

## Melanoma Cells Inhibit NK Cell Functions—Letter

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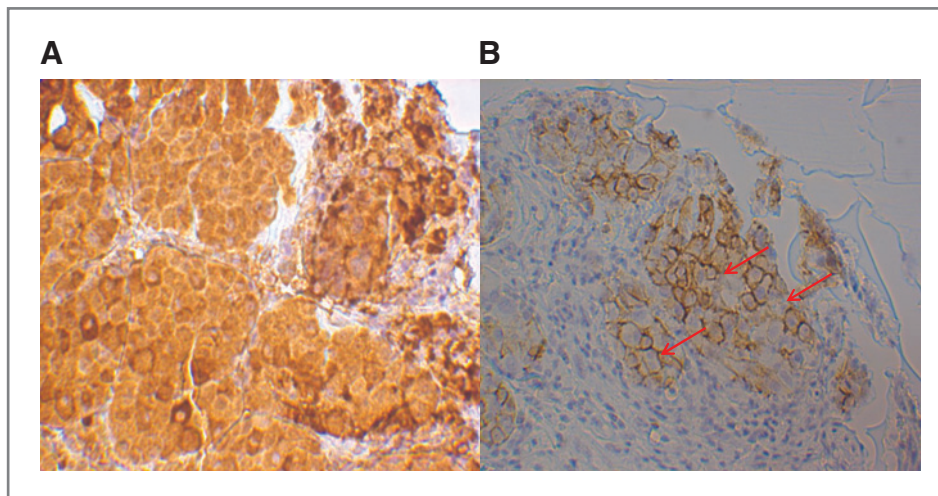
We have read with interest the recent paper by Pietra and colleagues who show that melanoma cells inhibit NKp30, NKp44, and NKG2D expression by allogeneic natural killer (NK) cells and their cytolytic activity (1). These results provide potential mechanistic insights for a number of observations previously made by others and by ourselves (2–5). Indeed, we found that NK cell infiltration is poor, if at all detectable, in various types of human cancers.

By taking advantage of a panel of tumor tissue microarrays (TMA), including hundreds of 0.6 mm punches from clinically annotated biopsies, in agreement with a recently published paper (4), we observed that no CD56+ cell infiltrate was detectable in 203 (71.4%) of 284 melanoma. Furthermore, among the 81 remaining punches, surface expression of CD56 antigen was exclusively detected on melanoma cells in 24 specimens (Fig. 1B). We also found that 310 (92%) of 336 hepatocellular carcinomas (HCC), 376 (97%) of 385 breast cancers (Sconocchia and colleagues, unpublished data), and

108 (92%) of 117 renal cell carcinomas (RCC; ref. 3) showed no evidence of CD56+ cell infiltration.

On the other hand, CD56+ cell infiltration with a mean number of 10 cells per punch or more was observed in 460 (38%) of 1,203 punches in colorectal cancers (CRC). Even in this case, however, CD56+ cell infiltration was devoid of prognostic significance (5). Similar results were obtained by using CD57 as a NK/NK-T cell marker. Notably, phenotypic analysis of freshly excised and enzymatically digested CRC specimens clearly indicated that CD56 and NKp46 were expressed in comparably ( $P = 0.09$ ) low percentages of tumor infiltrating cells (5), suggesting that our findings could not be merely attributed to a downregulated CD56 expression.

Importantly, more than 90% of RCC, HCC, CRC, and melanoma cells from the tumors included in the TMAs under investigation expressed high amounts of MHC class I-related chain molecule A/B (MICA/B; refs. 3, 5; Fig. 1A), thereby representing potentially excellent NK cell targets.



**Figure 1.** Melanoma microenvironment is rich in MICA/B positive cells and poor in CD56+ lymphocyte infiltration. A, a representative example of cytoplasmic and cell surface expression of MICA/B in a melanoma punch stained using WW6B7 mAb (6). B, CD56 is expressed on melanoma cells, whereas it is not expressed in the inflammatory infiltrate. Positive cells are stained in brown. Arrows indicate cell surface positive melanoma cells.

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In this respect, it is of interest that functional impairments of NK cell activities, possibly because of soluble factors released by tumor cells, including TGF- $\beta$ 1, have recently been observed also in patients with advanced breast cancers (2, 7).

Further studies using autologous cancer cells are warranted to clarify whether molecular mechanisms underlying impaired NK cell functions in a tumor setting are specifically related to neoplastic transformation (3). Nevertheless, the data by Pietra and colleagues, Mamessier and colleagues, and Erdag and colleagues (1, 2, 4, 7), together with our observations question

the relevance of NK cells in the control of solid tumor progression in humans.

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### Authors' Contributions

**Conception and design:** G. Sconocchia, S. Ferrone, G.C. Spagnoli

**Development of methodology:** G. Sconocchia

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** R. Arriga, L. Tornillo

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** G. Sconocchia, R. Arriga, L. Terracciano, G.C. Spagnoli

**Writing, review, and/or revision of the manuscript:** G. Sconocchia, R. Arriga, S. Ferrone, G.C. Spagnoli

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** G. Sconocchia, R. Arriga

**Study supervision:** G. Sconocchia, L. Terracciano, G.C. Spagnoli

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### References

- Pietra G, Manzini C, Rivara S, Vitale M, Cantoni C, Petretto A, et al. Melanoma cells inhibit natural killer cell function by modulating the expression of activating receptors and cytolytic activity. *Cancer Res* 2012;72:1407–15.
- Mamessier E, Sylvain A, Thibault ML, Houvenaeghel G, Jacquemier J, Castellano R, et al. Human breast cancer cells enhance self tolerance by promoting evasion from NK cell antitumor immunity. *J Clin Invest* 2011;9:3609–22.
- Sconocchia G, Spagnoli GC, Del Principe D, Ferrone S, Anselmi M, Wongsena W, et al. Defective infiltration of natural killer cells in MICA/B-positive renal cell carcinoma involves  $\beta_2$ -integrin-mediated interaction. *Neoplasia* 2009;11:662–71.
- Erdag G, Schaefer JT, Smolkin ME, Deacon DH, Shea SM, Dengel LT, et al. Immunotype and immunohistologic characteristics of tumor-infiltrating immune cells are associated with clinical outcome in metastatic melanoma. *Cancer Res* 2012;72:1070–80.
- Sconocchia G, Zlobec I, Lugli A, Calabrese D, Iezzi G, Karamitopoulou E, et al. Tumor infiltration by Fc $\gamma$ RIII (CD16+) myeloid cells is associated with improved survival in patients with colorectal carcinoma. *Int J Cancer* 2011;128:2663–72.
- Sconocchia G, Lau M, Provenzano M, Rezvani K, Wongsena W, Fujiwara H, et al. The antileukemia effects of HLA-matched NK and NK-T cells in chronic myelogenous leukemia involves NKG2D-target cell interaction. *Blood* 2005;106:3666–726.
- Mamessier E, Sylvain A, Bertucci F, Castellano R, Finetti P, Houvenaeghel G, et al. Human breast tumor cells induce self-tolerance mechanisms to avoid NKG2D-mediated and DNAM-mediated NK cell recognition. *Cancer Res* 2011;71:6621–32.

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