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REVIEW

Myeloid cell signatures in tumor microenvironment predicts therapeutic response in cancer

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Bhagelu R Achyut
Ali S Arbab

Tumor Angiogenesis Laboratory, Department of Biochemistry and Molecular Biology, Cancer Center, Georgia Regents University, Augusta, GA, USA

Abstract: Tumor microenvironment (TME) consists of several immune and nonimmune cell populations including tumor cells. For many decades, experimental studies have depicted profound contribution of TME toward cancer progression and metastasis development. Several therapeutic strategies have been tested against TME through preclinical studies and clinical trials. Unfortunately, most of them have shown transient effect, and have largely failed due to aggressive tumor growth and without improving survival. Solid tumors are known to have a strong myeloid component (eg, tumor-associated macrophages) in tumor development. Recent data suggest that therapeutic responses in tumor are characterized by alterations in immune cell signatures, including tumor-associated myeloid cells. Polarized tumor-associated myeloid cells (M1–M2) are critical in impairing therapeutic effect and promoting tumor growth. The present review is intended to compile all the literatures related to the emerging contribution of different populations of myeloid cells in the development of tumor and therapeutic failures. Finally, we have discussed targeting of myeloid cell populations as a combination therapy with chemo-, targeted-, or radiation therapies.

Keywords: tumor microenvironment, tumor-associated macrophage, myeloid-derived suppressor cells, therapies, macrophage polarization, radiation, antiangiogenic therapy

Introduction

Tumor microenvironment (TME) has profound contribution toward cancer development and metastasis.[1,2] Recent advancements in cancer research have made very clear that tumor is not a single entity, but consists of various host components such as stromal cells, growing blood vessels, and heterogeneous immune cell populations, in addition to the tumor cells.[1] Inflammatory cells that are recruited to the tumors from bone marrow significantly contribute to local inflammation.[3,4] Depending on the context, infiltrating inflammatory cells in the TME may exert a dual role on tumor growth and progression.[5,6] Initially, TME exerts antitumor immune responses by the immune cells that may inhibit tumor cell growth.[7] However, at advanced stages, protumoral factors and chemokines secreted by tumor recruit and regulate immune cells to favor tumor growth and progression.[6] Among tumor-infiltrating immune cells, heterogeneous populations of myeloid cells (eg, macrophages) are known as distinct critical players in TME to regulate tumor cell migration and metastasis.[8–12] The present review is intended to introduce heterogeneous subtypes of myeloid populations and compile the literatures related to the involvement of myeloid cells in the development of tumors and therapeutic failures. Finally, we have discussed targeting of myeloid cell populations as a combination therapy with chemo-, targeted-, or radiation therapies.

Correspondence: Ali S Arbab
Tumor Angiogenesis Laboratory, Biochemistry and Molecular Biology, Cancer Center, Georgia Regents University, 1410 Laney Walker Blvd, CN3141, Augusta, GA 30912, USA
Tel +1 706 721 8909
Fax +1 706 434 6406
Email aarbab@gru.edu

Tumor-associated macrophages

Tumor-associated macrophages (TAMs) are part of heterogeneous populations of immunosuppressive myeloid cells that produce chemokines for the activation and maintenance of inflammatory processes in TME.[4,9,10,13] TAM recruitment, localization, and phenotypes are regulated by the tumor-secreted factors at the hypoxic areas of the tumor.[14,15] Depending on the stimuli, macrophages undergo series of functional reprogramming as described by two different polarization states, known as M1 and M2.[15,16] In TME, M1 macrophages are activated by tumor-derived cytokines such as granulocyte monocyte colony-stimulating factor and tumor necrosis factor (TNF). M1 macrophages play an important role as inducer and effector cells in polarized T-helper type 1 cells (Th1) responses. M1 macrophages produce high amount of interleukin (IL)-12 and IL-23, and low IL-10.[16] M1 cells also produce reactive oxygen and nitrogen species, and IL-1β, TNF, and IL-6 inflammatory cytokines.[17] In addition, M1 macrophages release antitumor chemokines or chemokines that attract Th1 cells such as chemokine (C-X-C motif) ligand (CXCL)-9 and CXCL-10.[18–20] Th1 cells drive cellular immunity to eliminate cancerous cells. Studies suggest that recruitment and/or differentiation of M1 macrophages can be inhibited by the T-regulatory cells (Tregs) that promote tumor progression.[21] On the other hand, M2 macrophages are induced by IL-4, IL-13, IL-21, and IL-33 cytokines in the TME.[22,23] M2 macrophages release high levels of IL-10 and low levels of IL-12 and IL-23 (type 2 cytokines). M2 macrophages also produce chemokine (C-C motif) ligand (CCL)-17, CCL-22, and CCL-24 chemokines that regulate the recruitment of Tregs, Th2, eosinophils, and basophils (type 2 pathway) in tumors.[18,20] Th2 response is associated with the anti-inflammatory microenvironment, which promotes tumor growth. In comparison with M1 macrophages, M2 cells are poor antigen presenters, inhibit inflammation, and contribute to tumor progression by angiogenesis and tissue remodeling.[16,24,25]

TAMs infiltrating to the tumor may participate in local inflammation and may favor tumor progression by acquiring M2-like phenotype.[26] Tumor-secreted molecules were associated with the M2-type TAM polarization and tumor growths. For example, secretion of distinct TAM-associated molecules by tumor induces expression of vascular endothelial growth factor (VEGF), mannose receptor-1, arginase-1, IL-10, transforming growth factor-beta (TGF-β), and matrix metallopeptidase 9.[27] Overexpression of nodal protein (member of TGF-β superfamily) by tumor contributes to TAM polarization in cancer and contributes tumorigenesis, invasion, and metastasis.[28] Nodal protein promotes generation of M2-like macrophages and downregulates expression of IL-12. Interestingly, inhibition of nodal protein reprogrammed TAMs to classically activate M1 macrophages.[28] TAMs showed high levels of protumorigenic and hypoxia-associated genes compared with that of splenic myeloid cells.[29] Protumoral functions of TAMs are facilitated by inhibiting the antitumoral immune surveillance through participating in the extracellular matrix remodeling and enhancing angiogenesis, cancer cell proliferation, invasion, and metastasis.[11] In TME, TAMs are associated with the tumor vasculature development under hypoxic environment. A provascular program is triggered in TAMs by inducing expression of hypoxia-inducible factor-1 and hypoxia-inducible factor-2, and thus, overexpression of tumor-promoting VEGF, basic fibroblast growth factor, IL-8 chemokines, and lymphangiogenic factors.[30,31] Surprisingly, tumor cell-derived Sema3A, not VEGF, is responsible for accumulation of TAM into hypoxic niches, which cause TAM to escape antitumor immunity and to promote vasculature development.[32] On the other hand, different studies reported that hypoxia is not a major driver for the differentiation of TAM subset found in tumor infiltrate, but rather hypoxia fine-tunes the M2-like macrophage population.[33] Moreover, studies suggest that TAM employ antitumoral activities by releasing a wide range of growth factors, cytokines, and chemokines, which activate both the innate and adaptive immune responses.[11,21] Other type of myeloid population is known as myeloid-derived suppressor cells (MDSCs), which is critical in regulating TME and thus the tumor progression. We have discussed the characteristics, phenotype, and functions of MDSCs in the next section.

Myeloid-derived suppressor cells

MDSCs are immunosuppressive cells, which are abundant in TME and inhibit T-cell-mediated antitumor immunity.[34–36] Myeloid expansion in spleen and peripheral blood are seen in spontaneous and xenograft murine models of cancer.[34,37–39] Similar myeloid expansions have been observed in a range of human cancers.[40,41] In mice, MDSCs express $Gr1^+$ and $CD11b^+$ myeloid markers, which can be divided into monocytic and granulocytic MDSCs. Monocytic MDSCs express $CD11b^+Ly6G^-/Ly6C^+$ and granulocytic MDSCs express $CD11b^+Ly6G^+/Ly6C^{low}$ markers. On the other hand, human MDSCs express CD11b and CD33 markers. Monocytic MDSCs are characterized by expression of human leukocyte antigen-antigen D related ($HLA\text{-}DR^-$), $CD11b^+$, $CD33^+$, and $CD14^+$ markers in humans, whereas mature monocytes

express HLA-DR marker. Human granulocytic MDSC are usually characterized by the presence of HLA-DR$^-$, CD11b$^+$, CD33$^+$, and CD15$^+$ markers.[35] Gr1 antigen is absent in the human MDSCs. Interestingly, phenotypic characterization of MDSCs through surface markers is heterogeneous and depends on the site of tumor in human cancers.[42] Molecular signals that stimulate MDSCs to acquire immunosuppressive properties are signal transducer and activator of transcription (STAT)1, STAT3, and STAT6, and nuclear factor-κB transcription factors.[43,44] Arginase 1 (ARG1), NADPH oxidase, inducible nitric oxide synthase, indoleamine 2,3-dioxygenase, and immunosuppressive cytokines that inhibit cytotoxic T-lymphocytes (CTLs), dendritic cells, and natural killer cells are produced by activated MDSCs.[36] Surprisingly, expression of CD79a (B-cell receptor component) on immature myeloid cells contributes to their tumor-promoting effects.[45] Downregulation of CD40 expression also contribute to accumulation of MDSCs by facilitating MDSC's resistance to apoptosis.[46] In addition, CD4$^+$CD25$^+$FoxP3$^+$ Tregs are expanded due to release of MDSC-secreted factors to generate immunosuppressive TME.[47] Overall, it is evident that MDSCs share functional similarities with TAM in TME.

Summary

TME is intricate and consists of heterogeneous subsets of myeloid cells. Growing tumor is capable of modulating antitumor myeloid cells to protumor myeloid cells through secreted factors. M1–M2 polarization of myeloid cells resulted into immunosuppressive and protumor phenotypes. Other category of myeloid cells that exerts protumor function in microenvironment is called MDSCs. All the tumor-promoting myeloid subsets are characterized by the surface markers, secretory factors, and their functions in the microenvironment. Tumor-promoting myeloid cells inhibit antitumor immunity and thus, enhance tumor growth. Next, we have discussed the contribution of key myeloid populations in the therapeutic responses.

Myeloid cell signatures in therapeutic response

Myeloid cells are the key players of microenvironmental regulation of tumor growth and affects therapeutic responses in cancer.[48–50] Recently, the role of commensal microbiota on myeloid cell functions and their effect on the response to cancer therapy has been discussed.[51] In this section, we have discussed how cellular and molecular myeloid cell signatures are associated with the antiangiogenic therapy (AAT), chemotherapy, and radiotherapy responses.

Myeloid cells in AAT response

Vasculature development is considered one of the major cancer hallmarks in tumor progression, which mediates through VEGF–vascular endothelial growth factor receptor (VEGFR).[52,53] AATs have been tried against VEGF–VEGFRs pathways to inhibit the vasculature development in tumor. Surprisingly, most of the treatments resulted into transient decrease in tumor growth followed by enhanced vasculature and tumor growth, which are associated with the presence of MDSCs and TAMs (Table 1). Surprisingly, immune-suppressive myeloid cells mediate tumor resistance to anti-VEGF therapies.[54,55] Paracrine signaling network between Th17 and immature myeloid cells or MDSCs induces the expression of granulocyte colony-stimulating factor in the stromal compartment, which in turn attracts MDSCs that drive anti-VEGF-A resistance.[56] Recently, we found that myeloid cells mediate escape from AAT in preclinical chimeric mouse model of glioblastoma (GBM).[57] AAT through vatalanib, a VEGFR tyrosine kinase inhibitor, was associated with increased bone marrow-derived tumor-associated myeloid cells in GBM.[57] Therefore, targeting myeloid cells was proposed using anti-colony-stimulating factor 1 receptor (CSF1R) agents (eg, GW2580) to combat tumor evasion against AATs.[58] Depletion of CSF1R$^+$ myeloid cells with GW2580 decreased recruitment of tumor-associated myeloid cells in the tumor and reduced GBM growth. Interestingly, AAT increased expression of CXCL-7 chemokine and CSF1R blockade decreased CXCL-7 in TME. In addition, CXCL-7 expression was correlated with number of tumor-infiltrating bone marrow cells, phosphor-ERK mitogen-activated protein kinase, and proliferation of bone marrow cells in GBM.[57]

Adverse effect of AATs has been reported by other study, where bevacizumab (Avastin) and sunitinib initially reduced both infiltration of macrophages and tumor vascularity, and showed sign of improved animal survival. However, multi-targeted VEGFR tyrosine kinase inhibitors, but not VEGF inhibitor, rapidly created a vascular gradient in tumor and more rapidly induced hypoxia and reinfiltration of macrophages and CD11b$^+$/Gr1$^+$ myeloid cells. Tumors acquired aggressive mesenchymal features and expressed increased stem cell marker.[59] Other group investigated the role of macrophages in patients with recurrent GBM. Specimen from 20 patients with recurrent GBM who received AAT and chemoradiation, and specimen from eight patients who received chemotherapy and/or radiotherapy without AAT or no treatment, was compared.[60] Patients who received AAT and had recurrent GBMs showed an increased infiltration of myeloid cells in the tumor bulk and in the infiltrative

Table 1 Antiangiogenic therapy-induced myeloid cells attenuate antitumor response

Studies	Drugs	Cancer	Cellular and molecular biomarkers	Refs
Bone marrow-derived myeloid cells orchestrate antiangiogenic resistance in glioblastoma through coordinated molecular networks	Vatalanib	Glioblastoma (U251)	$Gr1^+CD11b^+$MDSCs and $CD68^+$ macrophages and CXCL-7	57
Increase in tumor-associated macrophages after antiangiogenic therapy is associated with poor survival among patients with recurrent glioblastoma	Bevacizumab, Vatalanib, Cediranib, Cabozantinib, and Thalidomide	Recurrent glioblastoma (patients)	$CD68^+$, $CD163^+$ macrophages	60
Glioblastoma resistance to anti-VEGF therapy is associated with myeloid cell infiltration, stem cell accumulation, and a mesenchymal phenotype	Bevacizumab and Sunitinib	Glioblastoma (U87)	$Gr1^+CD11b^+$ MDSCs	59
Intratumoral myeloid cells regulate responsiveness and resistance to antiangiogenic therapy	Sorafenib DC101	Neuroendocrine, RIP1-Tag2 (RT2) mice and PyMT breast tumor model	$Gr1^+CD11b^+$ MDSCs	49
An IL-17-mediated paracrine network promotes tumor resistance to antiangiogenic therapy	B20-4.1.1	LLC (EL4), colon (CT26) plasmacytoma (TIB6)	Bv8-positive granulocytes and G-CSF	56
Tumor refractoriness to anti-VEGF treatment is mediated by $CD11b^+Gr1^+$ myeloid cells	Bevacizumab	LLC (EL4) Melanoma (B16F1) Plasmacytoma (TIB6)	$Gr1^+CD11b^+$ MDSCs	55
KIT oncogene inhibition drives intratumoral macrophage M2 polarization	Imatinib	Gastrointestinal stromal tumors – sarcoma	CD68 and CSF1R	65

Abbreviations: CSF1R, colony-stimulating factor 1 receptor; CXCL, chemokine (C-X-C motif) ligand; G-CSF, granulocyte colony-stimulating factor; IL, interleukin; LLC, lymphoma lung cancer; MDSCs, myeloid-derived suppressor cells; VEGF, vascular endothelial growth factor; Refs, references.

regions. Higher numbers of $CD11b^+$ cells correlated with poor prognosis of these patients and TAMs may represent a potential biomarker of resistance and a potential therapeutic target in recurrent GBM.[60]

Similarly, intratumoral myeloid cells are thought to regulate responsiveness and resistance to AAT in other solid cancers.[49] The study found that the efficacy of antiangiogenic agents targeting the VEGF–VEGFR axis was dependent on induction of the angiostatic and immune-stimulatory chemokine CXCL-14 in pancreatic neuroendocrine and mammary tumors in mouse.[49] Once VEGF–VEGFR axis was blocked, tumor initiated angiogenesis and immune suppression by activating phosphoinositide 3-kinase signaling in all $CD11b^+$ cells, making tumors nonresponsive to VEGF–VEGFR inhibition. Adaptive resistance to AAT was also linked to an increased accumulation of $Gr1^+CD11b^+$ cells; however, targeting $Gr1^+$ cells was not sufficient to sensitize antiangiogenic effect. On the other hand, inhibiting phosphoinositide 3-kinase activity in $CD11b^+$ myeloid cells can create an angiostatic and immune-stimulatory environment in the tumor, where AAT can remain efficient. Moreover, studies suggest that AATs, particularly anti-VEGF–VEGFR2, are marked by the overrepresentation of immunosuppressive myeloid cells. Therefore, AAT with the combination of myeloid cell blockade may enhance the therapeutic success in inhibiting tumor growth.

Myeloid cells in chemotherapy response

Studies have reported the involvement of myeloid cell signatures-associated adverse responses with chemotherapeutic modalities (Table 2). Chemotherapy with paclitaxel caused upregulation of chemotactic factors for macrophage CSF1, CCL-8, and IL-34 and increased in CSFR1 expression in TAM in a transgenic mouse model of breast cancer.[18,61] Chemotherapy combined with inhibitors of CSFR1 showed enhanced therapeutic activity with decreased metastases, increased T-cells in the tumors, and increased mRNA for various cytotoxic effector molecules such as granzyme A and B and perforin-1.[61] When $CD8^+$ CTLs were depleted, the tumor-suppressive effects due to the blockage of macrophage infiltration disappeared, suggesting chemotherapeutic response to be dependent on the depletion of macrophages and activity of $CD8^+$ CTL.[61] Recruitment of chemokine (C-C motif) receptor 2 (CCR2)-expressing monocytes occurred following doxorubicin treatment via stroma-derived CCL-2, which contributed to suboptimal treatment response and tumor reemergence in breast cancer model.[62] Similarly, chemotherapies of murine breast cancers increased TAM accumulation, which enabled

Table 2 Chemotherapy-induced myeloid cells attenuate antitumor response

Studies	Drugs	Cancer	Cellular and molecular biomarkers	Refs
Immunosuppressive myeloid cells induced by chemotherapy attenuate antitumor $CD4^+$ T-cell responses through the PD-1–PD-L1 axis	Cyclophosphamide	B-cell lymphoma Colon cancer metastasis to lung	Monocytic ($Ly6C^+$ $CCR2^+$) Myeloid cells	64
Imaging tumor–stroma interactions during chemotherapy reveals contributions of the microenvironment to resistance	Doxorubicin	Breast cancer	CCL-2 and $CCR2^+$ monocytes	62
Leukocyte complexity predicts breast cancer survival and functionally regulates response to chemotherapy	Paclitaxel	Breast cancer	CSF1, MCP1, IL-34, and $CSF1R^+$ macrophages	61
Macrophages and cathepsin proteases blunt chemotherapeutic response in breast cancer	Paclitaxel, etoposide, and doxorubicin	Breast cancer	$Iba1^+$ and $CD68^+$ macrophages	63
B-cells regulate macrophage phenotype and response to chemotherapy in squamous carcinomas	αCD20 monoclonal antibody, paclitaxel, *cis*-diamminedichloroplatinum (II), and carboplatin	Head and neck, vulva and skin	$Gr1^+CD11b^+$ MDSCs	68
Chemotherapy alters monocyte differentiation to favor generation of cancer-supporting M2 macrophages in the tumor microenvironment	Cisplatin, carboplatin, and indomethacin	Cervical and ovarian cancers	$CD1a\text{-}CD14^+CD206^+CD163^+$ M2 macrophages	13
Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth	Gemcitabine and 5-fluorouracil	Melanoma (B16F10) LLC (EL4) 4T1 mammary gland cancer	$Gr1^+CD11b^+$ MDSCs	67

Abbreviations: CSF1, colony-stimulating factor 1; CSF1R, colony-stimulating factor 1 receptor; LLC, lymphoma lung cancer; MCP1, monocyte chemoattractant protein 1; MDSCs, myeloid-derived suppressor cells; PD-1, programmed death 1; PD-L1, programmed death ligand 1; Refs, references.

cathepsin protease B- and S-mediated chemoresistance to paclitaxel, etoposide, and doxorubicin.[63] Treatment with cyclophosphamide causes the expansion of inflammatory monocytic myeloid cells ($CD11b^+Ly6C^{hi}CCR2^{hi}$), which are immunosuppressive in nature. Ding et al[64] showed the initial robust antitumor immune response with adoptive transfer (AT) of tumor-specific $CD4^+$ T-cells following cyclophosphamide treatment (CTX^+CD4 AT) in mice with advanced lymphoma, but the combined treatment also resulted in enhanced expansion of monocytic myeloid cells. These therapy-induced monocytic myeloid cells caused failure in long-term tumor control and subsequently caused relapse by mediating functional tolerization of antitumor $CD4^+$ effector cells through the programmed death 1 (PD-1)–programmed death ligand 1 (PD-L1) axis. When PD-1–PD-L1 was blocked after CTX^+CD4 AT therapy, there was persistence of $CD4^+$ effector cells and antitumor effects.

In mice, established gastrointestinal stromal tumors contained M1-like TAMs, which were antitumoral. Imatinib therapy polarized TAMs to become M2-like through the activation of CCAAT/enhancer binding protein (C/EBP)β in this tumor model. Similar findings were observed in human, where TAMs behaved M1-like at baseline and became M2-like after imatinib therapy.[65] Macrophages polarized into M2 alternatively activated state of macrophages in response to distinct therapies including platinum-based agents,[13] and low-dose irradiation that promotes an inducible nitric oxide synthase-positive M1 phenotype[66] that allowed the recruitment of CTL in the tumor and thereby enhanced immunotherapy efficacy in animal models.[66] There are some reports that clearly showed that myeloid cells are capable of impairing chemotherapeutic antitumor response. For example, chemotherapeutic agents such as gemcitabine and 5-fluorouracil can activate the NOD-like receptor family (pyrin domain containing-3 protein [Nlrp3]-dependent caspase-1 activation complex [inflammasome]) in MDSCs, leading to production of IL-1β.[67] Then IL-1β induced secretion of IL-17 by $CD4^+$ T-cells, which impaired the anticancer efficacy of the chemotherapies.[67] In other study, investigators have shown that myeloid-based pathways regulated by humoral immunity limit squamous cell carcinoma responses to chemotherapy not only by fostering tumor angiogenesis but also by impairing $CD8^+$ T-cell infiltration into tumors.[68] Here, B-cells educated TAMs toward a tumor-supporting phenotype by the activation of the Fc receptor. Further, B-cell depletion resulted in increased recruitment of $CD8^+$ cells and an enhanced therapeutic response.[68] On the other hand, some reports showed that chemotherapy could limit or reverse the expansion of myeloid populations in tumor.[69–71] These paradoxical outcomes might be related to the differences in models as well

as schedules of the chemotherapy. However, majority of data point toward negative role of tumor-associated myeloid cells (TAMC)s in chemotherapy failures.

Myeloid cells in radiotherapy response

Macrophages accumulated into TME following radiotherapy plays dual roles. Initially accumulated macrophages participate in M1-type responses early in inflammation and then convert to M2 responses at later stages. A series of multiple cytokines cause and sustain the acute phase of radiation-induced inflammation,[72] and these cytokine patterns match the status of inflammatory macrophage differentiation in the site of radiation.[73] The proinflammatory cascade that is initiated following radiotherapy has been linked to production of cytokines, including the M1 cytokine TNF-α.[74,75] At later stages in this inflammatory cascade, the M2 cytokine TGF-β is expressed.[76] Studies have shown the mechanisms of radiation-induced inflammation followed by repair and the consequences to adaptive immune responses in the treatment site, and how radiation-induced myeloid cell response may impact immunotherapies designed to improve control of residual cancer cells.[77] The impact of radiation-induced myeloid cell response has been reported and discussed.[77,78] Peripheral MDSCs together with Treg PD-1-positive cells have shown to predict the response to short-course radiotherapy in rectal cancer patients.[79] Treatment with sunitinib increased the efficacy of stereotactic radiotherapy in patients with oligometastases by reversing MDSC and Treg-mediated immune suppression.[80] Commonly used nonhypofractionated radiotherapy induced stromal cell-derived factor-1 and caused accumulation of bone marrow-derived myeloid monocytic cells that contributed to vasculogenesis and increased tumor growth.[81,82] Similarly, the effect of radiotherapy can be limited due to accumulation of Th2-polarized $CD4^+$ T-cells and macrophages. By depleting macrophages using either a neutralizing monoclonal antibody to CSF1 or a small-molecule inhibitor of the CSF1R (PLX3397) significantly delayed tumor regrowth following radiotherapy in mammary tumor-bearing mice. Delayed tumor growth in this study was thought to be associated with increased accumulation of $CD8^+$ T-cells and reduction of $CD4^+$ T-cells, the main source of the Th2 cytokine IL-4 in mammary tumors.[83] Similarly, radiotherapy upregulated CSF1 in prostate cancers and increased myeloid cell numbers and blockade of CSF1R signaling decreased the number of myeloid cells and improved the efficacy of radiotherapy in prostate cancer.[84] Radiotherapy could be combined with immunotherapy to improve the antitumor responses.[85] On the other hand, one study reported that expansion of peripheral myeloid cells driven by 4T1 murine cancer progression was reversed by radiotherapy.[86] Altogether, studies suggested that myeloid cells modulate radiotherapy response and are bonafide target of cancer therapy.

Summary

Majority of tumors are characterized by the overrepresentation of tumor-promoting myeloid subsets. Recent studies suggest that therapies such as AAT, chemotherapy, and radiotherapy against tumors resulted into increased accumulation of myeloid cells. Current evidence suggests that myeloid cells impair antitumor immunity through secreted factors, which constitute immunosuppressive microenvironment. In some experimental studies, targeting myeloid cells by CSF1R inhibitors have improved antitumor immunity by increasing $CD8^+$ T-cells and thus, decreasing tumor growth. Therefore, combining conventional therapies with myeloid inhibitor could enhance the therapeutic efficacy in cancer.

Conclusion and future perspectives

There are many mechanisms known by which cancers can develop resistance to various therapeutic modalities. Therapeutic resistance could be added as an emerging area of interest and cancer hallmark. In addition, biomarkers that can predict response to any type of therapy are urgent to explore.[52,87] At this point, we are sure that heterogeneous macrophages are critical players in therapeutic resistance against cancer. Therefore, myeloid cell blockade in addition to AAT or chemotherapy or radiotherapy should provide better antitumor responses. Different myeloid cell blockers have been tested and discussed in literature.[50,88,89] Our biggest challenge is the limited understanding of the underlying mechanisms through which therapies modulate distinct subpopulations of macrophages within the TME. Recently, we initiated exploring cytokines, which take part in therapeutic resistance.[57] However, we may need complete understanding of the entire TME before and after therapeutic modalities to get clear changes in TME. In addition, we may take advantages of available large-scale therapeutic datasets to rule out gene expression profiles of heterogeneous populations of TAMs using data from whole-tumor samples from patients through bioinformatics approaches.[90–92]

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Disclosure

The authors report no conflicts of interest in this work.

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