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CURRENT STATUS REVIEW

Myeloid-derived suppressor cells: a double-edged sword?

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Summary

Myeloid-derived suppressor cells are important cell population with an immunoregulatory potential in both adaptive and innate immunity. Their immunosuppressive activity is widely accepted. However, emerging evidence suggests that this heterogeneous cell population can be, under some circumstances, immunostimulatory rather than suppressive. This finding can shed a new light on antitumour immunity which is believed to be impaired in immunosuppressive environments.

Keywords
antitumour immunity, immunoregulatory properties, myeloid-derived suppressor cells

Introduction

Myeloid-derived suppressor cells (MDSC), important innate regulators of immune response, have been investigated intensively in several recent studies. In mice, MDSC are a heterogeneous population of cells that express both CD11b and Gr-1 (Ly6G and Ly6C) and consists of early myeloid progenitors and immature myeloid cells [macrophages, granulocytes, dendritic cells (DC)] at different stages of differentiation. They lack or have reduced expression of markers of mature myeloid cells (Gabrilovich & Nagaraj 2009).

MDSC have the ability to suppress immune responses. The suppressive activity of MDSC is primarily associated with the metabolism of L-arginine, a substrate for inducible nitric oxide synthase, iNOS (NO generation) and arginase 1 (generation of urea and L-ornithine) and production of reactive oxygen species (ROS) (Mazzoni *et al.* 2002; Talmadge 2007, Kusmartsev *et al.* 2004). It has been proposed that they might play an important physiological role in preventing immune system from excessive activation and thereby limiting tissue damage during the immune response (Bronte & Zanovello 2005; Cripps *et al.* 2010; Dardalhon *et al.* 2010). In addition, MCSC accumulate in many pathological situations such as bacterial and parasitic infections, trauma, acute and chronic inflammation, autoimmunity (Goñi *et al.* 2002; Gómez-García *et al.* 2005; Ezernitchi *et al.* 2006; Makarenkova *et al.* 2006; Zhu *et al.* 2007; Iwata *et al.* 2010).

Numerous studies also point to a role of MDSC in cancer, where they negatively influence antitumour immunity. Although large body of evidence shows that MDSC accumulating in tumour bearers can inhibit immunosurveillance and contribute to tumour progression (both in patients and in tumour models) (Almand *et al.* 2001; Bunt *et al.* 2006; Nagaraj & Gabrilovich 2008; Liu *et al.* 2009), there emerge suggestions that myeloid $CD11b^{+}Gr\text{-}1^{+}$ cells could function paradoxically in an immunostimulatory way and even act against tumours (Table 2). The latter findings seem to be consistent with the fact that monocytes/macrophage lineage cells are highly plastic in nature. Their activities can be opposing depending on environmental influences (such as

cytokines, prostaglandins, chemokines, hormones, pathogen-associated molecular patterns).

A classification of macrophages based mainly on the response to Th cytokines has been proposed. Classically activated macrophages (M1) develop under the influence of Th1 cytokines (e.g. IFN-γ) or bacterial products. They are capable of killing microorganisms and tumour cells. Presence of Th2 cytokines (e.g. IL-4, IL-13) mediates the development of alternatively activated macrophages (M2) that act by enhancing Th2 adaptive immune response and limiting Th1 immune response. In contrast to M1, M2 macrophages are involved in immunosuppression and tissue repair and were shown to exhibit protumour activity. Interestingly, phenotype of monocytes/macrophage lineage cells adapted to environmental signals may be reversible (Mantovani *et al.* 2004; Stout & Suttles 2004; Guiducci *et al.* 2005).

Suppressive activity of MDSC

The suppressive activity of MDSC has been clearly demonstrated. Most studies on their function has been performed in tumour models (both *in vitro* and *in vivo*), in which MDSC reduce antitumour immune response. Importantly, there are also studies which suggest that accumulation of MDSC in patients with cancer may correlate with defectiveness of immunological reactions against tumour (Almand *et al.* 2001; Bunt *et al.* 2006; Nagaraj & Gabrilovich 2008; Diaz-Montero *et al.* 2009; Liu *et al.* 2009). Collectively, MDSC downregulate innate immunity by impairment of natural killer cells (NK) activity (Liu *et al.* 2007) and decrease in macrophage production of IL-12 (Sinha *et al.* 2007) and regulate adaptive immunity by reduction of T-cell function. MDSC inhibit T-cell response by multiple pathways that include NO and ROS production, amino acid metabolism, T-regulatory cell (T reg) induction and secretion of inhibitory molecules such as IL-10 and TGF-β (Mazzoni *et al.* 2002; Terabe *et al.* 2003; Kusmartsev *et al.* 2004; Huang *et al.* 2006; Sinha *et al.* 2007; Srivastava *et al.* 2010).

Accumulation of MDSC is also linked to the impairment of development and function of DC, which are at the interface between innate and adaptive immunity (Greifenberg *et al.* 2009; Hu *et al.* 2010).

Immune stimulation and antitumour activity: another face of MDSC?

Myeloid cells with suppressive function were firstly discovered in the late 1970s when they were referred as natural suppressor (NS) cells. They were described as cells with ability to inhibit T-cell responses *in vitro* and *in vivo* (Strober 1984; Holda *et al.* 1985). Surprisingly, it was found that NS cells exhibit antiproliferative activity not only for lymphocytes but also for tumour cells. The mechanism of tumour growth inhibition by NS cells was not clarified by the investigators (Sugiura *et al.* 1990). NO, which was found to be produced by early myeloid suppressor cells (Angulo *et al.* 2000b) and which is believed to have a potent tumoricidal activity (Umansky & Schirrmacher 2001; Mocellin *et al.* 2007), could be responsible. The antitumor potential of early myeloid suppressor cells producing NO was investigated by Peláez *et al.* (2001). They used a model of combined adoptive therapy (tumour-specific lymphocytes) with cyclophosphamide (CY) that is known to cause transient MDSC accumulation in the spleen after injection into mice (Angulo *et al.* 2000a). They have proved that cells with features of MDSC derived from CY-treated mice indeed are able to inhibit tumour growth *in vitro* by generation of NO. Administration of N^G-monomethyl-L-arginine (LMMA), an inhibitor of NO synthase, prevented nitrite production (end product of NO metabolism) and tumour cell growth inhibition. This study suggest that these effects may also occur *in vivo*; however, it has not been formally proved (Peláez *et al.* 2001).

Even though some reports suggest that MDSC have an ability to inhibit tumour cell proliferation by releasing NO, the majority of studies show the opposite effect. This could be partially explained by a dual role for this molecule. NO at high concentration can cause apoptosis of tumour cells, but on the other hand, at low concentration it can act as tumour promoter (indirectly promoting DNA damage) (Mocellin *et al.* 2007; Umansky & Schirrmacher 2001). Furthermore, tumour cells can acquire resistance to NO-induced apoptosis (Wang & MacNaughton 2005). Additionally, important effectors of antitumour immunity, lymphocytes, are sensitive to NO (Mazzoni *et al.* 2002). The presence of NO and superoxide anions leads to the generation of highly toxic peroxynitrate. Production of peroxynitrite during direct contact of MDSC with T cells results in the nitration of TCR and CD8 molecule, thus making T-cell unresponsive to antigen-specific stimulation (Nagaraj *et al.* 2010). Therefore, NO secreted by MDSC has a tumoricidal potential, but alone may not be sufficient to destroy tumour masses and its prolonged production can be more harmful than beneficial.

Interestingly, despite the strong evidence that MDSC can make lymphocytes defective, some studies demonstrate that the presence of MDSC is not necessarily related to a hampered function of T cells. Srivastava *et al.* (2008) observed that even if proliferation of $CD4^+$ cells from patients with lung cancer is initially inhibited by MDSC, MHC II positive lung cancer vaccines can prime and boost tumour-specific $CD4^+$ cells, which secrete IFN-γ. Similarly, Watanabe *et al.* have demonstrated that MDSC strongly inhibit the proliferation of T cells, but production of IFN-γ by these cells was still detected. Importantly, the same author has shown that MDSC do not inhibit function of T cells *in vivo* at the effector phase. After cotransfer of MDSC with activated T cells into tumour-bearing mice, tumour regression could still be observed (Watanabe *et al.* 2008). However, neither interaction between transferred lymphocytes and MDSC *in vivo* nor the phenotype of MDSC after cotransfer was investigated.

Apart from T cells, MDSC also affect NK cells, the second important effector cells in antitumour immunity. Several studies suggest that MDSC inhibit NK cells function by dif-

Table 1 Cytokines that drive differentiation of $CD11b^+$ $Gr\text{-}1^+$ cells into immunostimulatory cells *in vitro*

Cytokines	Phenotype after differentiation	Refs
IFN-γ + TNF-α	$CD11c^-CD86^+$ MHC II^+	Bronte *et al.* 2000
IL-12	$CD11c^-CD86^+$ MHC II^-	Bronte *et al.* 2000
GM-CSF + IL-4	$CD11c^+$ MHC II^+	Caquard *et al.* 2010
IFN-γ + IL-12 + GM-CSF + IL-3	$CD11c^+$MHC I^+ MHC II^+	Narita *et al.* 2009

ferent mechanisms (Liu *et al.* 2007; Hoechst *et al.* 2009; Li *et al.* 2009). However, one study using NK-sensitive tumour model, RMA-S lymphoma, unravelled an activating role for $CD11b^+Gr\text{-}1^+F4/80^+$ MDSC on NK cells. These suppressor cells express RAE-1, a ligand for the activating receptor NKG2D, and induce NK to produce IFN-γ. Depletion of MDSC (using anti-Gr-1 antibody) in this tumour model accelerates tumour growth (Nausch *et al.* 2008) in contrast to studies using other tumour models (Gabrilovich & Nagaraj 2009; Li *et al.* 2009). This report proves that even though MDSC are suppressive, they can also be immunostimulatory under some circumstances.

Development of immunostimulatory properties in MDSC could occur when these cells are placed in a proper cytokine environment. In the 1990s it was reported that a suppressive population of granulocyte-macrophage progenitor cells could be differentiated by using a combination of low doses of IFN-γ and TNF-α (Pak *et al.* 1995). The finding of Bronte *et al.* suggested that the same cytokines can drive differentiation of MDSC into antigen-presenting cell (APC)-like cells. They have demonstrated that suppressive $CD11b^+Gr\text{-}1^+CD31^+$ cells in the presence of IFN-γ and TNF-α or IL-12 get transformed into stimulatory cells (with upregulation of CD86) that enhance cytotoxic T lymphocytes (CTL) responses *in vitro* (Bronte *et al.* 2000). Similarly, Narita *et al.* (2009) showed that $CD11b^+Gr\text{-}1^+$ cells from tumour-bearing mice can differentiate *in vitro* into either functional $CD11c^+$ cells (which are able to generate CTL) or $F4/80^+$ suppressive macrophages depending on the environment (Th1 cytokines *vs.* tumour-derived factors). Myeloid-derived suppressor cell-like cells have also been shown to have ability to differentiate into immunostimulatory cells *in vivo* (Caquard *et al.* 2010). These cells had the $CD11b^+Ly\text{-}6G^-Ly\text{-}6C^+$ phenotype and were generated after CY injection into NOD mice (anti-Gr-1 antibody recognizes two epitopes: Ly-6G is expressed mainly on granulocytic fraction of MDSC and Ly-6C expressed mainly on monocytic fraction of MDSC). They resemble MDSC functionally as they exhibit immunosuppressive activity *in vitro* but have the morphology of inflammatory monocytes. In the model of prediabetic NOD/SCID, adoptive transfer of this cell population unexpectedly caused their conversion into $CD11c^+$ cells *in vivo*. When cultured with GM-CSF and IL-4, $CD11b^+Ly\text{-}6C^+$ cells were also able to differentiate into DC-like cells that were capable of stimulating T-cell response. Culture of $CD11b^+Ly\text{-}6C^+$ cells with IFN-γ or IL-4 results in the upregulation of NOS2 or ARG1 respectively (Caquard *et al.* 2010). This study, in agreement with previous studies (Bronte *et al.* 2000; Narita *et al.* 2009), demonstrates that cells with features of MDSC exhibit plasticity. This observation was used by Ko *et al.* (2009) who created an APC-based vaccine from MDSC. As it is known that NKT cells have potential to reduce the suppressive activity of MDSC (De Santo *et al.* 2008), α-galactosylceramide (αGalCer), the ligand for NKT cells, was used for the preparation of the vaccine. Thus the MDSC presenting tumour antigen (Ag) and αGalCer after injection into tumour-bearing mice were converted into APC and prolonged survival time. This vaccine was shown to lead to antitumour immunity, as illustrated by generation of CTL and NK responses (Ko *et al.* 2009). This suggests that not only cytokine *milieu* alone (Table 1) but also NKT cells can deliver signals to MDSC, thereby changing their function from immunosuppressive into immunostimulatory (Figure 1).

Table 2 Examples of immunostimulatory function of myeloid $CD11b^+Gr\text{-}1^+$ cells

	Function of myeloid $CD11b^+Gr\text{-}1^+$cells	Experimental model	References
1	Priming and expansion of antigen-specific B cells, optimal production of antibody	Immunization with alum	Jordan *et al.* 2004
2	Inhibition of tumour growth during adoptive immunotherapy with CY	Ehrlich tumour	Peláez *et al.* 2001
3	Activation of NK-cell effector functions	Lymphoma model RMA-S	Nausch *et al.* 2008
4	MDSC-based vaccine increases survival time & protects from metastases	Colon adenocarcinoma	Ko *et al.* 2009
5	Antigen-specific immunity and cross-priming	Ovarian carcinoma model	Tomihara *et al.* 2010
6	$CD11b^+$Ly-6C hi monocytes contributed to tumour growth inhibition	Chronic osteomyelitis in osteosarcoma model	Sottnik *et al.* 2010
7	$CD11b^+Ly\text{-}6C^+$ cells differentiated into DC that were able to stimulate T cells	Diabetes	Caquard *et al.* 2010
8	Enhancement of CTL response *in vitro* after differentiation into APC	Mammary adenocarcinoma	Bronte *et al.* 2000

APC, antigen-presenting cell; CTL, cytotoxic T lymphocytes; CY, cyclophosphamide; DC, dendritic cells; MDSC, myeloid-derived suppressor cells; NK, natural killer.

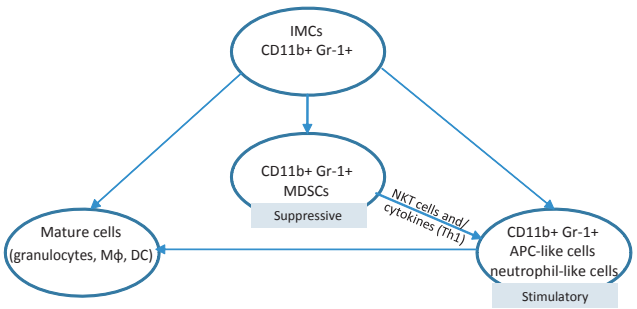

Figure 1 Simplified model for possible routes of differentiation of myeloid CD11b+Gr-1+ cells. (IMCs, immature myeloid cells; MDSCs, myeloid-derived suppressor cells; Mφ, macrophages; DC, dendritic cells; APC, antigen-presenting cells).

Myeloid cells with markers characteristic for MDSC were also found in the ascites of epithelial ovarian carcinoma in mice. However, these cells lack suppressive activity and resemble neutrophils, so they cannot be regarded as MDSC. Surprisingly, they are highly phagocytic and cross-prime Ag-specific T cells *in vivo*. Adoptive transfer of these cells delayed tumour development (Tomihara *et al.* 2010). Antitumour activity of $CD11b^{+}Gr\text{-}1^{+}$ neutrophils was also described in another study, where they were shown to infiltrate tumour site after TGF-β blockade (Fridlender *et al.* 2009). It is not known whether $CD11b^{+}Gr\text{-}1^{+}$ neutrophils could differentiate from MDSC.

Conditions for the differentiation of immune cells towards antitumour effector cells can be created during infection with microorganisms. The beneficial properties of bacterial infection in patients with cancer were already observed in the 19th century by William Coley as quoted in (McCarthy 2006) and constitute the basis for *Salmonella*-based cancer immunotherapies. These have shown to be very promising with impressive responses in preclinical trials (Pawelek *et al.* 1997; Avogadri *et al.* 2005; Bereta *et al.* 2007; Chen *et al.* 2009). Interestingly, it was observed that $CD11b^{+}Gr\text{-}1^{+}$ cells infiltrate a tumour tissue in tumour-bearing mice injected with *Salmonella*. The presence of $CD11b^{+}Gr\text{-}1^{+}$ cells at tumour site was correlated with the areas of tumour necrosis (Avogadri *et al.* 2005). However, the exact role of these cells has not been investigated, and it is not known whether these $CD11b^{+}Gr\text{-}1^{+}$ cells can be regarded as MDSC or MDSC-derived cells.

Concluding remarks

Taking together the data, despite the widely accepted immunosuppressive capacities of MDSC, a new function has emerged which is immune stimulation and antitumour activity. Why can MDSC be both immunosuppressive and immunostimulatory? Factors which should be responsible for their contradictory functions include the known dual role of NO, the cytokine *milieu*, interaction with NKT cells and the tumour microenvironment. Furthermore, we should also include heterogeneity and the presence of cells at different stages of maturation within a population of MDSC. This raises a possibility that under diverse conditions different subsets of MDSC can be expanded. We can expect that MDSC accumulating during pathologic situations can involve not only cells with phenotypic but also cells with functional diversity. It is known that some subpopulations of MDSC are more suppressive than others (e.g. the monocytic fraction of MDSC is generally more suppressive than the granulocytic one) and some do not show suppressive activity at all (e.g. the eosinophil subpopulation) (Ribechini *et al.* 2010). Examples introduced earlier do not indicate one specific subpopulation of MDSC that could exhibit stimulatory activity. Myeloid $CD11b^{+}Gr\text{-}1^{+}$cells phenotypically resembling both inflammatory monocytes and granulocytes were demonstrated to have this capacity.

There are still many open questions and challenges in research on MDSC. Lack of specificity of markers, (CD11b and Gr-1), and heterogeneity make this population of cells complex and difficult to analyse. The precise conditions for stimulatory activity of MDSC *in vivo* are not known. The exact role of NKT cells on MDSC is not clear, and future experiments should provide answers. Finally, the stimulatory abilities of MDSC have not been yet detected in humans.

This review presents our view, supported by some evidence, that MDSC can be successfully converted into stimulatory cells even if they were initially inhibitory (Figure 1). This is in contrast to another known population of suppressive cells, the regulatory T cells (T reg). Further detailed investigation into the phenomenon of dual differentiation ability of MDSC may reveal novel strategies for overcoming immunosuppression (which is detrimental in some pathological situations, e.g. in cancer) this would be without the need for elimination of suppressive cells, instead, it would involve redirecting them into beneficial cells.

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