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Targeting Tumor-Associated Macrophages (Tams) Reprogramming for Cancer Metastasis Therapy

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Abstract

Tumor-Associated Macrophages (TAMs) are critical components of the microenvironment of the majority of malignant tumors, associated with poor prognostic notably through various factors secreting. Thus they are emerging as novel targets for tumor metastasis therapy. In this review article, we describe how TAMs regulate tumor angiogenesis, invasion, metastasis, and then discuss the potential of applying TAMs-targeting treatment as a promising therapeutic strategy for metastatic cancer.

Keywords: Tumor-associated macrophages (TAM); Tumor microenvironment (TEM); Tumor metastasis; Target therapy

Introduction

Metastasis defined as the spreading of cancer cells from the primary tumor to surrounding tissues and distant organs, it is a foremost event leading to approximately 90% mortality of patients with cancer[1-3]. Despite the advent of effective cancer therapies by developing early diagnosis or applying cancer growth inhibition strategy in the past decades, conventional strategies of cancer therapy include surgical resection, chemotherapy, radiotherapy and immunotherapy, which have made significant contributions to cancer treatment. Limited success has been made in the treatment of metastasis owing to its systemic nature and the resistance of disseminated tumor cells to existing therapeutic agents. Metastasis suppression is still a crucial step for the success of cancer therapy[4,5]. On the basis of evidence from a growing body of research indicating tumor associated macrophages are crucial to cancer metastasis, we summarized the information that is currently at hand and discus the potential therapeutic strategies used to suppress metastatic process, our review highlights the combination therapeutic options to treat cancer metastasis. Because the cellular and molecular programs that drive cancer metastasis. Although our understanding of cellular and molecular programs that drive cancer metastasis remains quite incomplete. Thus, we here we summarized the information that is currently at hand and aiming to expecting a more efficient therapy strategy.

Tumor micro environment (TEM) and metastasis: Tumor metastasis usually goes through a series of sequential and interrelated steps that can be conceptualized as the invasion-metastasis cascade. Starting with a detachment of metastatic cells from the primary tumor, traveling to the surrounding sites or organs intravasation of these cells into the circulatory system and survival, arrest and extravasation through vascular walls into the parenchyma of distant tissues; formation of micro metastatic colonies in this parenchyma; and the subsequent proliferation of microscopic colonies into overt, clinically detectable metastatic lesions, this last process beingtermed colonization[6-9]. Tumor Micro Environment (TME) is intimately involved in all essential steps of the metastasis process through interacting with the tumor. Recently, increasing evidence shows that TME participates aberrant tissue function and promote the subsequent evolution of

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Abbreviations: TAMs: Tumor-associated macrophages; TEM: Tumor microenvironment; CAFs: Cancer-associated fibroblasts; PDGF: Platelet-derived growth factor; FAP: Familial adenomatous polyposis; FGFR: fibroblast growth factor receptor ; VDR: Vitamin D Receptor; ECM: Extracellular matrix; TNF-α:Tumor necrosis factor alpha; IL-10:Interleukin 10; IL-12: Interleukin 12; TGF-β :Transforming growth factor beta; $HMGB_1$: High mobility group box 1; CCL_{12}: Chemokine (C-C motif) ligand 12; CCL_7: Chemokine (C-C motif) ligand 7; FGF: Fibroblast growth factor; HGF: Hepatocyte growth factor; TN-C: tenascin C; MMP_2: Matrix Metallopeptidase 2; MMP_7: Matrix Metallopeptidase 7; MMP9: Matrix Metallopeptidase 9; EGF:Epidermal growth factor; WNT_5A:Wnt family member 5A; CSF-1:Macrophage colony-stimulating factor 1; Sema 4D: Semaphorin-4D; IL-1β: Interleukin 1β; CSTB: Cystatin B

more stubborn and advanced malignancies.

In general, TME mainly consists of genetically heterogeneous cancer cells, endothelial cells, cancer-associated fibroblasts(CAFs), and different populations of immune cells[2], establishing a complex cross-talk with tumor *via* producing growth factors, chemokines and matrix-degrading enzymes. For example, CAFs secrete PDGF, FAP, FGFR and VDR, which are participating in wound healing, Integrating collagen and protein to form the ECM fiber network or escaping damage; Immune cells produce TNF-α, IL-10, IL-12, TGF-β and HMGB1, which are not only treat wound healing, infection, clear dead cells and cellular debris but also promote cancer cell proliferating, showing a double effect on tumor formation[10-12].

CAFs are the dominant cell type in the tumor stroma, which exhibits mesenchymal-like features and are likely mesoderm-derived. They are recruited and activated by cancer cells. The interplay between CAFs and cancer cells within the TME is complicated, resulting in various impact on cancer progression and metastasis[13-17]. Large amounts of work described pro-tumorigenic influence of CAFs on cancer cells driven by altered secretome, such as, $CXCL_{12}$, CCL_7, TGF βs, FGFs, HGF, periostin (POSTN) and TN-C, these secreted factors enhance tumor progression by promoting the survival, proliferation, stemness, and the metastasis-initiating capacity of cancer cells, ultimately assisting cancer metastasis[18-20].

Besides CAFs, immune cells also exhibit crucial role in TEM, broad and comprehensive understanding of immune cells will primarily promote the cancer metastasis study. Among these immune cells, Tumor- Associated Macrophages (TAMs) are one of the most abundant infiltrated in solid tumors, which have been known to orchestrate the TME for tumor invasion and progression and contribute to the metastasis of tumor cells[21-23]. Specifically, TAMs are derived from circulating monocytes and differentiate into M_1 or M_2 macrophages, gaining specific functional properties within the TEM (shown as in Figure1). Classically activated M_1 TAMs suppress cancer progression, while M_2 type promotes it. However, the specific phenotype of TAMs depends on the tumor progression stage. In the early stages of tumors progression, TAMs adopt the M_1-like phenotype for the inhibition of angiogenesis in conjunction with the activation of tumor immunity. In contrast, TAMs shift to an M_2-like state to enhance tumor metastasis by secreting different factors (shown as in Figure1)[24-26]. The most comprehensively described mechanism by which M_2 TAMs promote cancer metastasis is to provide factors that enhance metastasis and the establishment of a premalignant niche of malignant cells, the elements are listed as below: Matrix Metallopeptidase 2(MMP_2), MMP_7, MMP_9, epidermal growth factor (EGF), wnt family member 5A(WNT_5A), macrophage colony-stimulating factor 1(CSF-1), Semaphorin-4D(Sema 4D), IL-1β, Cathepsin B, TNFα, VEGF,TGF-β[2-3]. Cystatin B (CSTB) and WNT_5A stimulate cancer cell migration and invasion; VEGF promotes cancer cell extravasation, and TGF-β stimulates cancer cell proliferation and metastasis through C-Jun and $SMAD_3$ pathway[27-32]. Per these findings, TAMs are therefore emerging as an attractive therapeutic target for the inhibition of tumor growth and cancer metastasis.

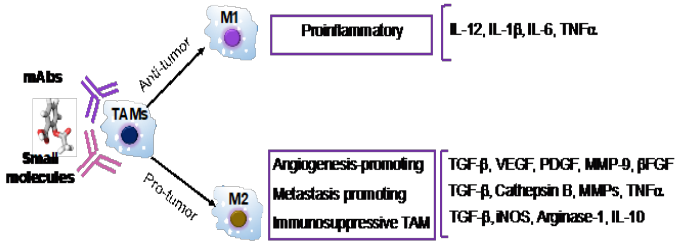

Figure1: The binary M_1 / M_2 classification of tumor-associated macrophages(TAMs), Pro-tumor M_1 type macrophage and anti-tumor M_2 type TAM secrete different factors to exact the specific functions.

Targeting TAMs therapeutic strategies: Currently, massive lines of research are being investigated for the effective targeting TAM therapies; the approaches are summarized as the following two routes:

- decreasing the quantity of TAMs in tumor tissue;
- Shifting TAMs from tumor-promoting to tumoricidal status.

A large number of successful attempts have been reported to target TAM *via* depleting or inhibiting TAMs recruitment[33-38]. The most typical approaches rely on TAM depletion *via* the inhibition of CSF-1 / CSF-1R or CCL_2–CCR_2 signaling pathways, based on evidence that these axes are essential for macrophage recruitment[39-41]. Up to now, a variety of small molecules and monoclonal antibodies (mAbs) directed at CSF1R or its ligand CSF1 are investigated for clinical development[34]. Among the class of small molecules, pexidartinib(PLX3397) showed a therapeutic effect in KIT-mutated advanced acral and mucosal melanoma in phase II clinical trial. ARRY-382, PLX7486, BLZ945, and JNJ40346527, are being investigated in solid tumors and cHL *via* targeting CSF1R[42,43]. MAbs in clinical development include emactuzumab, AMG820, IMC-CS4, cabiralizumab, MCS110, and PD-0360324, with the latter two being the only compounds targeting the ligand CSF_1[44-47]. A phase I clinical trial using a CSF-1R–blocking mAb (RG7155) in patients with diffuse-type giant cell tumors (DT-GCT), a proliferative disease caused by overexpression of CSF-1[48], yielded measurable clinical responses. Similarly, the inhibition of CCL_2 by an anti-CCL_2 monoclonal antibody (e.g., carlumab) or through its synthesis inhibition (e.g., bindarit, trabectedin) prevented the recruitment of macrophages into the tumor site and estimated in various metastatic cancertherapy[49,50]. Besides mAb targeting CCL_2, other compounds (e.g., bindarit, trabectedin) were found to inhibit the synthesis of CCL_2 / MCP-1. Bindarit reduced TAM and myeloid-derived suppressor cell infiltration in a breast cancer model and resulted in impaired metastatic disease in a prostate cancer model[51]. This treatment also targeted angiogenesis and tumor growth in human melanoma xenografts[52].

In comparison with depleting TAMs, functional reprogramming of TAMs is emerging as a more attractive strategy for cancer metastasis therapy. Bo Yang et al, have proved that Imatinib prevents lung cancer metastasis by interfering the reprogramming of M_2-like polarization of macrophages[53]. Enlightenby the relevance of TAMs for metastasis interference scientist's also sought to re-consider the immune modulatory function of the classical chemotherapeutic drugs. Wanderley CW et al. reported that paclitaxel reduces tumor growth by reprogramming TAMs to an M_1 profile in a TLR_4-Dependent Manner[54]. Trabectedin, a

marine-derived natural product, interferes with transcription and DNA repair but also targets TAMs and induces their depletion through mechanisms as yet obscure[55]. Brana I et al. show that combining Carlumab, a human monoclonal antibody against CCL_2, with other chemotherapy agents (docetaxel, gemcitabine, paclitaxel or carboplatin and pegylated liposomal doxorubicin) can significantly delay tumor regrowth following chemotherapy[56].

Despite the above mentioned monotherapies including depleting TAMs and re-educating to an M_2 phenotype, complementing and / or synergizing with the conventional anti-cancer treatment such as chemotherapy as well as other cancer-immunotherapy approaches. Floris Dammeijer et al. used CSF-1R kinase inhibitor PLX3397 (pexidartinib) to reduce TAMs amount effectively, and then combine with dendritic cell vaccination synergistically enhanced the survival in mice cancer model[57]. Furthermore, a combination clinical study of PLX3397 and Pembrolizumab to treat advanced melanoma and other solid tumors are undergoing[58,59]. Olson et al. improved therapeutic response by depleting of MHCIIlo TAMs in a preclinical breast cancer model which increased the ability of Taxol to induce apoptosis[60].

With the emerging experimental and clinical studies indicating a strong association between cancer metastasis and increased macrophage infiltration in various cancers, consistent with an unbiased transcriptome analysis, the underlying mechanism behind TAMs modulated cancer metastasis is widely explored and can be summarized as involvement intumor angiogenesis, growth, cell migration and invasion, which was assisted by secreting various chemotactic factors. E.g. Urokinase-Type Plasminogen Activator (uPA), Matrix Metallo Proteinase (MMP) and cathepsins are used to break down the basement membrane and remodel the stromal matrix. Meanwhile, various growth factors and chemokines like Epidermal Growth Factor (EGF), Transforming Growth Factor-B (TGF-β), Interleukin-8 (IL-8) and Tumor Necrosis Factor-A (TNF-α) are mostly promoting the migration of tumor cells towards vessels and provide proliferative and anti-apoptotic signals to these cells. Thus, strategies aimed at targeting TAMs for cancer metastasis therapy is gaining the most attention recently. A number of these agents are already currently under clinical investigation. Thus, either monotherapy or in combination with novel and standard cancer therapy strategies are worthwhile to explore.

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