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Tumor immune surveillance in the mouse: Effectors and regulators

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Abstract

Since Burnet and Thomas' immune surveillance hypotheses in the 1960's, debate has raged concerning the relevance of tumor immunity. Immunosuppression in humans can lead to the development of malignancy, however many of these tumor types have a viral origin and immunosurveillance of epithelial and other common malignancies in the absence of viral infection has been more difficult to ascertain. Early studies in immunodeficient mice challenged the validity of the immunosurveillance hypothesis, however a variety of factors compromised these studies, and the subsequent discovery of thymus-independent lymphocytes raised more intrigue. More recently, in methylcholanthrene (MCA)- and other spontaneous malignancy models, we and others have also illustrated the importance of anti-tumor immunity mediated by CD8+ T cells, NK cells, NKT cells, and gammadelta+T cells. Over the past decade, the production of gene-targeted mice for specific effector molecules has greatly aided our analysis of tumor immunosurveillance. Interferon (IFN)-gamma, perforin (pfp), and TRAIL, key molecules of the innate and adaptive immune systems, contribute to host protection from tumor metastasis and tumor initiation in mice; treated with the chemical carcinogen, MCA, expressing oncogenes, or deficient for tumor suppressors. Recently, we described the first study to evaluate spontaneous tumor development in aged gene-targeted mice lacking IFN-gamma and/or pfp, or the immunoregulatory cytokines, IL-12, IL-18, and TNF. Both IFN-gamma and pfp were critical for suppression of lymphomagenesis, and the immunoselection pressure of pfp expressed by CTL was evidently extremely strong. A significant incidence of late onset adenocarcinoma observed in both IFN-gamma- and pfp-deficient mice demonstrated that at least some epithelial tissues are also subject to immune surveillance. A critical step forward in tumor immunity has been the discovery of ligands expressed on stressed epithelial cells that recognize the innate activation receptor, NKG2D. The lectin-like NKG2D receptor expressed on NK cells, gammadelta-TCR+ T cells, CD8+ alphabeta-TCR+ T cells and activated macrophages. The retinoic acid early inducible-1 (Rae-1) gene products and a distantly related minor histocompatibility antigen, H60, have been reported as NKG2D ligands in mice. Recent studies show that the ectopic expression of NKG2D ligands in several tumor cell lines resulted in the rejection of the tumor cells, even when the tumor cells expressed normal levels of MHC class I molecule. We have investigated the primary immunity generated *in vivo* by MHC class I-deficient and -competent tumor cell lines that expressed the NKG2D ligand, Rae-1beta. Rae-1beta expression on class I-deficient RMA-S lymphoma cells enhanced primary NK cell-mediated tumor rejection *in vivo*, while RMA-Rae-1beta tumor cells were rejected by a combination of NK cells and CD8+ T cells. Rae-1beta expression stimulated NK cell cytotoxicity and IFN-gamma secretion *in vitro*, but not proliferation. Surprisingly only NK cell perforin-mediated cytotoxicity, but not production of IFN-gamma, was critical for the rejection of Rae-1beta expressing tumor cells *in vivo*. This distinct requirement for perforin activity contrasts the NK cell-mediated rejection of MHC class I-deficient RMA-S tumor cells expressing other activating ligands such as CD70 and CD80. Thus, NKG2D acted as a natural cytotoxicity receptor to stimulate perforin-mediated elimination of ligand-expressing tumor cells. The development of memory T-cell responses

downstream of NK cell- and CD70-mediated tumor rejection determined an important link between innate and adaptive immunity to tumors. Future goals will be the discovery of 1) how early and relevant are immune responses to transformed tissues, 2) what innate immune cell networks prime and regulate CTL anti-tumor function, and 3) what receptor/ligand pairs control lymphocyte effector function.

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