Cancer Immunity, Vol. 5 Suppl. 1, p. 10 (6 April 2005)

CANCER
IMMUNITY
Meeting Abstract

Relevance of NKG2D and its ligands in tumor immunity

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Ubiquitously expressed MHC class I molecules are ligands for diverse arrays of inhibitory receptors that control NK cells and, in some cases, modulate T-cell responses. With NK cells, these receptors collectively gauge impairments in the expression of MHC class I molecules that are frequently associated with tumor and virus-infected cells. This system is complemented by MHC class I-like molecules that are not constitutively but inducibly expressed and interact with the activating NKG2D receptor. Among these ligands are the closely related MICA and MICB glycoproteins, which have no role in antigen presentation, have a restricted tissue distribution, and can be induced in permissive types of cells by viral and bacterial infections, malignant transformation, heat shock, and proliferation. Under some of these conditions, *MIC* genes are regulated similarly to heat-shock protein 70 (*hsp70*) genes as their 5'-flanking regions share highly conserved heat-shock response elements (HSE) which can bind heat-shock factor 1 (HSF1). However, preliminary evidence also suggests that cellular stress is not the only determining factor in the regulation of expression of *MIC*. NKG2D is a C-type lectin-like receptor that signals through the associated DAP10 protein by activation of a PI-3 kinase-dependent or -independent pathway. Ligand engagement of NKG2D activates NK cells and costimulates effector CD8 T cells.

A dominant theme in the immunobiology of MIC is their abundant tumor-associated expression, including many lung, breast, kidney, ovarian, prostate, gastric and colon carcinomas, and melanomas (…). Experiments in mice have shown that NKG2D can effectively promote NK cell and T cell-mediated tumor rejection. In humans, however, tumors may subvert this system to the effect of immune evasion. Presumably due to the action of metalloproteinases, tumors shed substantial amounts of soluble MIC into the circulation, inducing a systemic downmodulation of NKG2D and thus impairment of the responsiveness of NK cells and tumor antigen-specific T cells. Moreover, preliminary studies suggest irregular expression of MIC by dendritic cells (DC) in tumors and their draining lymph nodes, possibly impairing the immunostimulatory capacities of these DC.

Because MIC represent uncommonly broad tumor markers, we investigated the ability of DC loaded with anti-MIC antibody opsonized melanoma, breast and ovarian tumor cells to prime multivalent anti-tumor T-cell responses. Quantitative and qualitative evaluations suggest that this could become an effective approach for immunization against a large variety of histologically distinct tumors that may also be applicable to adoptive T-cell therapy and as a platform for tumor antigen discovery.