30. Chouinard-Pelletier G, Jahnsen ED, Jones EA. Increased shear stress inhibits angiogenesis in veins and not arteries during vascular development. Angiogenesis. 2013;16(1):71-83.
31. Heinke J, Patterson C, Moser M. Life is a pattern: vascular assembly within the embryo. Front Biosci (Elite Ed). 2012;4:2269-88.
32. Choi K. Hemangioblast development and regulation. Biochem Cell Biol. 1998;76(6):947-56.
33. Huber TL, Kouskoff V, Fehling HJ, Palis J, Keller G. Haemangioblast commitment is initiated in the primitive streak of the mouse embryo. Nature. 2004;432(7017):625-30.
34. Vogeli KM, Jin SW, Martin GR, Stainier DY. A common progenitor for haematopoietic and endothelial lineages in the zebrafish gastrula. Nature. 2006;443(7109):337-9.
35. Jain S, Ward MM, O'Loughlin J, Boeck M, Wiener N, Chuang E, et al. Incremental increase in VEGFR1+ hematopoietic progenitor cells and VEGFR2+ endothelial progenitor cells predicts relapse and lack of tumor response in breast cancer patients. Breast Cancer Res Treat. 2012;132(1):235-42.
36. Plummer PN, Freeman R, Taft RJ, Vider J, Sax M, Umer BA et al. MicroRNAs regulate tumor angiogenesis modulated by endothelial progenitor cells. Cancer Res. 2013;73(1):341-52.
37. Gao D, Mittal V. The role of bone-marrow-derived cells in tumor growth, metastasis initiation and progression. Trends Mol Med;15(8):333-43.
38. Kirschmann DA, Seftor EA, Hardy KM, Seftor RE, Hendrix MJ. Molecular pathways: vasculogenic mimicry in tumor cells: diagnostic and therapeutic implications. Clin Cancer Res. 2012;18(10):2726-32.
39. Maniotis AJ, Folberg R, Hess A, Seftor EA, Gardner LM, Pe'er J, et al. Vascular channel formation by human melanoma cells in vivo and in vitro: vasculogenic mimicry. Am J Pathol. 1999;155(3):739-52.
40. Shirakawa K, Tsuda H, Heike Y, Kato K, Asada R, Inomata M, et al. Absence of endothelial cells, central necrosis, and fibrosis are associated with aggressive inflammatory breast cancer. Cancer Res. 2001 Jan 15;61(2):445-51.
41. Sood AK, Fletcher MS, Zahn CM, Gruman LM, Coffin JE, Seftor EA, et al. The clinical significance of tumor cell-lined vasculature in ovarian carcinoma: implications for anti-vasculogenic therapy. Cancer Biol Ther. 2002;1(6):661-4.
42. Sharma N, Seftor RE, Seftor EA, Gruman LM, Heidger PM Jr, Cohen MB, et al. Prostatic tumor cell plasticity involves cooperative interactions of distinct phenotypic subpopulations: role in vasculogenic mimicry. Prostate. 2002;50(3):189-201.
43. Bissell MJ. Tumor plasticity allows vasculogenic mimicry, a novel form of angiogenic switch. A rose by any other name? Am J Pathol. 1999;155(3):675-9.
44. Hendrix MJ, Seftor EA, Hess AR, Seftor RE. Molecular plasticity of human melanoma cells. Oncogene. 2003;22(20):3070-5.
45. Pollard JW. Tumour-educated macrophages promote tumour progression and metastasis. Nat Rev Cancer. 2004;4(1):71-8.
46. Leek RD, Hunt NC, Landers RJ, Lewis CE, Royds JA, Harris AL. Macrophage infiltration is associated with VEGF and EGFR expression in breast cancer. J Pathol. 2000;190(4):430-6.
47. Coussens LM, Tinkle CL, Hanahan D, Werb Z. MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. Cell. 2000;103(3):481-90.
48. Dirkx AE, Oude Egbrink MG, Wagstaff J, Griffioen AW. Monocyte/macrophage infiltration in tumors: modulators of angiogenesis. J Leukoc Biol. 2006;80(6):1183-96.
49. Studeny M, Marini FC, Dembinski JL, Zompetta C, Cabreira-Hansen M, et al. Mesenchymal stem cells: potential precursors for tumor stroma and targeted-delivery vehicles for anticancer agents. J Natl Cancer Inst. 2004;96(21):1593-603.
50. Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. Nat Rev Immunol. 2008;8(9):726-36.
51. Hall B, Andreeff M, Marini F. The participation of mesenchymal stem cells in tumor stroma formation and their application as targeted-gene delivery vehicles. Handb Exp Pharmacol. 2007;(180):263-83.
52. Liu S, Ginestier C, Ou SJ, Clouthier SG, Patel SH, Monville F et al. Breast cancer stem cells are regulated by mesenchymal stem cells through cytokine networks. Cancer Res. 2011;71(2):614-24.
53. Karnoub AE, Dash AB, Vo AP, Sullivan A, Brooks MW, Bell GW, et al. Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature. 2007;449(7162):557-63.
54. Ghajar CM, Peinado H, Mori H, Matei IR, Evason KJ, Brazier H, et al. The perivascular niche regulates breast tumour dormancy. Nat Cell Biol. 2013;15(7):807-17.
55. Taylor DP1, Clark A, Wheeler S, Wells A. Hepatic nonparenchymal cells drive metastatic breast cancer outgrowth and partial epithelial to mesenchymal transition. Breast Cancer Res Treat. 2014;144(3):551-60.

DISPARATE FUNCTIONS OF MYELOID-DERIVED SUPPRESSOR CELLS IN CANCER METASTASIS

Laura E Edgington-Mitchell and Belinda S Parker
Department of Biochemistry, La Trobe Institute for Molecular Science, La Trobe University, Melbourne, Australia.
Email: Belinda.Parker@latrobe.edu.au

Abstract

Myeloid-derived suppressor cells comprise a heterogeneous population of immature immune cells that expand during the course of cancer progression. These cells adopt an immunosuppressive phenotype that impairs the anti-tumour immune response through modulation of T cells, natural killer cells, dendritic cells and macrophages, as evidenced both in mouse models of cancer and patients. While much attention has been focused on the immunosuppressive roles of myeloid-derived suppressor cells, it is becoming increasingly clear that they can also promote tumour progression and metastasis via other immune-independent functions, including the regulation of angiogenesis and tumour invasiveness. Their arrival at metastatic sites prior to the arrival of tumour cells also contributes to the formation of a favourable pre-metastatic niche. This review will summarise the various roles for myeloid-derived suppressor cells, including new evidence that supports a role in promoting a favourable pre-metastatic environment for bone metastasis.

That cancer progression relies heavily on the interaction between malignant cells and host stromal cells within the tumour microenvironment, including fibroblasts, endothelial cells and immune cells, is now well accepted. Although initially thought to have anti-tumour roles, it is now well known that immune cells can also become influenced by tumour-derived and other microenvironmental factors and adopt a pro-tumorigenic, immunosuppressive phenotype. In the last three decades, much attention has been focused on the roles of myeloid-derived suppressor cells (MDSCs) in this process. Mostly known for their ability to suppress the anti-tumour immune response through

modulation of adaptive and innate immune activation, it is becoming increasingly clear that MDSCs have additional immune-independent pro-metastatic roles, including promoting angiogenesis and bone degradation, and that they play an integral part in the formation of a pre-metastatic niche.

MDSCs comprise a heterogeneous population of immature immune cells. In normal physiology, these cells differentiate into macrophages, dendritic cells, granulocytes and neutrophils. However, in cancer, tumour-derived factors such as vascular endothelial growth factor (VEGF), G-CSF, GM-CSF and the pro-inflammatory proteins S100A8 and S100A9 block this differentiation, leading to an expansion of immature myeloid cells in bone marrow, peripheral blood, spleen and tumour.[1-4] Murine MDSCs are most often characterised by co-expression of the cell surface markers CD11b and Gr-1, and they can be divided into subclasses based on differential expression of the Gr-1 epitopes Ly6G and Ly6C. Granulocytic MDSCs are $CD11b^+/Gr\text{-}1^+/Ly6C^{mid}/Ly6G^{high}$ while monocytic MDSCs are $CD11b^+/Gr\text{-}1^+/Ly6C^{high}/Ly6G^-$ (table 1).[2,5,6] In humans however, MDSCs are defined as $CD11b^+/CD14^-/CD33^+$ or $Lin^-/HLA\text{-}DR^-/CD33^+$.[1,2] Given the heterogeneity of these populations, it will be essential in the future to identify markers that further subdivide unique populations. At present, the most conclusive way to define an MDSC population is by demonstrating its functional ability to suppress anti-tumour immune responses.

Table 1: Summary of common cell surface markers for MDSCs.

Species	MDSC Markers
Mouse	$CD11b^+/Gr\text{-}1^+$ $CD11b^+/Gr\text{-}1^+/Ly6C^{mid}/Ly6G^{high}$ (Granulocytic) $CD11b^+/Gr\text{-}1^+/Ly6C^{high}/Ly6G^-$ (Monocytic)
Human	$CD11b^+/CD14^-/CD33^+$ $Lin^-/HLA^-/DR^-/CD33^+$ $CD14^-/Cd11c^{hi}/CD123^-$ (fibrocytes)[41]

Numerous studies have now demonstrated that MDSCs accumulate throughout disease progression. A small number of $CD11b^+/Gr\text{-}1^+$ cells are found in healthy naïve mice, however these cells are not true MDSCs because they do not exert immunosuppressive effects. During chronic inflammation and tumourigenesis however, these cells fail to differentiate and instead rapidly expand and adopt an immunosuppressive phenotype.[2,7] A correlation between MDSC accumulation in blood and metastatic progression has been observed in human patients with breast, colorectal, gastric, brain, prostate, pancreatic, oesophageal, liver and skin cancers.[8-13] For example, in the peripheral blood, MDSCs increase from an average frequency of 1.26% and 1.96% in healthy patients and early breast cancer patients respectively, up to 4.37% (and as high as 25%) in patients with advanced metastatic disease.[8] This correlation has been recapitulated in immunocompetent mouse models of cancer, where MDSC numbers in the spleen and peripheral blood correlate closely with tumour burden and metastatic potential.[14-17] One of the most exaggerated models of MDSC accumulation is the 4T1 murine model of metastatic breast cancer, in which MDSC levels can increase by >20-fold compared to naïve mice.[18] Although less pronounced, this accumulation is also observed in the MMTV-PyMT breast cancer model, with an increase in MDSC accumulation of approximately seven-fold in tumour bearing mice.[18] In general, MDSC accumulation is more pronounced in mouse models, since overall tumour and/or metastatic burden is often higher than in patients who have received therapeutic intervention.

Immunosuppressive roles for MDSCs

As suggested by their name, the most prominent role for MDSCs is their ability to suppress the anti-tumour immune response, as extensively reviewed elsewhere.[4,19,20] Both granulocytic and monocytic MDSCs can suppress the proliferation and activation of T cells. MDSCs perform this function through several mechanisms. They overexpress arginase-1, which converts L-arginine to ornithine and urea.[4] They also express high levels of the cystine transporter x_c^- for importing cystine and lack the ASC transporter required for exporting cysteine.[21] MDSCs therefore act as a sponge for arginine and cysteine, reducing the availability of amino acids that are essential for protein synthesis and proliferation of T cells. Additionally, granulocytic MDSCs produce high levels of reactive oxygen species and peroxynitrites, and monocytic MDSCs produce nitric oxide through expression of inducible nitric oxide synthase.[4,7,22] Peroxynitrites and nitric oxide impair DNA damage repair and protein synthesis and consequently lead to reduced T cell proliferation.

In addition to their effects on T cells, MDSCs interfere with anti-tumour responses by decreasing the prevalence and function of natural killer cells through TGFβ, IL-1β, or natural killer p30-dependent mechanisms.[23-25] They are also able to dampen the immune response by triggering the activation and expansion of another immune suppressive population, regulatory T (T_{Reg}) cells.[26-28] Furthermore, MDSCs can function to skew the polarisation of macrophages to a pro-inflammatory and tumour promoting M2 phenotype,[29] and impair the ability of dendritic cells to activate T cells.[30]

These multiple suppressive functions are likely to have important implications therapeutically. A number of therapeutic approaches for cancer rely on immune activation and therefore may not be efficacious in an immune-suppressed environment populated by MDSCs. A recent strategy has focused on improving the anti-tumour immune response by combining immunotherapies with agents that manipulate the function of MDSCs, either by eliminating them, deactivating them, blocking their formation or forcing their differentiation, as extensively reviewed elsewhere.[31,32] One agent trialled in the clinic is all-trans retinoic acid (ATRA), which functions to promote the maturation of MDSCs into mature myeloid cells such as macrophages, dendritic cells and granulocytes. In renal cell and small cell lung cancer patients, ATRA improved

anti-tumour immune effects in combination with vaccine therapy.[33,34] However, a new study in murine breast cancer models suggests that ATRA promotes the differentiation of MDSCs into CD11b^{+}/Gr-1^{-}/F4/80^{+} macrophages that are even more immunosuppressive than their precursors.[18] This increase in T cell-suppressive ability was associated with enhanced metastatic outgrowth in the lungs of ATRA-treated mice, suggesting that extreme caution should be taken when going forward with this therapeutic approach. Therapies such as 5-fluorouracil or gemcitabine that deplete MDSCs without inducing differentiation, might be more efficacious at preventing tumour progression.[32] In order to improve the outcome of combination therapies, more information is needed regarding the diverse functions of MDSCs, both within the primary tumour and in circulation. This will ensure the educated design of clinical trials that use combination therapies in the right setting based on mechanisms that maximise the likelihood of synergy.

Pro-angiogenic and pro-invasive roles for MDSCs

In addition to their presence in bone marrow, blood and spleen, MDSCs have been shown to infiltrate into the tumour microenvironment, where they concentrate at the periphery of the tumour and can exert effects on tumour growth.[16,18] MDSCs can mediate reduced sensitivity to anti-VEGF therapy,[35,36] suggesting an important role in promoting angiogenesis. In fact, it has been shown in models of colorectal cancer and Lewis lung carcinoma that MDSCs not only promote angiogenesis and tumour growth, but actually directly incorporate into the vasculature and express endothelial markers.[15] In this study, enhanced tumour growth and angiogenesis were reversed using matrix metalloprotease-9 (MMP9)-deficient MDSCs. Considering MMP9 has been implicated in VEGF activation,[37] this study suggests that apart from direct differentiation into endothelial cells, MDSCs are likely to be critical for promoting angiogenesis within the tumour microenvironment via production of MMP9.[15] This was supported in studies using mice lacking the MMP inhibitor TIMP2, whereby accumulation of MDSCs with high MMP activity increased angiogenesis and tumour growth rate in the Lewis lung carcinoma model.[38] Additionally, in the 4T1 breast cancer model, co-culture of tumour cells with MDSCs from late-stage tumour bearing mice enhanced tumour cell invasion in an MMP-dependent manner, and this was associated with enhanced metastasis to lung.[16]

The evidence linking MDSCs to angiogenesis is not limited to their expression of MMPs. Other potential promoters of MDSC-induced angiogenesis include regulator of G protein signaling-2 (Rgs2),[39] and Stat3, which governs MDSC-induced angiogenesis through upregulation of angiogenic genes such as VEGF, bFGF, IL-1β, MMP, CCL2 and CXCL2.[40] Human studies that support this pre-angiogenic role of MDSCs are lacking, however recent work in patients with metastatic paediatric sarcomas has reported a novel subset of human MDSCs called fibrocytes (CD14^{-}/Cd11^{chi}/CD123^{-}) that, apart from their immune suppressive activity, stimulate vessel growth in tube formation assays.[41]

Role of MDSCs in the pre-metastatic niche

In addition to their roles in promoting local invasion and angiogenesis within the primary tumour microenvironment, myeloid-derived suppressor cells have also been implicated in the formation of a pre-metastatic niche. The concept of a pre-metastatic niche involves tumour-induced changes to distant organs that make them well suited to support impending metastatic outgrowth. In 2005, Lyden and colleagues first described early events that initiate a pre-metastatic niche, whereby recruitment of hematopoietic progenitor cells into the lung promoted tumour cell recruitment and degradation of the extracellular matrix.[42] Studies in the last decade have focused on MDSCs as a subset of bone marrow-derived cells that is critical for establishing this favourable environment due to their roles in both angiogenesis and immunosuppression.

Hypoxia, or low oxygen levels, in the primary tumour has been linked with metastatic progression and is associated with the formation of a pre-metastatic niche at distant sites.[43] It has been demonstrated in mouse models of metastasis that hypoxia inducible factor (HIF)-dependent lysyl oxidase (LOX) secreted by hypoxic tumour cells, can remodel the extracellular matrix in secondary sites to promote the adhesion of CD11b+ bone marrow-derived cells.[43] In support of this, pre-injection of mice with conditioned media from hypoxic breast tumour cells prior to intravenous injection of tumour cells resulted in clustering of granulocytic MDSCs at the terminal bronchioles of the lung and increased lung colonisation, a phenomenon that was not observed using the normoxic conditioned media counterpart.[44] In this study, enhanced metastasis was associated with immune suppression, whereby NK cells had reduced cytotoxic activity.

MDSC accumulation in pre-metastatic lungs is also observed in the 4T1 mammary tumour model, where they have been associated with immune suppression via inhibition of interferon-γ (IFN-γ) production.[45] In this study, pre-metastatic lungs harbouring MDSCs had increased levels of growth factors, Th2 cytokines (IL-4, IL-5, IL-9 and IL-10) and inflammatory cytokines (IL-1β, SDF-1, MCP-1), which functioned collectively to create a proliferative, immunosuppressive and inflammatory environment optimal for tumour cell growth. Additionally, the vasculature of the pre-metastatic lung was more disorganised and leaky than the normal lung and more amenable to tumour cell extravasation and metastasis.[45] This confirmed an important role for MDSCs in vascular remodelling of the pre-metastatic niche. The evidence for a pre-metastatic niche extends beyond the lung in this model. MDSCs also infiltrate into the brain prior to the arrival of 4T1 tumour cells, where they have been implicated in tumour recruitment to the metastatic site.[46]

Role of MDSCs in bone metastasis

Apart from their role in supporting a pre-metastatic niche in soft tissues, recent evidence in breast cancer models suggests that MDSCs also function to promote a favourable microenvironment in bone, a common site of metastasis in patients. When MDSCs from tumour-bearing

mice were co-injected with MDA-MB-231 mammary tumour cells into the fat pad of nude mice, there was a 30% decrease in trabecular volume in femurs compared to tumour cells co-injected with naïve myeloid cells.[47] This phenomenon was observed prior to the outgrowth of bone metastases, suggesting that bone loss due to MDSCs may be integral in establishing a pre-metastatic environment in bone. To further confirm this, mice were injected intra-tibially with tumour MDSCs or naïve myeloid cells just prior to cardiac injection with MDA-MB-231 cells. Tumour MDSCs enhanced bone tumour growth and this was associated with enhanced bone degradation and an increased osteoclast activity.

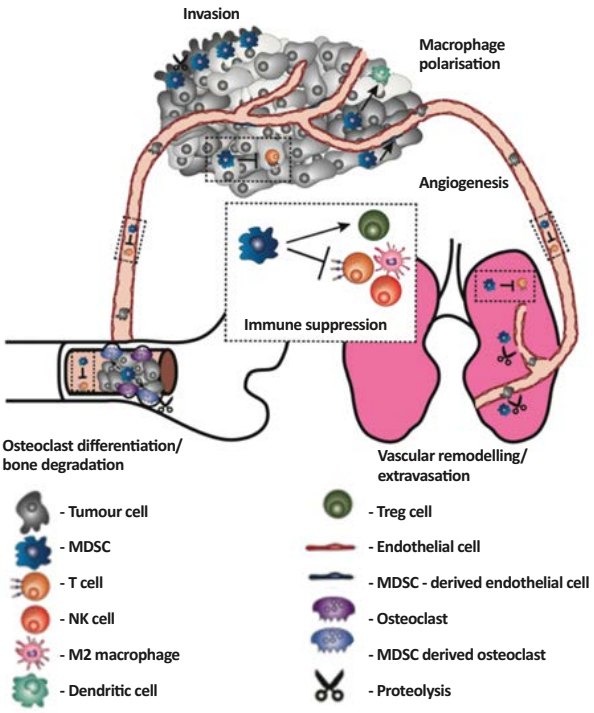
Surprisingly, when MDSCs were isolated from the bone marrow of tumour-bearing mice and cultured on dentine slices in the presence of RANK ligand, the cells differentiated into tartrate-resistant acid phosphatase positive ($TRAP^+$) osteoclasts with bone-degrading capabilities. This was confirmed *in vivo*, where GFP^+ MDSCs became $TRAP^+$ after intratibial injection, providing the first evidence that MDSCs can differentiate into osteoclasts in the bone microenvironment.

Other groups demonstrated that this phenomenon also exists in the 4T1 breast cancer model,[48] and in multiple myeloma.[49] In the 4T1 model, MDSCs that were isolated from the bone marrow of mice bearing bone metastases were able to differentiate into $TRAP^+$ osteoclasts, whereas those isolated from the metastatic lung, lymph node, spleen or blood of tumour bearing mice could not. This highlighted an importance for the bone microenvironment in this process. MDSC-derived osteoclasts also expressed other osteoclast markers such as cathepsin K, MMP9 and carbonic anhydrase-2, and were capable of resorption of bovine cortical bone slices in vitro and of tibias in vivo.[49] High levels of nitric oxide were shown to be critical for the differentiation of MDSCs to osteoclasts, as treatment of mice with 1400W, an inhibitor for inducible nitric oxide synthase, attenuated bone damage caused by MDSCs. Considering recent work by Kang and colleagues has revealed that metastatic outgrowth of disseminated breast tumour cells in bone is dependent on osteoclast activation,[50] MDSCs may represent an important subset of osteoclast progenitors that is crucial in the establishment of a pre-metastatic niche in bone.

Conclusion

We have provided a brief overview of the diverse functions of MDSCs in tumour growth and metastasis (figure 1). Most of the work to date has focused on the immune suppressive nature of these cells and their ability to extinguish the anti-tumour immune response through modulation of T cell proliferation and activation. There is now clear evidence however, that these cells have other functions in promoting angiogenesis and providing a favourable microenvironment for outgrowth in common metastatic sites such as lung and bone. Additionally, MDSCs have varying roles depending on the microenvironment from which they are derived. Therefore, further characterisation of specific markers that predict functional characteristics of MDSCs is necessary. Among many other factors, the secondary roles for MDSCs seem to be governed in large part by proteolytic enzymes such as MMPs, which are highly expressed in these cells and whose activity is critical for the cell signalling, matrix degradation and bone resorption necessary to promote metastasis. As the understanding of these diverse MDSC subtypes and functions continues to expand, therapies targeting MDSCs in combination with immunotherapy will continue to improve.

Figure 1: Diverse roles for myeloid-derived suppressor cells in cancer metastasis. MDSCs compromise the anti-tumour immune response through suppression of T cells, dendritic cells, and natural killer cells. Their stimulation of T_{REG} activation can also diminish the anti-tumour response. While much attention has been focused on these immune suppressive roles for MDSCs, they function in various other ways to promote metastasis. At the site of the primary tumour, MDSCs stimulate angiogenesis and can even become incorporated into the endothelium. They promote local invasion of tumour cells and can also polarise macrophages towards an M2 phenotype, which further augments angiogenic and invasive potential. At distant sites, MDSCs function to create an environment that is immune suppressed and primed for metastatic outgrowth. In lung, this includes remodelling the vasculature to support tumour cell extravasation. In the bone, MDSCs can differentiate into osteoclasts that are capable of degrading bone. Many of these non-immunosuppressive roles for MDSCs rely on proteases such as matrix metalloproteases, and in the case of bone degradation, cathepsin K.



References

1. Ye XZ, Yu SC, Bian XW. Contribution of myeloid-derived suppressor cells to tumor-induced immune suppression, angiogenesis, invasion and metastasis. J Genet Genomics. 2010;37(7):423-430.
2. Talmadge JE, Gabrilovich DI. History of myeloid-derived suppressor cells. Nat Rev Cancer. 2013;13(10):739-752.
3. Umansky V, Sevko A. Tumor microenvironment and myeloid-derived suppressor cells. Cancer microenvironment: official journal of the International Cancer Microenvironment Society. 2013;6(2):169-177.
4. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V. Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol. 2012;12(4):253-268.
5. Youn JI, Nagaraj S, Collazo M, Gabrilovich DI. Subsets of myeloid-derived suppressor cells in tumor-bearing mice. J Immunol. 2008;181(8):5791-5802.
6. Movahedi K, Guilliams M, Van den Bossche J, Van den Bergh R, Gysemans C, Beschin A, et al. Identification of discrete tumor-induced myeloid-derived suppressor cell subpopulations with distinct T cell-suppressive activity. Blood. 2008;111(8):4233-4244.
7. Qu P, Boelte KC, Lin PC. Negative regulation of myeloid-derived suppressor cells in cancer. Immunol Invest. 2012;41(6-7):562-580.
8. Diaz-Montero CM, Salem ML, Nishimura MI, Garrett-Mayer E, Cole DJ, Montero AJ. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. Cancer Immunol Immunother: CII. 2009;58(1):49-59.
9. Zhang B, Wang Z, Wu L, Zhang M, Li W, Ding J, et al. Circulating and tumor-infiltrating myeloid-derived suppressor cells in patients with colorectal carcinoma. PloS one. 2013;8(2):e57114.
10. Gabitass RF, Annels NE, Stocken DD, Pandha HA, Middleton GW. Elevated myeloid-derived suppressor cells in pancreatic, esophageal and gastric cancer are an independent prognostic factor and are associated with significant elevation of the Th2 cytokine interleukin-13. Cancer Immunol Immunother: CII. 2011;60(10):1419-1430.
11. Wang L, Chang EW, Wong SC, Ong SM, Chong DQ, Ling KL. Increased myeloid-derived suppressor cells in gastric cancer correlate with cancer stage and plasma S100A8/A9 proinflammatory proteins. J Immunol. 2013;190(2):794-804.
12. Vuk-Pavlovic S, Bulur PA, Lin Y, Qin R, Szumlanski CL, Zhao X, et al. Immunosuppressive CD14+HLA-DRlow/- monocytes in prostate cancer. The Prostate. 2010;70(4):443-455.
13. Weide B, Martens A, Zelba H, Stutz C, Derhovanessian E, Di Giacomo AM, et al. Myeloid-Derived Suppressor Cells Predict Survival of Patients with Advanced Melanoma: Comparison with Regulatory T Cells and NY-ESO-1- or Melan-A-Specific T Cells. Clin Cancer Res. 2014;20(6):1601-1609.
14. Bidwell BN, Slaney CY, Withana NP, Forster S, Cao Y, Loi S, et al. Silencing of Irf7 pathways in breast cancer cells promotes bone metastasis through immune escape. Nat Med. 2012;18(8):1224-1231.
15. Yang L, DeBusk LM, Fukuda K, Fingleton B, Green-Jarvis B, Shyr Y, et al. Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. Cancer Cell. 2004;6(4):409-421.
16. Yang L, Huang J, Ren X, Gorska AE, Chytil A, Aakre M, et al. Abrogation of TGF beta signaling in mammary carcinomas recruits Gr-1+CD11b+ myeloid cells that promote metastasis. Cancer Cell. 2008;13(1):23-35.
17. Younos I, Donkor M, Hoke T, Dafferner A, Samson H, Westphal S, et al. Tumor- and organ-dependent infiltration by myeloid-derived suppressor cells. Int Immunopharmacol. 2011;11(7):816-826.
18. Hamilton MJ, Bosiljcic M, Lepard NE, Halvorsen EC, Ho VW, Banath JP, et al. Macrophages are more potent immune suppressors ex vivo than immature myeloid-derived suppressor cells induced by metastatic murine mammary carcinomas. J Immunol. 2014;192(1):512-522.
19. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol. 2009;9(3):162-174.
20. Nagaraj S, Gabrilovich DI. Regulation of suppressive function of myeloid-derived suppressor cells by CD4+ T cells. Semin Cancer Biol. 2012;22(4):282-288.
21. Srivastava MK, Sinha P, Clements VK, Rodriguez P, Ostrand-Rosenberg S. Myeloid-derived suppressor cells inhibit T-cell activation by depleting cystine and cysteine. Cancer Res. 2010;70(1):68-77.
22. Raber PL, Thevenot P, Sierra R, Wyczechowska D, Halle D, Ramirez ME, et al. Subpopulations of Myeloid-Derived Suppressor Cells (MDSC) impair T cell responses through independent nitric oxide-related pathways. Int J Cancer. 2013.
23. Hoechst B, Voigtlaender T, Ormandy L, Gamrekelashvili J, Zhao F, Wedemeyer H, et al. Myeloid derived suppressor cells inhibit natural killer cells in patients with hepatocellular carcinoma via the NKp30 receptor. Hepatol. 2009;50(3):799-807.
24. Li H, Han Y, Guo Q, Zhang M, Cao X. Cancer-expanded myeloid-derived suppressor cells induce anergy of NK cells through membrane-bound TGF-beta 1. J Immunol. 2009;182(1):240-249.
25. Elkabets M, Ribeiro VS, Dinarello CA, Ostrand-Rosenberg S, Di Santo JP, Apte RN, et al. IL-1beta regulates a novel myeloid-derived suppressor cell subset that impairs NK cell development and function. Eur J Immunol. 2010;40(12):3347-3357.
26. Pan PY, Ma G, Weber KJ, Ozao-Choy J, Wang G, Yin B, et al. Immune stimulatory receptor CD40 is required for T-cell suppression and T regulatory cell activation mediated by myeloid-derived suppressor cells in cancer. Cancer Res. 2010;70(1):99-108.
27. Huang B, Pan PY, Li Q, Sato AI, Levy DE, Bromberg J, et al. Gr-1+CD115+ immature myeloid suppressor cells mediate the development of tumor-induced T regulatory cells and T-cell anergy in tumor-bearing host. Cancer Res. 2006;66(2):1123-1131.
28. Serafini P, Mgebroff S, Noonan K, Borrello I. Myeloid-derived suppressor cells promote cross-tolerance in B-cell lymphoma by expanding regulatory T cells. Cancer Res. 2008;68(13):5439-5449.
29. Sinha P, Clements VK, Bunt SK, Albelda SM, Ostrand-Rosenberg S. Cross-talk between myeloid-derived suppressor cells and macrophages subverts tumor immunity toward a type 2 response. J Immunol. 2007;179(2):977-983.
30. Hu CE, Gan J, Zhang RD, Cheng YR, Huang GJ. Up-regulated myeloid-derived suppressor cell contributes to hepatocellular carcinoma development by impairing dendritic cell function. Scand J Gastroenterol. 2011;46(2):156-164.
31. Wesolowski R, Markowitz J, Carson WE, 3rd. Myeloid derived suppressor cells - a new therapeutic target in the treatment of cancer. J ImmunoTher Cancer. 2013;1(10): eCollection 2013.
32. Baniyash M, Sade-Feldman M, Kanterman J. Chronic inflammation and cancer: suppressing the suppressors. Cancer Immunol Immunother: CII. 2014;63(1):11-20.
33. Mirza N, Fishman M, Fricke I, Dunn M, Neuger AM, Frost TJ, et al. All-trans-retinoic acid improves differentiation of myeloid cells and immune response in cancer patients. Cancer Res. 2006;66(18):9299-9307.
34. Iclozan C, Antonia S, Chiappori A, Chen DT, Gabrilovich D. Therapeutic regulation of myeloid-derived suppressor cells and immune response to cancer vaccine in patients with extensive stage small cell lung cancer. Cancer Immunol Immunother: CII. 2013;62(5):909-918.
35. Shojaei F, Wu X, Malik AK, Zhong C, Baldwin ME, Schanz S, et al. Tumor refractoriness to anti-VEGF treatment is mediated by CD11b+Gr1+ myeloid cells. Nat Biotechnol. 2007;25(8):911-920.
36. Finke J, Ko J, Rini B, Rayman P, Ireland J, Cohen P. MDSC as a mechanism of tumor escape from sunitinib mediated anti-angiogenic therapy. Int Immunopharmacol. 2011;11(7):856-861.
37. Nozawa H, Chiu C, Hanahan D. Infiltrating neutrophils mediate the initial angiogenic switch in a mouse model of multistage carcinogenesis. Proc Natl Acad Sci. 2006;103(33):12493-12498.
38. Guedez L, Jensen-Taubman S, Bourboulia D, Kwityn CJ, Wei B, Caterina J, et al. TIMP-2 targets tumor-associated myeloid suppressor cells with effects in cancer immune dysfunction and angiogenesis. J Immunother. 2012;35(6):502-512.
39. Boelte KC, Gordy LE, Joyce S, Thompson MA, Yang L, Lin PC. Rgs2 mediates pro-angiogenic function of myeloid derived suppressor cells in the tumor microenvironment via upregulation of MCP-1. PloS one. 2011, 6(4):e18534.
40. Kujawski M, Kortylewski M, Lee H, Herrmann A, Kay H, Yu H. Stat3 mediates myeloid cell-dependent tumor angiogenesis in mice. J Clin Invest. 2008, 118(10):3367-3377.
41. Zhang H, Maric I, DiPrima MJ, Khan J, Orentas RJ, Kaplan RN, et al. Fibrocytes represent a novel MDSC subset circulating in patients with metastatic cancer. Blood. 2013;122(7):1105-1113.
42. Kaplan RN, Riba RD, Zacharoulis S, Bramley AH, Vincent L, Costa C, et al. VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nat. 2005;438(7069):820-827.
43. Erler JT, Bennewith KL, Cox TR, Lang G, Bird D, Koong A, et al. Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche. Cancer Cell. 2009;15(1):35-44.
44. Sceneay J, Chow MT, Chen A, Halse HM, Wong CS, Andrews DM, et al. Primary tumor hypoxia recruits CD11b+/Ly6Cmed/Ly6G+ immune suppressor cells and compromises NK cell cytotoxicity in the premetastatic niche. Cancer Res. 2012;72(16):3906-3911.
45. Yan HH, Pickup M, Pang Y, Gorska AE, Li Z, Chytil A, et al. Gr-1+CD11b+ myeloid cells tip the balance of immune protection to tumor promotion in the premetastatic lung. Cancer Res. 2010;70(15):6139-6149.
46. Liu Y, Kosaka A, Ikeura M, Kohanbash G, Fellows-Mayle W, Snyder LA, et al. Premetastatic soil and prevention of breast cancer brain metastasis. Neuro Oncol. 2013;15(7):891-903.
47. Danilin S, Merkel AR, Johnson JR, Johnson RW, Edwards JR, Sterling JA. Myeloid-derived suppressor cells expand during breast cancer progression and promote tumor-induced bone destruction. Oncoimmunol. 2012;1(9):1484-1494.
48. Sawant A, Deshane J, Jules J, Lee CM, Harris BA, Feng X, et al. Myeloid-derived suppressor cells function as novel osteoclast progenitors enhancing bone loss in breast cancer. Cancer Res. 2013;73(2):672-682.
49. Zhuang J, Zhang J, Lwin S, Edwards JR, Edwards CM, Mundy GR. Osteoclasts in Multiple Myeloma Are Derived from Gr-1+CD11b+Myeloid-Derived Suppressor Cells. PLoS one. 2012;7(11): e48871.
50. Lu X, Mu E, Wei Y, Riethdorf S, Yang Q, Yuan M, et al. VCAM-1 promotes osteolytic expansion of indolent bone micrometastasis of breast cancer by engaging alpha4beta1-positive osteoclast progenitors. Cancer Cell. 2011;20(6):701-714.