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REVIEW

The human NK cell—a short over-view and an hypothesis on NK recognition

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INTRODUCTION

Natural killer (NK) cells have been, and continue to be, a favourite object of study for both basic and clinical immunologists. NK cells were discovered in the mid-1970s, after thymus-dependent and antibody-dependent killer cells (T and K cells respectively), by their capacity to kill directly tumour cell lines, infected host cells and some normal cell types (Takasugi, Mickey & Terasaki, 1973; Jondal & Pross, 1975; Kiessling, Klein & Wigzell, 1975). Based on this characteristic, NK cells were recognized as potentially important in protection against tumour cells and infections, and in immunoregulation. Experimental data seemed to support this notion (Herberman, 1982; Möller, 1979; Welsh, 1981) and a large number of studies have been reported on NK killing (Table 1). This short over-view addresses the question whether NK cells are still to be considered biologically relevant, and if so, how variations in NK killing in different diseases are to be evaluated. A hypothesis for NK cell recognition is also presented as the elusive 'NK cell receptors' have not been defined. Several comprehensive NK cell reviews have been published (Möller, 1979; Trinchieri & Perussia, 1984; Herberman, 1983; Hansson & Kiessling, 1983; Grossman & Herberman, 1986) and the 1984 article by Trinchieri & Perussia, including 415 references, is especially recommended (Trinchieri & Perussia, 1984).

DEFINITION OF THE NK FUNCTION

The concept of natural killing evolved from studies on specific cytotoxicity in cancer patients and in different infections. We studied specific killing of Epstein–Barr virus (EBV) infected cells using peripheral lymphocytes from patients with acute infectious mononucleosis (Svedmyr & Jondal, 1975). It was found, as in other studies (Takasugi, Mickey & Terasaki, 1973; Trinchieri & Perussia, 1984), that a non-T cell population was strongly cytotoxic to non-infected target cells. However, if these cells were removed, specific T cell killing against relevant targets was detected (Svedmyr & Jondal, 1975). The non-specific killers were given the designation spontaneous or natural killer (NK) cells in analogy with natural antibodies and with similar cells defined in the mouse (Herberman, 1982).

Natural killing is usually defined as cell-mediated lysis of some standard leukaemic target cell lines by normal, non-immune lymphocytes from blood or other lymphoid tissues. In our original papers we introduced the erythroleukaemic cell line K-562, established by Lozzio and Lozzio (Jondal & Pross, 1975; Pross & Jondal, 1975; Lozzio & Lozzio, 1973). This line is still used as a 'universal' NK target cell (Herberman, 1982; Trinchieri & Perussia, 1984). Other commonly used target cells include leukaemic T cells such as Molt-4. Lymphoblastoid B cell lines, transformed by

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Table 1. Med-Line recordings under searchwords 'natural' and 'killer' from 1971 to March 1987

File	Number of years	References NK	References Total
Med 71	4	0	882 903
Med 75	2	11	642 612
Med 77	2	203	775 043
Med 80	2	864	804 744
Med 83	2	1277	584 303
Med 85	1·5	1566	571 705

Table 2. Shared characteristics between T and NK cells

Characteristic	References
Partial or complete expression of phenotypic surface markers such as CD2-7-8-11a-16-18-25-38 and Leu-7-19	Trinchieri & Perussia (1984); Grossman & Herberman (1986); Krensky *et al.* (1983); Lanier *et al.* (1986); Lanier *et al.* (1985); Allavena *et al.* (1985)
Capacity to express IL-2 receptors (CD25) and responsiveness to IL-2	Grossman & Herberman (1986); Domzig, Stadler & Herberman (1983); Ortaldo *et al.* (1984)
A functionally similar lytic machinery and C9-like molecules in azurophilic granulae	Trinchieri & Perussia (1984); Blumenthal *et al.* (1984); Young *et al.* (1986)
May express a similar LGL morphology	Biron, Natuk & Welsh (1986)
Some T cell leukaemias have an NK-like activity	Bom-van Noorloos *et al.* (1980); Pandolfi *et al.* (1983)
Induction of NK-like killing in specific T cell lines by hyperactivation	Siliciano *et al.* (1985)
Production of similar lymphokines	Ortaldo & Herberman (1981); Alllavena *et al.* (1985)

EBV, are resistant to normal NK cells and can be used as negative controls. However, some normal cell types are killed by NK cells including stem cells in bone-marrow and thymus (Hansson & Kiessling, 1983). The characterization of NK cells has been problematical as they cannot be clearly assigned to any defined lineage within the haematopoietic cell system. However, as recently summarized by Grossman & Herberman (1986) there are many similarities between T cells and NK cells (Table 2).

A complicating fact is that activated T lymphocytes also can mediate NK-like or atypical non-MHC restricted killing (Siliciano *et al.*, 1985; Lanier & Phillips, 1986). Classical NK cells (in normal peripheral blood) are distinct from mature T cells as they do not express functionally rearranged T cell receptor genes (Lanier *et al.*, 1986a,b). For that reason, it may be more relevant to consider natural killing as a defined function which may be present in different lymphoid subpopulations depending on the immunoregulatory microenvironment. The concept that natural killing is not a characteristic of a defined cell type only, but can be expressed in different cells, will be further expanded below in discussing NK cell recognition.

QUANTIFICATION OF NK KILLING

Different stages can be distinguished in killing such as target cell binding, activation of the lytic machinery and effector cell recycling (Berke, 1983). These stages can be selectively evaluated by

combining different techniques (Ullberg, 1983). However, NK killing is most commonly tested in short-term (3 to 4 h) radioisotope release assays in microplates. A constant number of labelled target cells (e.g. 10^4) is mixed with different numbers of effector cells and killing is calculated by amount of radioisotope released into the supernatant (Ullberg & Jondal, 1981). This test is easy to perform but only gives an estimate of bulk NK killing. Results can be given either as a percentage of specific release or as the number of effector cells required to kill a given number of target cells (lytic units, LU).

To optimize the sensitivity, and give every NK cell the possibility to express its full lytic potential, the system may instead be saturated with target cells to measure a cytotoxic V_{max} (Ullberg, 1983; Ullberg & Jondal, 1981). If V_{max} measurements are combined with single cell assays, in agarose or by flow-cytometry, the number of NK cells with target cell receptors and their mean recycling capacity may be determined (Ullberg & Jondal, 1981; Grimm, Thomas & Bonavida, 1979). This test system has been used experimentally to demonstrate an increase of effector cell recycling after interferon treatment and a decrease of target cell binding after prostaglandin treatment (Ullberg, Merrill & Jondal, 1981; Ullberg *et al.*, 1983). Katz *et al.* (1982) have demonstrated an intrinsic defect in the lytic event in systemic lupus erythematosus and Golub *et al.* a select recycling defect among lymphocytes infiltrating human pulmonary tumours (Moy, Holmes & Golub, 1985).

MECHANISM AND IMMUNOREGULATION OF NK KILLING

NK cells, and other cytotoxic lymphocytes, have azurophilic granules with characteristics of primary lysosomes (Trinchieri & Perussia, 1984). In NK cells, these contain enzymes and cytolysin molecules which, upon receptor-induced degranulation, polymerize in the presence of external Ca^{2+} to form complement-like holes in the target cell membrane (Blumenthal *et al*, 1984; Young *et al.*, 1986). These holes may then create an osmotic imbalance and/or allow the passage of toxic factors into the target cells which degrade DNA and induce cell death. Alternatively, lytic molecules like 'natural killer cell factor' (NKCF), or lymphotoxin (TNF beta) may be deposited on the target cell membrane and induce death by damage to the cytoplasmatic cell membrane (Berke, 1983; Koren, 1986). Which mechanism is most important in NK cells, or whether alternative ways of target killing may be used, is not entirely clear at present. The lytic mechanism shares many characteristics with the stimulus-degranulation model as defined with secretory mast cells and depends on different cellular events (Table 3).

All hormones, lymphokines, antibodies and other factors which influence these cellular processes are thus potential up or down-regulators of NK cell activity (Table 4). The major NK enhancers are interferons and IL-2 and important suppressor effects are mediated by certain arachidonic acid metabolites, anti-lymphocyte antibodies and immune complexes (Trinchieri & Perussia, 1984; Jondal *et al.*, 1985; Ramstedt *et al.*, 1987). Thus, as NK cells are recirculating and

Table 3. Cellular events associated with NK killing

Events
Activation of membrane-associated serine proteases
Increased receptor mobility by trans-methylation
Functional cAMP/cGMP levels
Generation of lipoxygenation products from arachidonic acid
Phosphatidylinositol response: activation of PkC and release of intra-cellular Ca^{2+}
Influx of eternal Ca^{2+}
Activation of cytoskeleton, transport of granulae to cell membrane
Degranulation of cytolysins and other toxic molecules (like NKCF and TNF beta)
Cellular mobility for effector cell recycling

Table 4. Influence of some factors on NK killing

Factor	NK effect
Interferons	+
IL-2	+
β-endorphins	+
Some cyclo and lipoxygenase products from arachidonic acid	+/−
Some viral and bacterial products	+/−
IgG immune complexes	+/−
Anti-lymphocyte antibodies	−
VIP neuropeptide	−
Corticosteroids	−

continuously activated, and as they express receptors for many regulatory molecules, NK killing often reflects the general immune status of an individual. For that reason NK killing is a useful parameter in immune monitoring.

NK FUNCTION IN HEALTH AND DISEASE

All normal individuals have active NK cells with highest activity in blood and spleen (Trinchieri & Perussia, 1984). There are variations in NK activity with low and high responders and some linkage to certain MHC haplotypes, sex, age, smoking, exercise and other general factors (Herberman, 1982; Trinchieri & Perussia, 1984). The mean percentage of active NK cells in normal blood has been estimated to be around 2–5% (Ullberg & Jondal, 1981). In certain rare diseases selective NK cell deficiencies have been described (Trinchieri & Perussia, 1984). In the Chediak-Higashi syndrome NK cells are hyporesponsive due to defective lysosomal degranulation (Katz, Zaytoun & Fauci, 1982), and in some cases of severe combined immunodeficiency (SCID) there is a lack of lymphoid stem cells as reflected by the absence of both T and NK cell functions (Neudorf, Kersey & Filipovich, 1985; Peter *et al.*, 1983). In advanced solid malignancies there is often depressed NK killing in blood (Kadish *et al.*, 1981; Pross & Baines, 1976; Takasugi, Ramseyer & Takasugi, 1977) In leukaemias there is also often NK suppression which can not only be explained by dilution with malignant cells (Trinchieri & Perussia, 1984). Some cases of chronic T cell lymphocytosis, characterized by neutropenia and recurrent infections, have the typical NK cell morphology and have also retained some NK cell functions. These may reflect the effect of an expanded, hyperactive NK-like cell population on myeloid stem cells and, in some cases, on normal B cells (Bom-van Noorloos *et al.*, 1980; Pandolfi *et al.*, 1983). After transplantation of T cell depleted bone-marrow activated NK cells appear before the generation of functional T cells. NK cells are believed to be involved in graft rejection and GVH disease although activated NK cells have been reported in patients without any obvious symptoms (Ueda *et al.*, 1984; Rooney *et al.*, 1986). Apart from the conditions mentioned above, altered NK cell activity has been reported in a multitude of different clinical conditions including infectious, endocrinological, neurological and other diseases. The biological significance of aberrent NK activity is often unclear in terms of cause-effect relationships. Also, killing has most commonly only been measured by standard radioisotope release assay.

A HYPOTHESIS OF NK CELL RECOGNITION

Much has been learnt about different aspects of NK cells such as morphology, phenotype, mode of function and specificity but the important question of target cell recognition has not been resolved (Lanier & Phillips, 1986). T cells utilize combinations of glycoprotein receptors for antigen recognition which are formed by genetic rearrangements in similarity to immunoglobulin molecules

(Robertson, 1985). T cell receptors interact functionally in the cell membrane with the CD3 complex to generate transduction signals for cellular activation (Imboden & Stobo, 1985; Oettgen *et al.*, 1985). Reinherz and coworkers have demonstrated an alternative activation pathway for T cell through the CD2 receptor (sheep RBC receptor) and postulated that T cells use this pathway in the thymic gland before they mature to express specific receptors and CD3 (Reinherz, 1985). This is supported by the facts that CD2 is a phylogenetically old receptor and that certain combinations of anti-CD2 monoclonal antibodies stimulate T cells to proliferate (Letvin *et al.*, 1983; Bernard *et al.*, 1986; Meuer, Hutteroth & Meyer zum Buschenfelde, 1986). Recently Springer *et al.* have defined the CD2 binding ligand as LFA3, a 60 kD glycoprotein expressed in the thymic gland and on different haematopoietic cells (Vollger *et al.*, 1987; Plunkett *et al.*, 1987; Dustin *et al.*, 1987; Selvaraj *et al.*, 1987).

NK cells express a cell surface receptor for the Fc portion of IgG (CD16). By virtue of this receptor, NK cells may attach to target cell-associated IgG antibodies and mediate an antibody-dependent cellular cytotoxicity (ADCC) reaction. However, many receptor structures in the cell membrane have a resemblance to Ig and have been described as belonging to the 'Ig supergene family' (Hood, Kronenberg & Hunkapiller, 1985). This may indicate that an Fc receptor structure such as CD16 evolved primarily to interact with Ig-like membrane molecules possibly in the same way CD3 interacts with T cell receptors. Fc receptors, like CD3, have been shown to mediate transduction signals for NK cell activation (Jondal *et al.*, 1986).

The fact that NK cells express CD2, CD16 and adherence type receptors such as CD11a/CD18 (Tranchieri & Perussia, 1984; Krensky *et al.*, 1983) could form the basis for a hypothesis on NK cell recognition without the need to further define specific 'NK cell receptors'. It can be argued that NK cells express CD2 receptors in such steric configurations that they both bind and activate cells in combination with supporting receptors such as CD16, CD11a/CD18 and possibly others. This postulated dual binding and triggering function of CD2 receptors on NK cells is based on the demonstration of different functional epitopes within the CD2 receptor molecule (Bernard *et al.*, 1986; Meuer *et al.*, 1986). We would thus suggest that CD2 receptors are part of the NK cell receptor complex and that they have this function when expressed on cells at a certain level of activation. In other cells, the same CD2 receptors may trigger other functions depending on the maturity and phenotype of the particular subpopulation. In Table 5 we have listed some points in support of CD2 receptors in NK killing. This hypothesis requires experimental verification. Alternatively, specific NK cell receptors may exist and CD2 may only play a secondary, supporting role.

Table 5. CD2 receptors in NK killing

Argument	References
CD2 is expressed on both T and NK cells which are functionally close. CD2 is phylogenetically old, in support of a primitive surveillance function for NK cells	Trinchieri & Perussia (1984); Grossman & Herberman (1986); Krensky *et al.* (1983); Lanier *et al.* (1986); Lanier, Kipps & Phillips (1985); Allavena *et al.* (1985); Letvin *et al.* (1983)
CD2 express different epitopes which may have both binding and triggering functions during multi-point attachment to target cells. Alternatively, being part of the Ig supergene family, CD2 may interact with CD16 during triggering	Letvin *et al.* (1983); Bernard *et al.* (1986); Meuer *et al.* (1986)
Some anti-CD2 antibodies have an agonistic effect on NK-killing	Allavena *et al.* (1985); Uggla *et al.* (1987); Bolhuis, Roozemond & van de Griend (1986)
The CD2 ligand, LFA3, is widely expressed on different cells, in line with the broad specificity of NK cells	Krensky *et al.* (1983)
In SCID patients there may be a correlation between expression of CD2 and presence of NK function	Peter *et al.* (1983)

CONCLUSIONS

NK cells have been the subject of many studies during the last 10 years. Are they that important? Are clinical studies on NK killing in different conditions relevant? In the opinion of the author, the answer to both these questions is clearly yes, as long as clinical results are given a reasonable interpretation. Experimental data strongly support the notion that NK cells represent an early, primitive, non-adaptive surveillance population. The important biological function of these cells is to act as a control system for proliferating lymphocytes, haematopoietic stem cells, arising tumour cells and infected host cells. An unresolved issue is: by which receptor system do NK cells recognize and kill different target cells. We suggest that NK recognition may be explained in the context of known receptors such as CD2, CD16 and CD11a/CD18 and that CD2 receptors may be especially important. In support of this concept are the many similarities between T cells and NK cells and the proposed triggering function of CD2 receptors early in T cell differentiation. CD2 receptors are also phylogenetically old, in line with the postulated, primitive surveillance function of the NK system.

In clinical studies, NK cells may be directly involved in pathological events in a limited number of diseases but may serve as a useful parameter for immune monitoring in many other conditions due to their sensitivity to regulation by many different factors. NK measurements which discriminate between different phases such as target cell binding, lytic activation and effector cell recycling may reflect underlying pathological mechanisms. However, bulk measurements of NK killing in a small number of patients combined with unfounded aetiological speculations are clearly not acceptable in serious medical journals.

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