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Origin and Function of Tumor Associated Macrophages

[1]Sujatha S Reddy, MDS, PHD, Professor, Department of Oral Medicine, Diagnosis and Radiology, Faculty of dental sciences, M S Ramaiah University of applied sciences, MSRIT Post, New BEL Road, Bangalore, Karnataka, India.

[1]N Rakesh, MDS, PHD, Professor and Head of the Department, Department of Oral Medicine, Diagnosis and Radiology, Faculty of dental sciences, M S Ramaiah University of applied sciences, MSRIT Post, New BEL Road, Bangalore, Karnataka, India.

[1]T Pavan Kumar, MDS, Assistant Professor, Department of Oral Medicine, Diagnosis and Radiology, Faculty of dental sciences, M S Ramaiah University of applied sciences, MSRIT Post, New BEL Road, Bangalore, Karnataka, India.

[1]Shwetha V., MDS, Assistant Professor, Department of Oral Medicine, Diagnosis and Radiology, Faculty of dental sciences, M S Ramaiah University of applied sciences, MSRIT Post, New BEL Road, Bangalore, Karnataka, India.

[1]Sethu Sailaja M, Post graduates, Department of Oral Medicine, Diagnosis and Radiology, Faculty of dental sciences, M S Ramaiah University of applied sciences, MSRIT Post, New BEL Road, Bangalore, Karnataka, India.

[1]Haripriya P, Post graduates, Department of Oral Medicine, Diagnosis and Radiology, Faculty of dental sciences, M S Ramaiah University of applied sciences, MSRIT Post, New BEL Road, Bangalore, Karnataka, India.

Corresponding Author: Sethu Sailaja M, Post graduates, Department of Oral Medicine, Diagnosis and Radiology, Faculty of dental sciences, M S Ramaiah University of applied sciences, MSRIT Post, New BEL Road, Bangalore, Karnataka, India.

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Abstract

The tumor microenvironment is a complex ecosystem of cells that evolves alongside tumor cells and supports them as they progress toward malignancy. Macrophages are the most prevalent innate and adaptive immune cells drawn to the tumour site, and they are present at all phases of tumor growth. Tumor-associated macrophages (TAMs) are the primary cells that produce cytokines, chemokines, growth factors, and stimulate the release of inhibitory immunological checkpoint proteins in T cells, resulting in an immunosuppressive tumor microenvironment (TME). TAMs play a key role in promoting cancer cell metastasis cascades while also providing many targets for checkpoint blockade immunotherapies aimed at slowing tumor growth. Macrophages are also immunosuppressive, blocking natural killer and T cells from attacking tumour cells during tumour growth and after chemo- or

immunotherapy treatment. In preclinical models and early clinical trials, therapeutic effectiveness in addressing these pro-tumoral activities shows that macrophages are potential targets as part of cancer treatment combinations. In this article we summarized origin and function of Tumor Associated Macrophages and regulating networks of TAM polarization and the mechanisms underlying TAM-facilitated metastasis.

Keywords: TAM, TME, Tumor

Introduction

Tumor cells escape from primary sites, spread through lymphatic and/or blood circulations, and eventually disseminate to distant sites in the process of metastasis. The development of metastasis is one of the hallmarks of cancer, accounting for more than 90% of cancer-related deaths [1]. Tumor cell metastasis is usually a multistep process that includes (a) invasion at the primary sites, (b) intravasation into the vasculature, (c) circulation survival, (d) extravasation out of the vasculature, and (e) adaptation and growth in the metastatic sites [2,3]. Failure to complete any of these phases will prevent formation of metastasis. The development of metastasis is not dependent on tumour cells alone. In fact, tumour cells and other components of the tumour microenvironment (TME), as well as their complex interplay, are all implicated. [4,5]. Tumor-associated macrophages are macrophages that populate the TME surrounding the tumour. TAMs appear to be important metastasis promoters in the TME, according to a vast number of studies.

Macrophages, a type of white blood cell that belongs to the mononuclear phagocyte immune system, play a critical role in anti-infective immunity, tissue homeostasis, and body defense by engulfing and digesting foreign substances [6,7]. Tumor-associated macrophages (TAMs) are macrophages that infiltrate tumour tissues or populate the microenvironment of solid tumours. TAMs affect tumour growth, tumour angiogenesis, immunological modulation, metastasis, and chemoresistance as a crucial component of the tumour microenvironment. The majority of TAMs congregate near the vessel's leading edge and avascular sections, with a few others aligning along the abluminal side. [8,9]. It is generally believed that the blood monocytes derived from bone marrow hematopoietic stem cells are the primary resource of macrophages [10,11,12]. Macrophages are a diverse cell population that has traditionally been classified into two subgroups: M1 and M2. M1-type macrophages, which are classically activated, perform crucial roles in the innate defence against invading pathogens. Alternatively activated M2-type macrophages play a key role in tissue healing and tumour growth. Notch signaling has been found to be important in the polarisation of M2 macrophages in previous investigations. M1 macro phages secrete proinflammatory cytokines such as IL-12, tumor necrosis factor (TNF)-α, CXCL-10, and in terferon (IFN)-γ and produce high levels of nitric oxide synthase (NOS, an enzyme metabolizing arginine to the “killer” molecule nitric oxide), while M2 macrophages secrete anti-inflammatory cytokines such as IL-10, IL-13, and IL-4 and express abundant arginase-1, mannose receptor (MR, CD206), and scavenger receptors [14,15]. The change of M1 (anti-tumorigenesis) to M2 (pro-tumori genesis) macrophages in response to micro environmental signals is known as "macro phage polarisation." [16]. TAMs can exhibit any polarisation phenotype, according to studies, although researchers tend to think of them as M2-like phenotypic-acquired macrophages. The accumulation of macrophages in the TME is generally associated with a worse disease prognosis, which is consistent with these clinical data.

According to a recent study, mouse peritoneal macrophages can express the transcription factor Gata6, which can change macrophage phenotype by modifying their transcriptome, contributing to the inflammatory response and macrophage renewal in the inflammatory response [13]. Furthermore, the localization of tissue-specific macrophages and the polarization of macrophage function can be determined, at least partially, by this pathway. We will further define the molecular pathways enabling TAMs polarisation from M1-like to M2-like to better understand the relationship between TAMs, metastasis, and clinical implications in cancer therapy.

TAMs have been shown to secrete chemokines and cytokines that stimulate tumour growth in several studies, and research on IL-6, IL-8, and IL-10 (to name a few) has made significant progress in this area.

IL-6

By regulating the corresponding genes of the cell cycle, promoting tumour angiogenesis, aggravating local inflammation, and aiding stem cell self-renewal, IL-6, which is secreted by tumor-associated endothelial cells and TAMs, is thought to increase the possibility of carcinogenesis and the developmental progress of malignant tumours. Because signal transducer and activator of transcription 3 (STAT3) phosphorylation regulates the principal signalling pathway mediated by IL-6, and the epithelial-mesenchymal transition (EMT) is a key feature of tumour stem cells, the transcription factor Snail may play an important regulatory role [17]. As a result, researchers discovered that STAT3 phosphorylation and Snail expression in tumour cells interacted with TAMs and tumor-associated endothelial cells expressing or overexpressing B-cell lymphoma-2 (Bcl-2) to enhance IL-6 secretion. And at the same time, they added a STAT3 suppressor to the group that overexpressed Bcl-2 and contained more IL-6. To obtain the results, the researchers tested the landmarks of the EMT. The results shows that IL-6 promotes STAT3 phosphorylation and the expression of Snail. When the phosphorylation of STAT3 was suppressed, the expression of Snail decreased simultaneously. The experimental results suggest that IL-6 may mediate the EMT by the Janus kinase (JAK)/STAT3/Snail pathway. Another research also shows that IL-6 combined with IL-6R can activate STAT3 phosphorylation and lead to anti-apoptosis in tumors.

IL-8

IL-8 is secreted by TAMs and serum IL-8 levels can correctly monitor and predict clinical benefit from immune checkpoint blockade. And experiments also showed that angiogenesis, tumor invasion, and the depression of immunity were more remarkable at higher levels of IL-8 [19,20]. Engulfment and cell motility 1 (ELMO1) is an evolutionarily conservative protein expressed in tumor cells that mainly mediates cell phagocytosis, migration, and morphological changes. Studies have shown that IL-8 can escalate tumor metastasis by upregulating the expression of ELMO1 in tumor cells [21]. To a wide extent, the activation of the JAK2/STAT3/Snail pathway is considered to be another mechanism for the capability of IL-8 to promote carcinogenesis. With the increase in exogenous IL-8, the expression of p-JAK2, p-STAT3, and Snail shows extreme improvement. Hence, it is reasonable to speculate that IL-8 can promote EMT via the JAK2/STAT3/Snail pathway.

IL-10

TAMs release cytokines such as IL-10, transforming growth factor-β (TGF-β), and inflammatory mediators such as prostaglandin E2 (PGE2) and matrix metalloproteinase-7 (MMP-7) in the tumour

microenvironment to block the normal antigen-presenting process, causing T lymphocytes to lose their ability to recognised and even kill tumour cells. It is believed that IL-10 family cytokines play an important role in maintaining tissue homeostasis during infection and inflammation by upregulating innate immunity, limiting excessive inflammatory responses, and promoting tissue repairing processes [22]. Toll-like receptor 4 (TLR4) can trigger M2 to release the cytokine IL-10 during chronic inflammation. Furthermore, activation of TLR4 signaling by lipopolysaccharide significantly increased EMT in pancreatic cancer cells, and IL-10 promotes tumour aggressiveness in lung adenocarcinoma cells by increasing cancerous expression of inhibitor of PP2A (CIP2A) via the phosphatidylinositide 3-kinases (PI3K) signaling pathway [23,24]. Furthermore, the researchers discovered a positive correlation between IL-10 levels in the serum and tumour progression, indicating that IL-10 plays a role in tumour development [25]. Multiple microenvironmental cytokines, chemokines, growth factors, and other signals derived from tumour and stromal cells regulate TAM polarization [24]. The most well-documented macrophage recruiters and M2-stimulating factors are colony stimulating factor 1 (CSF-1) and C-C motif ligand 2 (CCL2) [14].

CCL2, CSF-1

CCL2 was earlier reported to shape macrophage polarization toward the protumor phenotype via the C-C chemokine receptor 2 (CCR2) expressed on the surface of macrophages. CCL2 was earlier reported to shape macrophage polarization toward the protumor phenotype via the C-C chemokine receptor 2 (CCR2) expressed on the surface of macrophages [26]. Blocking the CCL2-CCR2 interaction either by genetic ablation or antibodies obviously inhibits metastatic seeding and prolongs the survival of tumor-bearing mice along with the diminished protumor cytokine expression [26,27]. CSF-1 is another potent determinant factor of macrophage polarization. CSF-1 wide overexpression is observed at the invasive edge of various tumors and correlates with a significant increase in metastasis [14]. In addition, tumor graft models showed that CSF-1 depletion led to greatly reduced macrophage density, delayed tumor progression, and severely inhibited metastasis. And the restoration of expression of CSF-1 in CSF-1 null mutant mice with xenografts accelerated both tumor progression and metastasis [28]. Vascular endothelial growth factor A (VEGF-A) has long been considered as a powerful pro-tumor factor [29]. Other than its pro-angiogenic effects, VEGF-A also fosters the malignant growth of tumors by inducing TAM infiltration and M2 polarization in the presence of IL-4 and IL-10 [30]. Direct evidence came from the gain-of-function experiments in the xenograft model of skin cancer, whereby VEGF-A upregulation rescued the clodronate induced macrophage depletion and resulted in shortened xenograft survival [30]. Besides, the overactivation of the epidermal growth factor receptor (EGFR) signaling pathway by either overexpression or mutation is frequently involved in tumor initiation, growth, and metastasis [31].Actually, EGFR signaling not only promotes proliferation and invasiveness of tumor cells directly, but also adjusts the TME by regulating macrophage recruitment and M2-like polarization [32].Disrupted EGFR signaling by cetuximab or gene knockout resulted in less M2-polarized TAMs and correlated with better prognosis in colon cancer models of mice [33]. Beyond those well-investigated factors mentioned above, a number of new homeostatic factors have been described as TAM inducers recently. For example, prostaglandin E2 (PGE2) synergized with

CSF-1 to promote M2 polarization by transactivating the CSF-1R, and PGE2-elicited macrophage infiltration was significantly halted in the absence of CSF-1R [34].

Function of Tumor associated Macrophages

Tumor cells acquire the ability to invade and escape from the constraints of the basement membrane into the surrounding stroma, which is the beginning of metastasis. Loss of intrinsic polarity and loose attachment to surrounding tissue structures are always features of highly invasive tumour cells. This morphological transformation is characterised by epithelial-mesenchymal transition (EMT), which contributes to malignant biological features such as invasion and metastasis [41]. E-cadherin repression causes tumour cells to lose cell-cell connections and apical-basal polarity, resulting in a motile mesenchymal cell phenotype. TAMs have recently been implicated in the regulation of the EMT process, as shown in a number of studies [42-43]. Macrophages play a role in the EMT process by secreting soluble substances such as interleukin-1 (IL-1), interleukin-8 (IL-8), tumour necrosis factor (TNF-), and transforming growth factor (TGF-). The extracellular matrix (ECM) acts as both a scaffold and a barrier for tumour cell movement, with degradation being a key process in metastasis. TAMs have been found to secrete a variety of proteolytic enzymes, such as cathepsins, matrix metalloproteinases (MMPs, such as MMP7, MMP2, and MMP9), and serine proteases, all of which are significant components in ECM breakdown and cell-ECM interactions.

TAMs promote vascularization of tumor cells

Tumor vasculature is an effective route for malignant tumours to spread. When solid tumours reach a particular size, a process known as "angiogenic switch" is triggered by multiple mechanisms, causing a high-density vasculature to provide nutrients and remove wastes [45,46]. TAMs are important regulators of the "angiogenic switch." They congregate in intratumoral areas and invasive fronts, which are both hotspots for angiogenesis and metastasis. The absence of TAMs, on the other hand, resulted in a 40% reduction in vessel density [47,48]. TAMs induce the remodelling of the established vasculature to a more tortuous and leaky form in favours of tumour dissemination, in addition to impacting the development of new tumour vessels.FGF-2, CXCL8, IL-1, IL-8, cyclooxygenase (COX)-2, nitric oxides (iNOS), and MMP7 are some of the other proangiogenic molecules involved [48]. TAMs also have a role in lymph angiogenesis, a process that involves the VEGF-C (a ligand overexpressed by tumors)/VEGFR-3 (a VEGF-C receptor expressed on TAMs) axis that is required for tumour cells to spread to regional lymph nodes and distant metastases. The VEGF-C/VEGFR-3 axis promotes lymph angiogenesis either directly by altering the activity of lymphatic endothelial cells (LECs) or indirectly by increasing cathepsin secretion, which is a strong inducer of lymph angiogenesis [49, 50].

TAMs promote intravasation of tumor cells

Another essential stage in metastasis is tumour cells squeezing through microscopic gaps in vascular endothelium to obtain access to the host vasculature [51]. Intravital multiphoton imaging was used in an attempt tovisualise intravasation in a direct and kinetical manner. This experiment found that an intravasating tumour cell is usually accompanied by a macrophage within one cell diameter, indicating that TAMs are involved in tumour cell intravasation [52]. The mechanisms that underpin this synergistic relationship are complex. On the one hand, macrophages use a variety of proteolytic enzymes like as cathepsins, matrix metalloproteinases, and serine proteases to break down

the ECM around the endothelium. TAMs, on the other hand, use a positive feedback loop involving tumour cell-produced CSF-1 and TAM-produced EGF to trick tumour cells into entering the circulation [53]. The former cytokine increases macrophage motility and EGF synthesis, which signals tumour cells and causes chemotactic migration toward blood arteries. As a result, inhibiting either the CSF-1 or the EGF signaling pathways disrupts both cell types' motility while also lowering the quantity of circulating tumour cells.

TAMs promote tumor cell survival in the circulation

The tumour cells must be primed for survival and egress from the circulation once they have pierced the vascular. Clots packed around tumour cells in the systemic circulation and capillaries reduce survival stress from natural killer (NK) cells in a tissue factor (TF)-dependent manner [54]. In particular, genetically altering macrophage functions reduced tumour cell survival in pulmonary capillaries and prevented tumour invasion into the lung, despite the formation of clots, revealing that macrophages play an important role in this aspect [55]. This phenomenon could be explained by two different mechanisms. A recent study found that recruited macrophages activated the PI3K/Akt survival signaling pathway in newly disseminated breast cancer cells by engaging VCAM-1 via 4 integrins [56,57]. Cancer cells were protected from proapoptotic cytokines like TNF-related apoptosis-inducing ligand (TRAIL) by activating the PI3K/Akt survival pathway [56]. In another part, many tumour cells survive because they are shielded by macrophages' released chemokines or cytokines directly produced [55].

TAMs promote extravasation of tumor cells

The tumour cells would try to attach and extrude through the vessel walls with the help of macrophages once they had settled in the capillaries of the targeted organs. Within an intact lung imaging system, the intimate interactions between tumour cells and macrophages during extravasation were observed and quantitatively studied [58]. The researchers discovered that the extravasation rate dropped considerably after the loss of macrophages, which coincided with the failure of metastasis [58].

TAMs prepare sites for tumor cells: pre-metastatic niches

It is believed that metastasis is not necessary to be a late event in tumor progression [59]. The primary tumors are smart enough to “prime” the secondary organs and dictate organ-specific dissemination before the arrival of tumor cells. Those “primed” sites are predisposed to metastasis and introduced as the concept of pre-metastatic niches (PMNs) [59]. Studies clarified that macrophages were one of the key determinants for the formation of PMNs. They were mobilized to the bloodstream and then clustered in the pre-metastatic sites by a variety of tumor-secreted factors, such as CCL2, CSF-1, VEGF, PLGF, TNF-α, TGF-β, tissue inhibitor of metallopeptidase (TIMP)-1, and exosomes [59]. Besides, the tissue-resident macrophages, such as liver Kupffer cells, pulmonary alveolar macrophages, and osteoclasts, were also involved in orchestrating PMN formation upon stimulation [60]. The presence of those macrophages provides a road map for the homing of circulating tumor cells (CTCs) into the PMNs with enhanced expression of chemokines such as stromal derived factor (SDF)-1 and Ang-1 and remodel the ECM to the tumor cell-favoring direction by secreting ECM-shaping enzymes like MMPs, integrins, and lysyl oxidase (LOX), most of which have been mentioned above as critical inducers of angiogenesis, EMT, and extravasation [62,62,63]. Furthermore, macrophages also establish metabolic cross talk with immune cells like T

helper 1 (TH1) cells and dendritic cells and attenuate their tumoricidal and tumor antigen-presenting behaviors, ultimately promoting the prosperity of those newly lodged tumor cells in a way of immunosuppression.

Macrophages Targeting Therapy

It has long been recognised that using non-discriminatory medicine for the entire body in the treatment of tumours has numerous drawbacks, including compromising the immune system and disrupting the microenvironment's balance, if not the entire balance. As a result of this concern, the need for targeted therapy and modification of molecules in the expression pathways, has been evident for a long time in the search for a treatment that only harms the tumour.

CCL2 and CCL5

Activated macrophages, monocytes, and dendritic cells secrete a considerable amount of CCL2 (also known as monocyte chemotactic protein-1, MCP-1) when they are stimulated by proinflammatory mediators such IL-8 and TNF-α. To put this another way, the interaction between resident macrophages and freshly recruited macrophages is bidirectional, because resident TAMs can attract macrophages to exacerbate tumour spread. CCL2 is a viable target site for preventing TAMs from aggregating in the tissue as a peritumoral function of TAMs [35]. Researchers have discovered that zoledronic acid, a diphosphate molecule, can reduce CCL2/MCP-1 expression, reducing the number of recruited macrophages and acting as an antitumoral agent [36].In some situations, a high quantity of CCL5 might cause TAM recruitment by interacting with CCR2 on the surface of monocytes. Gefitinib, a tyrosine kinase inhibitor that reduces CCL5 release, inhibits cross-talk between TAMs and prostate cancer cells, resulting in tumour cell growth and docetaxel activity inhibition [37].

Colony Stimulating Factor-1 (CSF-1)

Many research on targeted therapy are based on an intentional strategy of CSF1/CSF1R, that is, tumour cells express CSF1 for the purpose of collecting TAMs by connecting CSF1 with CSF1R on macrophages, in order to focus on the recruitment of TAMs and the secretion of cytokines. CSF1 is involved in macrophage recruitment, differentiation, and repolarization, hence targeting CSF1/CSF1R is an effective way. The tyrosine kinase inhibitor PLX3397 was used to treat melanoma in animal models driven by BRAFV00E, as reported in a prior study. It has the ability to suppress CSF1R, and because of this, it is currently being utilised in clinical trials to treat patients with glioblastoma, breast cancer, and other cancers. These researchers discovered that the number of TAMs had significantly dropped, and so has the proportion of M2 [38]. Another study found that CSF1-deficient mice with the use of the inhibitor PLX3397 or a monoclonal antibody to CSF1 displayed particular changes, such as a reduction in the number of TAMs [39]. In contrast to uninfluential M1 macrophages, it is now widely speculated that the absence of the CSF1/CSF1R signal has the potential to provide absolute control for consuming M2 macrophages [40].

Related Kinase Signaling Blocking

According to the above explanation, IL-10 increases CIP2A expression via the PI3K signaling pathway, which promotes tumor growth and spread. The phosphorylation of cAMP response element binding protein (CREB) by IL-10 produced in E6-positive lung cancer cells is regulated by the pathway, according to studies, and the feedback of IL-10-CIP2A-phosphorylated-CREB is believed to effect tumor

progression. One of the focused therapies is blocking the signaling transduction system with particular inhibitors as wortmannin or LY294002 (PI3K inhibitors). Wortmannin, an ubiquitous cell biology reagent, has been used to inhibit DNA repair, receptor-mediated endocytosis, and cell proliferation in the past. [69].

Monoclonal Antibodies and Inhibitors

One of the most fundamental mechanisms of tumour formation and dissemination is immune escape. Monoclonal antibodies are currently the most extensively used tumour immunotherapy. Monoclonal antibodies can impair tumour escape pathways and hence act as an anticancer drug by blocking several pathways involved in TAMs and tumour detection. Researchers employed an anti-CD47 monoclonal antibody to perform out in vivo investigations on tumor-bearing mice after identifying the CD47-SIRP recognition mechanism of tumor cells and macrophages, and discovered the antibody can block the CD47-SIRP route to interdict the signal of anti-phagocytosis. This antibody displays tumour cell targeting, which promotes tumour cell macrophage phagocytosis while having no effect on normal cells [70]. Anti-CD47 mAb causes a high self-reaction since the CD47 molecule is also expressed on the surface of normal cells. [71,72,73]. Anti-CD47 monoclonal antibodies have been reported to cause temporary anaemia and modest neutrophil decrease, with no other noticeable side effects or the occurrence of autoimmune illnesses, according to current research. [74,75].

Conclusion

Cancer is more of a systemic disease since metastasis occurs in the majority of patients. Effectiveness achieved by existing therapeutics is far from satisfactory, since most of the current paradigms are designed to eliminate or interdict tumor cells themselves while the successful outgrowth of metastases is largely influenced by non-malignant cells of the tumor microenvironment (TME) [64,65,67]. As the major orchesters of the TME, TAMs tightly regulate tumor metastasis in all of the steps involved. In this review, we discussed the implicated regulation factors participating in recruitment and polarization of TAMs. In specific, we detailed Ly described the underlying mechanisms for TAM-involved tumor metastasis.

To begin with, TAMs play a wide range of roles in the modulation of metastasis. On the one hand, while TAMs are commonly classified as M2-like, they can exhibit behaviours that fall somewhere between tumoricidal M1 and pro-tumoral M2 type. How phenotypes switch over the course of tumor progression is not fully known. On the other hand, molecular and cell-biological details involved in promoting metastasis might be more complicated than what we expect. Various major points of regulation networks remain elusive. Therefore, it is of great necessity for us to explore the unknown mechanisms underlying TAM-facilitated metastasis and figure out more detailed TAM characterizations as well as associated molecular profiles in TME.

Next to this, in spite of inspiring clinical data obtained from numerous laboratories, the translational benefits of agents targeting TAMs are somewhat not satisfactory in clinical studies. No agent has received official approval for clinical use of cancer treatment so far [67,68]. There is an interguiting possibility that tumors with different histologic types and grading, different genetic background, as well as diverse local inflammatory profiles, might have heterogenous responses to the same treatment. Further explorations in both preclinical and clinical studies are in desperate need. In clinical practice, pathology reports do not routinely describe TAM features in tumor samples, making it difficult to identify

potential TAM-target beneficiaries and creating a gap in knowledge between the clinic and tumor immunology research. Hence, figuring out TAM-related features, such as amount, phenotypes, and cytokine profiles on the pathology reports, or even assessing circulating M2 macrophage numbers as well as systemic CSF1, CCL2 levels might provide a tool for better predicting cancer metastasis and stratifying patients.

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