Letter to the Editor

Melanoma Cells Inhibit NK Cell Functions—Response

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We appreciated the comments by Sconocchia and colleagues to our recent study describing a novel tumor escape mechanism that allows melanoma cells to prevent natural killer (NK)-mediated recognition and killing (1).

We agree with the authors that the altered receptor expression and the limited capability of NK cells of infiltrating the tumor tissues may represent a serious limitation to their efficacy in controlling solid tumors including melanomas. On the other hand, in different animal models, NK cells have been shown to limit tumor cell proliferation and metastatic spread (2), thus suggesting that NK cells may indeed effectively control the early steps of tumor growth. On the other hand, when a tumor has reached a critical size and/or has established an appropriate microenvironment, it can contrast the antitumor activity of NK cells. Indeed, at the tumor site, different soluble factors and/or cellular interactions can dampen NK cell function and enhance melanoma cell resistance to NK cell killing. We should stress that NK infiltration has been described in solid tumors (3). Notably, the NK cell infiltrate may not be univocally assessed for several reasons. Indeed, it may be subjected to (i) the sensitivity and specificity of reagents used to reveal NK cells, (ii) the tumor type, and (iii) the areas analyzed within the tumor. For example, we have recently analyzed 28 primary cutaneous melanomas and detected NK cell infiltration (CD56+CD3− cells with lymphoid morphology) in more than half specimens (a higher proportion than that reported by Sconocchia and colleagues; ref. 4). In addition, in a previous study on metastatic melanomas, we found that infiltrating NK cells were primarily localized in the fibroblast-rich peritumoral zone (5). If this observation will be further confirmed (experiments are in progress in our lab), this may suggest that the tumor stroma may inhibit the NK cell migration into the tumor nests. Remarkably, cultured NK cells can kill a wide growing spectrum of tumor cells (including cancer stem cells). Thus, although the tumor cells may inhibit the access of NK cells to tumor lesions and may dampen their cytolytic potential, there is little doubt that nevertheless NK cells represent strategic effectors for immunotherapy (6). For example, this is clearly indicated also by their central role in the successful therapy of high-risk leukemias in the haploidentical hematopoietic stem cell transplantation setting (7). A future challenge will be a better understanding of the mechanisms that inhibit NK cell activation and infiltration in solid tumors to define novel strategies to maintain the NK cell cytolytic potential in vivo.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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Writing, review, and/or revision of the manuscript: G. Pietra, M. Vitale, C. Manzini, M. Balsamo, L. Moretta, M.C. Mingari

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