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Editorial Open Access

Myeloid Derived Suppressor Cells: Fuel the Fire

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Abstract

Low oxygen tension, hypoxia, is a characteristic of many tumors and associated with the poor prognosis. Hypoxia invites bone marrow derived cells (BMDCs) from bone marrow to the site of tumor. These recruited CXCR4+ BMDCs provide favorable environment for the tumor growth by acquiring pro-angiogenic phenotype such as CD45+VEGFR2+ Endothelial Progenitor Cells (EPC), or CD45+Tie2+ myeloid cells. CD11b+CD13+ myeloid population of the BMDCs modulate tumor progression. These myeloid populations retain immunosuppressive characteristics, for example, myeloid derived suppressor cells (MDSCs), and regulates immune- suppression by inhibiting cytotoxic T cell function. In addition, MDSCs were observed at the premetastatic niche of the distant organs in other tumors. Protumorigenic and prometastatic role of the myeloid cells provides a basis for therapeutic targeting of immunosuppression and thus inhibiting tumor development and metastasis.

Keywords: Myeloid cells; Hypoxia; Suppressor Cells; Bone marrow; Tumor

Editorial

Bone Marrow Derived Cells (BMDCs) play a pivotal role in tumor microenvironment [1]. Tumor induced changes such as hypoxia is involved in the up-regulation of HIF1-α followed by induction of Stromal Cell Derived Factor-1 Alpha (SDF1α) and secretion of various pro-angiogenic factors and recruitment of CXCR4+BMDCs [2-5]. These recruited cells are characterized as pro-angiogenic CD45+VEGFR2+ Endothelial Progenitor Cells (EPC), or CD45+Tie2+ monocytes [6,7]. Interestingly, lin-ckit+Sca-1+ and their derived cells demonstrate significant recruitment to carcinomas in vivo but they do not functionally contribute to tumor neovascularization [8]. BMPC derived MMP9 modulates neovessel remodeling, thereby playing pivotal role in tumor growth [9,10]. Recent studies have shown that myeloid populations of BMPCs are critical in tumor development [11] e.g. CD11b+CD13+ myeloid cells constitute an immune population of BMPCs that promote angiogenesis, tumor progression and metastasis [12]. Myeloid cells regulate VEGF independent tumor growth and angiogenesis [13]. TGFβ signaling in BMPCs is important and recruits Myeloid Derived Suppressor Cells (MDSCs) via CCL2 in the tumor microenvironment [14]. Additionally, MDSC can be produced in the bone marrow in response to tumor derived factors i.e. Granulocyte Colony Stimulating Factor (G-CSF), IL-6, Granulocyte Monocyte Colony Stimulating Factor (GM-CSF), IL-1β, Prostaglandin E2 (PGE2) and Tumor Necrosis Factor A (TNFα) and are recruited to the tumor site by CXCL12 and CXCL5 [15].

In mice, MDSC express Gr1+ and CD11b+ myeloid markers. Human MDSC express myeloid cell markers such as CD11b+ and CD33+. Monocytic MDSC are usually characterized by HLA-DR-, CD11b+, CD33+ and CD14+ phenotype in humans, whereas mature monocytes express HLA-DR. In mice, monocytic MDSCs express CD11b+Ly6G-/Ly6C+ markers. Granulocytic MDSC are usually characterized by HLA-DR-, CD11b+, CD33+, CD15+ phenotype in humans. Gr1 antigen is absent in the human MDSCs. In mice, granulocytic MDSCs express CD11b+Ly6G+/Ly6Clow markers. Phenotypic characterization of MDSCs is heterogeneous and depends on the site of tumor in human cancers [16]. Signals that stimulate MDSC to acquire immunosuppressive properties are STAT1, STAT3 and STAT6 signal transducer and activator of transcription, and NF-κB transcription factors [17]. Activated MDSC produce Arginase 1 (ARG1), NADPH oxidase, inducible Nitric Oxide Synthase (NOS2), Indoleamine 2,3-Dioxygenase (IDO) and immunosuppressive cytokines that inhibit Cytotoxic T Lymphocytes (CTLs), Dendritic Cells (DC), and Natural Killer (NK) cells [18]. Expression of the B-cell receptor component CD79a on immature myeloid cells contributes to their tumor promoting effects [19]. Downregulation of CD40 expression may contribute to MDSC accumulation by facilitating MDSC resistance to apoptosis [20]. In addition, MDSCs secreted factors expand CD4+CD25+FoxP3+ regulatory T cells (Tregs) to generate immunologically suppressive tumor microenvironment [21].

MDSCs acquire Endothelial Cell (EC) properties in tumor microenvironment and promote tumor growth [22]. MDSC may impair the efficacy of cancer vaccines [23] and antiangiogenic therapy [24]. Peripheral blood MDSC levels associate with a higher tumor burden and a worse prognosis [25,26]. In addition, Gr-1+CD11b+ MDSCs are significantly increased in lungs of mice bearing mammary adenocarcinomas before tumor cell arrival. In the premetastatic lungs, these immature myeloid cells significantly decrease IFN-gamma production and increase proinflammatory cytokines [27]. TGF-β signaling in myeloid cells is required for tumor progression [28] and metastasis [29]. In mice, stromal abrogation of TGF-beta signaling induced accumulation of MDSCs in fore stomach tumors [30]. Thus, protumorigenic and prometastatic role of the myeloid cells provides a basis for therapeutic targeting of immunosuppression and thus inhibiting tumor development and metastasis [31]. In patients, uniform methodology such as computational algorithm-driven analysis is necessary for prospective testing of MDSCs as a biomarker before treatment [32].

So far, many MDSC inhibitors have been developed that are categorized into four groups: (1) deactivation of MDSCs, (2) promotion towards differentiated and mature cells from MDSC, (3) inhibition of development of MDSC, and (4) Depletion of MDSCs. Several of these potential inhibitors have shown the minimal to broad effect on MDSCs [31,33-35]. For example, inhibition of MDSCs enhances anti-tumor immunity by increasing responsiveness to interferon stimulation in murine models [36]. Inhibition of tumor-derived prostaglandin-E2 blocks the induction of MDSCs and recovers NK cell activity [37]. However, better inhibitors are required to increase the efficacy of MDSC inhibition and improve the immunosuppressive effect of MDSCs on tumor microenvironment [38].

References

1. Scarlett CJ (2013) Contribution of bone marrow derived cells to the pancreatic tumor microenvironment. Front Physiol 4: 56.
2. Aghi M, Cohen KS, Klein RJ, Scadden DT, Chiocca EA (2006) Tumor stromal-derived factor-1 recruits vascular progenitors to mitotic neovasculature, where microenvironment influences their differentiated phenotypes. Cancer Res 66: 9054-9064.
3. De Falco E, Porcelli D, Torella AR, Straino S, Iachininoto MG, et al. (2004) SDF-1 involvement in endothelial phenotype and ischemia-induced recruitment of bone marrow progenitor cells. Blood 104: 3472-3482.
4. Ceradini DJ, Kulkarni AR, Callaghan MJ, Tepper OM, Bastidas N, et al. (2004) Progenitor cell trafficking is regulated by hypoxic gradients through HIF-1 induction of SDF-1. Nat Med 10: 858-864.
5. Du R, Lu KV, Petritsch C, Liu P, Ganss R, et al. (2008) HIF1alpha induces the recruitment of bone marrow-derived vascular modulatory cells to regulate tumor angiogenesis and invasion. Cancer Cell 13: 206-220.
6. Deak E, Göttig S, Rüster B, Paunescu V, Seifried E, et al. (2010) Bone marrow derived cells in the tumour microenvironment contain cells with primitive haematopoietic phenotype. J Cell Mol Med 14: 1946-1952.
7. Ahn GO, Brown JM (2009) Role of endothelial progenitors and other bone marrow-derived cells in the development of the tumor vasculature. Angiogenesis 12: 159-164.
8. Shinde Patil VR, Friedrich EB, Wolley AE, Gerszten RE, Allport JR, et al. (2005) Bone marrow-derived lin(-)c-kit(+)Sca-1+ stem cells do not contribute to vasculogenesis in Lewis lung carcinoma. Neoplasia 7: 234-240.
9. Seandel M, Butler J, Lyden D, Rafii S (2008) A catalytic role for proangiogenic marrow-derived cells in tumor neovascularization. Cancer Cell 13: 181-183.
10. Ahn GO, Brown JM (2008) Matrix metalloproteinase-9 is required for tumor vasculogenesis but not for angiogenesis: role of bone marrow-derived myelomonocytic cells. Cancer Cell 13: 193-205.
11. Shojaei F, Zhong C, Wu X, Yu L, Ferrara N (2008) Role of myeloid cells in tumor angiogenesis and growth. Trends Cell Biol 18: 372-378.
12. Dondossola E, Rangel R, Guzman-Rojas L, Barbu EM, Hosoya H, et al. (2013) CD13-positive bone marrow-derived myeloid cells promote angiogenesis, tumor growth, and metastasis. Proc Natl Acad Sci U S A 110: 20717-20722.
13. Ferrara N (2010) Role of myeloid cells in vascular endothelial growth factor-independent tumor angiogenesis. Curr Opin Hematol 17: 219-224.
14. Fan Q, Gu D, Liu H, Yang L, Zhang X, et al. (2014) Defective TGF-Î² signaling in bone marrow-derived cells prevents hedgehog-induced skin tumors. Cancer Res 74: 471-483.
15. Sawanobori Y, Ueha S, Kurachi M, Shimaoka T, Talmadge JE, et al. (2008) Chemokine-mediated rapid turnover of myeloid-derived suppressor cells in tumor-bearing mice. Blood 111: 5457-5466.
16. Solito S, Marigo I, Pinton L, Damuzzo V, Mandruzzato S, et al. (2014) Myeloid-derived suppressor cell heterogeneity in human cancers. Ann N Y Acad Sci 1319: 47-65.
17. Gabrilovich DI, Nagaraj S (2009) Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 9: 162-174.
18. Gabrilovich DI, Ostrand-Rosenberg S, Bronte V (2012) Coordinated regulation of myeloid cells by tumours. Nat Rev Immunol 12: 253-268.
19. Luger D, Yang YA, Raviv A, Weinberg D, Banerjee S, et al. (2013) Expression of the B-cell receptor component CD79a on immature myeloid cells contributes to their tumor promoting effects. PLoS One 8: e76115.
20. Shen J, Chen X, Wang Z, Zhang G, Chen W (2014) Downregulation of CD40 expression contributes to the accumulation of myeloid-derived suppressor cells in gastric tumors. Oncol Lett 8: 775-780.
21. Almand B, Clark JI, Nikitina E, van Beynen J, English NR, et al. (2001) Increased production of immature myeloid cells in cancer patients: a mechanism of immunosuppression in cancer. J Immunol 166: 678-689.
22. Yang L, DeBusk LM, Fukuda K, Fingleton B, Green-Jarvis B, et al. (2004) Expansion of myeloid immune suppressor Gr+CD11b+ cells in tumor-bearing host directly promotes tumor angiogenesis. Cancer Cell 6: 409-421.
23. Malmberg KJ (2004) Effective immunotherapy against cancer: a question of overcoming immune suppression and immune escape? Cancer Immunol Immunother 53: 879-892.
24. Lu-Emerson C, Snuderl M, Kirkpatrick ND, Goveia J, Davidson C, et al. (2013) Increase in tumor-associated macrophages after antiangiogenic therapy is associated with poor survival among patients with recurrent glioblastoma. Neuro Oncol 15: 1079-1087.
25. Gabitass RF, Annels NE, Stocken DD, Pandha HA, Middleton GW (2011) 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 60: 1419-1430.
26. Montero AJ, Diaz-Montero CM, Kyriakopoulos CE, Bronte V, Mandruzzato S (2012) Myeloid-derived suppressor cells in cancer patients: a clinical perspective. J Immunother 35: 107-115.
27. Yan HH, Pickup M, Pang Y, Gorska AE, Li Z, et al. (2010) Gr-1+CD11b+ myeloid cells tip the balance of immune protection to tumor promotion in the premetastatic lung. Cancer Res 70: 6139-6149.
28. Li Z, Pang Y, Gara SK, Achyut BR, Heger C, et al. (2012) Gr-1+CD11b+ cells are responsible for tumor promoting effect of TGF-β in breast cancer progression. Int J Cancer 131: 2584-2595.
29. Pang Y, Gara SK, Achyut BR, Li Z, Yan HH, et al. (2013) TGF-β signaling in myeloid cells is required for tumor metastasis. Cancer Discov 3: 936-951.
30. Achyut BR, Bader DA, Robles AI, Wangsa D, Harris CC, et al. (2013) Inflammation-mediated genetic and epigenetic alterations drive cancer development in the neighboring epithelium upon stromal abrogation of TGF-β signaling. PLoS Genet 9: e1003251.
31. Wesolowski R, Markowitz J, Carson WE 3rd (2013) Myeloid derived suppressor cells - a new therapeutic target in the treatment of cancer. J Immunother Cancer 1: 10.
32. Kitano S, Postow MA, Ziegler CG, Kuk D, Panageas KS, et al. (2014) Computational Algorithm-Driven Evaluation of Monocytic Myeloid-Derived Suppressor Cell Frequency for Prediction of Clinical Outcomes. Cancer Immunol Res .
33. Bruchard M, Ghiringhelli F (2014) Impact of chemotherapies on immunosuppression and discovery of new therapeutic targets. Bull Cancer 101: 605-607.
34. Highfill SL, Cui Y, Giles AJ, Smith JP, Zhang H, et al. (2014) Disruption of CXCR2-mediated MDSC tumor trafficking enhances anti-PD1 efficacy. Sci Transl Med 6: 237ra67.
35. Alizadeh D, Larmonier N (2014) Chemotherapeutic targeting of cancer-induced immunosuppressive cells. Cancer Res 74: 2663-2668.

36. Mundy-Bosse BL, Lesinski GB, Jaime-Ramirez AC, Benninger K, Khan M, et al. (2011) Myeloid-derived suppressor cell inhibition of the IFN response in tumor-bearing mice. Cancer Res 71: 5101-5110.

37. Mao Y, Sarhan D, Steven A, Seliger B, Kiessling R, et al. (2014) Inhibition of Tumor-Derived Prostaglandin-E2 Blocks the Induction of Myeloid-Derived Suppressor Cells and Recovers Natural Killer Cell Activity. Clin Cancer Res .

38. Qin H, Lerman B, Sakamaki I, Wei G, Cha SC, et al. (2014) Generation of a new therapeutic peptide that depletes myeloid-derived suppressor cells in tumor-bearing mice. Nat Med 20: 676-681.