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Review

Immunosuppressive cells and tumour microenvironment: Focus on mesenchymal stem cells and myeloid derived suppressor cells

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Summary. Tumours have been compared to unhealed wounds that produce large amounts of inflammatory mediators, including cytokines, chemokines, and growth factors. These molecules participate in the formation of a rich and heterogeneous microenvironment by attracting non malignant cells that promote tumour progression and dissemination. Tumour infiltrating cells include macrophages, myeloid-derived suppressor cells (MDSCs), mesenchymal stromal cells (MSCs) and TIE2-expressing monocytes. Most of them are bone marrow-derived, although MSC are present in virtually every tissue. This review focuses on MDSCs and MSCs, both of which can exert pro-tumorigenic effects through negative regulation of immune responses. MDSCs represent a heterogeneous population of cells of myeloid origin that are expanded and activated in response to growth factors and cytokines released by tumours. Once MDSCs are activated, they accumulate in lymphoid organs and tumours where they exert T cell immunosuppression. Like MDSCs, MSCs can be mobilized from the bone marrow into the bloodstream and home in the tumour stroma, where they either help or hinder tumour growth. Here, we will discuss the origin, the functions and the mechanisms of action of MSCs and MDSCs, as well as the strategies to target these cells for the therapeutic benefit of cancer patients.

Key words: Tumour microenvironment, Immunosuppression, Mesenchymal stem cells, Myeloid-derived suppressor cells

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Introduction

The microenvironment of a developing tumour is composed of proliferating malignant cells, tumour stroma, blood vessels and infiltrating inflammatory cells. It is a unique environment created and dominated by tumour cells that establish specific interactions with the neighbouring cells in order to promote tumour progression and metastasis. Different types of cells are found in the stroma, including fibroblasts, vascular smooth muscle, epithelial and immune cells. The latter cells comprise effectors of both adaptative immunity, such as T and B lymphocytes, and innate immunity, i.e. macrophages, dendritic cells (DCs), polymorphonuclear leukocytes (PMN) and natural killer (NK) cells (Whiteside, 2008). In response to tumour-derived signals, immune cells not only fail to exert anti-tumour functions, but contribute to tumour progression. Of the various escape mechanisms, the accumulation in the tumour microenvironment of suppressor cells that dampen T cell functions has attracted particular interest (Whiteside, 2006). Tumour cells produce and release soluble molecules, such as inflammatory mediators, growth factors and metalloproteinase (MMPs) that act in a paracrine/autocrine manner, directly stimulating tumour growth and promoting the recruitment of immunosuppressive cells, including T regulatory cells, mesenchymal stromal cells (MSCs) and macrophages (Bissell and Radisky, 2001).

In this review we will focus on two cell populations derived from the bone marrow (BM) i.e. MSCs and myeloid-derived suppressor cells (MDSCs), that contribute to tumour progression through different mechanisms.

Mesenchymal stem cells and tumour microenvironment

Definition and functional characterization

MSCs are multipotent stromal cells usually isolated from the BM. MSCs were first identified by Friedenstein and colleagues, who described a population of plastic-adherent cells isolated from the BM with i) fibroblast-like morphology, ii) the ability to form colony-forming unit-fibroblasts (CFU-F), iii) self-renewal capability, and iv) potential of differentiation into adipocytic, chondrocytic, miocytic, and osteocytic lineages (Friedenstein et al., 1974). More recently, several studies demonstrated that MSCs are able to transdifferentiate *in vitro* into cells of ectodermic and endodermic lineages (Pittenger et al., 1999). Although the BM represents the main tissue from which MSCs are isolated, MSCs reside in virtually all post-natal organs (da Silva Meirelles et al., 2006). There is not a single and specific marker that characterizes MSC. MSCs *ex vivo* expanded are usually negative for the hematopoietic markers CD34, CD45 and CD14, and positive for surface markers such as CD105 (endoglin), CD73 (ecto-5'-nucleotidase), CD44, CD90, CD71 (transferrin receptor), the ganglioside GD_2, CD271 (low-affinity nerve growth factor receptor) and STRO-1 (Uccelli et al., 2008).

MSCs reside in the BM and are also distributed in various connective tissues, serving as a source of dormant stem cells for tissue maintenance and regeneration. During pathological conditions characterized by an injury, chronic inflammation or tumours, MSCs are mobilized and recruited to the damaged tissues (Hung et al., 2005; Spaeth et al., 2008). Like a wound repair, tumours release soluble factors that have the ability to recruit responsive cells including MSCs (Spaeth et al., 2008; Kidd et al., 2009). These latter molecules include: i) growth factors, such as epidermal growth factor (EGF), vascular endothelial growth factor-A (VEGF-A), fibroblast growth factor (FGF), platelet derived growth factor (PDGF), insulin growth factor-1 (IGF-1), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), ii) chemokines including CCL2, CCL5, CXCL8, and iii) cytokines such as IL-6 (Spaeth et al., 2008; Bergfeld et al., 2010). MSCs are known to express significant levels of functional chemokines receptors i.e. CCR1, CCR4, CCR7, CCR9, CCR10, CXCR4, CXCR5, CXCR6, CX3CR1, most of which are involved in MSCs tumour homing (Spaeth et al., 2008). Once they localize in the tumour, MSCs together with other cells like myofibroblasts, endothelial cells, pericytes and inflammatory cells, contribute to create a specific tumour microenvironment and modulate tumour growth and progression. In the last five years different studies have demonstrated that MSCs may have opposite effects on tumour growth, that is, MSCs favour or inhibit tumour, depending on the experimental model tested (Kidd et al., 2008). Figure 1 depicts the interactions between MSCs and tumour cells and the mechanisms used by MSC to influence tumour progression and metastasis.

Tumour promoting effects

Role in tumour vessel formation

Striking evidence indicates that MSCs contribute to tumour vasculogenesis mainly by producing pro-angiogenic factors and by (trans)-differentiating into endothelial-like and pericyte-like cells (Roorda et al., 2009). The first mechanism is supported by the fact that MSCs secrete specific pro-angiogenic factors such as VEGF, PDGF, FGF and CXCL12 acting on tumour and/or endothelial cells (Kinnaird et al., 2004). In this respect, MSCs, co-implanted with cancer cells in syngeneic animals accelerate tumour appearance, probably by favouring an angiogenic switch (Annabi et al., 2004; Galie et al., 2008).

MSCs can also differentiate into pericytes and endothelial-like cells and contribute to mature tumour vasculature formation (Galmiche et al., 1993; Annabi et al., 2004; Bexell et al., 2009). More recently, MSCs have been shown to represent the precursors of tumour-associated fibroblasts (TAF), which express factors involved in extracellular matrix (ECM) degradation, angiogenesis and promotion of tumour cell growth (Spaeth et al., 2009). In particular, MSCs express typical TAF markers, such as extracellular matrix (ECM) proteins (tenascin-c and thrombospondin), ECM remodelling enzymes and growth factors (Hepatic Growth Factor (HGF), EGF, VEGF, Transforming Growth Factor (TGF)-ß and IL-6) (Spaeth et al., 2009).

Immunosuppression

The immunomodulatory function of MSCs represents a further mechanism through which MSCs may promote tumour development and progression. In general, MSCs display immunosuppressive activities on the most important cell populations involved in the innate and adaptive immunity, such as T and B lymphocytes, DC and NK cells (Aggarwal and Pittenger., 2005; Uccelli et al., 2006; Nauta amd Fibbe, 2007). MSCs dampen generation of mature myeloid DC from monocytes and $CD34^+$ haematopoietic progenitors thus impairing antigen presentation to T cells (Jiang et al., 2005; Nauta et al., 2006). In addition, MSCs inhibit proliferation, cytokine production and cytotoxic activity of NK cells and reduce the pro-inflammatory potential of neutrophils while prolonging their survival (Spaggiari et al., 2006; Raffaghello et al., 2008). MSCs inhibit proliferation and cytokine production, as well as $CD8^+$ T cell mediated cytotoxicity against allogeneic cells, virally infected cells and tumour cells (Di Nicola et al., 2002; Rasmusson et al., 2003; Morandi et al., 2008; Prigione et al., 2009). MSCs dampen B cell proliferation and differentiation into antibody secreting cells, as well

as inhibit chemotaxis to the chemokines CXCL12 and CXCL13 by down-regulating the expression of the respective receptors CXCR4 and CXCR5 (Corcione et al., 2006). Finally, MSCs promote the generation of T regulatory (T reg) cells through direct and indirect mechanisms (Selmani et al., 2008).

The mechanisms whereby MSCs exert these immunosuppressive activities are complex but generally dependent on a cross-talk between the MSCs themselves and their target cells. In other words, MSCs are instructed by target cell derived-soluble factors to produce immunosuppressive molecules, including prostaglandin E_2 (PGE_2), nitric oxide, indoleamine 2,3-dioxigenase (IDO), soluble (s) HLA-G5 and others (Morandi et al., 2008; Selmani et al., 2008; Spaggiari et al., 2008; Uccelli et al., 2008).

Based on the immunosuppressive function, MSC (10^3-10^5 cells), coadministered with B16 melanoma cells (10^4 tumour cells), prevent the rejection of cancer cells in an allogeneic animal mode (Djouad et al., 2003). However, it has been shown that low MSC numbers (10^2 MSC with 10^4 tumour cells) induced unexpected tumour rejection (Djouad et al., 2006).

Recently, MSCs have been shown to protect breast cancer cells by expanding T reg cells, with concomitant decrease of Th1 and increase of Th2 cytokines (Patel et al., 2010). This effect is largely mediated by TGF-ß1 (Patel et al., 2010).

Establishment of distant metastasis

Different reports have demonstrated that MSCs can colonize metastatic tumours and in some models favour the metastatic potential of tumour cells localized in the primary tumour (Karnoub et al., 2007; Bergfeld and DeClerck, 2010). In this regard, an elegant study demonstrated that MSC co-injected subcutaneously with breast carcinoma cells increased the metastatic potency of primary tumour cells. This enhanced metastatic ability is dependent on the chemokine CCL5, which is secreted

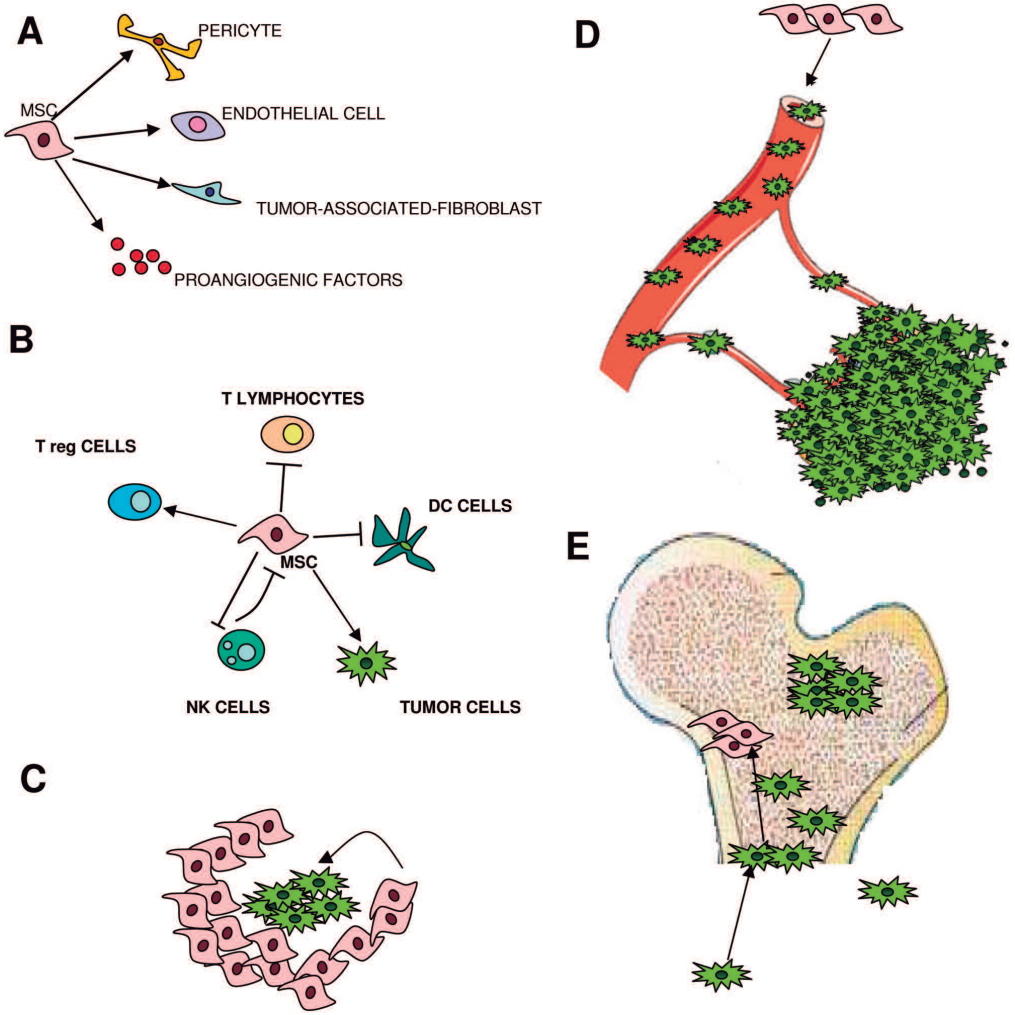

Fig. 1. Mechanisms of MSC-mediated pro-tumorigenic effects. **A.** MSCs contribute to tumour vasculogenesis by producing pro-angiogenic factors such as VEGF, PDGF, FGF, CXCL12 and by (trans)-differentiating into endothelial-like cells, pericytes and tumour-associated fibroblasts. **B.** MSCs exert immuno-suppressive activities by dampening the generation of mature myeloid DCs, by inhibiting the proliferation, cytokine production and cytotoxic activity of T and NK cells, by promoting the generation of T reg cells. Furthermore, MSCs induce tumour cell proliferation through secretion of factors including TGF-ß, VEGF, EGF, HGF and IL-6. **C.** MSCs may create a cancer stem cell niche in which tumour cells preserve their potential to proliferate and are protected against the cytotoxic effects of anti-tumour agents. **D.** MSCs can favour the metastatic potential of tumour cells localized in the primary tumour through the release of chemokines such as CCL5, which increases the motility, invasion and metastasis of tumour cells. **E.** MSCs secrete chemokines such as CXCL12 and CXCL13 that can attract tumour cells to the bone marrow, thus promoting osteolytic bone metastasis. This latter effect is mainly mediated by IL6.

by MSCs and increases the motility, invasion and metastasis of tumour cells (Karnoub et al., 2007). Similar studies demonstrated an increase of metastatic osteosarcoma lesions mediated by MSC-derived CCL5 (Xu et al., 2009).

Furthermore, MSCs contribute to create a pro-tumorigenic environment in the BM by promoting osteolytic bone metastasis and favouring tumour cell proliferation (Sohara et al., 2005; Bergfeld and DeClerck, 2010). BM-MSC secrete large amounts of CXCL12 and CXCL13 that attract different circulating different tumour cells, including breast, B leukaemia and myeloma cells (Urashima et al., 1997; Burger et al., 2002; Molloy et al., 2009) . The reciprocal interactions between tumour cells and MSCs lead to the production of soluble factors (i.e. PGE_2 and Galectin-3 binding protein) and cytokines like IL-6 (Michigami et al., 2000; Sohara et al 2005; Fukaya et al., 2008). IL-6 is a potent osteoclast-activating factor and also promotes tumour cell growth, survival and resistance to chemotherapy (Efferth et al., 2002; Brocke-Heidrich et al., 2004; Sohara et al., 2005).

Creation of cancer stem cell niche

MSCs have been proposed to form a cancer stem niche where tumour cells are protected and sustained in their growth (Ramasamy et al., 2007). In this regard, Ramasamy et al. demonstrated that tumour cells injected into nude mice in conjunction with MSCs grow faster as compared to those injected without MSCs (Ramasamy et al., 2007) . However, this *in vivo* pro-tumorigenic effect was not confirmed by *in vitro* experiments, where MSCs inhibited proliferation of tumour cells through induction of G1 phase arrest (Ramasamy et al., 2007). To explain this discrepancy between *in vitro* and *in vivo* behaviour, the authors suggested that MSCs may create a cancer stem cell niche in which tumour cells preserve their potential to proliferate.

According to this hypothesis, MSCs niches have been demonstrated not only to be essential for the long-term survival and expansion of leukemic lymphoblasts in vitro, but also to confer significant protection to the same tumour cells against asparaginase-induced cytotoxicity (Iwamoto et al., 2007).

Anti-tumour effects

Khakoo et al. were the first to demonstrate that MSCs exert a potent anti-neoplastic effect in a model of Kaposi's sarcoma (Khakoo et al., 2006). This activity is mediated by direct cell contact leading to inhibition of the activated isoforms of Akt protein kinase in tumour cells (Khakoo et al., 2006). MSC-mediated antineoplastic activities were also observed in SCID mice with disseminated Non-Hodgkin's lymphoma (Secchiero et al., 2010). Indeed, upon MSC injection, the tumour masses developed more slowly and were characterized by extensive areas of necrosis. *In vitro* experiments showed that MSCs induced migration of endothelial cells but also promoted endothelial cell apoptosis, interfering with angiogenesis (Secchiero et al., 2010). Similar anti-tumour effects mediated by MSCs were observed in an experimental model of pancreatic carcinoma (Kidd et al., 2010).

Since MSC exhibit intrinsic tropism to sites of inflammation such as tumours, these cells have been exploited as delivery vehicles to target antitumor agents to malignant cells. The efficacy of engineered MSCs has been tested recently in different experimental models and the results appear to be promising. MSCs transduced with the gene of interferon-beta inhibit the growth of melanoma, breast carcinoma and glioma cells *in vitro* as well as *in vivo* (Studeny et al., 2002, 2004; Nakamizo et al., 2005). Furthermore, the administration of MSCs engineered to express recombinant TRAIL or the suicide gene cytosine deaminase induces an antitumour effect in glioma and prostate carcinoma models, respectively (Sasportas et al., 2009; Cavarretta et al., 2010).

Clinical studies on cancer patients provide conflicting data about the effect mediated by MSC on cancer progression. Different reports indicated that MSCs do not affect the progression of breast and haematological malignancies (Koc et al., 2000; Lazarus et al., 2005). In contrast, a recent study demonstrated that patients suffering from haematological malignancies who were treated with chemotherapy and then co-transplanted with MSCs and hematopoietic stem cells (HSCs) showed greater incidence of disease relapse compared to those who received HSC alone (Ning et al., 2008).

We believe that, in spite of the antitumor effects mediated by MSCs convincingly demonstrated in some animal models, the use of MSCs in large scale clinical trials for cancer patients has to be considered with caution since MSCs may have a pro-tumorigenic function and the underlying mechanisms have not yet been fully elucidated.

Myeloid-derived suppressor cells and tumour microenvironment

Definition and functional characterization

MDSCs are a heterogenous population of cells of myeloid origin comprising myeloid progenitors and immature myeloid cells (IMC) (Gabrilovich et al., 2009). In healthy individuals, IMCs are generated in the BM and differentiate into mature granulocytes, DC, and macrophages (Gabrilovich et al., 2009). In contrast, in pathological conditions such as cancer, IMCs are blocked to differentiate into mature myeloid cells, and MDSC expansion and activation occur (Gabrilovich et al., 2009). MDSCs increase in response to various stimuli, including bacterial and parasitic infections, chemotherapy, experimentally induced autoimmunity, traumatic stress and cancer (Gabrilovich et al., 2009) . In tumour-bearing mice MDSCs accumulate in the BM,

spleen, peripheral blood (PB) and to a lesser extent in lymph nodes; in contrast in cancer patients MDSCs are found only in PB (Youn et al., 2008; Gabrilovich et al., 2009).

The soluble factors involved in expansion and activation of MDSCs can be divided into two main groups. The first group includes molecules primarily produced by tumour cells that mediate MDSC expansion through stimulation of myelopoiesis, such as VEGF, stem cell factor (SCF), GM-CSF, G-CSF, M-CSF, gangliosides, prostanglandins, IL-6, IL-10, IL-12, MMP9 and CCL2 (Talmadge 2007; Gabrilovich et al., 2009) . Most of these factors converge on the activation of the signal transducer and activator of transcription 3 (STAT3) that has a crucial role in: i) MDSC expansion, ii) contribution of MDSCs to angiogenesis, iii) MDSC accumulation in cancer patients, and iv) MDSC suppressive activity (Condamine et al., 2010). In contrast, the second group of soluble factors is produced by tumour stromal cells and activated T cells and is implicated in MDSC activation. These factors, including IFN-γ, ligands for Toll-like receptors, IL4, IL-13, and TGF-ß are responsible for activation of different pathways involving STAT6, STAT1 and nuclear factor-κB (NFκB) (Gabrilovich et al., 2009). MDSCs acquire immunosuppression activity only following activation. Figure 2 depicts a model of MDSC expansion and activation.

Two major classes of MDSCs have been identified i.e. granulocytic MDSCs (G-MDSCs) with polymorphonuclear phenotype and high levels of arginase expression, and monocytic MDSCs (M-MDSCs), which are mononuclear cells expressing arginase and inducible nitric oxide synthase (iNOS) (Movahedi et al., 2008; Youn et al., 2008).

In mice, both MDSC populations express the granulocyte marker Gr1 and the dendritic/macrophage marker CD11b (Gabrilovich et al., 2009). More recently, M-MDSCs positive also for CD54, F4/80 and Ly6G, and G-MDCS expressing high Ly6G levels have been identified (Ostrand-Rosenberg, 2010). In humans, M-MDSCs and G-MDSCs express CD33, CD11b and IL-4Rα and low levels of CD15 (Condamine et al., 2010). Furthermore, M-MDSCs are positive for CD14. Additional markers of MDSCs have been also identified in mice and humans (Nagaraj and Gabrilovich, 2010; Peranzoni et al., 2010).

MDSCs suppress adaptive and innate immunity by i) inhibiting antigen-specific and non-specific T cell activation (Bronte et al., 2000; Gabrilovich et al., 2001) ii) inducing the conversion of macrophages into M2 that contribute to tumour progression and invasion through

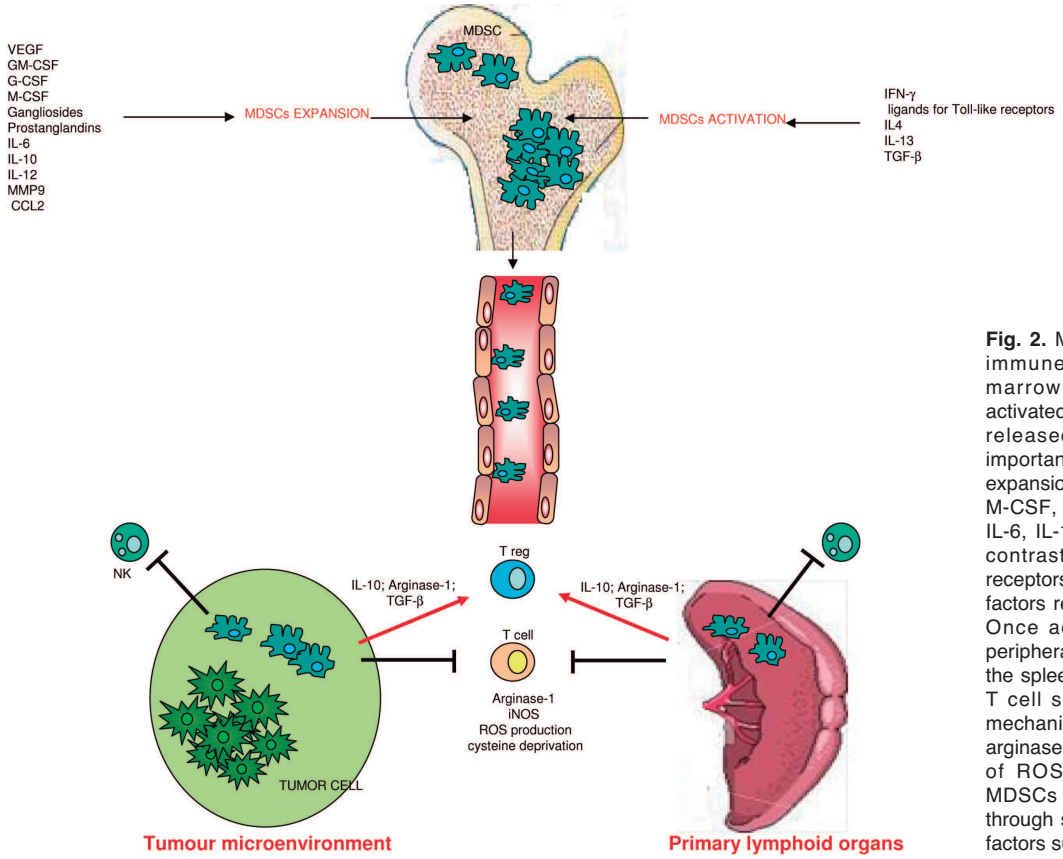

Fig. 2. Mechanisms of MDSC-mediated immune suppression. In the bone marrow, MDSCs are expanded and activated in response to soluble factors released by tumour cells. The most important molecules involved in MDSC expansion are VEGF, GM-CSF, G-CSF, M-CSF, gangliosides, prostanglandins, IL-6, IL-10, IL-12, MMP9 and CCL2. In contrast, IFN-γ, ligands for Toll-like receptors, IL-4, IL-13 and TGF-ß are the factors responsible for MDSC activation. Once activated, MDSCs migrate to peripheral blood, spleen and tumour. In the spleen and tumour, MDSCs mediate T cell suppression through different mechanisms, including up regulation of arginase-1 and iNOS activity, production of ROS, and cysteine deprivation. MDSCs promote T reg cell expansion through secretion of immunosuppressive factors such as TGF-ß and IL-10.

type 2 cytokine production (Sinha et al., 2005; Sinha et al., 2007), iii) by stimulating T reg expansion and iv) repressing NK cytotoxicity (Liu et al., 2007). However, the role of MDSCs on NK activity is controversial, since it has been reported that MDSCs can activate NK cells (Nausch et al., 2008).
In the following sections, we will describe the multiple mechanisms used by MDSCs to suppress T cell function (Fig. 2).

Mechanisms of MDSC immunosuppressive activity

Arginase 1, iNOS and reactive oxygen species (ROS)

L-Arginine is an essential amino acid that generates urea and L-ornithine upon reaction with the enzyme arginase (ARG), and NO and L-citrulline upon reaction with NOS. T cells require L-arginine for proliferation and activation (Bronte and Zanovello, 2005). MDSCs express high levels of intracellular ARG that depletes T cells of L-arginine (Rodriguez et al., 2004). This latter event inhibits T cell proliferation by i) decreasing T cell receptor (TCR)-associated CD3˙ chain, fundamental for antigen recognition and activation in T cells, and ii) preventing the induction of regulators of the cell cycle such as cyclin D3 and cyclin-dependent kinase 4 (Rodriguez et al., 2002, 2007). Among the main factors that induce ARG expression, much interest has been focused on cyclooxygenase-2 (COX2), whose expression is increased in many malignancies (Taketo 1998; Dannenberg and Subbaramaiah, 2003). COX2 stimulates the production of ARG, iNOS and PGE_2 (Rodriguez et al., 2005). The latter molecule contributes to create the inflammatory tumor microenvironment and has been shown to promote expansion of $CD11b^+/CD14^-/CD15^+$ MDSC in patients affected by renal cancer (Ochoa et al., 2007). Furthermore, an interesting study demonstrated that 3LL lung carcinoma cells produce high levels of PGE2 that induces ARG in tumour infiltrating MDSCs (Rodriguez et al., 2005). In this connection, blocking arginase I through the use of COX-2 inhibitors has been proposed as a promising strategy to improve antitumor T cell responses (Talmadge 2007 bis). The generation of NO by iNOS suppresses T cell function through inhibition of the IL-2 receptor pathway, by blocking STAT5 and JAK3 phosphorylation, and induction of apoptosis (Bingisser et al., 1998; Rivoltini et al., 2002). These mechanisms are mostly associated with M-MDSCs (Youn et al., 2008). In contrast, ROS are produced by NADPH-oxydase and are the main mediators of G-MDSC immunosuppression in tumour bearing mice and patients affected by cancer (Talmadge 2007; Movahedi et al., 2008; Youn et al., 2008) .

Among ROS, peroxynitrites represent the most relevant species that inhibit $CD8^+$ T cells by inducing the nitration of TCR and consequent alteration of TCR/MHC-peptide recognition (Nagaraj et al., 2007).

Several soluble factors released by tumour cells such as TGF-ß, IL-3, IL-6, IL-10, PDGF and GM-CSF can induce the production of ROS by MDSCs (Gabrilovich et al., 2009).

Induction of T reg cells

Different reports demonstrated that MDSCs mediate the development of T reg cells in tumor bearing hosts (Huang et al., 2006; Yang et al., 2006; Gabrilovich et al., 2009). The induction of T reg cells by MDSCs occurs through different mechanisms depending on the tumour model. In lymphoma bearing mice, MDSCs induce T reg cell expansion through a mechanism dependent on ARG and independent of TGF-ß (Serafini et al., 2008). By contrast, in a model of ovarian cancer, the induction of T reg cells by MDSCs is associated with the expression of cytotoxic lymphocyte 4 antigen (CTLA4) (Yang et al., 2006). Another group demonstrated that MDSCs induce T reg expansion by a mechanism that requires IL-10 and IFN-γ and is NO independent (Huang et al., 2006).

Depletion of cysteine

Cysteine is an essential aminoacid that serves as a fundamental substrate for generation of glutathione, a major intracellular molecule that protects cells from oxidative stress (Sakakura et al., 2007; Ostrang-Rosenberg 2010). Cysteine can be synthesized from intracellular methionine or alternatively can be imported as the oxidized form of cystine through ASC neutral amino acid plasma membrane transporter. T cells lack cystathionase, the enzyme responsible for cysteine synthesis, and are completely dependent on exogenous sources of cysteine (Ostrang-Rosenberg, 2010). MDSC, that do not express cystathionase and ASC transporter, generate cysteine from imported cystine. As a result, MDSCs deplete the environment of cistyne, do not export cysteine and consequently prevent T cell proliferation and activation (Srivastava et al., 2010).

In healthy mice, MDSCs are mainly localized in the BM, representing about 30% of normal BM cells. In contrast, in tumour bearing animals characterized by increased levels of tumor derived factors such as VEGF, GM-CSF, IL-3 M-CSF and IL-6, MDSCs are recruited from the BM to the spleen, PB and tumour microenvironment (Gabrilovich et al., 2009). At the latter site MDSCs can further differentiate into tumour-associated macrophages (TAM) via hypoxia inducible factor (HIF)-1α (Corzo et al., 2010).

MDSCs in cancer patients

In 2001, Almand et al. identified for the first time the accumulation of IMCs in the PB of patients affected by head and neck, breast and non-small cell lung cancer (NSCLC) (Almand et al., 2001). IMCs inhibit Ag-specific T cells through a NO independent mechanism and can differentiate into DC after treatment with all-trans retinoic acid (ATRA) (Almand et al., 2001).

In metastatic melanoma patients a new subset of MDSCs positive for CD14 and with low levels or absence of HLA-DR, exerted TGF-ß-mediated immune suppression and increased after administration of tumour-derived heat shock protein peptide complex gp96/GM-CSF vaccine (Filipazzi et al., 2007). In contrast, a subpopulation of activated granulocytes, $CD14^-/CD15^+/CD80^+/CD83^+/CD86^+/HLA\text{-}DR^+/CD66b^+/CD62L^{low}/CD16^{low}$ has been identified in the PB of renal carcinoma patients (Rodriguez et al., 2009). These latter cells release high amounts of arginase I, resulting in low levels of L-arginine in plasma and consequent T cell suppression. Furthermore, MDSCs isolated from renal carcinoma patients were also capable of suppressing antigen-specific T-cell responses *in vitro* through the secretion of ROS and NO upon interaction with cytotoxic T lymphocytes (CTL) (Kusmartsev et al., 2008).

More recently, it has been demonstrated that mononuclear and granulocytic fractions accumulate in the PB of patients affected by colon cancer and melanoma (Mandruzzato et al., 2009). Both cell fractions expressed typical MDSC markers, including IL4Rα, but only the mononuclear cells were endowed with immunosuppressive properties (Mandruzzato et al., 2009).

Similarly to the MDSC subpopulations found in melanoma patients, the frequency of $CD14^+/HLA\text{-}DR^{-/low}$ was also increased in the PB of multiple myeloma and hepatocellular carcinoma patients (Hoechst et al., 2008; Brimnes et al., 2010). In the latter patients, these mononuclear cells did not stimulate allogeneic T-cell responses, suppressed autologous T-cell proliferation, had high arginase activity and induced T reg cells when cocultured with autologous T cells (Hoechst et al., 2008). Notably, $CD11b^+/CD14^-/IL\text{-}4R^+/IFN\text{-}\gamma^+$ MDSC, identified in the PB of NSCLC patients, decreased in those patients who responded to chemotherapy and shortly after removal of the tumour (Liu et al., 2009).

A recent study performed on large cohorts of solid cancer patients identified the presence of a subset of leukocytes with high SSC that co-purified with mononuclear cells in density gradients (Brandau et al., 2010). This cell population expressed high amounts of CD66b, a member of the human CEA family uniquely expressed on human polymorphonuclear leukocytes, and exerted a potent suppressive activity on polyclonally stimulated T cells inhibiting proliferation and IFN-γ production (Brandau et al., 2010). The latter findings, together with the increased number of these cells in the PB of cancer patients, suggested that $SSC^{high}/CD66b^+$ can qualify as MDSC (Brandau et al., 2010)

Therapeutic targeting of MDSCs

Since immunosuppression has a crucial role in tumour progression and contributes to the failure of immunotherapy, therapeutic strategies aimed at eliminating suppressive factors such as MDSCs are being currently explored. MDSC targeting can be performed at different levels: i) by promoting myeloid differentiation, ii) by inhibiting MDSC expansion and function, and iii) by directly eliminating MDSCs. One of the most promising strategies is the induction of MDSC differentiation into mature myeloid cells without suppressive functions. In this regard, vitamin A and ATRA represent two examples of molecules used to induce differentiation of MDSCs into macrophages and DC in head and neck cancer, sarcoma, colon and metastatic renal-cell carcinoma patients (Kusmartsev et al., 2003; Lathers et al., 2004; Mirza et al., 2006). Different studies have reported the effects of agents able to neutralize the molecules involved in MDSC expansion, such as SCF, VEGF and MMP9 (Melani et al., 2007; Kusmartsev et al., 2008). In this regard, the VEGF specific blocking antibody avastin induced a decrease in the size of MDSC population in patients affected by metastatic renal-cell cancer (Kusmartsev et al., 2008). Another approach includes the inhibition of the signalling pathways that regulate the production of MDSC-derived soluble factors. COX2 inhibitor SC58236 and ROS inhibitors, such as nitroaspirin tested in tumour bearing mice improve antitumor immune response and enhance the therapeutic efficacy of immunotherapy (De Santo et al., 2005; Talmadge et al., 2007).

Finally, MDSCs can be also eliminated by chemotherapeutic agents such as gemcitabine, which decreases the number of MDSCs and improves antitumor responses induced by immunotherapy in animal models of lung cancer and mammary tumours (Suzuki et al., 2005).

Conclusions

We have reviewed the role and the molecular mechanisms of MSCs and MDSCs in favouring or inhibiting tumour progression. MDSCs represent a heterogeneous population of immature myeloid cells characterized by a relevant immunosuppressive activity; in contrast MSCs may have a split personality since they can favour or inhibit tumour progression, depending on the tumour model tested. The issue of whether MSCs and MDSCs could interact with each other, thus influencing their functional activity, remains to be elucidated. The understanding of the reciprocal interactions between MSCs and MDSCs may allow the design of promising therapeutic strategies useful for enhancing the antitumor efficacy of immunotherapies.

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