Functional Surface Structures on Human Natural Killer Cells*  **

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Summary. This manuscript reviews recent studies on the characterization of functional surface antigens on human NK cells. A series of cloned NK cell lines has been utilized for examination of these structures. These clones provide a relatively large number of cells with a stable phenotype and consistent specific cytotoxicity, which reflect the diversity of uncultured NK cells in normal peripheral blood. Almost all clones express the T11 antigen, some have a mature T-cell phenotype (T3+, T11+), and only one (JT1) does not reveal any T-cell antigen at all (T3-, T11+). Using NK clones to generate monoclonal antibodies specific for NK-associated antigens, two structures have been identified, NKH1 and NKH2. NKH1 appears to be exclusively expressed on large granular lymphocytes (LGL) of peripheral blood and was found to be a pan-NK cell antigen. NKH2 is also expressed primarily by LGL, but NKH2-positive LGL do not display a high level of NK activity. Another surface structure that has been found to play an important role in NK cell function is the T11 antigen/E rosette receptor complex, which is expressed in 80% of peripheral blood NK cells. The T11 antigen complex has been described as possessing the T111, T112, and T113 antigens and is an important alternate pathway for antigen-independent T-cell activation. Using anti-T112 and anti-T113 monoclonal antibodies, IL-2 receptor expression could be induced on various NK clones if they expressed the correct T11 antigenic epitope. As anti-T112/3 antibodies had a direct proliferative effect on NK cells with mature T-cell phenotype (T3+), it is proposed that the production of IL-2 by NK clones is largely dependent on the T-cell phenotype of NK cells. All NK clones expressed IL-2 receptor at low density and therefore needed a ten fold higher concentration for maximal proliferation than T-cell clones.

For some T-cell-like NK clones, the T3 antigen complex and a T-cell receptor-like structure, NKTa or NK Tb, have been shown to define the target cell specificity. The activation antigen, TnakTAR, was characterized as the recognition structure on the target cell for these NK cells. For both T3- and T3+ NK clones, the LFA-1 antigen has been shown to play an important role in effector/target cell interaction. As previously described for CTL, the LFA-1 molecule is involved in NK cytotoxicity as a nonspecific adhesion-strengthening molecule at the effector cell level.

In summary, NK cells have been found to have a number of unique surface antigens such as NKH1 and NKH2, which can be used to identify and characterize NK cells in vivo. In addition, analysis of surface antigens on NK cells has identified a number of functional structures, such as T11, T3, NKTa and LFA-1, which are shared by T-cells and which function in a fashion similar to both types of cells. Taken together, this analysis therefore indicates that NK cells have a strong functional relationship with T-cells and supports the conclusion that these cells are derived from the T-cell lineage.

Key words: Human NK cells – NK clones – Surface antigens, function, expression

Within the last 10 years, a small population of normal peripheral blood mononuclear cells (PBMC),
termed natural killer (NK) cells, has become the subject of extensive laboratory investigation [1, 45]. NK cells have been identified in many vertebrate species and have been operationally defined as cells capable of mediating spontaneous in vitro cytotoxicity against a variety of target cell populations without apparent prior sensitization. NK cells have been considered to be distinct from specific cytotoxic T lymphocytes (CTL) because they have not been shown to have clonally distributed specificity restriction for products of the major histocompatibility complex (MHC) at the target cell level, or immuneologic memory [45]. They have been implicated in a large number of diverse immuneologic functions. These functions include cytotoxicity against tumor cells and virally transformed cells, resistance to some microbial, fungal and parasitic agents, immune regulation through secretion of lymphokines such as IL-2 and interferon, regulation of hematopoiesis, and natural resistance to allogenic grafts [9, 11, 45]. Interestingly, morphologic analysis of NK cells has demonstrated that these cells have a homogeneous appearance of large granular lymphocytes (LGL) and distinctive physical characteristics that allow the enrichment of these cells on Percoll density gradients [40, 41]. These morphologic characteristics and unique functional capacities clearly distinguish NK cells from T-cells, B-cells, monocytes, and other hematopoietic and lymphoid elements. However, despite their homogeneous morphology, it has become apparent that NK cells are extremely heterogeneous and the precise relationships between NK cells and T-cells and myelomonocytic cells have not been clearly defined.

In part, the heterogeneity of NK cells has become apparent through characterization of the cell surface antigens expressed by these cells using various monoclonal antibodies [26]. These studies have shown that the majority of NK cells in human peripheral blood express antigens such as N901 [8], B73.1 (IgG-Fc receptor) [28, 29], T10 [32], Mo1 (C3bi receptor), and T11 (E rosette receptor) [6]. Approximately 60% of NK cells express HNK-1 antigen [1, 2] and approximately 30% express T8 [30]. Relatively few NK cells express T3, T4, or Ia antigens, and no NK cells are thought to express B-cell-restricted markers such as B1 and B2 and monocyte-restricted markers such as MY4 and Mo2. Thus, the majority of NK cells express markers characteristic of both T-cells (T11) and myeloid cells (Mo1, B73.1), and other antigens such as HNK-1 and T8 are only expressed on subsets of NK cells.

The heterogeneity of NK cells is also apparent from the wide variety of immunologic functions that have been attributed to these cells. As noted previously, these functions include resistance to tumor growth and metastasis, resistance to viral infections [13, 45], immunoregulation [3], and regulation of hematopoiesis [9]. In almost all instances, these NK cell activities in vivo are inferred from in vitro experiments and the precise role of these cells in vivo remains to be conclusively established. Moreover, it is not known whether all these functions can be mediated by the same cells or whether distinct functional subsets within the NK cell population have different activities. Since NK cells have been shown to secrete a variety of lymphokines, it is also not known which of these functions is mediated by direct cytotoxicity and which is mediated through lymphokine activity. At a structural level, it is presumed that the granules in NK cells contain cytotoxins that are capable of mediating target cell lysis, but the biochemical characterization and purification of these granule constituents has only recently begun [5, 22, 38]. With regard to the mechanisms whereby NK cells interact with target cells, they are only now beginning to be more fully understood. In most instances, the membrane target structures of NK cells have not been identified, and it is not known whether different NK cells react with the same or with different target antigens. At the effector cell level, it is not known which membrane molecules play important roles in effector/target cell binding or if all NK cells utilize the same membrane structures to interact with various target cells. With respect to regulation of NK activity, it has been established that both interferon [42, 43] and IL-2 [27, 44] are capable of activating NK cells and enhancing their cytotoxicity. At least some NK cells are capable of secreting interferon [43] and IL-2 [35], as well as other lymphokines, but the mechanism whereby NK cells can be triggered to secrete these lymphokines is not known. The purpose of this review is to summarize recent studies from our laboratory, in which we have begun to characterize functional surface structures of NK cells.

Development of the Cloning Strategy of NK Cells

Since NK cells represent only a small fraction of peripheral blood mononuclear cells (PBMC) and are themselves heterogeneous, it has been difficult to perform meaningful experiments with NK cells in normal peripheral blood. Therefore, the characterization of human NK cells was approached by first developing methods that allow the in vitro clonal expansion of cells with NK activity from