Myeloid Suppressors Decrease Melanoma Survival by Abating Tumor-Fighting T Cells

Rolf Kiessling, Yumeng Mao, and Yago Pico de Coaña

Disseminated malignant melanoma has a poor prognosis. Immunotherapy based on cytokines or checkpoint inhibitors has a protracted beneficial effect in a select group of patients. Understanding the mechanisms that inhibit tumor-specific T cells will help the development of biomarkers to formulate therapy for this disease. Clin Cancer Res; 20(6); 1401–3. ©2014 AACR.
course of disease before analysis (>24 months survival after first occurrence of distant metastases). In the present study, the presence of T cells responding to peptides from the tumor antigens NY-ESO-1 and Melan-A, together with percentages of peripheral MDSCs, was investigated in 94 patients, with a further 39 assessed only for MDSCs. The M-category, presence of NY-ESO-1–specific T cells, and levels of MDSCs were associated with better survival by Kaplan–Meier analysis, with the M-category and the presence of NY-ESO-1–specific T cells being independent prognostic factors. Other authors have shown that T-cell reactivity to NY-ESO-1 may also have a value for predicting beneficial outcome to ipilimumab treatment (9). One may argue that a relationship between tumor-reactive T cells and long-term survival may not necessarily be casual, and that patients who are generally more fit could be more prone to react to these tumor antigens.

In spite of this, the observation of a correlation between high levels of MDSCs and the absence of antigen-specific T cells strengthens the causal explanation rather than the indirect one, particularly because these were not independent risk factors. This is in line with several earlier observations supporting the concept that MDSCs can counteract the development of tumor-specific T cells (4, 5). The finding reported here of a “triple correlation” between high levels of MDSCs, the absence of antigen-reactive T cells and long-term survival may not necessarily be casual, and that patients who are generally more fit could be more prone to react to these tumor antigens.

In patients with advanced malignant melanoma, high levels of MDSCs (1) will block the induction of antigen-specific T cells via production of inhibitory mediators such as arginase 1, inducible nitric oxide synthase (iNOS), and ROS (2). These inhibitors can act either directly on the induction of antigen-specific T cells (3) or indirectly on the DC (4) via blocking presentation of melanoma antigen to the T-cell precursors. As a consequence, the melanoma antigen-specific T cells will not be able to eliminate the tumor which will progress (5) leading to poor prognosis for the patient. In patients with low levels of MDSCs (6), the tumor will be eliminated or kept in control by the T cells (7).
and to respond to ipilimumab therapy with a rapid decrease in number (12). Consequently, it will be important to know if also grMDSC will affect survival in patients with melanoma, although the task of measuring this will be a challenge as their fragility does not easily allow freezing.

Regardless of their prognostic importance, the negative influence of MDSCs on the development of tumor-specific T cells in patients with melanoma endorses novel combinatorial immune therapy strategies. Tumor vaccines administered together with drugs abrogating MDSCs or depleting their immunosuppressive products, such as arginase 1, reactive oxygen species (ROS), or TGF-β, are promising combinations to be tested in future clinical trials.

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

Authors’ Contributions
Writing, review, and/or revision of the manuscript: R. Kiessling, Y. Mao, Y. Pico de Coaña

Grant Support
R. Kiessling is supported by grants from The Swedish Cancer Society (12 0598), The Cancer Society of Stockholm (121103), The Swedish Medical Research Council (K2011-66X-15387-07-3), an ALF-Project grant from Stockholm City Council (20110070), and the "Torsten Soderbergs Stiftelse."

Received January 9, 2014; accepted January 13, 2014; published online March 14, 2014.

References
2. Sullivan RJ, Lorusso PM, Flaherty KT. The intersection of immune-directed and molecularly targeted therapy in advanced melanoma: where we have been, are, and will be. Clin Cancer Res 2013;19:5283–91.
Myeloid Suppressors Decrease Melanoma Survival by Abating Tumor-Fighting T Cells

Rolf Kiessling, Yumeng Mao and Yago Pico de Coaña


Updated version

Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-13-3388

Supplementary Material

Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2014/03/14/1078-0432.CCR-13-3388.DC1

Cited articles

This article cites 12 articles, 7 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/20/6/1401.full#ref-list-1

Citing articles

This article has been cited by 2 HighWire-hosted articles. Access the articles at:
http://clincancerres.aacrjournals.org/content/20/6/1401.full#related-urls

E-mail alerts

Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions

To request permission to re-use all or part of this article, use this link
http://clincancerres.aacrjournals.org/content/20/6/1401.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.