Research Artcile *Open Access*

Journal of Clinical Oncology & Advanced Therapy

DOI: *doi.org/10.63721/25JCOAT0104*

Deciphering the Role of Tumor-Associated Macrophages (TAMs) in Tumor Angiogenesis

Venketesh K. Panda[1,2*] and Sumant K. Mohanty[3]

[1]Khallikote University, Berhampur-76002, India
[2]School of Applied Sciences, KIIT Deemed to be University, Bhubaneswar-751024 India
[3]Utkal University, Bhubaneswar-751004, India

Citation: Venketesh K. Panda and Sumant K. Mohanty (2025) Deciphering the Role of Tumor-Associated Macrophages (Tams) in Tumor Angiogenesis. J of Clin Onco & Adv Thpy 1(2), 01-08. WMJ/JCOAT-104

Abstract

Breast cancer (BC) is among the top three cancers in the world. Age, hormonal imbalances, unhealthy lifestyles, family history, and genetic abnormalities are all significant risk factors for cancer development. Angiogenesis is a crucial step in this multifactorial process and involves various proangiogenic factors, such as VEGF, PDGF, HGF, MMPs, Angs, FGF, and TGF-β. In addition to angiogenic factors, stromal cells such as cancer-associated fibroblasts (CAFs), tumor-associated macrophages (TAMs), and cancer stem cells (CSCs) secrete secretory factors that aid endothelial cells (ECs) in the use of angiogenic factors, resulting in tumor vascularization. Hypoxia-responsive genes, such as osteopontin (OPN), regulate HIF1α-mediated VEGF production, promoting tumor development and angiogenesis. Despite significant breakthroughs in BC therapeutics, preventing disease recurrence and chemoresistance remains a challenge in treatment regimens. Several antiangiogenic medications, including bevacizumab and ramucirumab, are employed depending on the stage of the disease. Despite significant breakthroughs in BC therapeutics, no successful breakthrough treatment has been identified for preventing the metastasis and recurrence of this disease. This review focuses on understanding the mechanism of tumor angiogenesis and the role of TAMs in fostering angiogenesis.

***Corresponding author:** Venketesh K. Panda, School of Applied Sciences, KIIT Deemed to be University, Bhubaneswar-751024 India.

Submitted: 22.03.2025 **Accepted:** 29.03.2025 **Published:** 03.04.2025

Keywords: Breast cancer, angiogenesis, hypoxia, chemoresistance, antiangiogenic therapy

Introduction

According to the American Cancer Society, BC is the most common invasive malignancy and the leading cause of mortality worldwide in females. BC is a highly aggressive and metastatic cancer that spreads to distant organs such as the brain, bone, lung, and liver [1]. Early diagnosis of BC leads to a better prognosis and increases overall survival. The number of BC cases is gradually increasing in the US; however, the early detection mortality rate is relatively low [2]. The likelihood of developing BC can be increased by several risk factors, including age, hormonal imbalance,

family history, unhealthy lifestyles and gene mutations [3]. Aberrant mutations in mammary epithelial cells result in abnormal cell growth, thereby leading to the development of BC. Growth factors and chemokines stimulate various signaling cascades that interact within the tumor microenvironment (TME) to promote cancer development [4].

Within the tumor site, ECs support tumor growth by forming new blood vessels for the nourishment of cancer cells. This process eventually results in the migration of tumor cells from the primary tumor site to distant organs via metastasis [5]. Thus, angiogenesis is a critical step in the metastatic cascade [6]. In the process of angiogenesis and metastasis in BC, the TME plays an important role. ECs are the major component of the TME and contribute significantly to angiogenesis [6]. It is a multistep process associated with multiple proangiogenic and angiogenic factors, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), matrix metalloproteinases (MMPs), angiopoietins (Angs), fibroblast growth factor (FGF), and transforming growth factor-β (TGF-β) [6,7]. The VEGF family comprises five members: VEGF-A, B, C, D, and placental growth factor [8]. These ligands bind with their endothelial VEGF receptors (VEGFRs), VEGFR-1, 2, and 3, which are members of the receptor tyrosine kinase (RTK) family [6-9]. The microvasculature of blood vessels consists of perivascular and endothelial cells. Under physiological circumstances, endothelial cells were found to be dormant and nonproliferative. However, vascular angiogenesis can be triggered in response to inflammation, hypoxia, or injury through a series of well-controlled sequential manners. The activation of ECs is initially triggered by elevated levels of proangiogenic factors [10,11]. Blood vessels expand during the activation period as pericytes separate from the wall of blood vessels, and the tight connections of ECs are impaired, allowing ECs to elongate and multiply to form new blood vessels [12]. Tumor growth is typically aided by the expansion of blood vessels, which is compatible with the requirement of malignant cells to have access to the circulatory system to survive. Both co-opting the preexisting vasculature and the development of new blood vessels through the regulation of the expression of various genes and cellular pathways are two major ways in which tumors can become vascularized [13]. Numerous pro- and antiangiogenic factors control the homeostasis of the vascular system. Endothelial cells are nonproliferating, and the vasculature remains dormant when these cells are in equilibrium. When proangiogenic signaling predominates, blood vessel formation is stimulated; this process in tumors has been termed the “angiogenic switch” [14,15]. The angiogenic switch dislodges dormant tumors and stimulates the fast division of cancerous cells in conjunction with the formation of new blood vessels. The angiogenic switch could be activated by other genetic modifications of tumor cells, which may result in increased growth and hypoxia, the release of proangiogenic proteins, or tumor-associated inflammation and the attraction of immune cells.

Tumor-Associated Macrophage (TAM)-Mediated Angiogenesis

Among all immune cells, macrophages play crucial roles in the TME and are known to enhance several hallmarks of cancer. Macrophages exhibit a wide range of plasticity and an array of functional activities in the TME. TAMs are major players in driving the vascularization of various cancers, including solid tumors [16]. Macrophage polarization into the M2 phenotype is induced by several secretory factors. For example, colony stimulating factor 1 (CSF1) induces M2 polarization, and blocking CSF1 results in substantial attenuation of breast tumors angiogenesis and growth [17]. Furthermore, macrophage-produced WNT7b acts as an angiogenic switch that promotes VEGF-A mRNA and protein expression in BC [18]. TAM infiltration into breast tumors promotes angiogenesis via the S1PR1/NLRP3/IL-1beta axis [19]. TAMs enhance angiogenesis in tumors by producing angiogenic-promoting factors such as VEGF-A, PlGF, EGF, TGFβ, TNF-α, IL-8, IL-1β, CXCL12, CCL2 and CXCL8 [20,21].

For example, CCL18 secreted from TAMs enhances angiogenesis and tumor progression in BC [22]. Ablation of PKY2 reduces breast tumor growth and infiltration of TAMs, and targeting PKY2 effectively modulates TAMs [23]. TAMs trigger VEGF-1 phosphorylation through the associated Neuropilin-1 and PlexinA1/PlexinA4 in response to hypoxia-induced Semaphorin 3A. In a hypoxic environment, the expression of Nrp1 in TAMs is reduced, resulting in

TAM entrapment at the site [24]. In addition, TAMs promote tumor migration and metastasis by secreting MMPs through destabilization of the vasculature. For example, in human ovarian cancer, TAMs release MMP9, which is positively correlated with VEGF-A expression levels and promotes tumor angiogenesis and proliferation. [25]. TAMs are a robust source of various factors in mouse models and cancer patient samples, such as proangiogenic VEGF, TGF-β, PDGF, TGF-α, EGF, angiopoietin 1 and 2, and extracellular matrix-degrading mediators, such as MMP2, MMP9, and MMP12 [26]. In addition, TAMs have been reported to modulate angiogenesis by secreting members of the S100 family, SEMA family, SPP1, SPARC, COX-2, Tie-2, chitinase-like proteins (YKL-39, YKL-40) and others [27]. The proangiogenic properties of S100 family members have been reported to be associated with elevated protein levels in different cancers, including BC. S100A4, a member of the S100 family, enhances MMP13 expression in MDA-MB-231 cells, thereby promoting cell migration and angiogenesis [28]. Thus, the role of other family members (S100A7, S100A8, S100A9, and S100A10) in the context of TAMs remains unexplored. However, these factors potentially induce EC proliferation, migration, and tube formation in ovarian cancer, melanoma, cervical cancer, and other types of cancer. Several studies have indicated the pivotal role of the semaphorins in various cancers, including BC. Studies have reported that it reduces BC migration and invasion by inducing the expression of α2β1 integrin [29]. Among all the members of the SEMA family, class 3 semaphorins regulate VEGF-induced angiogenesis and cancer progression via plexin or neuropilins (NRPs) [30]. Furthermore, our group reported that SEMA 3A suppresses BC growth and angiogenesis by enhancing FOXO 3a-dependent MelCAM expression [31].

Recently, Radharani et al. reported that via the Stat-3 pathway, IL-6 enhances the cancer stem cell population and contributes to breast tumor progression and angiogenesis [32]. Another study reported that lactate induces BC progression and angiogenesis by inducing M2 polarization via the ERK/STAT3 signaling pathway. Additionally, the suppression of the ERK/STAT3 signaling pathway with the natural compound withanolide D reduces lactate-induced macrophage polarization [33]. In recent years, various studies have identified the role of miRNAs and long noncoding RNAs (lncRNAs) in modulating macrophage recruitment and polarization by inducing the expression of pro- and anti-inflammatory cytokines in macrophages, resulting in breast tumor growth and angiogenesis [34]. For example, miR-155 and miR-29b expressed in cancer cells or TAMs induce and/or inhibit angiogenesis, respectively, in BC models [35, 36]. Similarly, miR-107 and miR-15b expressed in TAMs inhibit the proangiogenic functions of TAMs [37]. Furthermore, lnc-PCAT6-expressing BC cells induce angiogenesis by inhibiting VEGFR2 degradation [38].

Numerous studies have been conducted to better understand the processes by which TAMs regulate tumor angiogenesis. There is substantial evidence that hypoxic tumor areas attract TAMs and release hypoxia-induced chemoattractants, including endothelins, vascular endothelial growth factor A (VEGFA), angiopoietin 2, CXCL12, and endothelial monocyte-activating polypeptide II (EMAPII), which can make TAMs proangiogenic [39]. TAMs release proangiogenic factors such as TNFα, MMPs, VEGF, and thymidine phosphorylase [40]. Furthermore, TAMs secrete growth factors such as VEGF, TGFβ, and PDGF, which promote angiogenesis in malignancies such as breast cancer [39]. Additionally, it has been discovered that the overexpression of CSF-1 promotes the recruitment of TAMs [41], whereas short-interfering RNA (siRNA)-induced knockdown of the CSF-1 receptor reduces macrophage vascularization and infiltration in vivo [40]. The TEK tyrosine kinase endothelial (TIE2) receptor is a recognized angiopoietin receptor that contributes significantly to angiogenesis [42]. One study revealed that TAMs express TIE2, which binds to angiopoietins and promotes angiogenesis in an in vivo model of breast cancer [43]. Furthermore, in vitro research has demonstrated that the CCL8 receptor PITPNM3 is necessary for the CCL8-mediated activation of angiogenesis in HUVECs [44]. The lymphatic endothelial cell marker podoplanin (PDPN), which is strongly expressed in TAMs, activates the promigratory integrin β1 to promote lymphangiogenesis and invasion [45]. TAMs produce the WNT family ligand WNT7B, which has been implicated in tumor growth and angiogenesis in a mouse model of breast cancer [46]. Furthermore, by inhibiting the angiogenic switch and lowering VEGFA, WNT7B suppression in macro-

phages reduces the formation of breast tumors in vivo [46].

The functional diversity of TAMs is strongly associated with cancer invasion, migration, increased tumor angiogenesis, therapy resistance, and tumor suppression [47]. Many studies are ongoing to target TAMs for immune therapy, antiangiogenic therapy, etc. However, novel technologies such as single-cell omics have explored the molecular and functional diversity of TAMs in various cancers. A recent study reported that seven TAM subsets based on their molecular signatures were preserved in almost all cancer types. Among the seven subsets, angio-TAMs play pivotal roles in multiple aspects of tumor development. These TAMs are characterized by VEGFA and SPP1 (OPN), which are highly expressed in Angio-TAMs. In addition, angiogenic factors such as VCAN, FCN1, and THBS1 also serve as molecular signatures. It has been reported that angio-TAMs also express other molecular signatures, including VCAN, in addition to SPP1 in breast and other cancers [48]. Another group reported that alterations in TAM transcription factors modulate the expression of various cytokines involved in tumor progression and angiogenesis [49]. The role of OPN (SPP1)-induced VEGF expression and its molecular mechanism in regulating breast tumor motility and angiogenesis have been reported [50]. In addition, SSP1 (OPN) promotes TAM-dependent melanoma growth and angiogenesis by upregulating cyclooxygenase-2 (COX2) via the ERK/MAPK/AP1 pathway [51]. A similar study reported that COX2 silencing via a lentivirus (replication incompetent) in combination with TAMs suppresses VEGF expression and angiogenesis [52]. Thus, targeting the molecular signatures of Angio-TAMs with antibody-based immunotherapies or in combination with other drug candidates could decrease TAM infiltration and tumor progression.

Angio TAM Diversity

Tumor-associated macrophages (TAMs) promote various oncogenic functions in breast and other cancers and hence constitute important therapeutic targets in cancer therapy. TAMs exhibit a wide range of functions, highlighting their diversity. Recent single-cell omics tools have made substantial contributions to our understanding of TAM molecular-diversity [47]. However, there is a lack of unified terminology for TAM diversity and molecular signature annotation. Advancements in single-cell omics are revealing the intricacy of TAM diversity in an unbiased manner. This is critical for not only macrophage research but also immune oncology to fully grasp the complexity of these powerful immune cells in cancer and, hopefully, employ this knowledge to improve precision diagnosis and therapy. A recent study reported seven TAM subsets on the basis of their signature genes, enriched pathways, and predicted functions: interferon-primed TAMs (IFN-TAMs), immune regulatory TAMs (Reg-TAMs), inflammatory cytokine-enriched TAMs (Inflam-TAMs), lipid-associated TAMs (LA-TAMs), proangiogenic TAMs (Angio-TAMs), RTM-like TAMs (RTM-TAMs), and prolif-TAMs [47]. Among them, Angio-TAMs play a pivotal role in the enrichment of blood vessels, thereby promoting tumor angiogenesis. Furthermore, on the basis of the molecular signature, Angio-TAMs can be characterized by high expression of an angiogenic signature including VEGFA and SPP1 or other angiogenic factors, such as VCAN, FCN1, and THBS1 [53-55]. Using SCENIC and single-sample gene set enrichment analysis (ssGSEA) of scRNA-seq data from various cancer types, the transcription factors CEBPB, FOSL2, and HIFA were predicted to influence the expression of this gene signature [53-57]. In other cancer types, instead of expressing SPP1, Angio-TAMs express different flag genes, such as VCAN in BRCA and melanoma, INHBA in gastric cancer and ESCA, and FN1 in kidney cancer. Previous research has shown that Angio-TAMs are typically found in hypoxic regions of the TME in a variety of human cancers as well as in the GL261 GBM animal model [58,59]. TAM-derived VEGFA, in particular, can promote metastasis by increasing tumor cell intravasation, extravasation and chemotherapy resistance in vivo breast cancer models utilizing both murine and human cancer cells [60,61]. As a result, Angio-TAMs may promote numerous aspects of tumor growth, and their abundance, including NSCLC, CRC, PDAC, OVC, kidney cancer, and melanoma, is consistently related to poor prognosis in The Cancer Genome Atlas (TCGA) datasets [53].

Conclusion

The notion of targeting angiogenesis as a therapeutic strategy is a major forward in cancer treatment and has led to the establishment of several therapeuticagents, such as bevacizumab, sorafenib, formononetin

and imatinib. Nevertheless, antiangiogenic therapeutic agents are unable to provide clinical benefits for several reasons. Even with increasing success in the treatment of cancer, the use of antiangiogenic agents might lead to more resistant tumors. This clinical insufficiency in the therapeutic approach could be analogous to preexisting resistance or adaptation to the effects of antiangiogenic agents. Angiogenesis is an elaborate process that involves a complex signaling mechanism, suggesting the importance of tumor-stroma interactions in mediating therapy resistance. It is understandable that numerous mechanisms of resistance prevail against angiogenic inhibitors (AIs), including the initiation of alternative angiogenic pathways, the contribution of stromal cells, adapting vessel co-option and vascular mimicry. Additionally, intratumoral hypoxia caused by AI-induced vascular regression increases resistance to AIs, radiotherapy and chemotherapy. The reduced tumor vasculature and blood flow resulting from AIs obstruct the delivery of chemotherapeutic agents into the tumor. All of these barriers in the utilization of AIs increase tumor growth and metastasis and may contribute to clinical limitations in drug development. However, non-VEGF targets, such as several growth factors and secretory factors from tumors as well as stromal cells, have now been introduced into clinical settings and have been shown to provide favorable results in experimental setups. In addition, more studies are warranted to explore tumor-specific antiangiogenic treatment resistance in the context of breast tumor angiogenesis. Hence, a better understanding of the interplay between stromal cells and tumor cells in modulating angiogenesis will help in the development of novel therapeutic treatment regimens.

Acknowledgements
Not applicable.

Authors' Contributions
The authors (V.K.P. and S.K.M.) wrote the manuscript together. V.K.P. conceptualized and significantly edited the entire manuscript. All the authors have read and agreed to the published version of the manuscript.

Funding
No funding was taken for the project, and there is no conflict of interest.

Data Availability
NA

Declarations
Ethics Approval and Consent to Participate
This is not applicable as this is a review article.

Consent for Publication
This is not applicable as this is a review article.

Competing Interests
The authors declare no competing interests.

References:
1. Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, et al. (2017) Risk Factors and Preventions of Breast Cancer. Int J Biol Sci 13: 1387-1397.
2. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, et al. (2016) Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. CA Cancer J Clin 66: 31-42.
3. Radharani NNV, Kundu IG, Yadav AS, Kundu GC (2021) Oxidative stress a key regulator of breast cancer progression and drug resistance. In: Chakraborti S, Ray BK, Roychowdhury S, Handbooks of oxidative stress in cancer: Mechanistics Aspects. Springer, Singapore 1-15.
4. Butti R, Das S, Gunasekaran VP, Yadav AS, Kumar D, et al. (2018) Receptor tyrosine kinases (RTKs) in breast cancer: signaling, therapeutic implications and challenges. Mol Cancer 17: 34.
5. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, et al. (2013) Panel members. Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. Ann Oncol 24: 2206-23.
6. Ayoub NM, Jaradat SK, Al-Shami KM, Alkhalifa AE (2022) Targeting Angiogenesis in Breast Cancer: Current Evidence and Future Perspectives of Novel Anti-Angiogenic Approaches. Front Pharmacol 13: 838133.
7. Rust R, Gantner C, Schwab ME (2019) Pro- and antiangiogenic therapies: current status and clinical implications. FASEB J 33: 34-48.

8. Ferrara N, Gerber HP, LeCouter J (2003) The biology of VEGF and its receptors. Nat Med 9: 669-676.
9. Yang J, Yan J, Liu B (2018) Targeting VEGF/VEGFR to Modulate Antitumor Immunity. Front Immunol 9: 978.
10. Karamysheva AF (2008) Mechanisms of angiogenesis. Biochemistry (Mosc) 73: 751-62.
11. Krüger-Genge A, Blocki A, Franke RP, Jung F (2019) Vascular Endothelial Cell Biology: An Update. Int J Mol Sci 20: 4411.
12. Mazurek R, Dave JM, Chandran RR, Misra A, Sheikh AQ, et al. (2017) Vascular Cells in Blood Vessel Wall Development and Disease. Adv Pharmacol 78: 323-350.
13. Kuczynski EA, Vermeulen PB, Pezzella F, Kerbel RS, Reynolds AR, et al. (2019) Vessel co-option in cancer. Nat Rev Clin Oncol 16: 469-493.
14. Hanahan D, Folkman J (1996) Patterns and emerging mechanisms of the angiogenic switch during tumorigenesis. Cell 86: 353-364.
15. Lugano R, Ramachandran M, Dimberg A (2020) Tumor angiogenesis: causes, consequences, challenges and opportunities. Cell Mol Life Sci 77: 1745-1770.
16. Chen Y, Song Y, Du W, Gong L, Chang H, et al. (2019) Tumor-associated macrophages: an accomplice in solid tumor progression. J Biomed Sci 26: 78.
17. Strachan DC, Ruffell B, Oei Y, Bissell MJ, Coussens LM, et al. (2013) CSF1R inhibition delays cervical and mammary tumor growth in murine models by attenuating the turnover of tumor-associated macrophages and enhancing infiltration by CD8+ T cells. Oncoimmunology 2: 26968.
18. 18. Yeo EJ, Cassetta L, Qian BZ, Lewkowich I, Li JF, et al. (2014) Myeloid WNT7b mediates the angiogenic switch and metastasis in breast cancer. Cancer Res 74: 2962-2973.
19. Weichand B, Popp R, Dziumbla S, Mora J, Elisabeth S, et al. (2017) S1PR1 on tumor-associated macrophages promotes lymphangiogenesis and metastasis via NLRP3/IL-1β. J Exp Med 214: 2695-2713.
20. Owen JL, Mohamadzadeh M (2013) Macrophages and chemokines as mediators of angiogenesis. Front Physiol 4: 159.
21. Hughes R, Qian BZ, Rowan C, Muthana M, Keklikoglou I, et al. (2015) Perivascular M2 Macrophages Stimulate Tumor Relapse after Chemotherapy. Cancer Res 75: 3479-3491.
22. Lin L, Chen YS, Yao YD, Chen JQ, Chen JN, et al. (2015) CCL18 from tumor-associated macrophages promotes angiogenesis in breast cancer. Oncotarget 6: 34758-34773.
23. Müller AK, Köhler UA, Trzebanski S, Vinik Y, Raj HM, et al. (2022) Mouse Modeling Dissecting Macrophage-Breast Cancer Communication Uncovered Roles of PYK2 in Macrophage Recruitment and Breast Tumorigenesis. Adv Sci (Weinh) 9 :2105696.
24. Casazza A, Laoui D, Wenes M, Rizzolio S, Bassani N, et al. (2013) Impeding macrophage entry into hypoxic tumor areas by Sema3A/Nrp1 signaling blockade inhibits angiogenesis and restores antitumor immunity. Cancer Cell 24: 695-709.
25. Huang S, Van Arsdall M, Tedjarati S, McCarty M, Wu W, et al. (2002) Contributions of stromal metalloproteinase-9 to angiogenesis and growth of human ovarian carcinoma in mice. J Natl Cancer Inst 94: 1134-1142.
26. Fu LQ, Du WL, Cai MH, Yao JY, Zhao YY, et al. (2020) The roles of tumor-associated macrophages in tumor angiogenesis and metastasis. Cell Immunol 353: 104119.
27. Larionova I, Kazakova E, Gerashchenko T, Kzhyshkowska (2021) J. New Angiogenic Regulators Produced by TAMs: Perspective for Targeting

Tumor Angiogenesis. Cancers (Basel) 13: 3253.
28. Wang L, Wang X, Liang Y, Diao X, Chen Q, et al. (2012) S100A4 promotes invasion and angiogenesis in breast cancer MDA-MB-231 cells by upregulating matrix metalloproteinase-13. Acta Biochim Pol 59: 593-598.
29. Pan H, Wanami LS, Dissanayake TR, Bachelder RE, (2009) Autocrine semaphorin3A stimulates alpha2 beta1 integrin expression/function in breast tumor cells. Breast Cancer Res Treat 118: 197-205.
30. Mishra R, Kumar D, Tomar D, Chakraborty G, Kumar S, et al. (2015) The potential of class semaphorins as both targets and therapeutics in cancer. Expert Opin Ther Targets 19: 427-442.
31. Mishra R, Thorat D, Soundararajan G, Pradhan SJ, Chakraborty G, et al. (2015) Semaphorin 3A upregulates FOXO 3a-dependent MelCAM expression leading to attenuation of breast tumor growth and angiogenesis. Oncogene 34: 1584-1595.
32. Radharani NNV, Yadav AS, Nimma R, Kumar TVS, Bulbule A, et al. (2022) Tumor-associated macrophage derived IL-6 enriches cancer stem cell population and promotes breast tumor progression via Stat-3 pathway. Cancer Cell Int 22: 122.
33. Mu X, Shi W, Xu Y, Xu C, Zhao T, et al. (2018) Tumor-derived lactate induces M2 macrophage polarization via the activation of the ERK/STAT3 signaling pathway in breast cancer. Cell Cycle 17: 428-438.
34. Benedetti A, Turco C, Fontemaggi G, Fazi F (2022) Non-Coding RNAs in the Crosstalk between Breast Cancer Cells and Tumor-Associated Macrophages. Noncoding RNA 8: 16.
35. Li Y, Cai B, Shen L, Dong Y, Lu Q, et al. (2017) MiRNA-29b suppresses tumor growth through simultaneously inhibiting angiogenesis and tumorigenesis by targeting Akt3. Cancer Lett 397: 111-119.
36. Kong W, He L, Richards EJ, Challa S, Xu CX, et al. (2014) Upregulation of miRNA-155 promotes tumor angiogenesis by targeting VHL and is associated with poor prognosis and triple-negative breast cancer. Oncogene 33: 679-689.
37. Donzelli S, Milano E, Pruszko M, Sacconi A, Masciarelli S, et al. (2018) Expression of ID4 protein in breast cancer cells induces reprogramming of tumor-associated macrophages. Breast Cancer Res 20: 59.
38. Dong F, Ruan S, Wang J, Xia Y, Le K, et al. (2020) M2 macrophage-induced lncRNA PCAT6 facilitates tumorigenesis and angiogenesis of triple-negative breast cancer through modulation of VEGFR2. Cell Death Dis 11: 728.
39. Mantovani A, Marchesi F, Malesci A, Laghi L, Allavena P, et al. (2017) Tumor-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol 14: 399-416.
40. Lin EY, Li JF, Gnatovskiy L, Deng Y, Zhu L, et al. (2006) Macrophages regulate the angiogenic switch in a mouse model of breast cancer. Cancer Res 66: 11238-11246.
41. Aharinejad S, Sioud M, Lucas T, Abraham D (2007) Target validation using RNA interference in solid tumors. Methods Mol. Biol 361: 227-238.
42. Komohara Y, Fujiwara Y, Ohnishi K, Takeya M (2016) Tumor-associated macrophages: Potential therapeutic targets for anticancer therapy. (Pt B) Adv. Drug Deliv. Rev 99: 180-185.
43. Mazzieri R, Pucci F, Moi D, Zonari E, Ranghetti A, et al. (2011) Targeting the ANG2/TIE2 axis inhibits tumor growth and metastasis by impairing angiogenesis and disabling rebounds of proangiogenic myeloid cells. Cancer Cell 19: 512-526.
44. Lin L, Chen YS, Yao YD, Chen JQ, Chen JN, et al. (2015) CCL18 from tumor-associated macrophages promotes angiogenesis in breast cancer. Oncotarget 6: 34758.
45. Bieniasz Krzywiec P, Martín Pérez R, Ehling M, García Caballero M, Pinioti S, et al. (2019) Podoplanin-expressing macrophages promote lymphangiogenesis and lymphoinvasion in breast cancer. Cell Metab 30: 917-936.
46. Yeo EJ, Cassetta L, Qian BZ, Lewkowich I, Li Jf, et al. (2014) Myeloid WNT7b mediates the angiogenic switch and metastasis in breast cancer.

Cancer Res 74: 2962-2973.

47. Ma RY, Black A, Qian BZ (2022) Macrophage diversity in cancer revisited in the era of single-cell omics. Trends Immunol 43: 546-563.
48. Cheng S, Li Z, Gao R, Xing B, Gao Y, et al. (2021) A pancancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. Cell 184: 792-809.
49. Yang Q, Guo N, Zhou Y, Chen J, Wei Q, et al. (2020) The role of tumor-associated macrophages (TAMs) in tumor progression and relevant advance in targeted therapy. Acta Pharm Sin B 10: 2156-2170.
50. Chakraborty G, Jain S, Kundu GC (2008) Osteopontin promotes vascular endothelial growth factor-dependent breast tumor growth and angiogenesis via autocrine and paracrine mechanisms. Cancer Res 68 :152-161.
51. Kale S, Raja R, Thorat D, Soundararajan G, Patil TV, et al. (2014) Osteopontin signaling upregulates cyclooxygenase-2 expression in tumor-associated macrophages leading to enhanced angiogenesis and melanoma growth via α9β1 integrin. Oncogene 33: 2295-2306.
52. Du Y, Shi A, Han B, Li S, Wu D, et al. (2014) COX-2 silencing enhances tamoxifen antitumor activity in breast cancer in vivo and in vitro. Int J Oncol 44: 1385-1393.
53. Cheng S, Ziyi L, Gao R, Xing B, Yang Y, et al. (2021) A pancancer single-cell transcriptional atlas of tumor infiltrating myeloid cells. Cell 184: 792-809.
54. Zilionis R, Engblom C, Pfirschke C, Savova V, Zemmour D, et al. (2019) Single-cell transcriptomics of human and mouse lung cancers reveals conserved myeloid populations across individuals and species. Immunity 50: 1317-1334.
55. Yang Q, Zhang H, Wei T, Lin A, Sun Y, et al. (2021) Single-cell RNA sequencing reveals the heterogeneity of tumor-associated macrophage in non-small cell lung cancer and differences between sexes. Front. Immunol 12: 756722.
56. Raghavan S, Winter PS, Navia AW, Williams HL, DenAdel A, et al. (2021) Microenvironment drives cell state, plasticity, and drug response in pancreatic cancer. Cell 184: 6119-6137.
57. Chen YP, Yin JH, Li WF, Chen DP, Zhang CJ, et al. (2020) Single-cell transcriptomics reveals regulators underlying immune cell diversity and immune subtypes associated with prognosis in nasopharyngeal carcinoma. Cell Res 30: 1024-1042.
58. Talks KL, Turley H, Gatter KC, Maxwell PH, Pugh CW, et al. (2000) The expression and distribution of the hypoxia-inducible factors HIF-1α and HIF-2α in normal human tissues, cancers, and tumor-associated macrophages. Am. J. Pathol 157: 411-421.
59. Pombo Antunes AR, Scheyltjens I, Francesca L, Messiaen J, Antoranz A, et al. (2021) Single-cell profiling of myeloid cells in glioblastoma across species and disease stage reveals macrophage competition and specialization. Nat. Neurosci 24: 595-610.
60. Harney AS, Arwert EN, Entenberg D, Wang Y, Guo P, et al. (2015) Real-time imaging reveals local, transient vascular permeability, and tumor cell intravasation stimulated by TIE2hi macrophage-derived VEGFA. Cancer Discov 5: 932-943.
61. Hughes R, Qian BZ, Rowan C, Muthana M, Keklikoglou I, et al. (2015) Perivascular M2 macrophages stimulate tumor relapse after chemotherapy. Cancer Res 75: 3479-3491.