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Review

Role of Tumor-Associated Macrophages in Breast Cancer Immunotherapy

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Abstract

Breast cancer (BC) is the second leading cause of death among women worldwide. Immunotherapy has become an effective treatment for BC patients due to the rapid development of medical technology. Considerable breakthroughs have been made in research, marking the beginning of a new era in cancer treatment. Among them, various cancer immunotherapies such as immune checkpoint inhibitors (ICIs), cancer vaccines, and adoptive cell transfer are effective and have good prospects. The tumor microenvironment (TME) plays a crucial role in determining the outcomes of tumor immunotherapy. Tumor-associated macrophages (TAMs) are a key component of the TME, with an immunomodulatory effect closely related to the immune evasion of tumor cells, thereby affecting malignant progression. TAMs also significantly affect the therapeutic effect of ICIs (such as programmed death 1/programmed death ligand 1 (PD-1/PD-L1) inhibitors). TAMs are composed of multiple heterogeneous subpopulations, including M1 phenotypes macrophages (M1) and M2 phenotypes macrophages (M2). Furthermore, they mainly play an M2-like role and moderate a variety of harmful consequences such as angiogenesis, immunosuppression, and metastasis. Therefore, TAMs have become a key area of focus in the development of tumor therapies. However, several tumor immunotherapy studies demonstrated that ICIs are effective only in a small number of solid cancers, and tumor immunotherapy still faces relevant challenges in the treatment of solid tumors. This review explores the role of TAMs in BC immunotherapy, summarizing their involvement in BC development. It also explains the classification and functions of TAMs, outlines current tumor immunotherapy approaches and combination therapies, and discusses the challenges and potential strategies for TAMs in immuno-oncology treatments.

Keywords: tumor-associated macrophages; breast cancer; immunotherapy

1. Introduction

Breast cancer (BC) is the leading cause of cancer-related deaths among women worldwide [1]. The tumor microenvironment (TME) comprises cancer cells and host-derived normal cells, such as lymphocytes, fibroblasts, and macrophages [2]. Macrophages are involved in homeostasis, inflammation, and progression. Tumor-associated macrophages (TAMs) play a significant role in cancer progression [3] by facilitating tumor metastasis and contributing to poor clinical outcomes. High levels of TAMs in BC are considered a poor prognostic factor [4,5]. Increased infiltration of M2 phenotypes macrophages (M2) in BC is associated with shorter survival times, whereas higher infiltration of M1 phenotypes macrophages (M1) is linked to longer lifespans across various BC subtypes (Fig. 1). These findings imply that modifying the function of TAMs might offer a prospective target for BC therapy. Immunotherapy of BC has attracted much attention recently [6], particularly for systemic treatments that involve targeting programmed death ligand 1 (PD-L1) [7]. However, immune-based cancer treatment, particularly immune checkpoint inhibitors (ICIs) ((PD-1/PD-L1) inhibitors), is efficient in only a minority proportion of patients with solid cancers. Studies reported [8–10] that TAMs influence the care process of PD-1/PD-L1 inhibitors, thus limiting the effect of the current treatment strategies for advanced malignancies. Thus, targeting TAMs could be an emerging area of interest, as these strategies may synergize with existing immunotherapies.

Status of Immunotherapy for Breast Cancer

Globally, BC is the most commonly diagnosed female cancer and the leading cause of cancer-related deaths, accounting for 23% of all female cancers [11]. The treatment selected is contingent upon the disease's stage and includes surgery, radiation therapy, and chemotherapy. Chemotherapy is designed to target cancer cells that are rapidly dividing; however, its toxicity can also harm healthy cells, leading to unwanted side effects. Though hormone therapy is a widely used unspecific treatment for BC, its effectiveness is limited to tumors that are responsive to hormones, and it is associated with significant side effects [12]. Thus, researchers are exploring potential treatment strate-

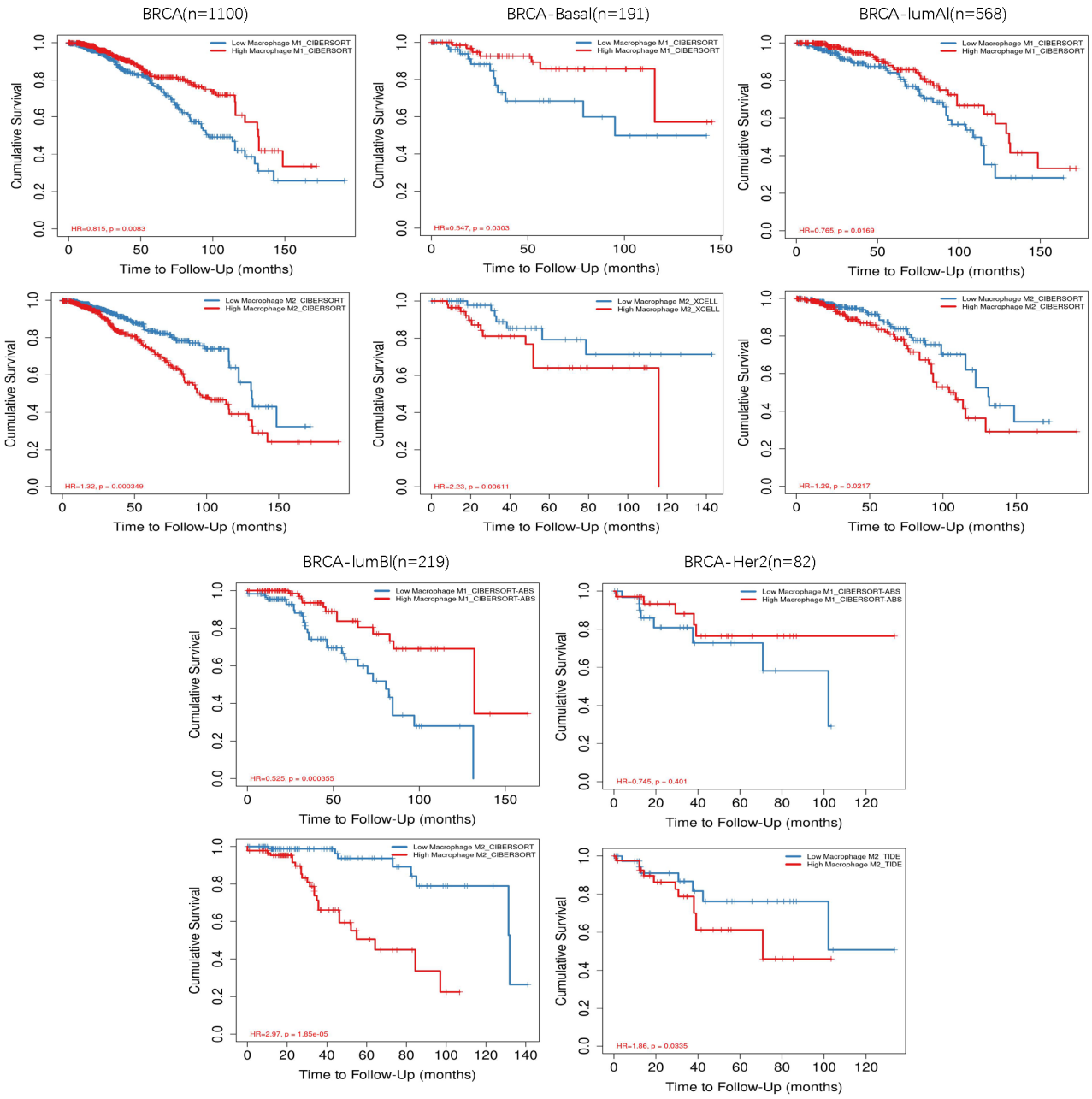

Fig. 1. M1 and M2 infiltration in breast cancer analyzed in the Timer 2.0 database. M1, M1 phenotypes macrophages; M2, M2 phenotypes macrophages; BRCA, breast cancer susceptibility gene; BRCA-basal, BRCA1-mutated basal-like breast cancer; BRCA lumB, BRCA1/2-mutated luminal B breast cancer; BRCA lumA, BRCA1/2-mutated luminal A breast cancer; BRCA HER2+, BRCA1/2-mutated HER2-positive breast cancer; HR, hazard ratio.

gies, including immunotherapy. Immunotherapy has been seen as a promising treatment method aimed at a specific protein found in cancer cells, holding great promise for the treatment of BC. Recent findings have uncovered the potential clinical efficacy of PD-1 and PD-L1 inhibitors in a subset of individuals with BC. For example, PD-L1 is the most commonly utilized biomarker for BC. In the phase II study (NCT02447003), monotherapy with pembrolizumab showed potential anti-tumor activity and a favorable safety profile in patients with PD-L1+ BC [13]. A phase III clinical trial (NCT02819518) revealed that the addition of pembrolizumab to conventional chemotherapy may enhance progression-free survival (PFS) in individuals with BC, as opposed to those who underwent chemotherapy alone [14]. Moreover, in the phase I trial (NCT01375842), atezolizumab as a single-agent treatment showed a tolerable safety profile and provided lasting therapeutic benefits for patients [15]. Atezolizumab combined with nab-paclitaxel

demonstrated an extension of recurrence-free survival in patients when compared to the subgroup treated solely with nab-paclitaxel in a phase III clinical trial (NCT02425891) [16]. The effects of atezolizumab and pembrolizumab are long-lasting in patients with BC, indicating that these therapies may improve the quality of life for those who respond positively. Antibodies targeting PD-1, including cemiplimab and nivolumab; those targeting PD-L1, including avelumab and durvalumab; and those targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), including tremelimumab and ipilimumab, have shown promise in therapy and have been cleared for treating a range of cancers, encompassing solid tumors. While ICIs like PD-1 and PD-L1 blockers are commonly used in clinical settings [17], there are also emerging therapies aimed at novel targets such as LAG3, TIM3, and ICOS that are in the developmental phase [18], which are suppressive receptors that negatively regulate T cell function and suppress immune cells, thereby promoting tumor escape immune surveillance; Challenges for effective use of ICIs persist such as the identification of definitive biomarkers and effective combinatorial strategies, inherent or acquired resistance to ICIs and some therapeutic side effects [19]. Given the remarkable clinical success of ICIs in many solid tumors, immunotherapy has become a new therapeutic approach and one of the significant landmarks in modern cancer research. In addition, ICIs synergized with chemotherapy have shown notable effectiveness in both early-stage as well as metastatic breast cancer (mBC), which has sparked interest in immune-based BC treatment and prevention strategies.

2. TAM Classification and Function

2.1 Classification

Under the guidance of chemokine ligand 2 (CCL2), chemokine ligand 18 (CCL18), chemokine ligand 20 (CCL20), colony-stimulating factor-1 (CSF-1), and vascular endothelial growth factor (VEGF)—cytokines and growth factors—monocytes from the blood convert into macrophages. A variety of factors alter the phenotypes and functions of macrophages. Lipopolysaccharide (LPS), tumor necrosis factor alpha (TNF-α), and interferon-gamma (IFN-γ) induce macrophages to develop into the pro-inflammatory M1 phenotype macrophage (main markers—human leukocyte antigen DR (HLA-DR) and cluster of differentiation 80 (CD80)/cluster of differentiation 86 (CD86), while interleukin-4 (IL-4), interleukin-10 (IL-10), and interleukin-13 (IL-13) drive their evolvement into M2 phenotype macrophage (main markers—macrophage mannose receptor 1 (CD206), cluster of differentiation 163 (CD163), cluster of differentiation 204 (CD204), and stabilin-1), also known as TAMs [20]. TAMs both eliminate tumor cells and promote tumor development (Fig. 2). M1 macrophages are widely regarded as tumor-killing cells capable of phagocytosis because they primarily possess anti-tumor and immune-promoting properties upon activation. They generate cytokines with pro-inflammatory effects, including interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-12 (IL-12) [21]. Their primary function is to capture external substances like apoptotic cellular fragments, thereby preserving organ and tissue integrity from external threats. They exert direct cytotoxic effects to eliminate tumor cells. This cytotoxicity involves multiple mechanisms, making it a gradual process that typically takes 24–72 h. An example of this is the release of tumoricidal molecules by macrophages, including reactive oxygen species (ROS) and nitric oxide (NO) [22].

In contrast, M2 macrophages, similar to TAMs in phenotype, facilitate cancer progression and metastasis and correlate with an adverse prognosis [20]. They contribute to the promotion of cancerous expansion, invasion, metastasis, and angiogenesis through the secretion of cytokines and growth factors. Moreover, M2 macrophages secrete immunosuppressive cytokines that suppress the action and metabolic activity of T cells [23]. They suppress T helper 1 cell (Th1) immunity, which is fundamental for healing injured tissues, thereby accelerating cancerous spread and neovascularization [24]. Furthermore, TAMs directly impede the expansion of CD8+ T cells by metabolizing L-arginine through arginase 1 (ARG-1), nitric oxide synthase 2 (Nos2), oxidative free radicals, or nitrogen-based compounds. They also lure Tregs with chemokine ligand 22 (CCL22), further restricting T cell tumor-inhibiting actions [25,26].

2.2 Function of TAMs in Breast Cancer

This section primarily depicts the features and functions of the M1 and M2 states in BC, to inspire tactics to hinder the M2 macrophage polarization and amplify the benefits of immunotherapy (Fig. 2).

2.2.1 Angiogenesis

The TME is an acidic anoxic environment [27]. Angiogenesis is vital to supply oxygen and nutrients to the tumor, and TAMs are involved in this process in many types of malignancies, such as ovarian carcinoma, melanoma, and BC [28]. TAMs sense intratumor hypoxia and react with vascular endothelial growth factor-alpha (VEGF-α), resulting in an upregulated matrix metalloproteinase 9 (MMP9) level in TAMs. MMP9 mediates the release of bioactive VEGF-α from cells and promotes intra-tumoral angiogenesis [29]. Furthermore, TAMs drive an anoxic environment through poor angiogenesis. TAMs secrete abnormal pro-angiogenic factors, including Ets transcription factors (ETs), angiopoietin-2 (Ang2), chemokine ligand 12 (CXCL12), and epithelial membrane antigen 2 (EMA-II), leading to leakage of the blood vessels and insufficient oxygen supply to cells, which in turn impacts TAMs that continue to secrete cytokines and drive TAM polarization, forming a vicious cycle [30]. In addition, M2-like

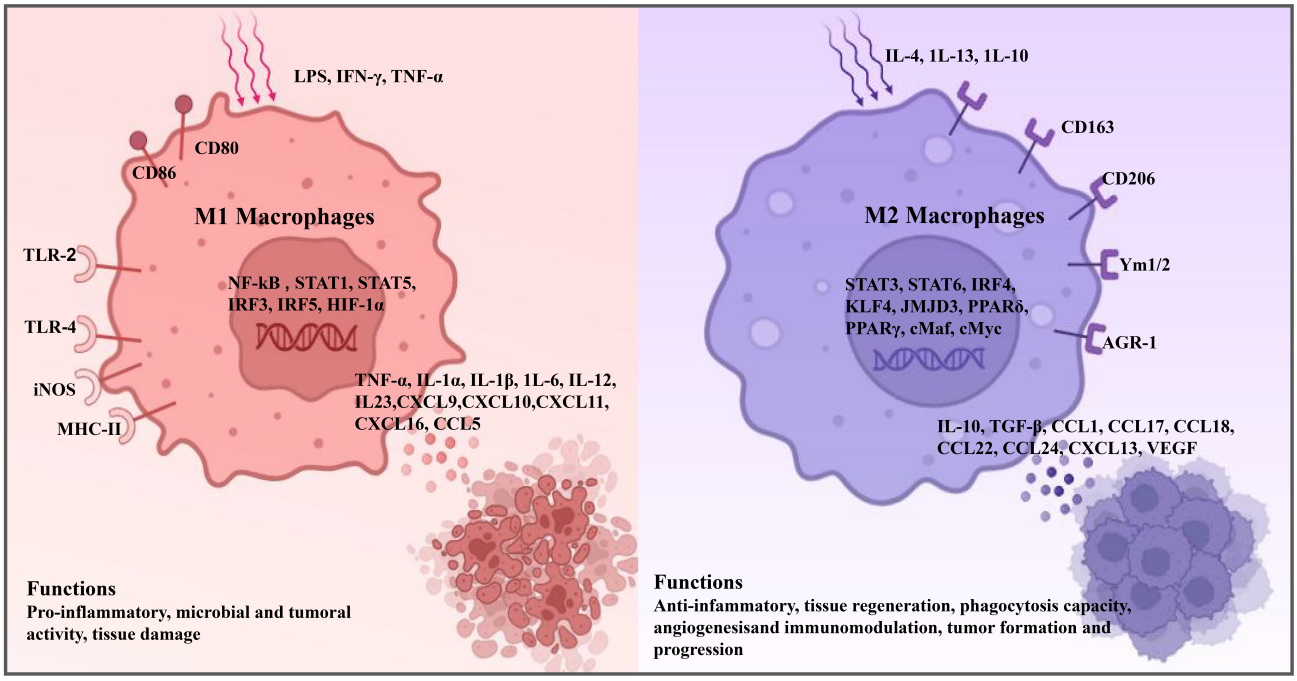

Fig. 2. TAM subtype: function of M1 and M2 macrophages. TAM, tumor-associated macrophage; LPS, lipopolysaccharide; IFN-γ, interferon-gamma; TNF-α, tumor necrosis factor alpha; CD80/86, cluster of differentiation 80/86; NK-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; STAT, signal transducer and activator of transcript; IRF3, interferon regulatory factor 3; HIF-1α, hypoxia-inducible factor 1-alpha; TLR, toll-like receptor; iNOS, nitric oxide synthase 2, called NOS2; MHC-II, major histocompatibility complex class II; IL, interleukin; CXCL, C-X-C motif chemokine ligand; CCL, C-C motif chemokine ligand; Ym1/2, chitinase-like protein Ym1/2; AGR-1, arginase 1; TGF-β, transforming growth factor-beta; VEGF, vascular endothelial growth factor; KLF, Kruppel-like factor; JMJD3, Jumonji domain containing 3; PPAR, peroxisome proliferator-activated receptor; cMaf, proto-oncogene c-Maf; cMyc, v-Myc myelocytomatosis viral oncogene homolog. Created with Biorender.

macrophages promote angiogenesis by closely binding to endothelial cells in the TME. Transforming growth factor beta (TGF-β) overexpression is present in the majority of epithelial tumors and is expressed by the M2-TAM phenotype, and induces epithelial-stromal transformation and promotes invasion and metastasis [24]. CSF-1 overexpression elevates the recruitment of TAMs, while the knockdown of CSF-1R by short-interfering RNA (siRNA) reduces vascularization and infiltration of macrophages *in vivo* [31]. Meanwhile, interleukin-8 (IL-8) is assumed to be a macrophage-derived mediator of angiogenesis [32]. The IL-8 signaling pathway stimulates blood vessel formation in endothelial cells, enhances the growth and survival of both endothelial and cancer cells, and strengthens the movement of cancer cells, endothelial cells, and neutrophils that have entered the tumor. Blocking the IL-8 signaling effects could be a crucial therapeutic strategy for targeting TAMs [33]. Angiogenesis allows the metastasis of cancer cells to other organs, resulting in poor treatment effects and reduced survival rates. Therefore, understanding the effect of TAMs on this process can help achieve a better therapeutic effect by targeting TAMs.

2.2.2 Immune Suppression

TAMs promote immunosuppressive changes by secreting immune-modulating anti-inflammatory factors, including TGF-β and IL-10, thereby inhibiting the cytotoxic functions of effector T cells and natural killer (NK) cells. A combined treatment approach using a TGF-β blocker (1D11 and galunisertib) along with anti-PD-1/PD-L1 leads to a rise in immune response, reviving the cytotoxic function of T cells and the cancer-inhibiting power of anti-PD-L1 [34,35]. Additionally, when tranilast, a TGF-β inhibitor, is combined with Doxil nanomedicine as part of a comprehensive treatment plan, it increases the presence of M1 macrophages in the malignancy, enhancing the impact of anti-PD-1 [36]. TAMs in mouse models release IL-10, which simultaneously inhibits CD8+ T cell responses and the dendritic cell production of IL-12. In addition to secreting cytokines, surface ligands of TAMs such as PD-L1, B7-H4, and CTLA-4 also inhibit T cell activity and recruitment of Tregs. B7-H4+ TAMs hinder the growth of CD4+ T cells and the secretion of IFN, which results in increased immune evasion and suppression [37]. Apart from these functions, TAMs directly prevent the expansion of CD8+ T cells by releasing ARG-1. Besides, TAMs attract Tregs via CCL22, further suppressing the T cell-mediated immune re-

action against tumors [25]. In short, TAMs release factors that weaken the killing capability for tumor cell lethality, contributing to immunosuppression and the promotion of tumor growth.

2.2.3 Resistance to Therapy

The presence of a macrophage population with a predominance of the M2 phenotype often leads to treatment resistance. According to Yang *et al*. [38], TAMs release IL-10, leading to hyperexpression of B-cell lymphoma 2 (BCL-2) and signal transducer and activator of transcript-3 (STAT3), which in turn triggers the IL-10/STAT3/BCL2 pathway in BC cells and boosts therapeutic barriers. TAMs are correlated with resistance to tamoxifen in postmenopausal women with BC, and they prevent the enlistment of CD8+ cytotoxic T cells, leading to the evolution of multidrug resistance [39]. M2 TAMs are more resistant to radiation therapy than M1 macrophages, yielding a challenge in the treatment of cancer.

The lack of response to PD-1/PD-L1 blockade treatment is partly due to the presence of TAMs. Monoclonal antibodies that target checkpoint ligands can be captured by TAMs due to the expression of these ligands on TAMs, such as PD-L1/2. This interaction can render the antibodies ineffective [40]. Paclitaxel or carboplatin treatment is counteracted by an increased IL-10 secretion by TAMs, leading to diminished IL-12 in DCs and an interruption of CD8+ T cell tumor-inhibiting capacity [41]. Understanding the resistance mechanisms of TAMs to therapy is crucial for crafting treatment approaches to overcome those problems and augment medical treatment potency without the risk of recurrence.

2.2.4 Tumor Metastasis and Proliferation

Epithelial cell mesenchymal transition (EMT) enables the transition of cancer cells from the primary site by entering the bloodstream and infiltrating other parts of the body, eventually developing tumor metastasis. M2 TAMs are involved in EMT during the development of cancer. They promote the EMT process through multiple pathways, for example, toll-like receptor 4 (TLR4) and IL-10 pathway, TGF-β/Smad family member 2 (Smad2) pathway, and microRNA 30a (miR-30a)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB)/Snail family transcriptional repressor 1 (Snail) signaling pathway [42]. Furthermore, an abundance of the M2 marker CD68 correlates with a reduction in the generation of E-cadherin, which typically prevents EMT and the spread of cancer cells [43]. TAM is constantly being recruited and differentiated while E-cadherin decreases continuously, forming a vicious cycle in the TME.

On the other hand, M2 macrophages release components that directly affect the expansion of malignant cells, like TGF-β and epidermal growth factor (EGF). TGF-β, which is typically engaged in the acceleration of cellular growth, is often overexpressed in cancer and associated with greater disease severity and unfavorable survival results. Furthermore, TGF-β plays additional roles in stimulating the growth of new blood vessels and suppressing the immune system, which helps tumors evade immune destruction and spread [34,44]. EGF receptor (EGFR) is excessive in malignant growths, leading to an increase in cell proliferation, angiogenesis, metastasis, and inhibition of apoptosis. Hagemann *et al*. [45] demonstrated that when tumor cells and macrophages are cultured together, there is an increase in the generation of MMP2 and MMP9, leading to the breakdown of extracellular matrix proteins and the enhancement of metastatic potential [46]. Metastasis-related macrophages in BC stimulate the production of CCL3 by secreting the CCL2 receptor (CCR2), which promotes lung metastasis [47]. Together, these functions offer new ideas for cancer treatment.

2.3 Development of TAMs in Breast Cancer

Macrophages play a key role in shaping tumor immunity, constituting over half of the solid tumor's mass and representing the predominant immune cell type infiltrating these tumors [48]. Meanwhile, exhaustion of T cells significantly hinders the immune response to tumors. This report demonstrated that the *in vivo* removal of TAMs alleviates the exhaustion programs of intratumoral CD8+ T cells [49]. Reciprocally, the exhaustion programs of T cells release signals that actively draw monocytes into the TME and influences their differentiation toward M2 macrophages to inhibit the TME. Therefore, blocking TAM polarization and relieving immunosuppression may be a future research direction in cancer therapy. CD8+ T cells act as suppressors of tumor growth, engaging with cancerous cells and triggering their destruction by initiating internal signaling pathways within the context of tumor immunity. In the TME, "immune exclusion" impedes cancer immunotherapy by preventing CD8+ T cells from accessing the area around tumor cells and suppressing their immune functions [50]. This leads to a scarcity of CD8+ T cells within the TME and allows tumor cells to evade immune detection [51–53]. Li *et al*. [54] demonstrated that membrane spanning 4-domains A4A (MS4A4A) blockade treatment on TAM reshapes the immune TME, to decrease the presence of M2-TAMs while enhancing the infiltration of active CD8+ T cells. The generation of PD-L1 on macrophages promotes breast tumor immune evasion. Fang and colleagues [55] found that the production of M2 markers and PD-L1 was raised in macrophages after the treatment with progranulin. However, the account of immune cells in progranulin–/– BC tissue were upregulated, and the infiltration of CD8+ T cells was also elevated. Furthermore, TAMs release anti-inflammatory cytokines such as TGF-β and IL-10, display immune checkpoint molecules such as PD-L1, and deprive cytotoxic CD8+ T cells of crucial amino acids by expressing arginase, thereby starving them. Additionally, TAMs at-

tract Tregs, which leads to the suppression of tumor immunity [56]. Tregs inhibited the release of interferon-gamma (IFN-γ) by CD8+ T cells, which, if not suppressed, would prevent the activation of sterol regulatory element-binding protein 1 (*SREBP1*) that drives fatty acid synthesis in M2 TAMs [57]. The level of PD-1 in TAMs is also linked to phagocytosis negatively against allogenic material [58]. Thus, a therapy targeting macrophages is a promising approach.

2.4 Status of Immunotherapy Targeting TAMs in Breast Cancer

Until recently, cancer prevention and intervention measures have primarily centered on factors intrinsic to cancer cells. However, recent research is increasingly focused on targeting various active immune cells like macrophages and neutrophils. Among the various cell types in BC, macrophages are considered the most critical, constituting more than half of the tumor's volume in many malignancies. Their anti-tumor activities include direct cytotoxicity toward cancer cells and the presentation of tumor antigens to cytotoxic T cells. TAMs also boost tumor development directly and/or indirectly by stimulating tumor angiogenesis and metastasis.

Immunotherapy strategies targeting the immune system are promising for BC treatment, even though BC is not generally considered highly responsive to immune-based interventions. Currently, a range of cancer immunotherapy approaches are being developed to target TAMs. Most research methods fall into four categories: The initial method aims to block TAMs from accumulating at the tumor's location. Pharmaceuticals, including carlumab [59], Bindarit [60], and thalidomide [61], prevent monocytes from being drawn to the tumor, halting their development into TAMs and their contribution to cancerous development. Trabectedin [62] also hamper carcinoma development by either destroying TAMs or lowering their survival rates through a range of mechanisms. To impede TAM-driven tumorigenesis, one can also aim to decrease the differentiation and polarization of macrophages. Compounds such as LPS and TLR agonists [63] can invert the differentiation of macrophages, steering them to resort to the M1 state that is adverse to tumors, while triterpenoid compounds [64] can prevent the early polarization of M1 into the M2 state. In conclusion, blocking the growth of new blood vessels is another potential method to address tumor progression. Combining anti-VEGF antibodies with treatments such as Avastin, bevacizumab [65], or other neutralizing antibodies makes it possible to inhibit the transition of macrophages into the tumor area and the formation of new blood vessels that tumors require. For example, TAMs in solid tumors regulate the angiogenesis process; therefore, their elimination by the medication clodronate [66] leads to a slump in the density of blood vessels within the tumor [67]. Additionally, elevated levels of CSF-1 recruit more TAMs. However, silencing the CSF-1 receptor (CSF-1R) using siRNA reduces angiogenesis and inhibits macrophage migration [68] (Table 1, Ref. [59–66]). However, the immune response varies according to the BC subtype, and not all patients may experience beneficial effects from the same immunotherapeutic strategy. Thus, new therapeutic strategies to inhibit tumor growth are needed, including anti-tumor vaccine, combined immunotherapy, and nano immunotherapy to enhance anti-cancer effects. This review mainly focuses on the role of TAMs in the development of BC, the challenges and coping strategies faced in tumor immunotherapy, and summarizes the current methods of tumor immunotherapy and combined therapy in detail.

3. Advancements in Immunotherapy for Breast Cancer

3.1 Immunotherapy for TNBC

Triple-negative breast cancer (TNBC) is a subtype of BC characterized by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression on the cancer cells. This subtype is the most invasive form of BC with the poorest prognosis [69]. Among the infiltrating immune cells, TAMs constitute the main fraction of the TME. Thus, treatments that target TAMs hold great promise as therapeutic strategies for TNBC. Not only does blocking the macrophage colony-stimulating factor (M-CSF)/CSF-1R signaling pathway reduce tumor growth in BC xenograft models [70], but CSF-1R blockade augments the movement and penetration of CD8+ T cells into tumors [71–74]. Furthermore, when in combination with anti-PD-1 treatment, it further promotes the buildup of CD8+ T cells around cancer cells and reducing tumor growth [53]. Another study indicated that a combination of CSF-1R inhibitor and an activated anti-CD40 antibody increases M2 to M1, inhibits the conversion of the G2/M cell cycle phase in cancer cells, promotes the production of TNF-α and reduces the capacity of malignant cells to survive [75]. In addition, CD24 expression is significantly higher in TNBC than ER+PR+ BC. In the BC tumor milieu, CD24 evades TAM-mediated killing by acting as an anti-phagocytic signal in breast and ovarian cancer [76]. One study also reported that many carcinomas upregulate CD24 and that TAMs exhibit elevated expression of sialic-acid-binding immunoglobulin-like lectin10 (Siglec-10) [77]. Moreover, it demonstrates a role for tumor-expressing CD24 in promoting immune evasion through its interaction with the inhibitory receptor siglec-10, which is expressed by TAMs. Therapeutic inhibition of CD24 results in a macrophage-dependent reduction of tumor growth *in vivo*. Recent research reports [78] that CD47 is widely expressed in TNBC, especially TAMs. There is a highly efficient treatment approach through the integration of CD47 blockade with cabazitaxel therapy, promoting the systematic removal of TNBC cells and impeding tumor development and its metastatic poten-

Table 1. Anti-tumor effects of drugs associated with TAMs.

Drug	Type	Adverse drug reactions and toxicity	Anti-tumor function	Reference
Carlumab	Human immunoglobulin G1 kappa monoclonal antibody with high binding affinity and specificity for CCL2	Shown to possess a favorable safety profile in previous phase 1 and phase 2 clinical studies when administered at up to 15 mg/kg	By binding with CCL2, the content of serum is reduced, thereby reducing the infiltration of CD68+ macrophages/monocytes in tumor tissues, thus slowing tumor growth and angiogenesis	[59]
Bindarit	Selective inhibitor of monocyte chemotactic protein with anti-inflammatory activity	Its safety and efficacy have been verified by phase II clinical trials in patients with lupus nephritis and coronary stent restenosis	Inhibits macrophage infiltration and activation	[60]
Thalidomide	Immunosuppressor	Severe teratogenicity in the infant	Immunomodulatory and anti-inflammatory effects. Inhibition of angiogenesis and anti-tumor effects: cytokines, such as VEGF and fibroblast factor, are angiogenesis stimulants, which bind to specific receptors to stimulate signal transduction and cause endothelial cell proliferation	[61]
Trabectedin	Tetrahydroisoquinoline alkaloid	Manifested as nausea, constipation, fatigue, vomiting, and headaches, yet in some cases, they can escalate to severe complications like cardiomyopathy, anaphylaxis, neutropenia progressing to sepsis, rhabdomyolysis, or tissue necrosis due to extravasation	Inhibits pro-inflammatory mediators produced by monocytes, macrophages and TAMs, such as CXCL8 and IL-6. In addition, trabectedin directly targets endothelial cells to upregulate metalloproteinase-tissue inhibitor-1, metalloproteinase-tissue inhibitor-2, and thrombin sensitive protein-1, and exerts antiangiogenic activity in myxoid lipoma coma	[62]
LPS	TLR agonists	No toxic, non-specific immunogen	Interacting with TLR4 to form LPS signaling complexes leads to the synthesis of pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, promoting macrophage aggregation and polarization towards the M1 state	[63]
Corosolic acid (CA) and oleanolic acid (OA)	Triterpenoid compounds	No cytotoxicity	Inhibited macrophage polarization to M2 phenotype by suppressing STAT3 activation	[64]
Avastin	Anti-VEGF antibodies	Anemia, pain, abdominal pain, headache, high blood pressure, diarrhea, nausea, vomiting, loss of appetite	Inhibit tumor angiogenesis by specifically binding and blocking VEGF, thereby inhibiting tumor growth and spread	[65]
Bevacizumab	Anti-VEGF antibodies	Gastrointestinal perforation, bleeding, arterial thromboembolism	Binds specifically to VEGF-A and prevents its interaction with VEGFR, thereby inhibiting endothelial cell proliferation, activating survival pathways, and the formation of new blood vessels and angiogenesis	[65]
Clodronate	Bisphosphonate drugs	Well tolerated orally, and the main side effects are lower digestive tract symptoms such as diarrhea	An effective macrophage removal tool that can remove macrophages from different tissue sites and blood in animals. It uses the macrophage endocytosis mechanism to bring clodronate into the cell, release and accumulate in the cell under the action of macrophage lysosomal phosphatase, and induce apoptosis of macrophages	[66]

CCL2, C-C motif chemokine ligand 2; TAM, tumor-associated macrophages; CXCL8, C-X-C motif chemokine ligand 8; IL-6, interleukin-6; LPS, lipopolysaccharide; TLR, toll-like receptor; TNF-α, tumor necrosis factor-alpha; VEGFR, vascular endothelial growth factor receptor; STAT3, signal transducer and activator of transcription 3.

tial in preclinical models [78]. Furthermore, the combination of anti-PD-L1 antibodies suppresses BC metastasis, increasing granzyme B (GZMB) and IFN-γ in CD8+ T cells while decreasing lymphocyte-activation gene 3 (LAG3 or CD223), CTLA-4, and T cell immunoglobulin mucin-3 (TIM-3) in CD8+ T cells [79].

In addition to the above treatment methods, several other effective methods exist. Phosphoglycerate mutase 1 (PGAM1) plays a pivotal role in the metabolic pathways of cancer, exhibiting highly abundant expression in TNBC and is correlated with an unfavorable prognosis. Inhibition of *PGAM1* works synergistically with anti-PD-1 immunotherapy, markedly reshaping the TME. This results in an elevation of immune effector subsets like CD8+ T cell and M1 and a downsize in the infiltration of suppressive immune cells, such as myeloid-derived suppressor cells, M2 macrophages, and Tregs [80]. Moreover, high-mobility group box 1 (HMGB1) is a dynamic redox-actuated protein involved in an array of intracellular activities (e.g., chromosomal architecture reorganization, DNA transcription, and autophagic processes) and extracellular processes (e.g., autoimmune inflammation and immune dysregulation). HMGB1 inhibition leads to a drastic reduction in myeloid-derived suppressor cell (MDSC) and Tregs, an elevated proportion of M1 relative to M2, along with heightened stimulation of DCs and pDCs and an improvement in the success rate of monotherapies using anti-PD-1 in cancer care [81]. Elevated levels of RNA binding motif single stranded interacting protein 1 (RBMS1) in BC are directly linked to higher PD-L1 expression. The absence of RBMS1 leads to the destabilization of beta-1,4-galactosyltransferase 1 (B4GALT1) transcript, preventing the glycosylation of PD-L1, enhancing its ubiquitination, and targeting it for degradation. When combined with CTLA-4 ICIs or chimeric antigen receptor T-cell immunotherapy (CAR-T) therapy, the loss of RBMS1 boosts anti-tumor T cell responses both *in vitro* and *in vivo* [82]. High long noncoding RNA NR_109 (lncRNA NR_109) expression is present in M2. NR_109 knockdown inhibits polarization of M2 and their activity in supporting the expansion and invasiveness of malignant cells both *in vitro* and *in vivo* [83]. The presence of T cell malignancy 1 (MCT-1) is an innovative predictor of disease progression in individuals with invasive BCs. Oncogenic MCT-1 activation promotes mammary tumor progression and increases M2 TAMs. In contrast, MCT-1 knockdown decreases M2 macrophages and increases tumor-suppressive M1 macrophages [42]. Overall, there are many targets that can regulate TAMs to control tumor progression.

Immunotherapy for BC has its limitations due to low tumor immunogenicity and an immunosuppressive TME. In recent years, researchers have integrated material science, chemistry, and medicine to obtain nanomedicine, which represents an emerging strategy for BC treatment. Nanocarriers transport chemotherapeutic drugs and natural substances, enhancing their lethal effect on BC cells and circumventing the onset of drug resistance [84]. One study introduces a lymphatic tumor homing peptide-1 (LyP-1) and chondroitin sulfate (CS) dual-modified liposome co-loaded with paclitaxel and cryptotanshinone, named CS/LyP-1-PC Lip, designed to bolster chemoimmunotherapy effects in TNBC through triggering immunogenic cell demise and suppressing signal transducer and activator of transcription 3 (STAT3) signaling [85]. This study offers a feasible combination regimen for the development of TNBC chemoimmunotherapy. Another study showed that Rhodiola rosea polysaccharide-based nanoparticles loaded with doxorubicin boost chemoimmunotherapy for TNBC by re-educating TAMs [86]. Combined with immunomodulatory drugs, these nanoparticles activate immune cells to achieve better therapeutic results. Recently, a study reported that these PD-L1-loading microparticles alleviated the suppressed state of the immune microenvironment, eventually impairing the TNBC progression due to boosting the activation and function of CD8+ T cells [87]. Others mediate the transformation of macrophages toward M1 through the interruption of the TANK-binding kinase 1/signal transducer and activator of transcription 6 (TBK1/STAT6) pathway and activity of the protein kinase B/ mammalian target of rapamycin (AKT/mTOR) pathway. Chen *et al*. [88] designed FA-CD@PP-CpG (FA-CuS/DTX@PEI-PpIXCpG) for synergistic phototherapy (including photodynamic and photothermal therapy) and docetaxel-enhanced immunotherapy. Moreover, loaded docetaxel in FA-CD@PP-CpG promotes the infiltration of cytotoxic T-lymphocytes (CTLs), improves the efficacy of anti-PD-L1 antibody, suppresses MDSCs, and competently polarizes them toward the M1 state, thereby reducing tumor burden and further enhancing the anti-tumor efficacy. In addition, the combination of chemotherapy with atezolizumab efficiently abrogates the state of immunosuppression, providing new insights into clinical TNBC immunotherapy [87].

3.2 Immunotherapy for HER2+ Breast Cancer

The hyperexpression of HER2, which occurs in about 15–20% of BC instances, is linked to an unfavorable prognosis and reduced PFS and overall survival (OS). Over the past few decades, HER2-targeting monoclonal antibodies and 3 inhibitors with CAR-T cells. The elimination of (TKI) have been part of the diverse treatment strategies for HER2+ BC. Not to mention, patients who undergo disease progression following multiple HER2-directed therapies frequently face a limited array of additional treatment choices [82,89]. Considering TAM's role, the selective targeting of TAMs could be a strategy to regulate the TME.

Tucatinib significantly inhibits tumor growth and increases the number of CD8+/PD-1+ and CD8+/TIM3+ T cells, CD49+ NK cells, monocytes, and DCs and macrophages, while decreases myeloid-derived suppressor

cells. Additionally, tucatinib effectively manages the TME, which is a significant aspect of its therapeutic impact on BC. Multitherapy with anti-PD-L1 or anti-PD-1 showed strengthened effectiveness in HER2+ patients [90]. Additionally, VEGF and placental growth factors are abundantly expressed in BC cells and M2 in the tissues, mediating tumor progression and immunosuppression. The study reported the application of VEGF siRNA and placental growth factor siRNA to both M2 and BC cells for successful anti-tumor immunotherapy [91]. Given that elevated sphingosine 1-phosphate receptor 3 (S1PR3) expression is linked to resistance to PD-1-based immunotherapy and higher levels of T cell exhaustion, employing an S1PR3 antagonist can boost the oncostatic efficacy of CAR-T cell therapy. This is achieved by curbing T cell exhaustion and reshaping the TME, which involves attracting pro-inflammatory macrophages [92]. The case further justifies the combination of S1PR3 inhibitors with CAR-T cells. The elimination of proline-rich tyrosine kinase 2 ch1 signaling and hinders CCL2 production by BC cells but co (PYK2) decreases the penetration of TAMs and simultaneously prevents angiogenesis and tumor growth. Specifically, PYK2 ablation not only hampers Notch1 signaling and hinders CCL2 production by BC cells but concurrently curbs the generation of chemokine receptor 2 (CCR2), chemokine receptor 4 (CXCR4), and interleukin-4 receptor subunit alpha (IL-4Rα), as well as signal transducer and activator of transcription 6 (Stat6) activation in macrophages [93]. Tumor-derived granulocyte-macrophage colony-stimulating factor (GM-CSF) is a crucial regulator of Arg-1 expression in myeloid cells and local immune suppression in BC. Consequently, blocking GM-CSF produced by tumors can boost the effectiveness of T-cell receptor-gene engineered T cells (TCR-T) therapy and ICIs [94]. Additionally, CKLF like MARVEL transmembrane domain-containing 6 (CMTM6) is a new immune checkpoint for tumor-induced immunosuppression. Individuals with HER2+ BC who exhibit high levels of CMTM6 tend to have poorer OS and PFS compared to those with lower CMTM6 levels. Suppressing CMTM6 also impedes the growth and movement of HER2+ BC cells and encourages self-destruction [95]. Moreover, the combination therapy with disitamab vedotin and zimberelimab has demonstrated successful control over recurrent HER2+ BC [96]. In conclusion, a combination of HER2-targeted antibody-drug conjugates (ADCs) with PD-1 inhibitors may be effective in patients with HER2+ BC, including those resistant to previous HER2-targeted ADCs.

4. Combination Therapy

Many treatments, including radiotherapy, chemotherapy, and targeted therapy, are not effective in a majority of cancer patients [97–99]. Immunosuppression is the primary barrier to fully realizing the therapeutic potential of immunotherapies [9,100]. Moreover, a higher degree of M2-like macrophage infiltration is related to immune suppression. Thus, seven combined treatment methods are summarized below to provide a reference for clinical treatments.

4.1 In Combination with Anti-Cancer Vaccines

The aim of vaccines designed for anti-tumor therapy is to provoke a highly specific cellular immune response against the cancer. Moreover, prompt T-cell reactions preempt the recurrence of tumors by establishing a long-term immune memory [101]. A DNA vaccine targeting the cysteine protease legumain, which is highly expressed within TAMs, has the ability to slump TAM density and inhibits cancerous growth, neovascularization, and metastasis [102]. A combination therapy of a DNA vaccination encoding the HER2 protein and trastuzumab demonstrates positive outcomes in the treatment of patients with HER2+ mBC [103]. The combination with GM-CSF is performed to increase DC function and to hamper Tregs. GM-CSF also promotes the polarization of macrophages toward the M1 phenotype and activates their anti-tumor functions. For example, the GVAX vaccine, an anti-tumor vaccine genetically modified with *GM-CSF* gene, combined with cyclophosphamide and trastuzumab, is utilized to treat HER2-negative mBC [104]. According to Garcia's findings [105], an anti-CD47 antibody along with PD-L1 blockade increases the frequency of innate and adaptive immune regulatory reactions and strengthens the vaccinal effect of treatments. In addition, immunotherapeutic vaccination triggers immune identification and elimination of BC by embedding malignant antigens such as HER2. HER2/neu-based vaccination combined with GMCSF vaccine amplifier and trastuzumab is an effective treatment for TNBC [106].

4.2 In Combination with Immune Checkpoint Inhibitors

Thus far, numerous immunological checkpoint inhibitors have been documented, yet the predominant ones utilized in clinical settings are those targeting PD-1 and PD-L1. The PD-1/PD-L1 axis and CTLA-4 both act as suppressive signals that dampen the immune response of T cells. Preventing the PD-1/PD-L1 axis to boost the cytotoxic capabilities of T cells has shown efficacy in resolving malignancies [107]. Administering pembrolizumab alongside standard chemotherapy enhances PFS in individuals with TNBC when compared to those undergoing chemotherapy alone [14]. Moreover, pre-treatment with cisplatin and doxorubicin followed by nivolumab leads to a more effective therapeutic outcome, a result linked to the chemotherapeutic drugs' ability to modulate the immune system and create a supportive TME for PD-1 inhibitors. Tumor cells stimulate macrophages to upregulate the expression of IL-15 receptor alpha subunit (IL-15Rα). IL15Rα+ TAMs reduce the protein expression of C-X3-C motif chemokine ligand 1 (CX3CL1) in tumors and hinder the gathering of CD8+ T cells by producing the IL-15/IL-15Rα substance. Implementation of an IL-15Rc block-

ing peptide slows down malignant growth and resolves the drug tolerance of oncogenic cells to immunotherapy using a PD-1 antagonist [108]. Targeting the CSF-1/CSF-1R axis may also be an efficient method to regulate macrophage activity. Treatment with the monoclonal antibody RG7155 in clinical trials blocks the dimerization and activation of CSF-1R, decreases TAM accumulation, and increases the number of CTLs [109]. Several studies have indicated that anti-VEGF antibodies can reduce TAM invasion and prevent TAMs from releasing pro-angiogenic factors, thereby increasing the efficacy of anti-vascularization treatments [110,111]. The combination of anti-HER2 therapy with ICB improves the survival in preclinical models of HER2+ BC. Neoadjuvant trastuzumab therapy augments PD-L1 in TAMs of HER2+ individuals, suggesting that the treatment effect is poor. However, anti-HER2 antibodies with inhibitors targeting PD-L1 and indoleamine 2, 3-dioxygenase (IDO) have demonstrated an enhanced anti-tumor immune response and improved the effectiveness of anti-HER2 therapies [112]. It is essential to recognize that although these methods show potential, the clinical effectiveness can vary among patients, and there is also a need to continue to explore the effects of combining different drugs.

4.3 In Combination with Nanomaterial Drugs

Remodeling the TME with nanocarriers represents a promising approach to boost the efficacy of immunotherapy. CCL2 attracts macrophages and monocytes, which then evolve into M2 and MDSCs. Lipid-protamine nanostructures are designed to deliver a plasmid that traps CCL2 and inhibits its ability to recruit M2 and MDSCs, thereby enhancing anti-tumor immunity and impeding cancer advancement [113]. Cationic nanoparticles encapsulating siRNA-CCR2 (CNP-siCCR2) target the *CCL2-CCR2* signaling pathway, which leads to the downregulation of CCR2 in monocytes [114], these nanoparticles can alter the TME, thereby inhibiting both tumor expansion and spreading. Jung *et al.* [115] developed 7C1 nanoparticles that are packed with CX3CL1. These nanoparticles have been successful in reducing the level of CX3CL1 and preventing the gathering of macrophages in the TME. In addition, liposomal formulations of zoledronic acid have been shown to deplete TAMs, reduce the presentation of the M2 marker CD206, inhibit the expression of CD31, and consequently decreasing neovascularization and breast tumor growth in TNBC. Like zoledronic acid, liposomal nanoparticle-delivered guano-sine monophosphate–adenosine monophosphate (GAMP) also suppresses TNBC development by the reprogramming of the M2 phenotype back to the M1 state [116,117]. Although signal regulatory protein alpha (SIRPα) binding to CD47 prevents the macrophages from engulfing tumor cells, the design of cell membrane-coated magnetic nanostructures hampers SIRPα and CD47 communication to ensure macrophage movement in phagocytosing BC cells, enhancing immune response and increasing the survival and prognosis of BC patients [118]. Furthermore, nanostructures, which are self-assembled and equipped with dual-targeting drugs, work to block the CSF1 and SH2 domain-containing protein tyrosine phosphatase-2 (SHP2) pathways, thereby promoting polarization to the M1 state and enhancing phagocytosis [119]. A recent study reports that the strategy of nanoparticles delivering small interfering RNA YTH N6-methyladenosine RNA binding protein 1 (YTHDF1) suppresses the secretion of IL-10, increases the production of IL-12 and IFN-γ, enhances the penetration of CD8+ T cells and increases the presence of M1 TAMs while decreasing the number of Tregs and M2 TAMs [120].

4.4 In Combination with Signaling Pathway Inhibitor Therapies

Inhibitors, such as poly ADP ribose polymerase (PARP), HER2, PI3K, AKT, mTOR, EGFRs, and VEGF, could serve as treatments to prevent the advancement of BC due to their roles in the cell cycle, angiogenesis, and metastasis [121,122]. Rapamycin, a mTOR inhibitor, has a positive therapeutic effect on hormone-resistant metastatic ER+ BC. A synergy regimen of everolimus with exemestane or trastuzumab yields favorable therapeutic outcomes in both HER2+/– BC [123]. Early-phase research suggests that PARP inhibitors increase cytoplasmic DNA and activate stimulator of interferon genes (STING) protein, which increases INF-α and T cells [124]. The inhibition of carlumab and PF04136309, leronlimab, and maraviroc indicate anti-tumor effects by reducing M2 infiltration and angiogenesis [125]. The control of signal transduction pathways can influence how macrophages become polarized. The NF-κB, STAT3, and STAT6 factors are involved in guiding the transition of TAMs into the M2 phenotype [126]. In addition, the inhibitors trebananib, emactuzumab, and pexidartinib inhibit macrophage recruitment and tumor growth [127]. A new HER2 tyrosine kinase inhibitor, tucatinib, with immune modulating therapies and/or chemotherapy treatments for advanced stage/metastatic HER2+ BC, had been approved. Tucatinib showed clinical benefits in patients with trastuzumab resistance in an advanced stage. In short, the combination of inhibitors plays an important role in clinical practice.

4.5 In Combination with Chemotherapy Drug Therapy

The use of paclitaxel in BC leads to an increase in CSF-1, which in turn boosts the migration of TAMs [3]. When CSF-1 inhibitors are administered with paclitaxel, it not only raises the number of T cells in the tumor and improves the treatment's effectiveness but also curbs metastasis [4]. The CSF-1R inhibitor BLZ-945 and the chemotherapeutic drugs doxorubicin and epirubicin specifically target and eliminate TAMs [128,129]. Pembrolizumab in association with chemotherapy drugs for locally recurrent unresectable or metastatic TNBC patients. Atezolizumab and

nab-paclitaxel prolong PFS among patients with metastatic TNBC and PD-L1–positive subgroup [16]. Blocking the CCL2 pathway with anti-CCL2 antibodies in BC models has been shown to reduce both tumor growth and migration. This approach is even more effective when the monoclonal antibody against CCL2 (such as carlumab) is used with other chemotherapy drugs for patients [47,59]. In addition, PLX3397 with radiotherapy suppresses the variation of monocytes into TAMs and inhibits STAT6 tyrosine phosphorylation, consequently reducing drug resistance [130, 131]. The inhibition of the CD47-SIRPα interaction by CD47 antibodies strengthens phagocytosis of TAMs and boosts the effectiveness of immunotherapy, chemotherapy, and combination strategies [132].

4.6 In Combination with Oncolytic Viruses

Oncolytic viruses (OVs) represent a promising category of cancer treatments that proliferate within cancerous cells and elicit anti-tumor reactions. OVs trigger immunogenic cell death in cancer cells, stimulating T-cell activation, and fostering an immune response that protects against tumor growth, such as the HSV-derived oncolytic virus T-VEC has successfully passed Phase III clinical trials and has received approval from the FDA (U.S. Food and Drug Administration) for utilization in immunological cancer treatments [133]. Furthermore, studies in the early phases of clinical research, encompassing various solid tumor types such as BC, have indicated that OVs possess therapeutic potential with low toxicity [134–137]. Given their therapeutic benefits, safety profiles, and minimal side effects, the deployment of these engineered viruses in immunological cancer treatments could mark a significant advancement in oncology. OVs have demonstrated the ability to stimulate the anti-tumor activities of specific immune cells, such as T cells. Research has shown that HSV1716 is capable of reconfiguring TAMs towards a phenotype that is less suppressive to the immune response. Administration of HSV1716 elevated the count of F4/80+ TAMs that displayed pro-inflammatory, M1 markers, like IL-12 and NOS2, compared to the controls without the virus. In addition, treatment with HSV1716 markedly decreased the quantity of F4/80+ MRC1+ TAMs [138]. This transformation of TAMs could potentially shift the balance within the TME, converting M2 into M1, which in turn facilitates the attraction of adaptive immune cells and enhances cytotoxic capabilities. In addition, OVs have been shown to increase sensitivity to immune checkpoint blockers. For instance, treatment with OVs makes typically unresponsive TNBC susceptible to immune checkpoint inhibitors, preventing recurrence in the majority of animals that received the treatment. The combination of OV therapy with ICIs serves as a potential neoadjuvant strategy within the interval between the diagnosis of TNBC and surgical removal [139]. Hedberg *et al*. [140] demonstrated through single-cell analysis that the presence of TAMs was elevated following HSV-C134 treatment, and these TAMs exhibited higher levels of the pro-inflammatory marker STAT1, a transcription factor that plays a role in the expression of interferons. Denton *et al*. [141] demonstrated that treatment with liposomal clodronate led to a reduction in TAM infiltration, which enhanced this OVs' anti-tumor effectiveness without an increase in viral replication. Finally, OVs designed to target specific anti-tumor functions of TAMs hold great promise. Nevertheless, to amplify the interaction between TAMs and OVs for enhanced anti-tumor immunity, it will be essential to leverage the distinctions between TAMs' anti-tumor and antiviral reactions.

4.7 Other Therapies

A pair of herbs, Hedyotis diffusa and Scutellaria barbata, have been discovered to curb the differentiation of TAMs towards M2 *in vitro*. This effect hampers the migration of BC cells, suggesting a potential role in impeding the spread of BC [142].

The application of hyperthermia directly to the breast tumor environment is an additional potential approach for immunotherapy, as it can lead to the direct elimination of cancer cells [143,144]. It is thought that hyperthermia augments immune cells, such as NK cells and CD8+ T cells, to eliminate tumor cells. Moreover, treatment of macrophages with CD40 agonists such as sotigalimab and selicrelumab has been shown to significantly enhance the generation of inflammatory factors, activate DCs, and promote the polarization of M1 TAMs. This approach is of particular interest in cancer immunotherapy due to its potential to reshape the TME and enhance the immune response against cancer cells.

In addition, CAR-Ps or chimeric antigen receptors for phagocytosis, is an innovative approach that engineers macrophages to directly engulf tumor cells or facilitate the degradation of the ECM components, thereby inhibiting the growth and progression of solid tumors. Zhang and colleagues [145] developed a HER2-specific CAR macrophage therapy, which contains an adjustable domain that binds to HER2 to elevate MMP production for the degradation of the ECM and another intracellular region consisting of CD147, which amplifies T cell infiltration within the TME, subsequently slowing down tumor growth. Overall, these approaches represent a promising new direction in cancer immunotherapy, providing a potential strategy to enhance the immune system's ability to target and eliminate tumors.

In summary, we have compiled a list of several drugs and the efficacy of combination therapies in Table 2, while treatment strategies are outlined in Table 3.

5. Challenges in Tumor Immunotherapy Targeting TAMs in Breast Cancer

The buildup of TAMs is also linked to poor clinical outcomes in a range of solid malignancies [146–148]. Fur-

Table 2. Combination treatment methods for breast cancer.

Drugs	Combinations	Functions
GM-CSF immunoadjuvant and trastuzumab	DNA vaccine against the cysteine protea selegumain; HER2/neu-based vaccination; Sipuleuce l-T vaccine	Decreases M2 and blocks tumor growth, angiogenesis and metastasis; triggers immune recognition and destruction; prolongs the survival of patients
IL-2, GM-CSF, and trastuzumab treatment	HER2-plasmid DNA vaccination	Induce M1 macrophage polarization; enhances DC functions and limits Treg regulation
Cyclophosphamide and trastuzumab	A granulocyte-macrophage colony-stimulating factor gene-transfected tumor vaccine	/
Anti-CD47 antibody	PD-L1 blockade	Enhances the anti-tumor effect
Pembrolizumab	Standard chemotherapy	Improves PFS in patients with metastatic TNBC
Nivolumab treatment	Cisplatin and doxorubicin	boost the gathering of CD8+ T cells
PD-1 antibody	IL-15Rc blocking peptide	Suppresses tumor growth and prevents oncogenic escape from treatment
Anti-VEGF-antibody	Avastin or Bevacizumab	Inhibits macrophage infiltration; prevents TAMs from releasing pro-angiogenic factors
Neoadjuvant trastuzumab	Anti-HER2 antibody, PD-L1 antagonist and IDO	Enhances anti-tumor immunity
Blocking SIRPα and CD47 interaction	Lipid-protamine nanostructures for the delivery of plasmids that trap CCL2	Prevents its action in recruiting M2 and MDSCs
CSF-1R blocking	siRNA-CCR2 encapsulated cationic nanoparticles	Prevents the recruitment of macrophages to the tumor region
PD-1 antibody	Nanoparticle delivering small interfering RNA YTHDF1	Boosts CD8+ T cell infiltration and M1-type TAMs, and reduces Tregs and M2-type TAMs in the TME
Everolimus	Exemestane or trastuzumab	/
PARP inhibitors	PD-1 antibody	Increases INF-α and T cell intratumoral infiltration
Estradiol	Inhibition of CCL2 and CCL5	Increases macrophage influx and angiogenesis
Tucatinib	Immunotherapy or chemotherapeutic agents	Clinical benefits in patients with trastuzumab resistance
Paclitaxel	CSF-1 inhibitors	Increases CCL8, IL-34, and CSF-1
Chemotherapy drug	Anti-CCL2 antibodies	Decreases both tumor growth and migration
BLZ-945 (a CSF-1R inhibitor), CD47 antibodies	Chemotherapeutic drug	Strengthen phagocytosis of TAMs and heighten immunotherapy, chemotherapy, and combination strategy
Pembrolizumab Atezolizumab	Chemotherapy Nab-paclitaxel	Prolongs PFS among patients with metastatic TNBC and PD-L1–positive subgroup

GMCSF, granulocyte-macrophage colony-stimulating factor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; IDO, indoleamine 2,3-dioxygenase; SIRPα, signal regulatory protein alpha; MDSCs, myeloid-derived suppressor cells; CSF-1R, colony-stimulating factor 1 receptor; TME, tumor microenvironment; PARP, poly ADP-ribose polymerase; CCR2, C-C chemokine receptor type 2; INF-α, interferon-alpha; CSF-1, colony-stimulating factor 1; siRNA, short-interfering RNA; PFS, progression-free survival; PD-1, programmed death 1; PD-L1, programmed death ligand 1.

Table 3. Immunotherapy targeting strategies.

Current field of therapeutic direction	Combined to inhibit angiogenesis
	Combined to inhibit immunosuppressive cell recruitment
	Combined to inhibit the production of tumor promoting factors
	Combined anticancer vaccine
	Combined immune checkpoint inhibitors
	Combination with Oncolytic viruses
	Combined nanomaterial drugs
	Joint signaling pathway target inhibitor
	Combination chemotherapy drug
	Combined with herbal medicine treatment
Potential therapeutic directions	Modified CAR-T to secrete chemokines and cytokines to enhance T cell killing and intratumoral infiltration
	Regulate TAM lipid metabolism and promote M1 polarization
	Screening old drugs for new ones

CAR-T, chimeric antigen receptor T-cell.

thermore, the abundance of TAMs shows a positive link with malignant inflammation, estrogen receptor, and E-selectin expression [149]. This indicates the importance of TAMs for tumorigenesis and is also key to whether tumor treatment is effective. Studies revealed that TAMs have evolved to the M2 and activate β-catenin signaling by the CCL2/AKT pathway, promoting EMT and cancer stem cell attributes [150,151]. Importantly, the infiltration of TAMs is also negatively correlated with E-cadherin levels in TNBC tissues [152]. In summary, TAMs labeled with either pan-macrophage markers or specific M2 markers reflect a poor patient prognosis.

Targeting TAMs offers hope for successful disease control, but their therapeutic response is not optimal, and a personalized treatment regimen may be required due to the heterogeneity of TAMs. Moreover, M2-type TAMs can inhibit the activity of T cells and NK cells by secreting immunosuppressive factors, thus promoting the immune escape of tumors and reducing the clinical therapeutic effect. For instance, TAMs express a variety of cytokines to reduce the cytotoxic immune response of T cells and NK cells, including the ligands of EGFR family [153], TNF, MMPs, TGF-β and IL-10, VEGF and thymidine phosphorylase [44,153]. TAMs also promote cancer cells' immune evasion tactics by gathering immune-suppressive white blood cells to the TME, such as MDSCs, monocytes, DCs, and Tregs, to inhibit T cell tumor-killing mechanisms [100]. Therefore, a deeper understanding of the intrinsic complexities of TAMs in immune modulation provides new insights. At the same time, developing new treatment strategies is challenging. Recently emerging nanotechnology and metal ion immunotherapy provided new possibilities for targeted therapy of TAMs, and can inhibit the recruitment of TAMs, eliminate TAMs, reprogram M2 TAMs to M1 TAMs, and regulate the phagocytosis of TAMs on tumor cells. However, the efficacy, safety and human tolerability of nanoparticles requires careful evaluation. Overall, targeting TAMs in BC immunotherapy is a complex process that requires overcoming numerous technical and scientific issues. It also necessitates a deeper understanding of the heterogeneity, function, and interaction of TAMs with other cells in the TME.

6. Conclusions and Perspectives

BC is the most common cancer worldwide and the leading cause of cancer-related mortality among women. Present therapeutic selections are limited to surgery, adjuvant chemotherapy, and radiotherapy. However, some patients do not qualify for surgical measures at initial diagnosis. Immunotherapy represents a promising treatment option by targeting TAMs, or the inhibitors of signaling pathways [154,155] and agonists [156,157]. This review summarized the immunosuppressive and immune escape role of macrophages in the TME. The proposed targeting of TAMs presents a promising therapeutic strategy. The changes in the TME following the targeting TAMs, with a focus on TNBC and HER2+ BC, are also described. The review concludes with an overview of several combination therapies, aiming to provide a breakthrough in clinical treatments. Immunotherapy has made significant advances in the treatment of BC, with agents such as atezolizumab and pembrolizumab showing partial benefits. However, these therapies are not yet sufficient to eradicate the disease in all patients. In summary, combination immunotherapy may offer a more effective approach to enhance the treatment outcomes for BC.

Although many treatments for TAMs have been reported, new treatments are urgently needed. For example, actively screening existing drugs for new therapeutic uses is a promising strategy. As the discovery of new drugs is challenging, it is beneficial to actively explore new approaches for screening targeted drugs with FDA approval. In addition, Treg cells deter the secretion of INF-γ by CD8+ cells, thereby promoting the activation of the immunosuppressive

fatty acid synthesis in TAMs mediated by SREBF1. The inhibition of this protein enhances the potency of ICIs, suggesting that targeting Treg cells or the regulation of M2-like TAM lipid metabolism could improve cancer immunotherapy [57,158–160]. Finally, CAR T cell therapy is a type of immunotherapy developed from adoptive T cell transfer. Recent studies [161,162] reported CAR T cells engineered to secrete cytokines and chemokines to kill tumor cells. For example, IL-10-expressing CAR T cells resist dysfunction and mediate durable clearance of solid tumors and metastases [161,162] (Table 3). This review elucidates how high expression of PD-L1 and a high level of M2 TAMs in BC correlates with poor prognosis. The involvement of macrophages in inhibiting the TME consequently diminishes the effectiveness of immunotherapy. Finally, the methods of targeting TAMs and combined therapy in recent years were summarized, aiming to improve the TME and offering renewed hope for patients. In the future, therapeutic strategies targeting M2-TAMs will need to be further studied and developed to find the most appropriate combination of therapy and individualized treatment regimens. At the same time, the application of nanotechnology in cancer therapy has a broad prospect. Nanomaterials can improve drug accumulation and intratumoral penetration in tumor tissues and reduce adverse effects on healthy tissues. Future research must address complex challenges, such as the clinical transformation of nanomedicine, in order to promote clinical development. In conclusion, future research must achieve breakthroughs at multiple levels to enhance the efficiency and effectiveness of cancer treatments, ultimately offering new hope to patients.

Author Contributions

YH: conceptualization, methodology, software, investigation, data curation, visualization, resources, writing—original draft, writing—review and editing. QL: supervision, visualization, writing—review, and editing. ZHL: conceptualization, methodology, software. QH & LW: conceptualization, methodology. ZFG: (i) made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; (ii) been involved in drafting the manuscript or reviewing it critically for important intellectual content, and (iii) given final approval of the version to be published. All authors have read and agreed to the published version of the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors contributed to editorial changes in the manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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