

# NK cell-mediated tumor immune surveillance

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## Abstract

There is emerging evidence that the innate arm of the immune system mediates and regulates tumor immunity. Importantly, coordination of innate and adaptive responses is very much controlled by interactions between NK cells and dendritic cells (DCs) and the regulatory role of specialized T cell populations such as NKT cells and CD4+CD25+ regulatory T cells. NK cells are regulated by both cells and cytokines in their immediate environment and when interacting with tumor directly, a delicate balance between inhibitory signals mediated by MHC class I molecules and activating signals triggered by specific ligands. The activation NKG2D receptor has been shown to play an important role in the control of experimental tumor growth and metastases expressing ligands for NKG2D, however a function for this recognition pathway in host protection from *de novo* tumorigenesis has never been demonstrated. We have now shown that neutralization of NKG2D enhances the sensitivity of wild-type C57BL/6 and BALB/c mice to methylcholanthrene (MCA)-induced fibrosarcoma. The importance of the NKG2D pathway was additionally illustrated in mice deficient for either IFN- $\gamma$  or TRAIL, while mice depleted of NK cells, T cells, or deficient for perforin did not display any detectable NKG2D phenotype. While NKG2D ligand expression was variable or absent on sarcomas emerging in wild-type mice, sarcomas derived from perforin-deficient mice or those mice neutralized for NKG2D were universally Rae-1+ and immunogenic when transferred into wild-type syngeneic mice. These findings suggest an important early role for the NKG2D in controlling and editing tumor formation. Furthermore, IL-12 therapy preventing MCA-induced sarcoma formation was also largely dependent upon the NKG2D pathway. This was consistent with our observation that some cytokines, such as IL-2, IL-12 and IL-21 mediate much of their anti-tumor activity via NKG2D activation when the tumor expresses the appropriate ligands. Despite our knowledge of NK cells as anti-tumor effector cells, and more recently as potential regulators of adaptive immunity, the composition of the mature NK cell population is very poorly understood. We now report that the mature NK cell pool can be dissected into two functionally distinct subsets. Comparatively, one subset displays non-NKG2D-mediated cytotoxic function, exhibits a distinct tissue distribution and responsiveness to chemokines, and interacts productively with DC. Importantly, similar subsets also appear to exist in humans. We are now beginning to discern the different roles of these NK cell subsets in immune responses in mice to cancer. Furthermore, we have recently illustrated an important role for CD4+CD25+ regulatory T cells in controlling NKG2D-mediated cytotoxicity and suppression of tumor growth and metastases by NK cells. Using the knowledge we have gained from using cytokines and depleting regulatory T cells, we have begun to rationally design combined therapies that optimize NK cell-mediated tumor destruction.