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 prognosis 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 discuss 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 microcolonic cells into overt, clinically detectable metastatic lesions, this last process being termed 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
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[29], 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, CXCL12, CCL5, TGF βs, FGFs, HGF, peroxin (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 TME, 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 M1 or M2 macrophages, gaining specific functional properties within the TEM (shown as in Figure 1). Classically activated M1 TAMs suppress cancer progression, while M2 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 M1-like phenotype for the inhibition of angiogenesis in conjunction with the activation of tumor immunity. In contrast, TAMs shift to an M2-type displaying anti-tumor activity and contribute to metastasis of tumor cells[21-23].

In comparison with depleting TAMs, functional reprogramming of TAMs is more attractive for cancer metastasis therapy. Bo Yang et al, have proved that Imatinib prevents lung cancer metastasis by interfering the reprogramming of M2-like polarization of macrophages[33]. Enlighten by 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 M₁ phenotype in a TLR4-Dependent Manner. Tra-pectedin, a marine-derived natural product, interferes with transcription and DNA repair but also targets TAMs and induces their depletion through mechanisms as yet obscure. Brana I et al. show that combining Carlumab, a human monoclonal antibody against CCL2, with other chemotherapy agents (docetaxel, gemcitabine, paclitaxel or carboplatin and pegylated liposomal doxorubicin) can significantly delay tumor regrowth following chemotherapy.

Despite the above mentioned monotherapies including depleting TAMs and re-educating to an M₁ phenotype, complementing and/or synergizing with the conventional anti-cancer treatment such as chemotherapy as well as other cancer-immuno-therapy approaches. Floris Dammeijer et al. used CSF-1R kit
treatment such as chemotherapy as well as other cancer-immu-
menting and/or synergizing with the conventional anti-cancer

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 in tumor angiogenesis, growth, cell migration and invasion, which was assisted by secreting various chemotactic factors. E.g. Urokinase-Type Plasminogen Activator (uPA), Matrix Metalloproteinase (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-α (TNF-α) are mostly pro-
moting 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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