Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population consisting of myeloid cells in their early developmental stages. Immature myeloid cells bearing the same phenotype as MDSCs naturally occur in healthy individuals in low frequencies but lack immunosuppressive functions. In contrast, MDSCs are found to accumulate in high numbers in tumor-bearing animals and cancer patients, as well as patients that are suffering from inflammation and infections. These cells carry potent immune suppressive functions against anti-tumor T-cell immunity through the production of immune regulatory cytokines, arginase-1, or reactive oxygen species (ROS). In mice, MDSCs are identified by the co-expression of CD11b and Gr-1. However, a number of MDSC phenotypes have been associated with different human cancer types. We and others reported the accumulation of a CD14⁺HLA-DR⁻/lo myeloid sub-population in the peripheral blood of advanced stage melanoma patients and characterized them as monocytic MDSCs. These cells showed increased surface expression of CD80, CD83, and DC-SIGN, and could suppress autologous T cell functions in a STAT-3 dependent manner. It is likely that the activation of transcription factor STAT-3 in these myeloid cells is induced by tumor-derived inflammatory factors, given that a variety of these molecules have been shown to be responsible for the induction and expansion of MDSCs, i.e., IL-1β, IL-6, GM-CSF, as well as prostaglandin E2 (PGE₂).

In a recent study, we investigated the detailed mechanisms of how MDSCs could be induced by tumor cells, when healthy donor-derived monocytes were co-cultured with early-passage melanoma tumor cell lines. The resulting tumor-educated monocytes bear a striking resemblance to the previously characterized CD14⁺HLA-DR⁻/lo monocytic MDSCs identified in advanced stage melanoma patients. In this co-culture system, inhibition of cyclooxygenase-2 (COX-2) enzymatic functions with a selective COX-2 inhibitor was sufficient to abrogate the suppressive activity of the MDSC-like cells on autologous T cells. COX-2 is an enzyme that is responsible for the synthesis of PGE₂, which has been shown to be one of the important immune regulatory factors produced by tumor cells, as well as a number of immune cell types. Importantly, treatment of monocytes with PGE₂ alone was sufficient to convert them into potent suppressors of autologous T cells.

A positive feedback loop of MDSC-derived COX-2 and PGE₂ has been proposed, where Obermajer et al. demonstrated the importance of PGE₂ in inducing and maintaining the suppressive functions of MDSCs in ovarian cancer patients. Indeed, MDSC-like cells generated by our tumor co-culture model, but not the control monocytes, exhibit a significant upregulation of intracellular COX-2 expression (Mao Y., unpublished data). Pre-treatment of the MDSC-like cells with COX-2 inhibitor before adding T cells could significantly rescue T-cell functions. Moreover, monocytes retrieved from the blood of advanced stage melanoma patients utilize PGE₂ as a major suppressive mechanism, in addition to superoxide production and STAT-3 signaling.

Together, these 2 studies provide convincing evidence in support of COX-2/PGE₂ being the master regulator of suppressive capacity of MDSCs in cancer. Expression of COX-2 could be a distinct molecular signature that is associated with the suppressive functions of MDSCs in cancer patients. Thus, we believe that during the MDSC induction phase, tumor-derived factors could activate the COX-2/PGE₂ pathway on healthy monocytes, conferring them with a MDSC phenotype and triggering the production of a number of suppressive mechanisms. Moreover, during the MDSC effector phase, secretion of PGE₂ by MDSCs...
Counteracting immune suppression induced by MDSCs has been proposed as a promising therapeutic possibility for cancer. The essential role of the COX-2/PGE2 pathway in the induction, expansion, and maintenance of MDSCs in cancer provides an attractive target for clinical immune intervention. Various selective COX-2 inhibitors or antagonists interfering with the PGE2 receptors may consolidate and enhance the current immunotherapy in cancer patients.

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

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Figure 1. A schematic illustration of how COX-2/PGE2 pathway is steering the functions of MDSCs in cancer. (A) In the MDSC induction phase, tumor-derived factors activate the expression of COX-2 in healthy monocytes, triggering the immune suppressive functions of these monocytes. (B) In the MDSC effector phase, PGE2, as well as other suppressive mechanisms are produced at a high level by MDSCs. In addition, MDSC-derived PGE2 maintains and enhances MDSC suppressive functions in an autocrine manner.

can directly suppress anti-tumor T cell functions, as well as stabilize the suppressive capacity of the MDSCs via the positive feedback loop (Fig. 1). Yet, it still remains to be elucidated to what extent the COX-2/PGE2 pathway in tumor cells could contribute to the induction of MDSCs, as COX-2 has been reported to be overexpressed in various cancer types and has been proposed as a negative prognostic factor for melanoma patients.9

Triggering anti-tumor immunity in cancer patients utilizing autologous dendritic cell (DC)-based therapy is currently under investigation in a number of clinical trials (including several performed at our institution). Even though the detailed DC production and treatment strategies vary among laboratories, most of the procedures involve isolation of monocytes from patient blood as the precursors for generating DCs. It is of particular interests to evaluate whether the presence of pathologic frequencies of MDSCs (>50%) could impair the quality of the DC vaccines. Of note, we have previously shown the negative impact of MDSCs on the overall quality of DC maturation,10 which might be dependent on the over-production of COX-2/PGE2 during early-stage of DC maturation, as suggested by the above-mentioned mechanisms.
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