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

Rolf Kiessling, Yumeng Mao, and Yago Pico de Coaña

In this issue of *Clinical Cancer Research*, Weide and colleagues (1) report on the prognostic impact of myeloid-derived suppressor cells (MDSC) and regulatory T cells (Treg) in patients with advanced melanoma. Malignant melanoma has a dismal prognosis once metastasized to distant organs. Presently, there is great optimism in the clinical management of this disease due to a number of breakthroughs in molecular biology and immune therapy (2). There is substantial evidence that the immune system can recognize and eliminate melanoma cells, particularly when impelled to do so by immunotherapy. Systemic therapy with high-dose IFNα is approved for the adjuvant treatment of melanoma, and high-dose interleukin-2 can cause long-lasting regression in a small but significant proportion of patients with melanoma. Therapy with ipilimumab, an antibody to the “checkpoint” molecule CTLA-4, was recently approved by the U.S. Food and Drug Administration and is already standard treatment for metastatic melanoma, and approval for several second-generation checkpoint inhibitors is imminent. Melanoma lesions contain tumor-infiltrating lymphocytes, which, when expanded to large numbers and reinfused to patients pretreated with low-dose chemotherapy, can cause clinical effects in approximately 50% of patients. Circulating T cells targeting defined melanoma-associated antigens have a strong prognostic impact in patients with melanoma, as shown earlier by Weide and colleagues (3). Collectively, these observations necessitate an explanation about why the T cells in the tumor microenvironment or periphery do not function to destroy the melanoma target cells. In this issue, Weide and colleagues describe how cellular control mechanisms restricting T-cell functions can explain why some patients fare worse in their disease than others. The main protagonists in their report are MDSCs, which constitute a heterogeneous group of cells of granulocytic (grMDSC) or monocytic (moMDSC) lineage (4, 5). They share the capacity to suppress T cells and natural killer cells and are also able to promote angiogenesis and act as osteoclast progenitors. Peripheral moMDSCs (CD14⁺CD11b⁺HLA-DR⁻low) were previously shown to correlate with tumor burden in malignant melanoma (6). The same type of moMDSCs has now been shown by Weide and colleagues to have a strong prognostic impact in a cohort of 94 patients with advanced melanoma. A circulating frequency greater than 11% was independently associated with poor survival and was as important as the M-category in predicting outcome according to the Cox regression analysis. Because their enumeration of MDSCs by flow cytometry is a robust and easy-to-perform assay, this method holds promise to be applied in a clinical setting, in which it could be of importance in determining choice of therapy.

An additional aim of their study was to investigate the prognostic relevance of Tregs. Tregs are known to be enriched in the blood of patients with metastatic melanoma and other tumor types, possibly due to their greater resilience to oxidative stress (7). Yet, in the cohort studied by Weide and colleagues, no differences in disease outcome according to the frequency of Tregs were found. But as the role of Tregs in cancer is not clear, with the frequency and functions of Treg associated with a poor prognosis in some cancers but with favorable outcome in others (8), this comes as no great surprise. One may surmise that at least for malignant melanoma, MDSCs are of greater importance than Tregs in affecting clinical outcome, and accordingly therapies targeting the enhanced level of MDSC seem worthwhile pursuing.

A strong correlation was noted between high levels of MDSCs and the absence of antigen-specific T cells, as assessed by intracellular cytokine flow cytometric assays against peptides derived from the tumor antigen NY-ESO-1 or Melan-A. The T-cell data were similar to their earlier report (3), in which they examined 112 patients with advanced melanoma, of which one cohort was composed of 18 long-term survivors with an extraordinarily favorable
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 the 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 causal, 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 poor clinical prognosis is, however, novel and suggests a causal relationship in which moMDSCs counteract the development of tumor-specific T cells (Fig. 1). There are, however, two different ways of interpreting this correlation. One explanation is that the observed frequencies of NY-ESO-1–specific memory T cells mirror true in vivo differences, in which case the interaction between the moMDSCs and the T cells takes place in the patient. But the ambiguity of the interpretation of the correlation lies in that the low precursor frequency of the tumor-specific T cells does not permit the direct ex vivo assessment of T-cell frequencies but requires a 12-day in vitro prestimulation before applying the cytokine release assay. Therefore, an alternative and equally likely interpretation is that this interaction takes place in vitro during the preculturing period when the MDSCs will have the chance to negatively influence the T-cell induction. MDSCs have been shown to negatively influence CD4+ as well as CD8+ T cells directly (4, 5), and can also indirectly do so via their negative influence on antigen-presenting dendritic cells (DCs) (10). These possibilities were discussed and their inability to obtain conclusive data supporting one or the other of these alternatives was commented. Yet, the prognostic value of these blood-derived parameters remains also in the absence of knowledge on the exact underlying mechanism. If confirmed they could complement the lactate dehydrogenase which presently is the only established blood biomarker.

Granulocytic MDSCs were not analyzed. Yet, their frequency is enhanced in advanced melanoma, and they have been suggested to possess a powerful suppressive capacity.

Figure 1. High levels of MDSC lead to absence of melanoma antigen-specific T cells and to tumor progression and poor prognosis. 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 DC (4) 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

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