Monocytic myeloid-derived suppressor cells in advanced melanoma patients
Indirect impact on prognosis through inhibition of tumor-specific T-cell responses?

Alexander Martens, Henning Zelba, Claus Garbe, Graham Pawelec, and Benjamin Weide

1Department of Internal Medicine II; Section for Transplantation Immunology and Immunohematology; University of Tübingen; Tübingen, Germany; 2Department of Dermatology; University Medical Center; Tübingen, Germany; 3Department of Immunology; University of Tübingen; Tübingen, Germany

Keywords: antigen-specific T cells, melanoma, Melan-A, MDSCs, NY-ESO-1, prognostic marker
Abbreviations: M, monocytic; MDSC, myeloid-derived suppressor cells; PMN, polymorphonuclear

The percentage of circulating CD14+CD11b+HLA-DRlow myeloid-derived suppressor cells (MDSCs) inversely correlates with survival among advanced melanoma patients. High levels of MDSCs are associated with the absence of T lymphocytes specific for melanoma-derived antigens, implying a causal and clinically relevant interaction between these cell subsets. MDSCs might therefore represent prognostic markers as well as targets for the development of novel therapeutic interventions against melanoma.

T cells are important effectors of the adaptive immune response. Indeed, they can destroy or maintain under control virus-infected as well as malignant cells upon recognition of specific peptides presented in complex with MHC molecules. Since the discovery of tumor-associated antigens (TAAs) more than 25 y ago, many groups worldwide have developed approaches to combat cancer through the activation of specific T-cell responses. Effective strategies of this type include adoptive T-cell transfer, a direct means to provide high amounts of tumor-specific T cells, as well as less direct manipulations such as the administration of immune checkpoint blockers or high-dose interleukin-2. Immunotherapeutic regimens that manipulate the T-cell response in melanoma patients can result in long-term tumor regression, yet clinical benefits are generally limited to a rather small subset of patients.

Fascinated by the favorable clinical course of some patients with unresectable advanced melanoma treated with cytotoxic T lymphocyte-associated protein 4 (CTLA4)-targeting antibodies at our department, we aimed to identify factors associated with potentially curative outcomes in long-term survivors that would set them apart from the majority of patients who do not experience such response. Initially, we identified melanoma antigen-specific T cells in the peripheral blood of most long-term survivors but few of the patients experiencing the usual clinical course (short-term survivors). An analysis of the prognostic relevance of this finding in unresectable stage IV melanoma patients revealed that T cells, in particular those responding to NY-ESO-1- or Melan-A-derived antigens, are strong independent predictors of survival, even more robust than the M category of the AJCC staging system. Thus, patients with T cells responding to more than one of the 4 different melanoma-associated antigens that we tested had a better clinical outcome than individuals whose T cells responded to one or none. In a subsequent study, we focused on the prognostic impact of cells that are capable of downregulating T-cell responses, notably regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs). Circulating CD4+CD25+FOXP3+ Tregs had no impact on prognosis but a high frequency of CD14+CD11b+HLA-DRlow MDSCs was strongly associated with survival in 133 late-stage melanoma patients bearing distant metastasis. The median survival time of patients with a low frequency of circulating MDSCs was 13 mo vs. 8 mo for others. In this study, we confirmed the strong impact of melanoma-specific T cells and compared the relative prognostic effect of MDSCs, T cells and the M category by multivariate analyses. Despite the strong association with survival in univariate analyses, the circulating levels of MDSCs did not add independent prognostic information in Cox regression models. The reason

*Correspondence to: Alexander Martens; Email: alexander.martens@uni-tuebingen.de
Submitted: 01/10/2014; Accepted: 01/14/2014; Published Online: 02/14/2014
Citation: Martens A, Zelba H, Garbe C, Pawelec G, Weide B. Monocytic myeloid-derived suppressor cells in advanced melanoma patients: Indirect impact on prognosis through inhibition of tumor-specific T-cell responses?. OncoImmunology 2014; 3:e27845; http://dx.doi.org/10.4161/onci.27845
for this unexpected finding is probably the strong correlation between the presence of melanoma-specific T cells and low MDSC levels implying a causal interaction between these cell types. We cannot say whether the amount of functional T cells detected in our experiments reflects the in vivo levels of antigen-specific T cells or is significantly influenced by the amounts of MDSCs present during the 12 d of re-stimulation in vitro (Fig. 1).

Further experiments are ongoing to clarify the impact of MDSCs on the detection of functional, antigen-specific T cells during in vitro expansion. We expect to observe a substantial influence of MDSCs in this setting. If this indeed turns out to be the case, the effects of MDSCs will have to be evaluated in assays commonly employed for the quantification of antigen-specific T cells after re-stimulation in numerous settings (e.g., ELISPOT assays).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Weide B, Zelba H, Derhovanessian E, Pflugfelder A, Eigentler TK, Di Giacomo AM, Maio M, Aarnzen EH, de Vries IJ, Sucker A, et al. Functional T cells detected in our experiments reflects the in vivo levels of antigen-specific T cells or is significantly influenced by the amounts of MDSCs present during the 12 d of re-stimulation in vitro (Fig. 1).

2. Weide B, Martens A, Zelba H, Stutz C, Derhovanessian E, Di Giacomo AM, Maio M, Sucker A, Schilling B, Schadendorf D, et al. Myeloid-derived suppressor cells predict survival of advanced melanoma patients: comparison with regulatory T cells and NY-ESO-1- or Melan-A-specific T cells. J Clin Oncol 2013; Forthcoming; PMID:23473958; http://dx.doi.org/10.1038/nri3175

3. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol 2012; 12:253-68; PMID:22437938; http://dx.doi.org/10.1038/1158

4. Mao Y, Poschke I, Wennerberg E, Pico de Coaña Y, Ethyazhi Brage S, Schulz I, Hansson J, Masucci G, Lundequist A, Kiersling R. Melanoma-educated CD14+ cells acquire a myeloid-derived suppressor cell phenotype through COX-2-dependent mechanisms. Cancer Res 2013; 73:3877-87; PMID:23633486; http://dx.doi.org/10.1158/0008-5472.CAN-12-4115
5. Filipazzi P, Valenti R, Huber V, Pilla L, Canese P, Iero M, Castelli C, Mariani L, Parmiani G, Rivoltini L. Identification of a new subset of myeloid suppressor cells in peripheral blood of melanoma patients with modulation by a granulocyte-macrophage colony-stimulation factor-based antitumor vaccine. J Clin Oncol 2007; 25:2546-53; PMID:17577033; http://dx.doi.org/10.1200/JCO.2006.08.5829

6. Diaz-Montero CM, Salem ML, Nishimura MI, Garrett-Mayer E, Cole DJ, Montero AJ. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. Cancer Immunol Immunother 2009; 58:49-59; PMID:18446337; http://dx.doi.org/10.1007/s00262-008-0525-4

7. Solino S, Falsi E, Diaz-Montero CM, Doni A, Pintoni L, Rosato A, Francescato S, Basso G, Zanovello P, Onicescu G, et al. A human promyelocytic-like population is responsible for the immune suppression mediated by myeloid-derived suppressor cells. Blood 2011; 118:2254-65; PMID:21734236; http://dx.doi.org/10.1182/blood-2010-12-325753

8. Walter S, Weinschenk T, Stenzl A, Zdrojowy R, Pluzanska A, Szczylk C, Stoehler M, Brugger W, Dietrich PF, Mendrzyk R, et al. Multiparticle immune response to cancer vaccine IMA901 after single-dose cyclophosphamide associates with longer patient survival. Nat Med 2012; 18:1254-61; PMID:22842478; http://dx.doi.org/10.1038/nm.2883

9. Filipazzi P, Pilla L, Mariani L, Paruzzo R, Castelli C, Camisaschi C, Maurichi A, Cova A, Rigamonti G, Giardino F, et al. Limited induction of tumor cross-reactive T cells without a measurable clinical benefit in early melanoma patients vaccinated with human leukocyte antigen class I-modified peptides. Clin Cancer Res 2012; 18:6485-96; PMID:23032742; http://dx.doi.org/10.1158/1078-0432.CCR-12-1516