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In Brief: Myeloid-derived suppressor cells in cancer

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Abstract

The role of myeloid-derived suppressor cells (MDSCs) in cancer development has become clear over recent years and MDSC targeting is an emerging opportunity for enhancing the effectiveness of current anti-cancer therapies. Since MDSCs are not only able to limit anti-tumour T cell responses, but also to promote tumour angiogenesis and invasion, their monitoring has prognostic and predictive value. Herein we review the key features of MDSCs in cancer promotion.

Keywords: myeloid-derived suppressor cells; tumour promotion; immune suppression

Myeloid-derived suppressor cells in the tumour microenvironment

The phenotype of a tumour microenvironment is shaped not only by the epithelial component, but also by the interaction with mesenchymal cells and the inflammatory infiltrate. In recent years, the contribution of these components to cancer progression has been evaluated, including ligands, cell-cell adhesion molecules, metabolites, oxygen and multiple soluble factors together with the expansion of immune cells (such as B cells, NK cells, macrophages, Th2, Th17 and Treg). Given the prominence of the immune infiltrate in the tumour microenvironment, evaluating the so-called “immunoscore” has been proposed as a computer-based analysis to quantify the immune component for improved patient management [1].

Myeloid-derived suppressor cells (MDSCs) represent a major population of regulatory cells that are expanded in different types of cancer and impair anti-tumour innate and adaptive immune responses. Many studies have underscored complex MDSC phenotypes that are not restricted to a single defined myeloid cell population, but rather exhibit a plastic phenotype responsive to tumour-derived soluble factors. These phenotypes can be reduced to three main subsets: granulocytic (PMN)-MDSCs, monocytic (M)-MDSCs and early stage (e)-MDSCs [2, 3 and Figure 1]. MDSCs originate from myeloid progenitors in the bone marrow and are expanded and activated by stromal and tumour-derived factors; the different composition of soluble factors mobilizing MDSCs dictates the phenotypical features of MDSC subsets observed in each patient. The pathological activation of myeloid precursors causes their acquisition of suppressive activity toward immune cells through a number of mechanisms depending on cell-surface interactions, the release of short-lived soluble mediators and the activation of enzymes (such as PD-L1/2, release of ROS and RNS, and activation of ARG1, IDO, iNOS; reviewed in [2]). Besides these strategies of immune suppression, MDSCs are also able to promote

tumour growth by acting on cancer cells or by triggering mechanisms responsible for tumour dissemination (Figure 1). Here, we will discuss some new advances in the field, documenting an enlargement of the sphere of influence of MDSCs.

Direct effects of MDSCs on cancer cells.

MDSCs may enhance the stemness of cancer cells [4, 5]. In particular, MDSCs triggered miRNA101 expression in ovarian cancer cells and promoted cancer stemness by targeting corepressor C-terminal-binding protein 2 (CtBP2). High levels of miRNA101 were associated with reduced overall survival in ovarian cancer patients; moreover, high $CD33^+$ MDSC infiltration correlated with low CtBP2, suggesting that the combination of CtBP2 and MDSCs allow for improved prognostic stratification of ovarian cancer [4]. In line with these data, $STAT\text{-}3^+$ Mo-MDSCs expanded after exposure to human pancreatic cancer (PC) cells and increased the frequency of aldehyde dehydrogenase-1^+ (ALDH1) cancer stem cells; PC patients with a predominant $CD14^+$ tissue infiltrate had reduced survival and the $CD14^+$ cell subset correlated with tumour ALDH1 expression [5]. MDSCs may also promote tumour progression in PTEN null prostate tumour models by opposing senescence of cancer cells through the release of IL-1RA in the tumour microenvironment and the consequent effects on IL-1Rα signalling [6]. Of note, IL-1RA inhibited docetaxel-induced senescence also in human prostate cancer cells, and patients with high levels of intratumoural IL-1RA did not respond to docetaxel and had a short disease free survival compared with patients with normal IL-1RA, and tumour-infiltrating $CD33^+$ myeloid cells were inversely correlated with the presence of $p16^{INK4A+}$ senescent cells [6].

Promotion of angiogenesis.

MDSCs may also have a profound influence on tumour angiogenesis; in fact, murine MDSCs are not only a rich source of MMP9, which can increase the bioavailability of

VEGF, but also have the potential to differentiate into endothelial-like cells [7]. In this context, the cytokine Bv8 appears to be an important mediator of myeloid cell mobilization and myeloid cell-dependent tumour angiogenesis, since Bv8 expression is upregulated in MDSCs following implantation of tumour cells and anti-Bv8 treatment of mice implanted with human tumours reduced angiogenesis and tumour growth. Moreover, MDSCs mediated tumour refractoriness to bevacizumab, an anti-VEGF neutralizing monoclonal antibody, and the molecular mechanisms responsible for resistance to anti-VEGF therapy induced by MDSCs reside in the release of cytokines, such as G-CSF and MCP-1 and proinflammatory factors MIP-2 and IL-1R [7].

Effects on the pre-metastatic niche.

There is increasing evidence from preclinical studies that MDSCs play an important role in the pre-metastatic niche. An example derived from a spontaneous model of uveal melanoma, in which PMN-MDSCs attracted by CXCL5 and infiltrating primary tumours were able to actively promote cancer cell dissemination by inducing epithelial-mesenchymal transition (EMT); transcriptome analysis revealed that the main inducers of EMT were Hepatocyte Growth Factor (HGF) and Transforming Growth Factor-β1 (TGF-β1) secreted by PMN-MDSCs, and Epidermal Growth Factor (EGF) released by tumour cells [8]. In addition, in another spontaneous model of breast cancer, tumour-induced IL-17-producing γδ T cells drove systemic expansion and polarization of neutrophils to PMN-MDSCs that, in turn, contributed to suppress a $CD8^+$ response and metastasis formation in distant organs [9].

These data indicate that MDSCs, historically recognized as the most potent inhibitors of T cell response, are actually able to orchestrate more potent strategies to redefine the outcome of tumour development, by contributing to cancer progression and metastasis.

Future studies are required to unveil the role of MDSC activity in the pre-metastatic niche and provide new immune target therapies to improve metastatic disease management.

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Author contributions statement

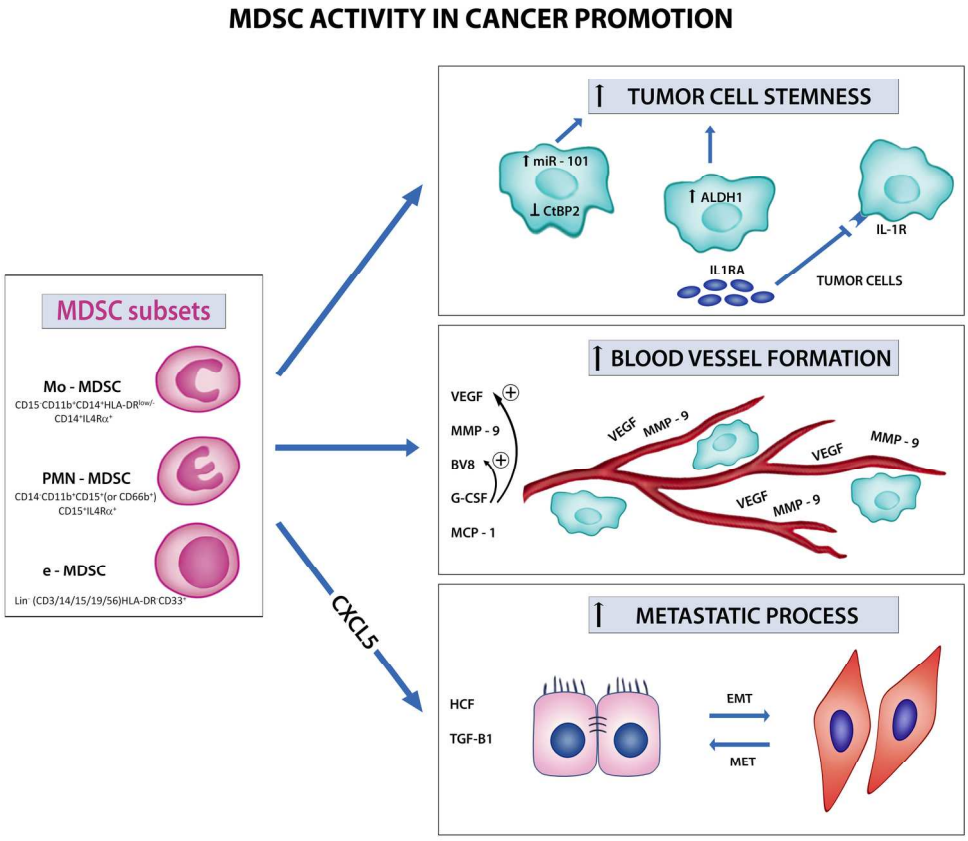
S.S, L.P and S.M wrote the manuscript,

References

1. Galon J, Mlecnik B, Bindea G*, et al.* Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. *J Pathol*. 2014;Sect. 199-209.
2. Bronte V, Brandau S, Chen SH*, et al.* Recommendations for myeloid-derived suppressor cell nomenclature and characterization standards. *Nat Commun* 2016; **7**: 12150.
3. Solito S, Marigo I, Pinton L*, et al.* Myeloid-derived suppressor cell heterogeneity in human cancers. *Ann N Y Acad Sci* 2014; **1319**: 47-65.
4. Cui TX, Kryczek I, Zhao L*, et al.* Myeloid-derived suppressor cells enhance stemness of cancer cells by inducing microRNA101 and suppressing the corepressor CtBP2. *Immunity* 2013; **39**: 611-621.
5. Panni RZ, Sanford DE, Belt BA*, et al.* Tumor-induced STAT3 activation in monocytic myeloid-derived suppressor cells enhances stemness and mesenchymal properties in human pancreatic cancer. *Cancer Immunol Immunother* 2014; **63**: 513-528.
6. Di Mitri D, Toso A, Chen JJ*, et al.* Tumour-infiltrating Gr-1+ myeloid cells antagonize senescence in cancer. *Nature* 2014; **515**: 134-137.
7. Shojaei F, Zhong C, Wu X*, et al.* Role of myeloid cells in tumor angiogenesis and growth. *Trends Cell Biol* 2008; **18**: 372-378.
8. Toh B, Wang X, Keeble J*, et al.* Mesenchymal transition and dissemination of cancer cells is driven by myeloid-derived suppressor cells infiltrating the primary tumor. *PLoS Biol* 2011; **9**: e1001162.
9. Coffelt SB, Kersten K, Doornebal CW*, et al.* IL-17-producing gammadelta T cells and neutrophils conspire to promote breast cancer metastasis. *Nature* 2015; **522**: 345-348.

Legend

Figure 1. MDSC activity in cancer promotion. Different subsets of MDSCs are recruited to the tumor microenvironment and promote tumor progression in several ways: 1) by acting directly on tumor cells (upper panel on the right), they can sustain tumor cell stemness; 2) through the secretion of pro-angiogenetic factors, thus promoting blood vessel formation (central panel on the right); 3) MDSCs support EMT, shown in the lower panel on the right.



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