Myeloid-derived suppressor cells as a Trojan horse
A cellular vehicle for the delivery of oncolytic viruses

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Myeloid-derived suppressor cells (MDSCs) consist of a heterogeneous population of immature myeloid cells and play an important role in the evasion of immune responses by cancer cells. Thus, MDSCs represent one of the main obstacles against successful anticancer (immuno)therapies. MDSCs stimulate tumor growth and promote metastasis by suppressing antitumor immune responses as well as by stimulating neangiogenesis.1,3 MDSCs, which can be recruited to neoplastic lesions and inflammatory sites by chemokine gradients, have been shown to suppress antitumor immunity through a number of mechanisms, including the production of arginase 1, reactive oxygen species and nitric oxide (resulting in the production of nitric oxide (NO)), and nitric oxide (resulting in the production of nitric oxide (NO)) species and nitric oxide (resulting in the production of nitric oxide (NO)). This resulted in a significant increase in the long-term survival of mice bearing metastatic colon carcinomas, when compared with systemic administration of VSV alone, in the absence of significant toxicity.

Oncolytic viruses can specifically infect and kill tumor cells while leaving normal cells largely unaffected. Although the greatest strength of oncolytic virus consists in their selective and efficient replication within cancer cells, leading to their lysis, our limited ability to deliver oncolytic viruses specifically and efficiently to neoplastic lesions still constitutes a major hindrance against the success of oncolytic virotherapy. The intratumoral injection of oncolytic viruses has been shown to effectively prolong the survival of mice bearing metastatic tumors. Still, this type of therapy cannot be employed in humans affected by multifocal or inaccessible tumors. Conversely, the systemic administration of oncolytic viruses would allow for their dissemination to occult metastases, but this approach requires high viral doses, which may cause toxic effects, and is often limited by the neutralizing activity of pre-existing circulating antibodies. To circumvent these issues, chemokine-dependent cellular vehicles have been explored as a means to deliver oncolytic viruses to neoplastic lesions. Various immune cell types have been investigated in this respect, including tumor-antigen specific TCR-transgenic T cells, cytokine-induced killer cells and macrophages.

MDSCs have the unique ability to specifically migrate to neoplastic lesions and promote tumor growth. Ablation of signaling from leukocyte immunoglobulin-like receptor, subfamily B (with TM and ITIM domains), member 3 (LILRB3, also known as PIRB) not only significantly limits the immunosuppressive functions of MDSCs, but also bestows them with type-1 macrophage (M1)-like activities, namely, an M1 cytokine secretion profile and tumoricidal functions. Interestingly, the tumor tropism of Lirb3–/– MDSCs is not significantly affected. Moreover, polyinosinic-polycytidylic acid (polyl:C), a synthetic Toll-like receptor 3 (TLR3) agonist, has been shown to convert tumor-supporting myeloid cells into tumoricidal M1-like effector cells. We hypothesized that the viral transduction could change the phenotype of MDSCs from that of tumor-promoting M2 cells to that of antitumor M1 cells without significantly affecting their tropism for malignant neoplastic lesions.4 This resulted in a significant increase in the long-term survival of mice bearing metastatic colon carcinomas, when compared with systemic administration of VSV alone, in the absence of significant toxicity.
The use of MDSCs as a cellular vehicle for the tumor-targeted delivery of oncolytic viruses has several advantages over that of other immune cells. In our study, we found that MDSCs exhibit an improved tumor-tropism as compared to many other immune cells analyzed. The administration of VSV-loaded MDSCs to tumor-bearing mice significantly prolonged their survival as compared with systemic viral therapy. Since MDSCs express CD16 (FcγRIII receptor) and CD32 (FcγRII receptor), a non-neutralizing monoclonal antibody specific for the VSV G-protein further enhanced VSV binding to MDSCs by bridging the virus to Fc receptors. To understand whether the adoptive transfer of MDSCs might promote tumor growth and metastasis, we analyzed the phenotype of MDSCs in the presence or absence of viral loading. Importantly, upon loading with VSV, MDSCs acquired an M1-like functional phenotype and exerted direct tumoricidal functions, which might (at least in part) contribute to therapeutic effects observed in tumor-bearing mice. Therefore, in this setting MDSCs served not only as tumor-targeting carriers for VSV but also as tumoricidal effector cells (Fig. 1). Recently, it has been shown that MDSCs can be infected with attenuated *Listeria monocytogenes* and selectively deliver the tumoricidal bacteria to primary tumors and metastases. Interestingly, upon bacterial infection, a subpopulation of MDSCs also acquired an immunostimulatory phenotype.

Despite their well-documented tumor-promoting functions, MDSCs—at least in some circumstances—can be used as a Trojan horse for the treatment of cancer and possibly several other inflammatory diseases. At least theoretically, MDSCs might also be used to deliver other anticancer (immuno)therapeutics, including TLR ligands, nanoparticles, chemotherapeutic agents, antibody-conjugated radionuclides and tumor-associated antigens. Moreover, the robust immunosuppressive activity of MDSCs may provide ample opportunities for the treatment of graft rejection and autoimmune diseases. However, the limited availability of MDSCs, reflecting the paucity of these cells in healthy hosts, as
well as safety concerns surrounding the use of MDSCs recovered from tumor-bearing hosts constitute an obstacle against the use of MDSCs as therapeutic agents. We have devised a system in which functionally active MDSCs can efficiently be generated from embryonic cells and bone marrow hematopoietic stem cells. Currently, efforts to derive human MDSCs from mobilized hematopoietic stem cells are underway and should facilitate the utilization of MDSCs in clinical settings.

Disclosure of Potential Conflicts of Interest
S-H.C. has filed a patent application based on the use of myeloid-derived suppressor cell as a cellular vehicle for tumor targeting. The other authors declare no conflicts of interest.

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