

The Role of the NKG2D Immunoreceptor in Immune Cell Activation and Natural Killing

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ABSTRACT:

Target cell recognition by NK cells is thought to be determined by a delicate balance between stimulatory and inhibitory receptors. NK cells express inhibitory receptors specific for MHC class I molecules, and consequently have the ability to lyse cells that have reduced surface expression levels of MHC class I. However, the sensitivity of target cells to NK lysis does not always correlate with the absence of MHC class I expression. It is thought that target cell lysis also depends on the interaction of NK activating receptors with stimulatory ligands. Little is known concerning the stimulatory receptors responsible for tumor cell lysis by NK cells. NKG2D is one such NK cell activating receptor. The ligands for NKG2D are expressed in embryonic tissues and by many tumor cells. The role of murine NKG2D was investigated with a new anti-NKG2D monoclonal antibody. Blocking of NKG2D inhibited natural cytotoxicity of all tumor cells tested that express ligands for the receptor. Staining analysis showed that NKG2D is also expressed by activated CD8⁺ T cells and macrophages, and subsets of TCR $\alpha\beta$ ⁺ and NK1.1⁺ T cells. NKG2D is expressed at maximal levels on the surface of virtually all NK cells as early as fetal day 15. NKG2D functions to activate many of these cell subsets analyzed. Contradicting reports that NKG2D is solely a costimulatory receptor, we observed that crosslinking of NKG2D directly stimulates NK cells and activated macrophages. In contrast, NKG2D costimulates activated CD8⁺ T cells. Thus, NKG2D engagement directly stimulates NK cells and macrophages, costimulates CD8⁺ T cells, and plays a substantial role in natural killing. Given its broad expression pattern, functional activity, and role in tumor cell lysis, the NKG2D receptor ligand system appears to play an important role in both acquired and innate immunity.