Target Cell Recognition by Natural Killer Cells: The NKG2D Receptor-Ligand System

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Natural killer (NK) cells are able to recognize and lyse transformed and infected cells. Until recently, NK cell recognition of target cells was considered to be largely "missing-self" recognition. Specifically, the primary function of NK cells was thought to be to attack cells that have downregulated self-MHC class I expression and spare normal class I^+ cells. For this purpose NK cells express a variety of inhibitory receptors that recognize self-MHC class I molecules delivering an inhibitory signal to the NK cell. However, NK cells are able to efficiently attack some target cells that express normal levels of class I MHC molecules, while some other cells are not sensitive to NK cell-lysis despite low or absent class I MHC expression. These findings imply that stimulatory receptors and their ligands may play an important role in target cell recognition by NK cells. While stimulatory receptors expressed by NK cells have been identified over the years, the ligands for most of these receptors remain unknown.

Only recently, ligands for the stimulatory receptor NKG2D have been identified. Interestingly, NKG2D-ligands (e.g., MIC and Rae1 proteins) are not expressed by most normal cells but are strongly upregulated on transformed or infected cells. Recently, we established the function of NKG2D and its ligands during anti-tumor responses *in vivo*. We could demonstrate that ectopic expression of the murine NKG2D ligands Rae1 or H60 in several tumor cell lines resulted in dramatic rejection of the tumor cells mediated by NK cells and/or $CD8^+$ T cells. Strikingly, mice exposed to live or irradiated tumor cells expressing Rae1 or H60 were specifically immune to subsequent challenge with tumor cells lacking NKG2D ligands, suggesting application of the ligands in the design of tumor vaccines.

This receptor-ligand system provides strong support for the notion that regulated expression of stimulatory ligands plays a central role in regulating NK-cell activity. These findings have led us to propose a second mode of immune recognition by NK cells, represented by the capacity of NK cells (and other immune cells) to recognize "induced-self" ligands (e.g., Rae1 and MIC proteins), expression of which is regulated by various forms of cellular abuse.

References

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