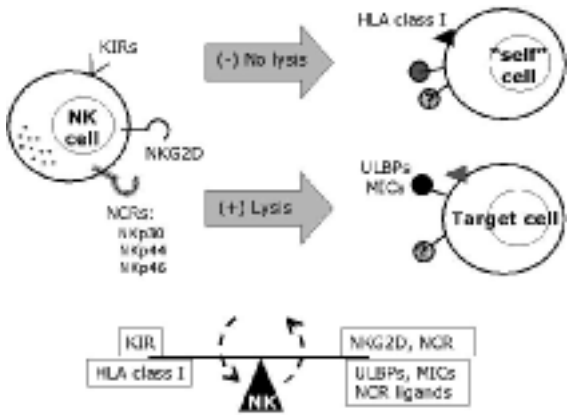

Figure 1

Mechanism of NK cell-mediated cytotoxicity. NK cell function is determined by a balance of inhibitory and activating signals delivered upon an interaction of NK cell receptors with cognate ligands on potential target cells. "Self cells" express high levels of HLA class I protecting them from NK attack, while cells become NK targets after downregulation of HLA class I and upregulation of ligands for the activating receptors.

surface ligands [4, 8]. Cells are protected from killing by expression of HLA class I molecules recognised as "self" by the receptors with inhibitory function. In the absence of this self-recognition and presence of molecules interacting with the activating receptors, cells become susceptible to lysis by NK cells. Consequently, a balance of activating and inhibitory signals defines the outcome of NK cell recognition (figure 1). Although many of the receptors have been discovered in the last few years, their ligands remain often unknown, leaving many unresolved questions as to the biological relevance and molecular basis of the positive and negative signalling pathways in NK cells.

Inhibitory NK cell receptor signalling

The recognition of polymorphic HLA class I is a hallmark of NK cell tolerance [9]. Human inhibitory receptors belong to two families of transmembrane glycoproteins, containing the immunoglobulin (Ig)- and lectin-like extracellular domains [10]. Among them, Killer Ig-like Receptors (KIRs) are the most important in determing the specificity towards the different alleles of classical HLA-A, -B and -C molecules. KIRs contain 2 or 3 Ig-like domains, designated 2D or 3D, and most of them contain long (L) cytoplasmic tails harbouring the immunoreceptor-tyrosine-based inhibition motifs (ITIMs). Individual KIRs have specificity for a number of different HLA alleles, eg KIR2DL1 for HLA-Cw2, 4, 5, 6, and KIR2DL2/3 for HLA-Cw1, 3, 7, 8, resulting in a complex receptor-ligand recognition system (table 1). Upon the engangement of clonally distributed KIRs by an appropriate HLA class I molecule, ITIMs become tyrosine phosphorylated and recruit phosphatases to counteract cellular activation signals. The predominant phosphatases associated with KIRs are SH2 domain-containing tyrosine phosphatases SHP-1 and -2, and the inositol-5-phosphatase, SHIP [11, 12]. The substrates specific for these phosphatases in NK cells have only began to be defined and they might depend upon which of the activating receptors are being modulated (figure 2).

Table 1

Human NK cell receptor-ligand specificities*.

Inhibitory receptors	Ligands
KIR2DL1 (CD158a)	HLA-Cw2, 4, 5, 6
KIR2DL2/3 (CD158b)	HLA-Cw1, 3, 7, 8
KIR3DL1 (CD158e)	HLA-Bw4
KIR3DL2 (CD158k)	HLA-A3, -A11
KIR3DL5	unknown
KIR3DL3	unknown

Activatory receptors	Ligands
NKG2D	ULBP-1, 2, 3, 4; MIC-A, -B
NKp30	unknown
NKp44	unknown
NKp46	unknown

* For comprehensive receptor-ligand list, see ref. 4.

Phosphatases mediate a strong inihibition of NK-mediated cytolysis, which is dominant over signals elicited from activating receptors. Accordingly, the NK-dependent killing is impaired in both naturally-occurring murine mutants and phosphatase-knockouts. Of particular interest are SHIP-1-deficient knockout mice that have a restricted repertoire of NK receptors and a profoundly activated PI3-kinase/akt pathway in NK cells. As a consequence, $SHIP^{-/-}$ NK cells fail to recognise the allogeneic targets and do not reject grafts of fully mismatched bone marrow, suggesting that SHIP plays an important role in graft rejection limiting the success of bone marrow transplantation [13]. A recent study demonstrated that SHIP-1 functions also as a negative regulator of IFN-γ production by primary human NK cell subsets [14].

Activating NK cell receptor signalling

NK cells have evolved a large series of activating receptors which trigger positive signals upon recognition of target cells [15]. At present many of these receptors are still orphans regarding the ligands which they recognise. An important family of receptors is represented by the natural cytotoxicity receptors (NCR), which include NKp30, NKp44, and NKp46 [16]. Surface density of these receptors correlates with the capacity of NK cells to kill a large variety of tumour cells [17]. The haemagglutinin protein of influenza virus has recently been suggested to interact with NKp44 and NKp46 [18, 19]. However, the cellular ligands for NCR receptors have not been identified. The

lectin-like receptor NKG2D forms a homodimer expressed by all NK cells, a subset of $CD8^+$ and TCR $\gamma\delta^+$ T cells [20]. The cellular ligands for NKG2D have been recently identified [21, 22]. In humans, these ligands belong to two distinct families: the MHC class I chain-related (MIC) antigens containing a short transmembrane domain, and the UL16 binding proteins (ULBPs) linked to the membrane through the GPI anchor (table 1). Activating signals can also be elicited by KIR receptors with short (S) cytoplasmic domains lacking the ITIM sequence motif (KIR2DS and KIR3DS).

Activating signals from NCRs and NKG2D and several activating NK co-receptors are transmitted by non-covalently associated small transmembrane adaptor proteins that possess immunoreceptor tyrosine-based activation motifs (ITAMs) in their cytoplasmic domains. NK cells express the ITAM-bearing CD3ζ, FcεRIγ, and DAP12 adaptor proteins [8]. The downstream events include phosphorylation of PI3-kinase, phospholipase C, Syk, Zap70 and other signalling elements commonly employed by leukocytes (figure 2) [23–25]. It remains not defined how ligand recognition by individual receptors is delegated to independent pathways and how it is assembled to produce relevant NK cell responses.

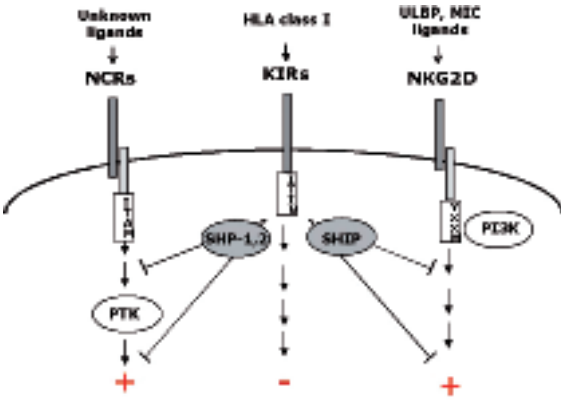

Figure 2

NK cell receptor-dependent signalling pathways. ITAM-bearing adaptor proteins (CD3ζ, DAP12); YxxM-bearing adaptor protein DAP10; PTK, protein tyrosine kinases; PI3K, phosho-inositol-3 kinase; SHP and SHIP, phosphatases. Positive signalling (+) by the activating receptors is counteracted by the negative signalling (–) by the inhibitory receptors.

Due to unknown ligands for most of the activating receptors, including all NCRs and some KIR2/3DS receptors, the knowledge of ligand-dependent NK cell activation is largely derived from studies on NKG2D ligands. In humans, these ligands are expressed on B- and myeloid-progenitor cells (26). MIC proteins are upregulated by various forms of cellular stress, by viral infection and on tumour cells of epithelial origin [21, 27, 28]. An important characteristic of MICs is that they can be shed by some tumour cells and become detectable in the serum [29, 30]. This may lead to a permanent downregulation of NKG2D receptor, together with its functional blockade. This strategy represents a new escape tool used by tumours otherwise killed upon NKG2D recognition. The expression pattern of ULBP and MIC proteins often differs in tumours of various tissue origin, suggesting functional differences between these ligands [31, 32]. Therefore, a wide ligand reactivity of NKG2D may represent a strategy of how NK cells prevent possible escape mutants which have downregulated only one ligand.

NK cells and the recognition of human leukaemia

Acute leukaemias are rapidly progressing blood cell malignancies with a poor prognosis. High-dose chemotherapy and transplantation of allogeneic stem cells offer the best chance of cure, but relapses are frequent and often fatal [33]. High incidence of disease recurrence suggests that leukaemic blasts can escape recognition by the immune system. The mechanism of immune evasion from the NK surveillance may be related to an inadequate function of NK cells, caused by abnormalities either at the level of receptors or cognate ligands. Recent studies began to unravel the reactivity of NK cells in primary human leukaemias. In acute myeloid leukaemia (AML), NK cell number is profoundly reduced [34] and expression of some of the activatory NCR receptors may be downregulated resulting in low NK cell cytotoxicity against autologous leukaemic cells [35]. In chronic myeloid leukaemia (CML), NK cells are reduced in numbers and their cytokine-induced cytotoxicity is inhibited by CML blasts [36]. Unlike in many solid tumours, expression of HLA class I molecules is usually not strongly downregulated, resulting in tolerance of NK cells towards the autologous blasts. Furthermore, ligands triggering the NKG2D receptor and the putative molecules recognised by NCRs are expressed at low levels, thus contributing to poor recognition of malignant cells [26, 37]. We have recently demonstrated that inadequate ligand expression is a consequence of haematopoietic maturation arrest associated with malignant transformation [26]. This is in contrast to findings with tumours of epithelial origin, in which the stress-inducible MIC ligands are upregulated, marking the tumour tissue for destruction by NK cells [27]. In conclusion, although still fragmented, these results suggest that NK cells are important for tumour surveillance in leukaemia, providing the rationale for studies on their therapeutic value [38].

The therapeutic potential of NK cells in human leukaemia

The cure of leukaemia and other malignant blood diseases by transplantation of haematopoietic stem cells (SCT) is achieved by two mechanisms: the cytoreductive chemoradiotherapy which reduces the bulk of leukaemic blasts, and the graft-versus-leukaemia (GvL) effect exerted by donor-derived immune effector cells which eradicate residual malignant clones. Despite 3 decades of continued progress in the transplantation field, the relapse rate approaches 30% following allogeneic SCT and as much as 50% after SCT of autologous cells. In patients who are not eligible for SCT and undergo a conventional high-dose chemotherapy only, the recurrence rate of the disease is even more dramatic [39]. These clinical results underscore, on the one hand, the need for better understanding of tumour clearance mechanisms, and on the other hand, the search for new therapeutic approaches to enhance the GvL effect and improve the cure rates. Recent findings on NK receptor – ligand specificities, have reawakened an interest in the possibility of applying the NK cell-based strategies to treat leukaemia.

Anti-leukaemic effect of alloreactive NK cells

Clinical results, initiated by Ruggeri et al. [40], suggest that NK cells may represent a unique therapeutic tool for clearance of leukaemia, in particular in conjunction with allogeneic SCT. In AML patients grafted with stem cells from haploidentical donors, the mismatch between KIRs on NK cells of the graft and HLA class I specificities of the recipient has facilitated NK cell-mediated killing of tumour cells, thus resulting in higher remission rates. This benefit of KIR receptor-ligand alloreactivity to promote engraftment and GvL effects without causing clinically overt graft-versus-host disease (GvHD) is increasingly recognised also in other SCT settings. The survival advantage associated with KIR ligand incompatibility has been reported in numerous haematological malignancies and with grafts derived from unrelated donors [41] as well HLA-matched siblings [42, 43]. Anti-leukaemic effects of KIR/HLA class I mismatches are also suggested by the experimental finding that blocking of murine inhibitory receptors Ly-49C with specific antibody increases NK cell-mediated killing of leukaemic cells *in vitro* and in tumour-bearing mice [44]. In addition to the anti-leukaemic NK cytotoxicity exerted through KIR-HLA disparity, NKG2D receptor-ligand interactions were shown to play a role in the cytolytic effect of HLA-matched NK cells againstst CML blasts [45]. A clinical impact of leukaemia recognition by NK activating receptors awaits further evaluation.

NK cell adoptive immunotherapy in treatment of leukaemia

The field of tumour immunotherapy is dominated by T cell-based approaches while clinical trials to utilise the anti-tumour effect of NK cells had little success in the past. This may rapidly change with a significant progress in identification of NK cell receptors and some of their ligands involved in selective recognition and lysis of tumour cells. The cellular immunotherapy by infusion of immune competent cells in the clinical SCT setting is expected to amplify the GvL effect exerted by the transplanted immune system. The clinical feasibility and efficacy of adoptive transfer of donor-derived T lymphocytes has been documented in CML; consequently, donor lymphocyte infusion (DLI) after SCT has become an established therapy in haematological malignancies [46, 47]. Adoptive transfer of activated NK cells in an allogeneic murine transplant model has shown the participation of these cells in GvL without inducing clinically overt GvHD [48]. Pilot clinical studies of an adoptive transfer of donor-derived NK cells to consolidate engraftment in AML patients transplanted from haploidentical donors have recently been reported [49, 50]. NK cell infusions were well tolerated, none of the patients developed GvHD, and importantly, donor-type chimerism was increased in some recipients. These studies, although involving a limited number of patients, documented the feasibility of NK cell DLI, opening the way for future graft engineering to exploit the clinical benefit of anti-leukaemic NK cells.

Future perspectives

Alloreactive NK cells may become an integral part of treating leukaemia with SCT from unrelated and from family donors. Based on in vitro and preclinical studies, NK cells are capable of promoting engraftment, protecting against GvHD, and exerting GvL effects [40, 51]. Therefore, including NK cells into a conditioning regimen and infusing them after SCT may prevent the progress of leukaemia, facilitate stem cell engraftment, and perhaps even serve to treat GvHD and relapse [52–54]. Many open issues include not only appropriate selection of donors and recipients, but also NK cell dose, timing of infusions and possible ex-vivo manipulations of NK cells prior to DLI. Expansion of clinical grade NK cells has been reported [55] and the use of ex-vivo cytokine-activated NK cells awaits clinical evaluation.

Also the antileukaemic potential of autologous NK cells deserves a therapeutic consideration. A number of studies documented a susceptibility of leukaemic blasts to autologous cytotoxicity by NK cells [56, 57]. According to our recent studies [33], AML-derived NK cells can be substantially expanded and activated in vitro, and are fully functional against autologous AML blasts by effectively reducing the tumour load when infused to AML-bearing NOD/SCID mice (figure 3). Adoptive transfer of autologous NK cells may represent a novel immunotherapeutic strategy in the managment of leukaemia in patients not eligible for SCT, due to age or lack of a suitable donor. Clinical translation of a continuing progress in understanding the mechanisms involved in NK cell-mediated immunity will define the importance of NK cells as specialised cellular tools for enhancing the antileukaemic immune response.

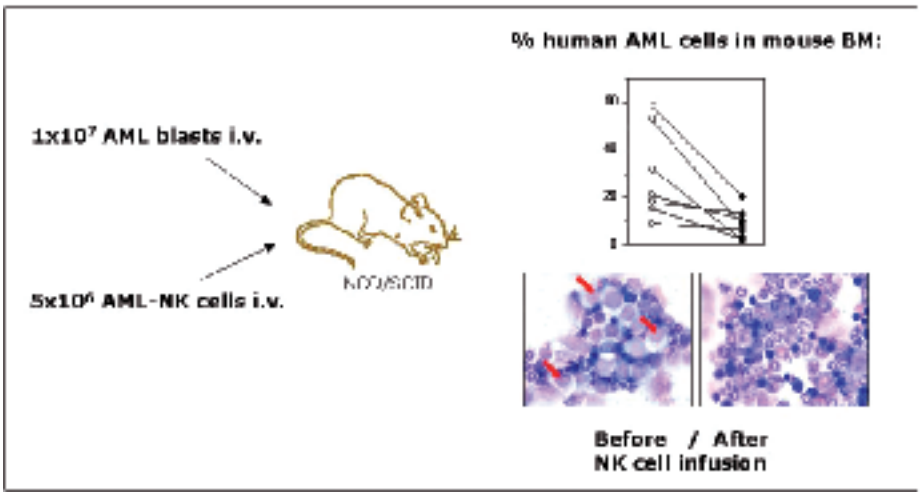

Figure 3

NK cell immunotherapy in NOD/SCID mice: Adoptive transfer of activated AML-NK cells eradicates human AML blasts in vivo. NOD/SCID mice were transplanted with human AML blasts and subsequently infused with AML-derived NK cells. The blasts content in the bone marrow (open circles) was dramatically reduced at 1 week after adoptive transfer of NK cells (closed circles), and AML blasts in the bone marrow (arrows) were not visible after NK cell infusions [33].

References

1 Trinchieri G. The choices of a natural killer. Nat Immunol 2003;4:509–10.
2 Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol 2001;22:633–40.
3 Raulet DH. Interplay of natural killer cells and their receptors with the adaptive immune response. Nat Immunol 2004;5:996–1002.
4 Lanier LL. NK Cell Recognition. Annu Rev Immunol 2005;23: 225–74.
5 Vivier E, Nunes JA, Vely F. Natural killer cell signaling pathways. Science, 2004;306:1517–9.
6 Waller EK. Cellular immunotherapy and cancer. Semin Oncol 2004;31:87–90.
7 Smyth MJ, Hayakawa Y, Takeda K, Yagita H. New aspects of natural-killer-cell surveillance and therapy of cancer. Nat Rev Cancer 2002;2:850–61.
8 Lanier LL. Natural killer cell receptor signaling. Curr Opin Immunol 2003;15:308–14.
9 Bottino C, Moretta L, Pende D, Vitale M, Moretta A. Learning how to discriminate between friends and enemies, a lesson from Natural Killer cells. Mol Immunol 2004;41:569–75.
10 Long EO. Regulation of immune responses through inhibitory receptors. Annu Rev Immunol 1999;17:875–904.
11 Bolland S. Ravetch JV. Inhibitory pathways triggered by ITIM-containing receptors. Adv Immunol 1999;72:149–77.
12 Galandrini R, Tassi I, Mattia G, Lenti L, Piccoli M, Frati L, et al. SH2-containing inositol phosphatase (SHIP-1) transiently translocates to raft domains and modulates CD16-mediated cytotoxicity in human NK cells. Blood 2002;100:4581–9.
13 Wang JW, Howson JM, Ghansah T, Desponts C, Ninos JM, May SL, et al. Influence of SHIP on the NK repertoire and allogeneic bone marrow transplantation. Science 2002;295:2094–7.
14 Trotta R, Parihar R, Yu J, Becknell B, Allard Ii J, Wen J, et al. Differential expression of SHIP1 in CD56bright and CD56dim NK cells provides a molecular basis for distinct functional responses to monokine co-stimulation. Blood 2005;105:3011–8.
15 Colucci F, Di Santo JP, Leibson PJ. Natural killer cell activation in mice and men: different triggers for similar weapons? Nat Immunol 2002;3:807–13.
16 Moretta A, Bottino C, Vitale M, Pende D, Cantoni C, Mingari MC, et al. Activating receptors and coreceptors involved in human natural killer cell-mediated cytolysis. Annu Rev Immunol 2001;19:197–223.
17 Sivori S, Pende D, Bottino C, Marcenaro E, Pessino A, Biassoni R, et al. NKp46 is the major triggering receptor involved in the natural cytotoxicity of fresh or cultured human NK cells. Correlation between surface density of NKp46 and natural cytotoxicity against autologous, allogeneic or xenogeneic target cells. Eur J Immunol 1999;29:1656–66.

18 Mandelboim O, Lieberman N, Lev M, Paul L, Arnon TI, Bushkin Y, et al Recognition of haemagglutinins on virus-infected cells by NKp46 activates lysis by human NK cells. Nature 2001;409:1055–60.
19 Arnon TI, Lev M, Katz G, Chernobrov Y, Porgador A, Mandelboim O. Recognition of viral hemagglutinins by NKp44 but not by NKp30. Eur J Immunol 2001;31:2680–9.
20 Raulet DH. Roles of the NKG2D immunoreceptor and its ligands. Nat Rev Immunol 2003;3:781–90.
21 Bauer S, Groh V, Wu J, Steinle A, Phillips JH, Lanier LL, Spies T. Activation of NK cells and T cells by NKG2D, a receptor for stress-inducible MICA. Science 1999;285:727–9.
22 Cosman D, Mullberg J, Sutherland CL, Chin W, Armitage R, Fanslow W, et al. ULBPs, novel MHC class I-related molecules, bind to CMV glycoprotein UL16 and stimulate NK cytotoxicity through the NKG2D receptor. Immunity 2001;14:123–33.
23 Sutherland CL, Chalupny NJ, Schooley K, VandenBos T, Kubin M, Cosman D. UL16-binding proteins, novel MHC class I-related proteins, bind to NKG2D and activate multiple signaling pathways in primary NK cells. J Immunol 2002;168: 671–9.
24 Billadeau DD, Upshaw JL, Schoon RA, Dick CJ, Leibson PJ. NKG2D-DAP10 triggers human NK cell-mediated killing via a Syk-independent regulatory pathway. Nat Immunol 2003;4: 557–64.
25 Zompi S, Hamerman JA, Ogasawara K, Schweighoffer E, Tybulewicz VL, Di Santo JP, et al. NKG2D triggers cytotoxicity in mouse NK cells lacking DAP12 or Syk family kinases. Nat Immunol 2003;4:565–72.
26 Nowbakht P, Ionescu M-C S, Rohner A, Kalberer CP, Rossy E, Mori L, et al. Ligands for natural killer cell-activating receptors are expressed upon the maturation of normal myelomonocytic cells but at low levels in acute myeloid leukemias. Blood 2005;105:3615–22.
27 Groh V, Bahram, S, Bauer S, Herman A, Beauchamp M, Spies T. Cell stress-regulated human major histocompatibility complex class I gene expressed in gastrointestinal epithelium. Proc Natl Acad Sci U S A 1996;93:12445–50.
28 Groh V, Rhinehart R, Secrist H, Bauer S, Grabstein KH, Spies T. Broad tumor-associated expression and recognition by tumor-derived gamma delta T cells of MICA and MICB. Proc Natl Acad Sci U S A 1999;96:6879–84.
29 Groh V, Wu J, Yee C, Spies T. Tumour-derived soluble MIC ligands impair expression of NKG2D and T-cell activation. Nature 2002;419:734–8.
30 Salih HR, Rammensee HG, Steinle A. Cutting edge: down-regulation of MICA on human tumors by proteolytic shedding. J Immunol 2002;169:4098–102.
31 Salih HR, Antropius H, Gieseke F, Lutz SZ, Kanz L, Rammensee HG, Steinle A. Functional expression and release of ligands for the activating immunoreceptor NKG2D in leukemia. Blood 2003;102:1389–96.
32 Pende D, Rivera P, Marcenaro S, Chang CC, Biassoni R, Conte R, et al. Major histocompatibility complex class I-related chain A and UL16-binding protein expression on tumor cell lines of different histotypes: analysis of tumor susceptibility to NKG2D-dependent natural killer cell cytotoxicity. Cancer Res 2002;62:6178–86.
33 Brenner MK, Pinkel D. Cure of leukemia. Semin Hematol 1999;36:73–83.
34 Siegler U, Kalberer CP, Nowbakht P, Sendelov S, Meyer-Monard S, Wodnar-Filipowicz A. Activated natural killer cells from patients with acute myeloid leukemia ary cytotoxic against autologous leukemic blasts in NOD/SCID mice. Leukemia 2005;19:2215–22.
35 Costello RT, Sivori S, Marcenaro E, Lafage-Pochitaloff M, Mozziconacci MJ, Reviron D, et al. Defective expression and function of natural killer cell-triggering receptors in patients with acute myeloid leukemia. Blood 2002;99:3661–7.
36 Mellqvist UH, Hansson M, Brune M, Dahlgren C, Hermodsson S, Hellstrand K. Natural killer cell dysfunction and apoptosis induced by chronic myelogenous leukemia cells: role of reactive oxygen species and regulation by histamine. Blood 2000;96:1961–8.
37 Pende D, Spaggiari GM, Marcenaro S, Martini S, Rivera P, Capobianco A, et al. Analysis of the receptor-ligand interactions in the natural killer-mediated lysis of freshly isolated myeloid or lymphoblastic leukemias: evidence for the involvement of the Poliovirus receptor (CD155) and Nectin-2 (CD112). Blood 2005;105:2066–73.
38 Caligiuri MA, Velardi A, Scheinberg DA, Borrello IM. Immunotherapeutic approaches for hematologic malignancies. Hematology (Am Soc Hematol Educ Program) 2004;337–53.
39 Burnett AK. Current controversies: which patients with acute myeloid leukaemia should receive a bone marrow transplantation? – an adult treater's view. Br J Haematol 2002;118:357–64.
40 Ruggeri L, Capanni M, Urbani E, Perruccio K, Shlomchik WD, Tosti A, et al. Effectiveness of donor natural killer cell alloreactivity in mismatched hematopoietic transplants. Science 2002;295:2097–100.
41 Giebel S, Locatelli F, Lamparelli T, Velardi A, Davies S, Frumento G, et al. Survival advantage with KIR ligand incompatibility in hematopoietic stem cell transplantation from unrelated donors. Blood 2003;102:814–9.
42 Cook MA, Milligan DW, Fegan CD, Darbyshire PJ, Mahendra P, Craddock CF, et al. The impact of donor KIR and patient HLA-C genotypes on outcome following HLA-identical sibling hematopoietic stem cell transplantation for myeloid leukemia. Blood, 2004;103:1521–6.
43 Hsu KC, Keever-Taylor CA, Wilton A, Pinto C, Heller G, Arkun K, et al. Improved outcome in HLA-identical sibling hematopoietic stem-cell transplantation for acute myelogenous leukemia predicted by KIR and HLA genotypes. Blood 2005;105:4878–84.
44 Koh CY, Blazar BR, George T, Welniak LA, Capitini CM, Raziuddin A, et al. Augmentation of antitumor effects by NK cell inhibitory receptor blockade in vitro and in vivo. Blood 2001;97: 3132–7.
45 Sconocchia G, Lau M, Provenzano M, Rezvani K, Wongsena W, Fujiwara H, et al. The antileukemia effect of HLA-matched NK and NK-T cells in chronic myelogenous leukemia involves NKG2D-target-cell interactions. Blood 2005;106:3666–72.
46 Collins RH Jr, Shpilberg O, Drobyski WR, Porter DL, Giralt S, Champlin R, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. J Clin Oncol 1997;15:433–44.
47 Kolb HJ, Schmid C, Barrett AJ, Schendel DJ. Graft-versus-leukemia reactions in allogeneic chimeras. Blood 2004;103:767–76.
48 Asai O, Longo DL, Tian ZG, Hornung RL, Taub DD, Ruscetti FW, et al. Suppression of graft-versus-host disease and amplification of graft-versus-tumor effects by activated natural killer cells after allogeneic bone marrow transplantation. J Clin Invest 1998;101:1835–42.
49 Passweg JR, Tichelli A, Meyer-Monard S, Heim D, Stern M, Kuhne T, et al. Purified donor NK-lymphocyte infusion to consolidate engraftment after haploidentical stem cell transplantation. Leukemia 2004;18:1835–8.
50 Miller JS, Soignier Y, Panoskaltsis-Mortari A, McNearney SA, Yun GH, Fautsch SK, et al. Successful adoptive transfer and in vivo expansion of human haploidentical NK cells in patients with cancer. Blood 2005;105:3051–7.
51 Ruggeri L, Mancusi A, Capanni M, Martelli MF, Velardi A. Exploitation of alloreactive NK cells in adoptive immunotherapy of cancer. Curr Opin Immunol 2005;17:211–7.
52 Ruggeri L, Capanni M, Mancusi A, Martelli MF, Velardi A. The impact of donor natural killer cell alloreactivity on allogeneic hematopoietic transplantation. Transpl Immunol 2005;14:203–6.
53 Moretta L, Bottino C, Pende D, Vitale M, Mingari MC, Moretta A. Human natural killer cells: Molecular mechanisms controlling NK cell activation and tumor cell lysis. Immunol Lett 2005;100:7–13.
54 Passweg JR, Stern M, Koehl U, Uharek L, Tichelli A. Use of natural killer cells in hematopoetic stem cell transplantation. Bone Marrow Transplant 2005;35:637–43.
55 Koehl U, Sorensen J, Esser R, Zimmermann S, Gruttner HP, Tonn T, et al. IL-2 activated NK cell immunotherapy of three children after haploidentical stem cell transplantation. Blood Cells Mol Dis 2004;33:261–6.
56 Cervantes F, Pierson BA, McGlave PB, Verfaillie CM, Miller JS. Autologous activated natural killer cells suppress primitive chronic myelogenous leukemia progenitors in long-term culture. Blood 1996;87:2476–85.
57 Torelli GF, Guarini A, Palmieri G, Breccia M, Vitale A, Santoni A, Foa R. Expansion of cytotoxic effectors with lytic activity against autologous blasts from acute myeloid leukaemia patients in complete haematological remission. Br J Haematol 2002;116: 299–307.

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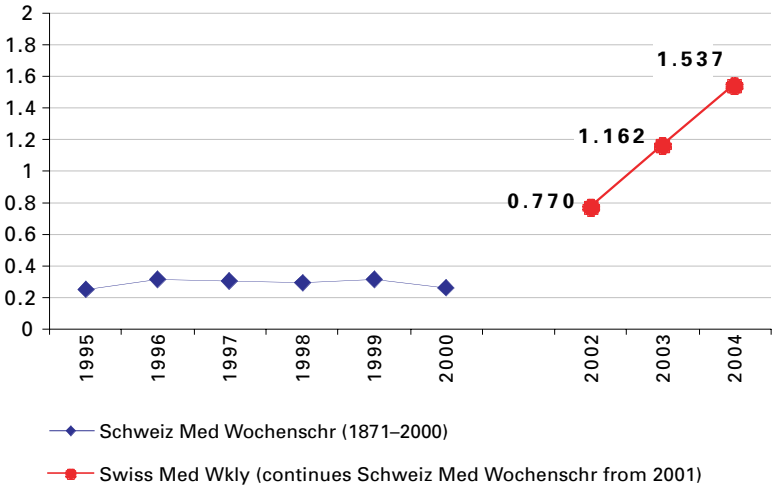

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