How melanoma cells inactivate NK cells

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Keywords: NK cells, melanoma cells, tumor escape, IDO, PGE2

NK cells are the most potent effectors against different tumors in vitro. However, their efficacy in vivo is compromised by suppressive signals delivered by tumor or tumor-associated cells. This study unravels the molecular mechanisms by which melanomas disarm NK cells and offers clues to revert such inhibitory effect.

Besides specific T lymphocytes, also natural killer (NK) cells are thought to play a role in cancer immunosurveillance. NK cells are effector lymphoid cells belonging to the innate immune system which are capable of recognizing and killing virus-infected cells and a wide variety of tumor cells, while sparing normal cells. In addition, once activated, they produce cytokines and chemokines that regulate both innate and adaptive immunity. Emerging evidences suggest that NK cells may shape downstream adaptive immune responses toward a Th1 profile, thought to favor the anti-tumor responses.

NK cell response to target cells depends on the balance between activating and inhibitory signals delivered by cell surface receptors. Inhibitory receptors are represented mainly by HLA Class I-binding receptors (KIR, NKG2A and LIR-1/ILT2), while activating receptors, which include Nkp46, Nkp30, Nkp44, NKG2D and DNAM-1, recognize ligands that are generally poorly expressed or absent on normal cells, but that can be induced by tumor transformation, virus infection or stress. The susceptibility of tumor cells to NK cell activity would thus largely depend on the high expression levels of activating receptor-ligands but it can be further increased by the downregulation of HLA Class I expression, which occurs on transformed cells either spontaneously or under the pressure of the HLA-I-restricted T-cell response. Therefore, NK cells might play a further important role in the elimination of tumors that evade T-cell killing by MHC Class I antigen loss or downregulation.

A number of studies in mice, genetically deficient of NK effector molecules or depleted of NK cells, suggest that these cells may represent major players in the control and killing of tumor cells. In humans, Imai et al. reported that a low degree of natural cytotoxicity correlates with an increased incidence of cancer. In addition, the presence of NK cell infiltration has a prognostic value in certain solid tumors because it correlates with a better prognosis. However, in many clinical trials in which NK cells have been used for adoptive immunotherapy, clinical responses were unfrequent. In particular, this holds true in the case of solid tumors, suggesting that mechanisms of resistance at the level of the tumor microenvironment may be prevailing in many cases. Indeed, various cytokines, growth factors and enzymes synthesized either by tumor or stromal cells have been shown to exert a suppressive effect on immune response. Thus, TGFβ, IL-10, PGE2, macrophage migration inhibitory factor (MIF), and the enzyme indoleamine 2,3-dioxygenase (IDO) (overexpressed by some tumor cells) may contribute to the establishment of immune tolerance in the tumor microenvironment. In this context, recent studies reported that tumor-infiltrating NK cells display an impaired functional capability. Also in melanoma lesions infiltrating NK cells were frequently detected. However, in this case, no information is available on the functional status of such infiltrating effectors.

In a recent study, we investigated the effect of co-culturing NK and melanoma cells on the phenotypic and functional properties of NK cells. We showed that IL-2-activated NK cells displayed a marked downregulation of the Nkp30, Nkp44 and NKG2D activating receptors. In addition, the content of cytolytic granules (i.e., granzyme A) and the NK cytotoxicity were sharply impaired. We could identify mechanisms possibly involved in inhibition of NK cell functions. By the use of specific inhibitors of TGFβ, PGE2, MIF and IDO, we showed that melanoma-derived IDO and PGE2 played a major role (Fig. 1). Remarkably, two out of three melanoma cell lines expressed IDO after interaction with activated NK cells. Transwell cultures showed that IDO expression was induced by NK-derived IFNγ. Immunofluorescence analysis in biopsies of skin lesions in patients with metastatic melanoma, revealed the expression of IDO, thus suggesting that IDO may play a relevant immunosuppressive role also in vivo. Also the production of PGE2 by melanoma cells was increased in the presence of NK cells. Thus, paradoxically, NK cell responses against tumor cells may result in amplification of the suppressive effect. Another paradoxical effect is that when NK cells could not promptly eliminate target cells, they induce HLA Class I upregulation on melanoma cells,
which in turn become resistant to further NK lysis.

Notably, the inhibitory effect of melanoma on NK cell function is reminiscent of previous data on mesenchymal stem cell (MSC)-NK cell interactions. Indeed, also MSCs inhibited the expression of NKp30, NKp44 and NKG2D through the production of IDO and PGE2. This finding may not be surprising in view of the origin of mesenchymal and melanocytic cells from common precursors belonging to the neural crest. Recently, our group reported that also melanoma-associated fibroblasts could inhibit NK cell function by modulating the surface expression of NKp30, NKp44 and DNAM-1. Interestingly, DNAM-1 downregulation relies on cell-to-cell interactions and does not involve soluble factors. Thus, one could speculate that tumor cells and their stroma may have evolved different mechanisms that act on different activating receptors to favor NK-cell tolerance toward tumors.

The impaired expression of NKp30 in “melanoma-conditioned” NK cells may have a negative effect also on the crosstalk between NK and dendritic cells (DC), possibly resulting in an altered DC editing. This, in turn, could favor T-cell tolerance toward tumors.

A good piece of news is that, based on this study, new strategies aimed at the restoration of NK cell function may be developed to treat melanoma. Since IDO and PGE2 play a major role in melanoma-mediated immunosuppression, drugs that can target these molecules may represent useful tools for novel immunotherapeutic approaches.

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