ORIGINAL RESEARCH PAPER
Volume - 15 | Issue - 07 | July - 2026 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

TUMOR-ASSOCIATED MACROPHAGES IN BREAST CARCINOMA: CURRENT UNDERSTANDING, THERAPEUTIC IMPLICATIONS, AND FUTURE PERSPECTIVES

Pathology

Dr. Kavipriyaa P* Post Graduate*Corresponding Author
Dr. Ather fatima Professor
Dr Naval kishore bajaj HOD & Professor

ABSTRACT

Breast carcinoma remains the most commonly diagnosed malignancy among women worldwide and is a major cause of cancer-related mortality. While genetic alterations within tumor cells are critical for carcinogenesis, increasing evidence suggests that the tumor microenvironment (TME) plays a pivotal role in tumor progression, metastasis, and therapeutic response [1,2]. Among the various immune cell populations present in the TME, tumor-associated macrophages (TAMs) represent one of the most abundant and functionally significant components [3]. TAMs display remarkable phenotypic plasticity and are broadly categorized into classically activated M1 macrophages and alternatively activated M2 macrophages. M2-polarized macrophages, commonly identified by CD163 expression, contribute to angiogenesis, immune suppression, extracellular matrix remodeling, epithelial-mesenchymal transition, and metastatic dissemination [4,5]. Recent advances in single-cell transcriptomics, spatial transcriptomics, and multiplex immunohistochemistry have improved understanding of macrophage heterogeneity within breast tumors [6,7]. Furthermore, therapeutic strategies targeting TAM recruitment, polarization, and immune checkpoint interactions are emerging as promising approaches in breast cancer treatment [8]. This review summarizes the role of TAMs in breast carcinoma, their molecular mechanisms, clinical significance, recent research developments, therapeutic implications, and future prospects in precision oncology.

KEYWORDS

Breast Carcinoma, Tumor Microenvironment, Tumor-associated Macrophages, Cd163, Immunotherapy, Macrophage Polarization.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer among women and remains one of the leading causes of cancer-related deaths worldwide [1]. Despite significant advances in screening, molecular classification, targeted therapy, and immunotherapy, disease progression and metastasis continue to be major challenges in clinical management [2].

Traditionally, cancer research focused primarily on tumor cell-intrinsic genetic alterations. However, contemporary evidence indicates that cancer progression is strongly influenced by the surrounding tumor microenvironment (TME), a complex ecosystem composed of stromal cells, immune cells, blood vessels, extracellular matrix proteins, cytokines, and growth factors [3,4].

Among immune cells within the TME, tumor-associated macrophages (TAMs) are particularly important because of their ability to regulate multiple hallmarks of cancer simultaneously, including angiogenesis, immune evasion, invasion, metastasis, and therapeutic resistance [5]. Consequently, TAMs have emerged as attractive prognostic biomarkers and therapeutic targets in breast carcinoma [6].

TUMOR MICROENVIRONMENT IN BREAST CARCINOMA

The tumor microenvironment consists of both cellular and acellular components that interact dynamically with malignant cells to influence tumor behavior [3].

Cellular components include:

1. Cancer-associated fibroblasts
2. Endothelial cells
3. Pericytes
4. T lymphocytes
5. B lymphocytes
6. Natural killer cells
7. Dendritic cells
8. Myeloid-derived suppressor cells
9. Tumor-associated macrophages

The acellular compartment consists of extracellular matrix proteins, cytokines, chemokines, and growth factors [4].

The TME is now recognized as a major determinant of cancer progression. Chronic inflammation within the microenvironment promotes genomic instability, tumor proliferation, angiogenesis, and immune escape [7]. Continuous crosstalk between tumor cells and stromal elements creates a permissive niche for disease progression and metastatic dissemination [3,7].

TUMOR-ASSOCIATED MACROPHAGES IN BREAST CANCER

Macrophages originate from circulating monocytes recruited into tumor tissues through chemokines such as CCL2 and colony-stimulating factor-1 (CSF-1) [8]. Following recruitment, these cells undergo polarization in response to local environmental signals.

Classically activated M1 macrophages exhibit antitumor functions through production of pro-inflammatory cytokines, reactive oxygen species, and nitric oxide [9]. Conversely, M2 macrophages support tissue repair, angiogenesis, and immune suppression [9].

Most TAMs within breast carcinomas exhibit an M2-like phenotype characterized by expression of CD163, CD204, and CD206 [10]. CD163-positive macrophages have been associated with aggressive tumor behavior and unfavorable clinical outcomes in multiple studies [11].

MOLECULAR MECHANISMS OF TAM-MEDIATED TUMOR PROGRESSION

CSF1-CSF1R Pathway

The CSF1-CSF1R signaling axis regulates macrophage recruitment, survival, and differentiation. Overexpression of CSF1 by breast cancer cells promotes accumulation of TAMs and facilitates tumor progression [5,12].

CCL2-CCR2 Axis

CCL2 is a potent chemoattractant that recruits CCR2-positive monocytes into tumor tissues. Elevated CCL2 expression is associated with increased TAM infiltration and metastatic potential [13].

IL-6/STAT3 Signaling

IL-6-mediated activation of STAT3 promotes M2 polarization, angiogenesis, and immune suppression. Persistent activation of this pathway contributes to treatment resistance and poor prognosis [14].

TGF-β Signaling

Transforming growth factor-beta (TGF-β) promotes epithelial-mesenchymal transition (EMT), immune evasion, and metastatic dissemination [15].

VEGF-Mediated Angiogenesis

TAM-derived vascular endothelial growth factor (VEGF) stimulates neovascularization and supports tumor growth under hypoxic conditions [16].

PD-1/PD-L1 Immune Regulation

Emerging evidence suggests that TAMs contribute significantly to immune checkpoint-mediated suppression by expressing PD-L1 and modulating T-cell activity [17].

CLINICAL SIGNIFICANCE OF TUMOR-ASSOCIATED MACROPHAGES

Numerous studies have demonstrated that increased TAM infiltration is associated with poor clinical outcomes in breast carcinoma [11,18].

High densities of CD163-positive macrophages have been linked to:

1. Increased tumor aggressiveness
2. Enhanced angiogenesis
3. Higher metastatic potential
4. Reduced disease-free survival
5. Reduced overall survival [11,18]

Furthermore, TAM-rich tumors frequently exhibit resistance to chemotherapy, endocrine therapy, and immunotherapy, highlighting their role in treatment failure [19].

The prognostic significance of CD163-positive macrophages has generated interest in their potential use as biomarkers for risk stratification and therapeutic decision-making [10,18].

RECENT ADVANCES IN TAM RESEARCH

Recent technological innovations have transformed the understanding of TAM biology.

Single-Cell RNA Sequencing

Single-cell sequencing studies have revealed substantial heterogeneity among TAM populations, demonstrating that macrophages exist along a continuum of activation states rather than a strict M1/M2 dichotomy [6].

Spatial Transcriptomics

Spatial transcriptomic approaches have identified distinct macrophage populations localized at invasive fronts, metastatic niches, and immunosuppressive regions of breast tumors [7].

Multiplex Immunohistochemistry

Multiplex immunohistochemistry allows simultaneous evaluation of multiple immune markers and has improved characterization of macrophage subsets within the TME [20].

Artificial Intelligence and Digital Pathology

AI-assisted image analysis is increasingly being used to quantify immune infiltrates and predict clinical outcomes based on TME characteristics [20].

THERAPEUTIC IMPLICATIONS

Recognition of TAMs as central regulators of tumor progression has stimulated development of several therapeutic strategies [8].

TAM Depletion

CSF1R inhibitors reduce macrophage recruitment and survival within tumors and are currently being investigated in clinical trials [12].

Inhibition of Monocyte Recruitment

CCR2 antagonists aim to block monocyte migration into tumor tissues and reduce TAM accumulation [13].

Macrophage Reprogramming

Emerging therapies seek to convert M2 macrophages into tumoricidal M1 macrophages, thereby restoring antitumor immunity [8].

Combination Immunotherapy

Combining TAM-targeted therapies with PD-1/PD-L1 inhibitors may enhance immune responses and improve treatment efficacy [17].

Nanomedicine

Nanoparticle-based delivery systems targeting macrophages have shown promise in improving drug specificity while minimizing systemic toxicity [21].

FUTURE PERSPECTIVES

Future research should focus on comprehensive characterization of macrophage heterogeneity through integration of genomics, transcriptomics, proteomics, and spatial biology technologies [6,7]. Development of TAM-specific biomarkers may facilitate patient stratification and personalized treatment approaches. Additionally, combining TAM-targeted therapies with conventional chemotherapy, endocrine therapy, and immunotherapy may provide synergistic benefits [8].

The incorporation of artificial intelligence, digital pathology, and multi-omics analysis into routine clinical practice may further enhance understanding of macrophage dynamics and improve therapeutic decision-making [20].

CONCLUSION

Tumor-associated macrophages are among the most influential immune cell populations within the breast cancer microenvironment. Through regulation of immune suppression, angiogenesis, extracellular matrix remodeling, and metastatic progression, TAMs significantly contribute to breast cancer pathogenesis [5,8]. Recent advances in molecular profiling and immunotherapy have expanded understanding of TAM biology and highlighted their potential as prognostic biomarkers and therapeutic targets. Continued investigation into macrophage heterogeneity and TAM-targeted therapeutic strategies may contribute substantially to the development of precision medicine approaches in breast carcinoma.

REFERENCES

1. 1) Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020. CA Cancer J Clin. 2021;71(3):209-249.
2. 2) Harbeck N, Penault-Llorca F, Cortes J, et al. Breast cancer. Nat Rev Dis Primers. 2019;5:66.
3. 3) Hinshaw DC, Shevde LA. The tumor microenvironment innately modulates cancer progression. Cancer Res. 2019;79(18):4557-4566.
4. 4) Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nat Med. 2013;19(11):1423-1437.
5. 5) Mantovani A, Marchesi F, Malesci A, et al. Tumour-associated macrophages as treatment targets in oncology. Nat Rev Clin Oncol. 2017;14:399-416.
6. 6) Cassetta L, Pollard JW. Targeting macrophages: therapeutic approaches in cancer. Nat Rev Drug Discov. 2018;17(12):887-904.
7. 7) Noy R, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. Immunity. 2014;41(1):49-61.
8. 8) Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. Cell. 2010;141(1):39-51.
9. 9) Etzerodt A, Moestrup SK. CD163 and inflammation. Antioxid Redox Signal. 2013;18(17):2352-2363.
10. 10) Cassetta L, Kitamura T. Macrophage targeting in cancer therapy. Nat Rev Cancer. 2023;23(3):157-173.
11. 11) Cheng S, Li Z, Gao R, et al. Landscape of immune microenvironment in breast cancer. Cell Res. 2021;31:157-170.
12. 12) Wu SZ, Al-Eryani G, Roden DL, et al. A single-cell and spatially resolved atlas of human breast cancers. Cell. 2021;184:1845-1858.
13. 13) Mantovani A, Allavena P, Marchesi F, Garlanda C. Macrophages as tools and targets in cancer therapy. Nat Rev Clin Oncol. 2022;19:93-106.
14. 14) Guerriero JL. Macrophages: their untold story in T-cell activation and function. Trends Cancer. 2018;4(9):593-604.
15. 15) Binnewies M, Roberts EW, Kersten K, et al. Understanding the tumor immune microenvironment. Nat Med. 2018;24:541-550.