Dean&Francis
ISSN 2959-409X

Tumor-associated Macrophages in Breast Cancer: Potential Therapeutic Strategies and Future Prospects

Ruoxuan Wang[1, *]

[1]The Fourth Clinical Medical College of Harbin Medical University, Harbin Medical University, Harbin, 150081, China
*Corresponding author: 422498991@gmail.com

Abstract:

Among women, breast cancer (BC) ranks as one of the most prevalent malignant tumors and is the primary cause of mortality from cancer. Circulating monocytes and embryonic tissue-resident cells give rise to tumor-associated macrophages (TAMs). TAM represents the major immune cell population in the breast tumor microenvironment and are closely associated with BC onset, progression and metastasis. This review highlights that TAM cells are classified into M1 and M2 types, and the two subtypes can be transformed into each other under certain conditions with a high degree of plasticity. TAM can contribute to BC growth by promoting the growth of cancer cells, facilitating tumor immune escape and enhancing cancer drug resistance. In addition, this review emphasized that immune resistance in BC can be overcome by inhibiting TAM recruitment, reprogramming TAM, removing existing TAM and blocking the immunosuppressive function of TAM. In the future, the combination of TAM and immune checkpoint inhibitors will become the mainstream direction for improving the survival cycle of patients with advanced breast cancer.

Keywords: Tumor-associated macrophages; Breast cancer; Tumor microenvironment; Target therapy.

1. Introduction

In the female population, breast cancer (BC) is a highly common malignant tumor and represents the foremost factor in cancer-associated fatalities. Although some treatments for BC have made progress, the prognosis for patients with advanced or recurrent disease remains unsatisfactory. Therefore, new treatment strategies need to be discovered. Among them, emerging therapies targeting tumor-associated and macrophage cells have shown hopeful results in treating BC.

Macrophages are critical cells in the innate and adaptive immunity. It is an immune phagocyte which the first immune line of defense is provided. It not only prevents the infection but also plays roles in regulating the wound healing and tissue homeostasis, presenting foreign and self-antigen post-injury, and

ISSN 2959-409X

alleviating inflammatory responses. As an important cellular component in the tumor microenvironment(TME), TAMs4er is a highly plastic immune cell and actively involved in the TME formation. Recently, it was shown that TME and the TAMs can take a central part in the tumor progression, the metastasis formation, the resistance to treatments. TAMs are the most populous immune cells within the TME of a BC. These cells may be polarized either into a tumorinhibiting (M1-like) or to a tumor-promoting (M2-like) phenotype, according to the local stimuli. An abundance of the TME (and especially M2-like) TAMs was found to be strong linked to aggressive BC, overmetastatic propensity, and resistance to treatment. TAMs further induce immune suppression, angiogenesis, metastatic dissemination and phenotypic plasticity of BC cells.

This review will summarize the origin of the TAM,the common TAM subtypes in the BC TME and their functions in BC development, assess current challenges and controversies, and outline future research directions.

2. Origin and Polarization of TAM

2.1 Origin of TAM

TAMs originate from two primary sources. One is circulating monocytes derived from hematopoietic stem cells (HSCs), another is embryonic tissue-resident macrophages. HSCs differentiate into bone marrow progenitor cells, which further develop into monocytes and M-MDSCs. These monocytes migrate to tissues and mature into macrophages. Additionally, embryonic tissue-resident macrophages, originating from yolk sac and fetal liver progenitors, proliferate in situ in organs like the brain and spleen. In the TME, monocytes are recruited by chemokines (such as CCL2, CCL5) secreted by tumor cells and other stromal cells, where they differentiate into TAMs. This dual origin contributes to the heterogeneity and functional diversity of TAMs, enabling them to adapt to various roles in tumor progression and immune modulation [1].

2.2 Polarization of TAMs

M1-type polarization is driven by IFN-γ, LPS, or GM-CSF, activated through the STAT1/NF-κB pathway, with high expression of iNOS, IL-1β, IL-12, and TNF-α. M2-type polarization is polarized to a pro-tumorigenic phenotype in response to stimulation with IL-4, IL-13, IL-10, or TGF-β, through the STAT6/PPARγ pathway, secreting Arg-1, VEGF, and IL-10. Reprogramming of glucose metabolism and lipid metabolism in TAM directly regulates its M1/M2 polarization. When stimulated by cytokines, M1-type macrophage metabolism changes to glycolysis, reducing the rate of oxygen consumption. In addition, succinate and citrate accumulate under tricarboxylic acid cycle (TCA) interruption and inhibit prolyl hydrogenase activity, thereby stabilizing IL-1β and driving the inflammatory response. Unlike M1-type macrophages, M2-type macrophages have an intact TCA cycle and have a marked increase in oxygen consumption in the activated state, with energy supply relying mainly on OXPHOS and fatty acid oxidation (FAO). In addition to this, a number of other polarized subtypes exist [2]. For example, hypoxia induces TAMs to express CD206 and VEGF via HIF-1α; tumor metabolites (such as lactate) promote M2-like polarization by acidifying the microenvironment.

3. The Phenotype and Function of TAM in TME

The common way of TAMs is divided into the two kinds of TAM phenotypes, proinflammatory TAM (M1)and anti-inflammatory TAM (M2). M1 type TAM has antitumor activity by recognizing tumor cells and killing tumor cells directly through killing action and ADCC,M1-type TAM expresses CD80/CD86, and directly killed tumor cells by recognizing tumor cells and tumor killing factor such as NO and reactive oxygen species (ROS).The process of antibody-dependent cytotoxicity-mediated tumour killing on tumour surface. During the early stage of tumour development, the highly expressed IL-12 and low IL-10 expression on M1 type TAMs can produce a stronger immune response to destroy and kill cancer cells [3].

There is substantial evidence indicating that, as tumors progress to advanced stages, TAMs in tumor tissues undergo a significant shift from M1-type to M2-type TAMs. M2-type TAMs exhibit low IL-12 expression and high IL-10 expression, leading to reduced tumor cell killing capacity. M2-type TAMs express CD163 and CD206 and secrete cytokines such as IL-4, TGF-β, and M-CSF. They create an immunosuppressive microenvironment that promotes tumor cell growth and participates in tumor invasion, metastasis and angiogenesis [4].

4. The Role of TAM in BC Progression

4.1 The Role of TAM in BC Progression

First, in the early phase of the tumor development, TAMs make microenvironment suitable for tumor cells by secret-

ing some growth factors (such as EGF and FGF), pro-inflammatory cytokines (such as IL-6 and TNF-α) or other useful chemical substances to promote tumor growth. Second, TAMs facilitate tumor cells to growth by secreting matrix metalloproteinases (MMPs) to degrade the extracellular matrix. Another important role of TAMs is in angiogenesis.TAMs promote cancer by secreting large amounts of VEGF, which binds to the VEGFR2 in vascular endothelial cells and results in activation of the downstream PI3K-Akt, RAS-MAPK signaling, which is used to induce vasculogenesis of endothelial cells, proliferation, migration and the survival of new tumor blood vessels [5]. As can be seen from these combined mechanisms, there is regulatory relationship between TAMs and BC microenvironment.

4.2 TAMs Promote Tumor Immune Evasion

TAMs suppress antitumor immune responses through multiple mechanisms, reshaping the tumor microenvironment to aid BC in evading immune surveillance. First, TAMs highly express immune checkpoint molecules such as PD-L1 and B7-H4. By binding to receptors on T cell surfaces, these molecules induce T cell functional exhaustion and even apoptosis. Additionally, TAMs suppress the cytotoxic activity of T cells and NK cells by secreting immunosuppressive cytokines (IL-10 and TGF-β). Second, TAMs actively recruit regulatory Tregs and MDSCs by secreting chemokines like CCL17 and CCL22, forming an immunosuppressive network that further weakens anti-tumor immune responses [6]. Beyond these mechanisms, TAMs can also degrade L-arginine which is a nutrient critical for T cell survival in the microenvironment and highly express arginase-1 (Arg-1). This reduces expression of the T cell receptor CD3ζ chain and impairs T cell responses.

4.3 TAMs Enhance Drug Resistance in BC Cells

TAMs facilitate BC cell drug resistance through various mechanisms. Through a series of secreted soluble factors, TAMs directly protect BC cells against drugs' induced apoptosis. Tumor cells in which TAMs release cytokines like IL-6, IL-8, TNF-α can be activated to exert pro-survival signaling pathway like NF-kB and STAT3.Activation these pathways results in the upregulation of anti-apoptotic proteins (Bcl-2, Bcl-xL) and inhibition of pro-apoptotic proteins, thereby allowing cancer cells to survive in the face of drug challenge. In terms of resistance against the hormone therapy, TAM-secreted CCL2 activates PI3K/AKT/mTOR pathway, upregulates the expression of sodium-glucose cotransporter(SGLT), stimulates glycolytic metabolism, subsequently leads to tamoxifen resistance and contributes to tumors to grow faster.Second, TAMs trigger a cascade of transcriptional programs in cancer cells through secretion of inflammatory cytokines/chemokines, including CCL18 and IL-6, and interaction with cancer stem cells (CSCs) that help to boost CSC self-renewal capacity and maintenance of the stem cell features [7]. For example, TAMs upregulated Sox-2 expression in BC cells through the EGFR/STAT3/Sox-2 signaling axis, the important transcription factor for maintaining the stem cell traits.In addition, TAMs can compete with cancer cells for available nutrients in the TME, and this additional level of stress might be indirectly conducive to selecting for drugresistant cell subpopulations that are more able to withstand stress.

5. TAM Therapy in BC

5.1 Inhibition of TAM Recruitment

Inhibiting TAM recruitment is the primary approach to reducing TAM levels. Driven by signaling pathways involving cytokines, chemokines (such as CCL2), and colony-stimulating factors (CSF-1), monocytes or macrophages from the peripheral circulation are recruited into the TME, thereby promoting BC growth and metastasis. Blocking these signaling pathways effectively reduces TAM recruitment, thereby inhibiting tumor growth. Inhibitors targeting the CCL2-CCR2 axis disrupt the CCL2/CCR2 signaling pathway, thereby suppressing tumor growth by enhancing T cell-mediated antitumor immunity [8]. CSF-1R inhibitors (such as Pexidratinib) block the CSF-1/CSF-1R signaling pathway, converting pro-tumor M2-type TAMs into anti-tumor M1 phenotypes, and further enhance antigen presentation and T cell activation. A phase II trial is currently underway to study the combination of eribulin and Pexidarnitib in the treatment of metastatic TNBC. Additionally, CSF-1R inhibitors can be combined with CXCR2 antagonists to achieve antitumor effects and produce synergistic effects with chemotherapy or immune checkpoint inhibitors. What is more, Anti-CCL2/CCL5 therapy can suppress elevated CCL2/CCL5 levels in BC, thereby inhibiting macrophage infiltration and angiogenesis. Using VEGF antibodies (such as bevacizumab) or VEGFR2 inhibitors (such as apatinib) can block VEGF/VEGFR2 binding, inhibit the angiogenesis signaling pathway, leading to the regression of existing blood vessels and preventing the formation of new ones. Tumors become oxygen-deprived and nutritionally deficient due to insufficient blood supply, ultimately hindering their growth. Therefore, the VEGF/VEGFR2 axis can ef-

ISSN 2959-409X

fectively inhibit the growth of BC.

5.2 Reprogramming Tumor-Associated Macrophages

The macrophage plasticity allows them to be phenotypically remodeled to adapt to the tumor niche. Thus reprogramming TAMs towards an anti-tumoral phenotype is an emerging approach for the treatment of cancer. Stimulation of the CD40 signaling pathway drives TAMs to a M1 phenotypes that favors anti-tumor immunity. For example, CD40 agonists (e.g., Selicrelumab) have been shown to cooperate with chemotherapy, immunotherapy, anti-angiogenesis. The PI3Kγ pathway is highly relevant to M2 polarization, and pharmacological PI3Kγ inhibition could reprogram macrophages and improve T cell responses. PI3Kγ inhibitors such as IPI-549 could be used together with T cell Checkpoint blockade [9].PI3Kγ inhibitors are synergistic with PLG-CA4, extending cancer patients' mean survival time by a considerable amount. mTOR modulates macrophage polarization by monitoring nutrient cues and activating glycolysis.Activation of the mTORC1 signaling is another important pathway that promote conversion of the M2 macrophages into M1 macrophages. For example, under the pro-tumor microenvironment, stimulation by a variety of TLR agonists and IFN-γ triggers a strong mTORC1 activation and downstream mTORC1-dependent HIF-1a- and NF-κB-driven transcription cascades that induce a shift in the metabolic phenotype towards glycolysis and sets off an M1 gene program (the so-called "reprogramming" of pro-tumor M2 macrophages into anti-tumor M1 phenotypes).Another mTOR inhibitor, another promising clinical results for advanced BC trial. And other combination regimen, of nanoparticles can directly impact macrophage polarizations used for immuno therapeutical strategies, as a promising new paradigm for reprogramming the TAMs.It was revealed that some nanoparticles could have immune-boosting effects. For example, in mouse BC model, iron oxide nanoparticles stimulate M2-type TAM repolarization toward M1-type TAMs. Gold and silver nanoparticles inhibit TNF-α and IL-10 but activate IL-12 in a M-type polarization-correcting modulated reprogramming of TAMs.

5.3 Clearing Existing TAMs

The intention of destroying pre-existing TAMs is directly lowering population of already existing pro-tumor macrophages in TME. Anti-CSF-1R antibody (e.g. Emactuzumab) can directly kill CSF-1R+ TAMs via ADCC and ADCP. ADCC depend on NK cells which recognizes antibody-bound TAMs and releases perforin and granzyme to induce apoptosis.ADCP refer to antibody-mediated TAM phagocytosis. BsAbs can bind TAM surface markers (CD206, F4/80, or CSF-1R) and T cell or NK cells' activation receptors (CD3 or CD16) simultaneously and achieve clearance of TAMs. To reduce TAM numbers, it is possible to also trigger TAM apoptosis.TRAIL induces apoptosis in TAMs by upregulating the death receptor DR5.Besides, in BC, ADCs could target and kill TAMs [10]. ADCs is an antibody targeted to TAMs surface antigens combined with cytotoxic drugs. ADCs bind to TAMs and internalizes, which releases toxins and selectively killing TAMs. ADCs targeted to CD206 or FOLR2 could eliminate TAMs in BC effectively and improve the effect of PD-1 inhibitor.Synthetic oncolytic virions (e.g., herpes virus or adenoviruses) can also be engineered to express as to replicate only in the M2-type TAMs and then lysed by the TAMs to trigger their targeted eradication. Additionally, it is shown clinically that TAM can internalize bisphosphonates (BP), inducing apoptosis as well as function deficiencies, suppress tumor growth and extend survival in breast cancer.

5.4 Blocking the Immunosuppressive Function of TAM

ARG1 inhibitors replenish arginine in the TME and enhance CD8+ T cell responses. ARG1 inhibitors may also be applied in combination with immune checkpoint inhibitors (anti-PD-1 antibodies) to improve the antitumor efficacy synergistically. Preclinical data indicate that CB-1158 inhibits tumor growth in BC mouse models by itself and in combination with anti-PD-1 therapy. TAMs upregulated high levels of IDO, which catalyzes degradation of tryptophan, to kynurenine, which leads to tryptophan depletion and accumulation of toxic metabolites such as leading to T cell suppression. The IDO inhibitor epacadostat, which increases the levels of tryptophan and provides anti-suppressive activity restores T cell anti-tumor immunity. IDO inhibitors synergistically boost the antitumor activity of the anti-PD-1 antibodies. TAMs exhibit high expression of CD39 and CD73, exoenzymes that catalyze ATP to adenosine. Adenosine exerts T cell and NK cell suppression through A2A receptors [11]. Hence, people can inhibit adenosine production by modulating the adenosine metabolism pathways using anti- CD73 antibodies(oleclumab). Moreover, TAMs directly suppress T cells through the cell–cell contact and disrupting TAM-T cell interactions can block TAMs immunosuppressive effects. Anti-FasL antibodies antagonize TAM-mediated T cell apoptosis. Anti-B7-H4 antibodies rescue T cell functions.

6. Conclusion

As the most abundant immune cells within the TME, TAMs actively participate in key processes of BC, including its initiation, progression, metastasis, and response to treatment. TAMs differentiated from tissue-resident embryonic macrophages or from circulating monocytes, have plastic pro-inflammation M1 and immunosuppressive M2 phenotypes. In advanced BC M2-polarized TAMs are dominant.TAMs fuel angiogenesis in TME and metastasis of cancer cell. And progress tumor malignancy based on multi-dimensional mechanisms. TAMs mediating immune escape and cancer drug resistance by secreting anti-immune effectors (i.e. IL-10, TGF-β), disrupting the antigen presentation, remodeling their polarization phenotype, and interacting with cancer stem cells.TAM-targeted treatment is a highly promising future- direction for BC therapy. The focus of the existing dominant strategy is on depletion and/or blocking the TAM recruitment to tumours, the induction of TAM repolarization to M1 phenotype, clearance of the already resident TAM and establishment of the immunosuppression.As mentioned above, future TAM-targeting therapy will certainly attach more importance to a multi-agent approach by the combined use of chemotherapy, radiation therapy, and targeted therapy, especially the immune checkpoint inhibitors, such as, PD-1/PD-L1 antibody, instead of single-agent therapy. Multidimensional restoration of immunosuppressive tumor microenvironment, reversal of T-cell exhaustion and synergy of a powerful antitumor effect.Therefore, along with the antitumor immunity therapy, targeting TAMs to BC patients, especially the BC patients suffering from refractory subtypes such as TNBC, it will be more encouraging for a better and more lasting therapy to help BC patients extending long-term survival in the future.

References

[1] Huang, X., Cao, J., & Zu, X. (2022). Tumor-associated macrophages: An important player in breast cancer progression. Thoracic cancer, 13(3), 269–276. https://doi.org/10.1111/1759-7714.14268

[2] Yang, Y., Li, S., To, K. K. W., Zhu, S., Wang, F., & Fu, L. (2025). Tumor-associated macrophages remodel the suppressive tumor immune microenvironment and targeted therapy for immunotherapy. Journal of Experimental & Clinical Cancer Research, 44(1), 145. https://doi.org/10.1186/s13046-025-03377-9

[3] Munir, M. T., Kay, M. K., Kang, M. H., Rahman, M. M., Al-Harrasi, A., Choudhury, M., Moustaid-Moussa, N., Hussain, F., & Rahman, S. M. (2021). Tumor-Associated Macrophages as Multifaceted Regulators of Breast Tumor Growth. International journal of molecular sciences, 22(12), 6526. https://doi.org/10.3390/ijms22126526

[4] Saeed, A. F. (2025). Tumor-Associated Macrophages: Polarization, Immunoregulation, and Immunotherapy. Cells, 14(10), 741. https://doi.org/10.3390/cells14100741

[5] Jin, H., Meng, X. Y., & Feng, J. W. (2025). Mechanisms of tumor-associated macrophages in breast cancer and treatment strategy. Frontiers in Immunology, 16, 1560393. https://doi.org/10.3389/fimmu.2025.1560393

[6] Binnewies, M., Roberts, E. W., Kersten, K., Chan, V., Fearon, D. F., Merad, M., Coussens, L. M., Gabrilovich, D. I., Ostrand-Rosenberg, S., Hedrick, C. C., Vonderheide, R. H., Pittet, M. J., Jain, R. K., Zou, W., Howcroft, T. K., Woodhouse, E. C., Weinberg, R. A., & Krummel, M. F. (2018). Understanding the tumor immune microenvironment (TIME) for effective therapy. Nature medicine, 24(5), 541–550. https://doi.org/10.1038/s41591-018-0014-x

[7] Ren, B., Cui, M., Yang, G., Wang, H., Feng, M., You, L., & Zhao, Y. (2018). Tumor microenvironment participates in metastasis of pancreatic cancer. Molecular cancer, 17(1), 108. https://doi.org/10.1186/s12943-018-0858-1

[8] Nagarsheth, N., Wicha, M. S., & Zou, W. (2017). Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. Nature reviews. Immunology, 17(9), 559–572. https://doi.org/10.1038/nri.2017.49

[9] DeNardo, D. G., & Ruffell, B. (2019). Macrophages as regulators of tumour immunity and immunotherapy. Nature reviews. Immunology, 19(6), 369–382. https://doi.org/10.1038/s41577-019-0127-6

[10] Kundu, M., Butti, R., Panda, V. K., Malhotra, D., Das, S., Mitra, T., Kapse, P., Gosavi, S. W., & Kundu, G. C. (2024). Modulation of the tumor microenvironment and mechanism of immunotherapy-based drug resistance in breast cancer. Molecular cancer, 23(1), 92. https://doi.org/10.1186/s12943-024-01990-4

[11] Rumney, R. M. H., Coffelt, S. B., Neale, T. A., Dhayade, S., Tozer, G. M., & Miller, G. (2017). PyMT-Maclow: A novel, inducible, murine model for determining the role of CD68 positive cells in breast tumor development. PloS one, 12(12), e0188591. https://doi.org/10.1371/journal.pone.0188591