Rethinking the role of myeloid-derived suppressor cells in adoptive T-cell therapy for cancer

Ainhoa Arina

Department of Pathology; The University of Chicago; Chicago, IL USA

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The expansion of cancer-induced myeloid cells is thought to be one of the main obstacles to successful immunotherapy. Nevertheless, in murine tumors undergoing immune-mediated destruction by adoptively transferred T cells, we have recently shown that such cells maintain their immunosuppressive properties. Therefore, adoptive T-cell therapy can, under certain conditions, overcome myeloid cell immunosuppression.

A myriad of studies have demonstrated the immunosuppressive capabilities of cancer-induced myeloid cells, including myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages (TAMs). The general notion in the field is that when cancer immunotherapy strategies fail to cure cancer, it is very likely that MDSCs and/or TAMs are involved. However, a careful review of the literature uncovers a litany of unresolved questions regarding such a notion (see references in Ref. 1). For instance, most studies use in vitro assays to characterize the immunosuppressive properties of MDSCs/TAMs, raising questions about the extent to which such assays reflect the actual contribution of MDSCs/TAMs to a poor antitumor immune response occurring in vivo. Also, the effects of cancer-induced myeloid cells on naïve vs. effector/memory T-cells differ markedly in vitro. In vivo, MDSCs have been reported to suppress naïve T-cell responses in some models, but it is unclear how effector/memory T cells are affected, which is more relevant for tumor-infiltrating T cells.

We recently showed that adoptively transferred immune (memory) but not naïve T cells eliminated well-established tumors that expressed natural (i.e., non-artificially overexpressed) antigens. However, mice bearing such tumors had increased levels of MDSCs and abundant TAMs that were strongly immunosuppressive by the standard in vitro suppression assay. Conceptually, there were three possible explanations accounting for the success of T cells in eliminating tumors, despite the presence of cancer-induced myeloid cells: (i) myeloid cells were eventually abolished, (ii) myeloid cells shifted to a more “benign” phenotype, or (iii) the myeloid cells were neither eliminated nor shifted, but simply failed to prevent tumor eradication by T cells.

In prior studies from our lab, we demonstrated that stromal myeloid cells can cross-present antigen during T-cell destruction of tumor cells overexpressing artificial model antigens, a process leading to stromal cell death. In such in vivo models, myeloid cells acted as “double agents” cross-presenting antigen to activate T cells more efficiently than cancer cells, despite retaining immunosuppressive potential as characterized in vitro. In other studies, tumor immunotherapy has been shown to stimulate changes in the composition of myeloid infiltrate required for optimal antitumor function of T cells. Such beneficial deviations could affect the distribution of myeloid cells in favor of more proinflammatory subsets, or alter the function of TAMs to elicit T cells to produce antitumoral cytokines (original references in Ref. 1). Nevertheless, in our native antigenic tumor model, we found that concurrently with T-cell tumor infiltration and tumor destruction, most myeloid cells retained viability, appeared relatively stable in their subset distribution and production of cytokines, and maintained their ability to suppress T-cell function in vitro. Thus, our adoptively transferred T cells were able to overcome the immunosuppression imposed by the biological activity of MDSCs and TAMs present in the tumor. This finding does not necessarily dictate that the myeloid cells present during tumor destruction were the exact same that were there prior to T cell infiltration. In fact, our in vivo longitudinal imaging data have revealed morphological changes in stromal cells during tumor destruction in response to adoptively transferred T cells, possibly suggesting infiltration of new myeloid cells from the circulation. T-cell mediated tumor elimination was also characterized by the destruction of cancer cells and tumor vasculature following parallel kinetics (Fig. 1).

There are several practical implications arising from these findings. First, the observation that MDSCs and TAMs can exhibit strongly immunosuppressive activities in vitro does not necessarily mean that they actually will be immunosuppressive in vivo. Concerns about the applicability of findings derived from in vitro murine suppression assays to the
pathophysiology of patient responses in the clinic have been raised. 7 In support, the recent study demonstrated that myeloid cells were ineffective if the mice became old prior to use. Furthermore, the collaboration of CD8+ and CD4+ T cells is crucial for the optimal efficacy of antitumor T-cell responses,9 and our ongoing work supports that this paradigm also holds true in the case of adoptive T-cell therapy (unpublished observations). Finally, the choice of antigen to be targeted by CD8+ T cells is of utmost importance. In these regards, we have recently shown that upon adoptive T cell transfer, only peptides with high-affinity for MHC class-I are efficiently cross-presented by tumor stroma, thereby inducing T cell cytokine secretion and associated stromal cell death, and culminating in relapse-free regression of tumors.2 New methods to identify mutated epitopes based on whole-exome sequencing of tumors will permit the identification of truly tumor-specific antigens10 with the highest potential affinity for MHC class-I, leading to a new generation of engineered T cells for cancer immunotherapy.

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

References

1. Arina A, Schreiber K, Binder DC, Karrison TG, Liu RB, Schreiber H. Adoptively transferred immune T cells eradicate established tumors despite cancer-induced immune suppression. J Immunol 2014; 192:1286-93; PMID:24367029; http://dx.doi.org/10.4049/jimmunol.1202498
2. Schreiber K, Arina A, Engels B, Spiotto MT, Sidney J, Sette A, Karrison TG, Weichselbaum RR, Rowley DA, Schreiber H. Splenic cells from young but not old immunized mice eradicate large established cancers. Clin Cancer Res 2012; 18:2526-33; PMID:22445314; http://dx.doi.org/10.1158/1078-0432.CCR-12-0127
3. Spiotto MT, Rowley DA, Schreiber H. Bystander elimination of antigen loss variants in established tumors. Nat Med 2004; 10:294-8; PMID:14981514; http://dx.doi.org/10.1038/nm999
4. Zhang B, Zhang Y, Bowerman NA, Schietinger A, Fu TX, Krantz DM, Rowley DA, Schreiber H. Equilibrium between host and cancer caused by effector T cells killing tumor stroma. Cancer Res 2008; 68:1563-71; PMID:18316622; http://dx.doi.org/10.1158/0008-5472.CAN-07-5324
5. Engels B, Engelsland YH, Sidney J, Sette A, Binder DC, Liu RB, Krantz DM, Meredith SC, Rowley DA, Schreiber H. Relapse or eradication of cancer is predicted by peptide-major histocompatibility complex affinity. Cancer Cell 2013; 23:516-26; PMID:23957565; http://dx.doi.org/10.1016/j.ccr.2013.03.018
6. Schietinger A, Arina A, Liu RB, Wells S, Huang J, Engels B, Bindokas V, Barkowski T, Lee D, Herrmann A, et al. Longitudinal confocal microscopy imaging of solid tumor destruction following adoptive T cell transfer. Oncimmunology 2013; 2:e26677; PMID:24482756; http://dx.doi.org/10.4161/onci.26677
7. Gross A, Turiotte S, Wunderlich JR, Ahmadzadeh M, Dudley ME, Rosenberg SA. Myeloid cells obtained from the blood but not from the tumor can suppress T-cell proliferation in patients with melanoma. Clin Cancer Res 2012; 18:5212-23; PMID:22857179; http://dx.doi.org/10.1158/1078-0432.CCR-12-1108
8. Schmidt K, Zilio S, Schmollier JC, Bronte V, Blankenstein T, Willimsky G. Differently immunogenic cancers in mice induce immature myeloid cells that suppress CTL in vitro but not in vivo following transfer. Blood 2013; 121:1740-8; PMID:23305737; http://dx.doi.org/10.1182/blood-2012-06-436568
9. Schietinger A, Philip M, Liu RB, Schreiber K, Schreiber H. Bystander killing of cancer requires the cooperation of CD4+ and CD8+ T cells during the effector phase. J Exp Med 2010; 207:2469-77; PMID:20921286; http://dx.doi.org/10.1084/jem.20092450
10. Weck X, Wala V, Lin JC, Tee JK, Prickett TD, Garnett J, Davis S, Stemke-Hale K, Davies MA, Getzenfelder JE, et al.; NISC Comparative Sequencing Program. Exome sequencing identifies GRIN2A as frequently mutated in melanoma. Nat Genet 2011; 43:442-6; PMID:21499247; http://dx.doi.org/10.1038/ng.810