Innate immunity to carcinomas?


Abstract

Human MHC class I-related molecules, MICA and MICB, are stress-induced antigens that are recognized by a subset of gamma delta T cells expressing the variable region Vdelta1. This functional association has been found to be limited to intestinal epithelium, where these T cells are prevalent and where MICA and, presumably, MICB are mainly expressed. However, increased frequencies of Vdelta1 gamma delta T cells have been observed in various epithelial tumours; moreover, MICA/B are expressed on diverse cultured epithelial tumour cells. With freshly isolated tumor specimens, expression of MICA/B was documented in many, but not all, carcinomas of the lung, breast, kidney, ovary, prostate, and colon. In tumors that were positive for MICA/B, the frequencies of Vdelta1 gamma delta T cells were significantly higher than in those that were negative. Vdelta1 gamma delta T cell lines and clones derived from different tumors recognized MICA/B on autologous and heterologous tumor cells. In accord with previous evidence, no constraints were observed in these interactions, such as those imposed by specific peptide ligands. Thus, MICA/B are tumor-associated antigens that can be recognized, in an apparently unconditioned manner, by a subset of tumor-infiltrating gamma delta T cells. These results raise the possibility that an induced expression of MICA/B, by conditions that may be related to tumor homeostasis and growth, could play a role in immune responses against tumors. Allergen, 45 identified an activating receptor complex NKG2D-DAP10 that is expressed by most γδ T cells, CD8+ αβ T cells, and NK cells. These NKG2D expressing γδ T cells and NK cells, but not the CD8+ αβ T cells, were shown to have cytolytic activity against transfected and tumour cell lines expressing MICA. This activity could be abrogated by addition of monoclonal antibody to NKG2D. The relationship between the NKG2D receptor and Vδ1 receptor is unclear, as the cytolytic activity could also be inhibited by a monoclonal antibody to the γδ TCR. The authors suggest that for the most efficient lysis of MICA+ target cells by γδ T cells, engagement of both receptors may be necessary.

What practical significance does this work have? It is not yet known what importance the MICA system has for in vivo control of tumours. The frequency of γδ T cells within epithelial tumours is very low, and so can they really make a significant contribution to the antitumour response? There is certainly no sign of a running battle in vivo; tumour infiltrating γδ T cells are not commonly surrounded by cellular debris of lysed target cells. Tumour cells are known to have many mechanisms allowing them to evade or suppress the immune response. Perhaps there are factors in vivo which restrict expression of the cytolytic response through MICA, so that the full potential of the antitumour activity mediated by this receptor ligand system is only be observed in vitro. Of course the number of tumours which might be prevented by the activity of the MICA binding sentinels is not quantifiable, and it may be possible that when tumour growth is observed, we are witnessing a failure of the system. Someday it may be possible to enhance the cytolytic response in vivo, or to boost the numbers of γδ and NK cells reaching the tumour sites,
allowing the patient’s own cells to destroy the tumour. For now however, it remains to be seen whether the MICA/NKG2D/DAP10 system will prove to be a useful weapon in the war against epithelial tumours and their metastases.

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