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Editorial

# Editorial: **PGE2-producing MDSC: a role in tumor progression?**

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APCs play a fundamental role in the initiation and outcome of the immune response. Depending on their nature and/or properties, they can promote the differentiation and/or expansion of $CD4^+$ T cells toward a type 1, type 2, type 17, or regulatory phenotype and promote or suppress CTL proliferation and activity. Seminal work from the group of Gabrilovich [1] clearly demonstrated that TDFs restrain DC maturation and promote the accumulation of MDSCs in tumor-bearing hosts. Indeed, VEGF, GM-CSF, PG, and other factors secreted by tumors promote extramedullary hematopoiesis and lead to MDSC accumulation in the neoplastic bed and in the secondary lymphoid organs. In these sites, MDSCs induce T cell anergy, restrain the effector phase of the $CD8^+$ T cell, and can promote antigen-specific Treg proliferation [1, 2] by mechanisms that require arginase and/or NOS expression or TGF-$\beta$ and/or ROS production.

The appearance of cells with similar properties and phenotype can be obtained from GM-CSF-driven, BM-derived cultures by the addition of tumor-conditioned media [3]. Although in the absence of TDFs, BM precursors differentiate into myeloid DCs; in the presence of conditioned media, $CD11c^{low}$, $Gr1^+$, MHC class $II^{low/-}$, and $F4/80^+$ MDSCs are generated [4].

In this issue, Eruslanov and colleagues [5] suggest that TDFs promote MDSC function and differentiation by inducing the intracellular production of PGE2.

PGE2 is one of the best-characterized and studied isoform of eicosanoids that possesses proinflammatory and immunosuppressive properties and that is produced during the course of inflammation following cellular stresses, in response to growth factors, hormones, endotoxin, and inflammatory cytokines or by growing tumors.

This eicosanoid is synthesized by COX2, which converts arachidonic acid into PGH2 and PGES1, which isomerizes PGH2 in PGE2, and PGE2 can be catabolized in biologically inactive 15-keto-PGs by 15-PGDH and carbonyl reductase or secreted by the transporter MRP4 (**Fig. 1**).

The group of Kusmartsev showed that TDFs induce COX2, PGES1, and MRP4 and down-regulate the expression of 15-PGDH in BM-derived MDSCs [5]. These data indicate that MDSCs can actively produce and secrete PGE2. This production and secretion correlate with arginase overexpression, STAT3 and STAT1 phosphorylation, and IL-10 and MIP-2 production, a phenotype typically associated with MDSC suppressive activity. Importantly, COX2 pharmacologic inhibition reverts this suppressive phenotype and partially restores the differentiation of BM cells into myeloid DCs (Fig. 1).

PGE2 is a pleiotropic molecule involved in numerous (and sometimes opposite) biological processes, including angiogenesis, apoptosis, inflammation, and immune suppression. Its presence in the tumor microenvironment seems to favor tumor progression. By producing this biological mediator, the role of tumor-associated MDSCs can become more prominent in many neoplastic processes (Fig. 1). Tumor angiogenesis has been correlated with the intratumoral concentration of PGE2. This prostaglandin can influence VEGF mobilization and the incorporation of fibroblast and endothelial cells into a tumor vessel through the binding of EP-2 receptors [6]. Similarly, MDSCs were shown to regulate VEGF bioavailability though MMP9 expression and to promote angiogenesis by being incorporated in tumor vessels. As MDSCs express the PGE2 receptors EP-2 and EP-4, it is possible that they play an even more important role in tumor angiogenesis: in an autocrine manner, by being activated to express MMP9 and in a paracrine manner, by influencing other populations in the tumor stroma [7]. Prevention of apoptosis of neoplastic cells has been associated with PGE2, which in fact,
can increase the expression of the anti-apoptotic factor BCL-2 and can activate the PI3K/AKT, ERK, EGFR, and cAMP pathways that mediate prosurvival signaling in tumor cells [8]. Thus, it is possible that tumors that are able to recruit and differentiate MDSCs in their stroma

Abbreviations: 15-PGDH=15-hydroxy-PG dehydrogenase, BCL-2=B-cell chronic lymphocytic leukemia/lymphoma 2, BM=bone marrow, EP=E-prostanoid, MDSC=myeloid-derived suppressor cell, MMP9=matrix metalloproteinase 9, MRP4=multidrug resistance protein 4, PG=prostaglandin, PGES1=PGE synthase 1, TDF=tumor-derived factor, Treg=regulatory T cell

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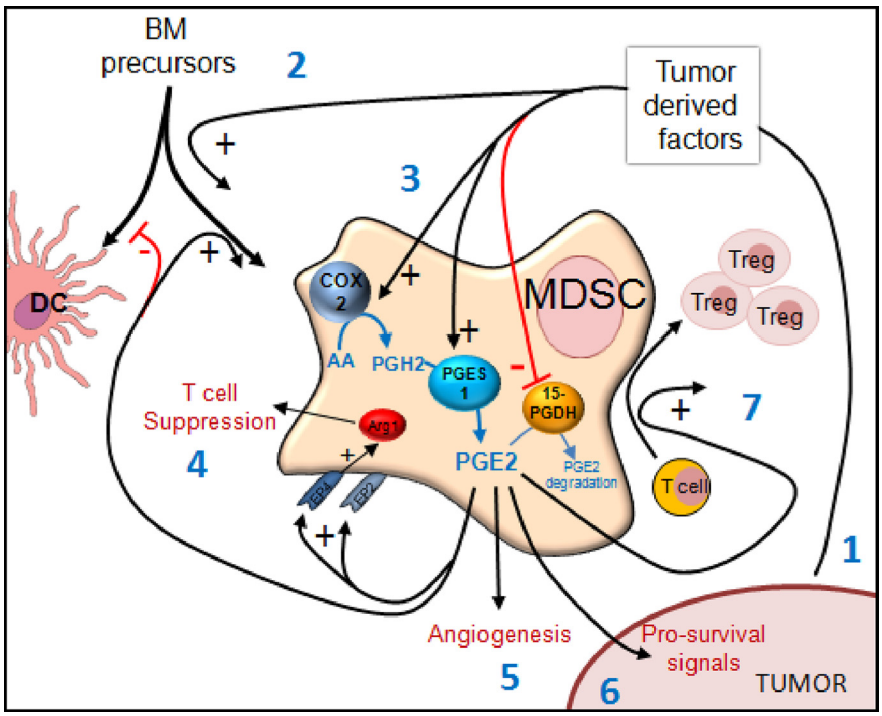


**Figure 1. Possible role of PGE2-expressing MDSCs in tumor progression.** (1) Tumor-derived factors promote the differentiation of BM precursors into MDSCs and (2) increase the expression of PGE2-producing enzymes COX2 and PGES1, while inhibiting the catabolizing enzyme 15-PGDH. The resulting increase in PGE2 production and secretion autocrinally activates Arg1 expression and MDSC-suppressive activity (4) and angiogenic potential. Paracrinally, PGE2 secretion can promote tumor angiogenesis further (5) by activating stromal endothelial cells and fibroblast. Furthermore, (6) MDSC-produced PGE2 inhibit tumor apoptosis by providing pro-survival signals (i.e., BCL-2). Finally, (7) PGE2 could potentiate the MDSC-mediated Treg proliferation.

could benefit directly from PGE2 production. Finally, PGE2 production by MDSCs can be seen as an additional mechanism of immunosuppression used by this myeloid-derived population: PGE2 can inhibit tumor immunity by numerous mechanisms, some of which are still not fully understood. This eicosanoid can restrain DCs by inhibiting their maturation, the expression of co-stimulatory molecules, and the production of IL-12, leading to an imbalance in Th1 and Th2 responses. Moreover, PGE2 can promote the differentiation of tolerogenic DC-producing IL-10 and IDO promoting the conversion of $CD4^+$ T cells into Tregs [6]. Also, PGE2 directly affects the capacity of $CD8^+$ T cells to recognize the cognate antigen expressed by tumor cells. Finally, PGE2 stimulates arginase 1 expression and the suppressive activity of MDSC after binding the EP-4 receptor [9]. Interestingly, we previously showed that MDSCs can promote the antigen-specific Treg proliferation directly by a mechanism that requires arginase expression and cross-presentation of tumor antigens [2]. As PGE2 enhances the suppressive activity of Tregs, and it is involved in the conversion of $CD4^+CD25^-$ into Tregs (even when T cells are stimulated in the absence of APCs by the anti-CD3 antibody) [10], it is possible that the autocrine secretion of this eicosanoid participates or potentiates MDSC-dependent Treg proliferation. These considerations suggest that PGE2-producing MDSCs and PGE2 metabolism could play a prominent role in tumor progression. This hypothesis is sustained by the fact that forcing PGE2 catabolism in the tumor environment by using an adenoviral vector encoding for 15-PGDH is sufficient to restore tumor immunity and reduce tumor progression significantly [11].

Despite these data and hypotheses, the plethora of data indicating PGE2 as an important mediator of inflammation must not be forgotten. Indeed, in the last year, numerous reports indicate a prominent role of PGE2 in inducing a Th17 and Th1 inflammatory response. These observations culminated last year in the work of Yao et al. [12], showing that IL-12 and PGE2 promote the differentiation of $CD4^+$ T cells toward a Th1 phenotype; PGE2 can enhance IFN-γ and IL-17 production in $CD4^+$ T cells after engagement of EP-2 and EP-4; and PGE2 induces DCs to produce IL-23 by a mechanism that requires the endogenous activation of COX2. Although these findings were shown to be relevant in mice subjected to experimental autoimmune encephalomyelitis or contact hypersensitivity [12], the importance in tumor biology cannot be underestimated, as DCs transduced with IL-23 have been described as capable of triggering powerful antitumor activity [13]. Furthermore, previous studies indicate that PGE2, by up-regulating the OX40 ligand, CD70, and 41BB on DCs, enhances T cell proliferation and promotes inflammation [6].

Taken together, these reports indicate a prominent role of PGE2 in APC differentiation; however, it is still not clear how PGE2 induces tolerogenic APCs, MDSCs, or immunogenic DCs. It is possible that depending on the PGE2 concentration in the microenvironment, this eicosanoid exerts different functions. Alternatively, the binding of PGE2 to the different EP receptors can promote selected differentiation pathways on APCs. Finally, additional cytokines or factors present in the differentiation milieu can integrate PGE2 signaling determining the APC phenotype.

In conclusion, a better understanding of how PGE2 signaling is fine-tuned is necessary to fully understand the molecular basis of APC differentiation that could lead to a new era for the treatment of cancer and autoimmune diseases.

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