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Investigation of NK cell function and their modulation in different malignancies

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Abstract NK cells have become a subject of investigation not only in the field of tumor immunology and infectious diseases, but also within all aspects of immunology, such as transplantation, autoimmunity, and hypersensitivity. Our early studies aside from investigating NK cell activity in experimental animals and humans included studies of perforin expression and modulation in this lymphocyte subset. As NK cell activity is modified by their environment, we showed clinical stage–dependent impairment of their activity and in vitro effect of different sera, Th1 cytokines, and their combination in breast cancer, Hodgkin's disease, and non-Hodgkin's lymphoma patients, especially with respect to metabolic and cell membrane changes of peripheral blood lymphocytes evaluated by spontaneous release of the enzyme lactate dehydrogenase (LDH) that led to the correction of the LDH enzyme release assay for natural cytotoxicity. By long-term immuno-monitoring of patients with malignancies, we also showed the kinetics of NK cell modulation during chemo-immunotherapy. In our more recent studies, we give data of NK function and novel families of NK cell receptor expression in healthy individuals that may be of help in NK cell profiling, by giving referent values of basic and cytokine-induced expression of some NK cell receptors either in evaluation of disease or in immuno-monitoring during cytokine therapy of patients with malignancies. Moreover, we give novel aspects of modulation of NK cell activity by cytokines approved for immunotherapy, IFN and IL-2, in melanoma and other malignancies with respect to alterations in new activating (NKG2D and CD161) and inhibitory (CD158a and CD158b) receptor characteristics and signaling molecules in CD16- and CD56-defined NK cells and their small immunoregulatory and large cytotoxic subsets in peripheral blood and lymph nodes, as NK cell-mediated killing of tumor cells depends on the balance between stimulatory and inhibitory signaling.

Keywords NK cells · Malignancies · Perforin · Cytokine modulation · Activating and inhibitory receptors

Natural killer cells

During 1980s, early investigations have started on a newly defined subpopulation of peripheral blood lymphocytes, natural killer cells (NK cells), that have been shown to be large granular lymphocytes distinct from T and B cells and initially regarded as an "experimental artifact" in T-cell cytotoxicity assays. NK cells were shown to be important effectors of the innate immune system that have a unique ability to directly lyse transformed or virus-infected cells without prior sensitization or MHC class restriction. NK cells were first discovered in mice by Kiessling et al. [1], who named them natural killer cells and in parallel by Herberman et al. [2]. Human NK cells were initially described as non-adherent, non-phagocytic, CD16 (low affinity FcγR+), large granular lymphocytes [3]. The identification of the NKR-Pl and NK1.1 [4] made it possible to define the murine NK cells roughly as NK1.1+ TCR-sIg-CD16+. Today, human NK cell are defined as

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