Breast Cancer: Targets and Therapy

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REVIEW

Current Status of Breast Cancer Immunotherapy and Prognosis-Related Markers

Yirong Xu[1,2,*], Bingchen Zhang[3,*], Hongyuan Wu[2,4,*], Yifen Wu[1]

[1]The First School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, 510000, People's Republic of China; [2]Cancer Center, The Tenth Affiliated Hospital of Southern Medical University (Dongguan People's Hospital), Southern Medical University, Dongguan, Guangdong, 523059, People's Republic of China; [3]Department of Laboratory Medicine, Dongguan Institute of Clinical Cancer Research, Department of Oncology, The Tenth Affiliated Hospital of Southern Medical University (Dongguan People's Hospital), Dongguan, Guangdong, 523059, People's Republic of China; [4]Dongguan Institute of Clinical Cancer Research, Dongguan Key Laboratory of Precision Diagnosis and Treatment for Tumors, The Tenth Affiliated Hospital, The First School of Clinical Medicine, Southern Medical University (Dongguan People's Hospital), Dongguan, Guangdong, 523059, People's Republic of China

*These authors contributed equally to this work

Correspondence: Yifen Wu, The First School of Clinical Medicine, Southern Medical University, Guangzhou, Guangdong, 510000, People's Republic of China, Tel +8613423158632, Email 31200195@smu.edu.cn

Abstract: Breast cancer, being the most common type of cancer globally, stands out as the primary malignant tumor affecting females. With the advent of breast cancer immunotherapy, inhibitors targeting immune checkpoints such as anti-PD-1 (Programmed cell death protein 1) / PD-L1 (Programmed cell death-Ligand 1) and CTLA-4 (Cytotoxic T Lymphocyte-Associated Antigen-4) have demonstrated promising outcomes for breast cancer patients across all molecular subtypes, particularly those with advanced breast cancer and triple-negative breast cancer (TNBC). Our current focus lies in accurately predicting the prognosis of breast cancer patients and the effectiveness of immunotherapy. This article provides a review of emerging biomarkers for breast cancer, encompassing immune-related markers, metabolic indicators, and potential prognosis-related markers. The primary emphasis of the article is to review immune-related tumor biomarkers in breast cancer. Our goal is to summarize relevant studies capable of forecasting breast cancer prognosis and immunotherapy effectiveness. Lastly, we delve into the future directions of breast cancer immunotherapy development.

Keywords: breast cancer, immunotherapy, markers, prognosis

Introduction

Breast cancer rates have been steadily climbing worldwide over the past four decades. According to the American Cancer Society in 2024, the incidence rose by 1.0% annually from 2012 to 2021.[1] Despite advancements in cancer therapy, the global mortality rate has seen a consistent decline between 2019 and 2022. However, this positive trend may be hampered by the increasing occurrence of breast cancer, among other factors. Studies have revealed racial disparities in breast cancer incidence,[2] with significant differences in survival rates among female patients of various racial and ethnic backgrounds.[3] China contributes to 12.2% of newly diagnosed breast cancer cases and 9.6% of breast cancer-related deaths worldwide.[4] In recent years, researchers have paid greater attention to the interactions between tumor cells and immune cells. Primary tumors can suppress the body's anti-tumor immune response by enhancing the expression of inhibitory receptors known as "immune checkpoints". This mechanism can facilitate tumor progression, metastasis, and further development. Consequently, immune checkpoint inhibitor therapy has become a focal point in cancer treatment and a significant milestone in oncology. Notably, therapies targeting the PD-1/PD-L1 pathway have revolutionized tumor immunotherapy. PD-1 antibodies hinder T-cell receptor-mediated cytotoxicity by binding to PD-L1 ligands, concurrently inhibiting the proliferation of CD8+ T-cells. As a result, tumors can evade immune surveillance and elimination, facilitating tumor growth. Moreover, tumor-associated macrophages with a tumor-promoting phenotype (M2-TAM) are implicated in T-cell depletion mediated by PD-1/PD-L1, contributing to immune tolerance during anti-PD-1/PD-L1

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treatment. Hence, investigating the tumor immune microenvironment and tumor-infiltrating cells is pivotal for advancing immunotherapy. Today, immune checkpoint inhibitors like Ipilimumab (CTLA-4 monoclonal antibody), Pembrolizumab, and Nivolumab (PD-1 monoclonal antibodies), and Atezolizumab (PD-L1 inhibitor) have gained approval for treating various tumors, with their applications expanding. For instance, Pembrolizumab has shown significant anti-tumor efficacy in treating metastatic triple-negative breast cancer that is PD-L1-positive, with a proven safety record. Furthermore, PD-L1 expression is detected in 20%-64% of triple-negative breast cancers, making the use of PD-L1 monoclonal antibodies highly advantageous for patients with this breast cancer subtype. Avelumab, a human anti-PD-L1 IgG1 monoclonal antibody, sets itself apart from other PD-L1/PD-1 monoclonal antibodies due to its ability to induce antibody-dependent cell-mediated cytotoxicity (ADCC) on tumors, suggesting a distinct anti-tumor mechanism. In a Phase Ib trial, avelumab demonstrated a manageable safety profile in patients with PD-L1-positive triple-negative breast cancer. Moreover, its therapeutic remission rates are comparable to those of pembrolizumab and atezolizumab.[5] However, mounting evidence indicates that only a small subset of patients benefit from immunotherapy. Given the existence of multiple molecular subtypes of breast cancer, limited immunogenicity, and the possibility of multiple breast cancer subtypes coexisting within the same tumor, a single immunotherapy approach cannot be expected to effectively treat tumors with diverse molecular subtypes.[6–10] The urgent need for biomarkers capable of predicting therapeutic response is evident. Currently, PD-L1 has been established as an empirical biomarker for guiding clinical treatment. And numerous clinical trials have confirmed its predictive capacity.[7] Expression of PD-1/PD-L1 indicates a favorable prognosis and correlates with heightened sensitivity to cancer chemotherapy. Hence, exploring additional markers that can forecast the response to immunotherapy and integrating them into clinical practice holds significant value for the treatment and prognosis of breast cancer patients. This review focuses on discussing biomarkers linked to breast cancer prognosis and the prediction of immunotherapy outcomes.

The Immune Microenvironment of Breast Cancer and Tumor-Infiltrating Lymphocytes (TILs) in It

The tumor microenvironment (TME) comprises various biologically active components, with common features such as tumor cells, immune cells, stromal cells, extracellular matrix, and blood vessels, although their specific composition may vary depending on the tumor type. Among these components, the immune elements collectively constitute the Tumor Immune Microenvironment.[11] Breast cancer, being an immunostatic tumor, often exhibits limited response to immunotherapy.[12] However, promising results from preclinical trials and recent clinical data suggest that immunotherapy holds potential to revolutionize clinical interventions in breast cancer. Particularly noteworthy is the mounting evidence indicating that immune infiltration within the tumor immune microenvironment serves as a crucial predictor of breast cancer prognosis, offering hope for improved treatment outcomes.[13] Exploring the immune microenvironment of breast cancer is paramount, especially considering its variation across different subtypes. Lymphocyte infiltration varies significantly among different subtypes, with triple-negative breast cancer (TNBC) often characterized by abundant CD8+ T-lymphocyte infiltration, strongly associated with favorable disease-free survival (DFS). Conversely, the predominance of FoxP3+ regulatory T cell infiltration in estrogen receptor-positive (ER+) and human epidermal growth factor receptor 2-positive (HER2+) breast cancer tissues typically indicates a poor prognosis for patients.[14] However, immune cells exhibit a dual role within the tumor microenvironment, both promoting and suppressing tumor activity. Studies have shown that the epithelial-mesenchymal transition (EMT) process in tumors can create an immunosuppressive microenvironment, protecting tumors from anti-tumor immune responses in vivo. Conversely, myeloid dendritic cells contribute to immune activation through antigen presentation and subsequent activation of CD4+ and CD8+ T cells.[15] Immune cells or immune-related genes can serve as early predictors of cancer patient outcomes and prognosis. Notably, tumor-infiltrating cells (TILs) have demonstrated a robust prognostic effect in patients with early-stage TNBC and HER2-positive breast cancer.[16] However, the prognostic impact of TILs varies across different breast cancer subtypes, with elevated TIL levels correlating with a survival benefit in HER2+ breast cancer and TNBC. In patients with HER2-negative breast cancer, their prognosis demonstrates an inverse relationship with elevated levels of tumor-infiltrating lymphocytes (TILs), indicating a distinct biological basis for immune infiltration in HER2-negative breast cancer.[17] Immune checkpoint inhibitor (ICI) therapy has exhibited promising efficacy in treating other types of breast cancer but faces limitations in treating triple-negative breast cancer

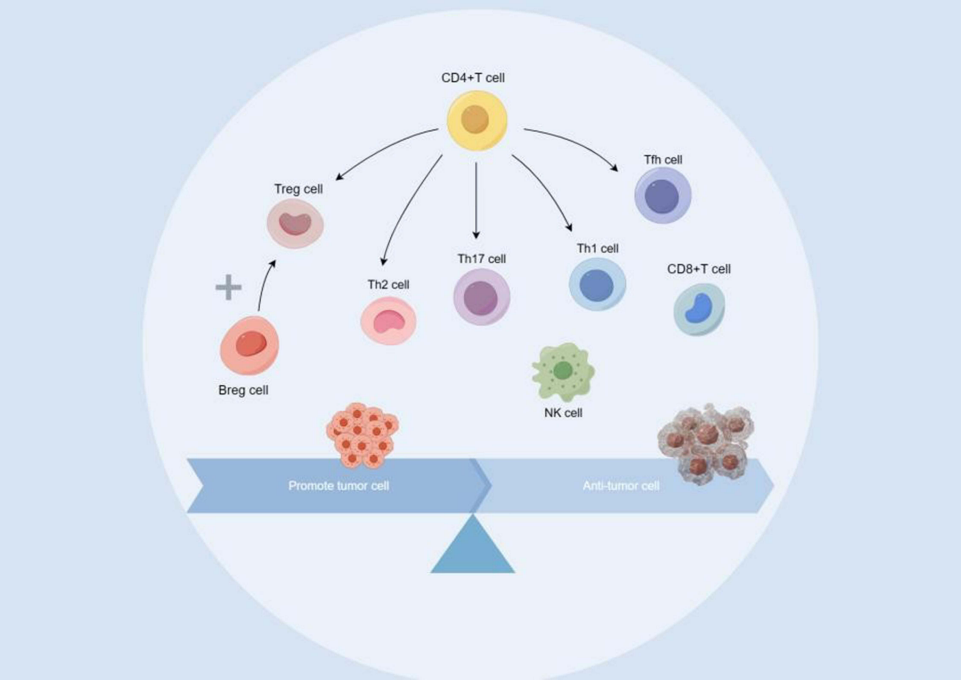

Figure 1 In breast cancer, tumor-infiltrating lymphocytes (TILs) within the immune microenvironment are broadly categorized into pro-tumor and anti-tumor cells, which restrict each other to maintain balance. Naive CD4+ T cells can differentiate into five distinct subtypes: Th1, Th2, Th17, Treg, and Tfh. Notably, Th17 cells exhibit a dual role. Both Breg and Treg cells are tumor-promoting, with Breg cells inducing the differentiation of Treg cells and establishing a microenvironment that supports tumor growth.

(TNBC) due to the lack of functional TILs in the "non-inflammatory" or "cold" tumor immune microenvironment (TIME). Although the exact mechanism remains unknown, the significance of TILs in the tumor immune microenvironment is strongly suggested. Various tumor-infiltrating cells in breast cancer play different roles, broadly categorized into pro-tumor and anti-tumor effects (Figure 1 and Table 1).[18,19] An increase in tumor-infiltrating lymphocytes (TILs), particularly CD8+ T cells, in the immune microenvironment predicts the outcome and prognosis of patients with early-stage TNBC. Yamashita et al,[20] investigated the combination of IFN-γ pathway activation with the immunosuppressive tumor microenvironment and found that

Table 1 Pro- and Anti-Tumor Roles of TILs in Breast Cancer

Tumor Infiltrating Cells (TILs)	Functionality
Initial CD4+ T lymphocytes	Secretion of IL-2, IL-4, IL-6, TGF-β, IFN-γand other cytokines and differentiation into a variety of lymphocytes and other ancillary effects, inhibition of BC cancer cell cycle, direct anti-tumor effects
Th1 cell	Secretion of INF-γ, anti-tumor immune response, inhibition of Th17 cell differentiation
Th2 cell	Secretion of IL-4 promotes tumor growth and inhibits Th17 cell differentiation
Th17 cell	Secretion of CCL2, CC20L or CXCL1 with dual action
CD8+ T lymphocytes	Identifying and destroying tumor cells predicts a good prognosis for breast cancer
Tfh cell (follicular helper T cell)	Cytotoxic effects, mediates humoral immune response
Treg cell	Promoting immune escape of tumor cells
Breg cell	Recognition of PD-L1, suppression of immune response, promotion of Treg cell differentiation, and prognosis of worse prognosis
B cell	Antigen presentation, mediates humoral immune response
Nk cell	(1) CD 56 dimCD 16 high NK cells mediate cytotoxicity;
	(2) CD 56 highCD 16 dimNK cells release cytokines to induce other immune cells to attack target tumor cells.

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MUC1-C integrates IFN-γ pathway activation with TIL depletion in TNBC. These findings suggest that targeting MUC1-C may enhance the immunotherapy effectiveness of TNBC by counteracting its immunosuppressive effect.[20]

Suppressive Immune Microenvironment of Breast Cancer and Its Remodeling by Immune Cells

Immunotherapy holds significant promise in breast cancer treatment, yet it faces obstacles such as the immunosuppressive microenvironment, the influence of cancer-associated fibroblasts (CAFs), and the inherently "cold tumor" nature of breast cancer. Activated CAFs play a pivotal role in promoting various aspects of tumor progression, including growth, angiogenesis, invasion, metastasis, extracellular matrix remodeling, and even resistance to chemotherapy. They not only interact with tumor cells but also contribute significantly to the establishment of the tumor's immunosuppressive microenvironment. Previously overlooked innate immune cells like NK cells have emerged as promising targets for breast cancer treatment. Under normal circumstances, cells in the body express sufficient levels of MHC-I-like molecules to dampen NK cell activity, preventing their destruction. However, reduced or absent expression of these molecules in cancer cells renders them susceptible to elimination by NK cells. Nevertheless, in the immunosuppressive microenvironment of breast cancer, NK cell function can be compromised by inhibitory signals produced by cancer cells. Additionally, CAFs can directly or indirectly inhibit NK cell activity through various pathways. Consequently, numerous studies are underway to reprogram NK cell function with the aim of reshaping the tumor immune microenvironment.[21–23]

Breast cancer is often characterized as a "cold tumor" with low immunogenicity, largely attributed to the immunosuppressive microenvironment it fosters.[12] Within breast cancer tissues, the tumor suppressor miR-204-5p plays a crucial role in regulating both the autonomous behavior of cancer cells and the immune microenvironment.[24] Overexpression of miR-204-5p leads to a reduction in myeloid-derived suppressor cells (MDSCs), macrophages, and natural killer cells, while increasing the prevalence of CD4+ T cells, CD8+ T cells, and regulatory T cells.[24] Cancer tissues actively remodel the immune microenvironment to support their growth and proliferation, presenting a viable target for cancer treatment. Transforming "cold tumors" into "hot tumors" holds significant promise for the clinical management of breast cancer. Macrophages play a crucial role in the immune response within the tumor microenvironment. M1 macrophages exhibit anti-tumorigenic activity by producing ROS, mediating antibody-dependent cytotoxicity, and releasing tumor necrosis factor (TNF). Conversely, M2 macrophages promote tumor progression by facilitating tumor angiogenesis, suppressing immune function, aiding invasion and metastasis, and remodeling the extracellular matrix (ECM).[22] Ginsenoside Rg3 possesses both antitumor and immunomodulatory properties. It demonstrates antitumor activity when combined with chemotherapeutic agents such as paclitaxel, docetaxel, and doxorubicin across various malignancies.[25] For example, Rg3-loaded liposomes combined with docetaxel can activate the immune microenvironment of breast cancer by shifting the balance towards M1 macrophages, increasing the presence of CD4+ and CD8+ T cells in the tumor microenvironment, and consequently transforming the tumor from a "cold" to a "hot" state, thereby enhancing the therapeutic efficacy of docetaxel.[26] Additionally, Professor Huo Jiege's team at Nanjing University of Traditional Chinese Medicine (NJUTCM) encapsulated Rg3 using chitosan and membrane-penetrating peptide copolymers. This approach reduced solid stress and degraded the extracellular matrix of the tumor, enabling better penetration into deeper tumor regions. As a result, treatment with Rg3 proved more effective, leading to significant progress in tumor treatment.[27]

Crosstalk Between Breast Cancer Biomarkers and Immunotherapy Prognosis

Immune-Related Prognostic Markers

Cancer-associated fibroblasts (CAFs) play a pivotal role in the progression of tumors, particularly solid tumors like breast cancer. Extensive research has shown that CAFs contribute to breast cancer progression through various mechanisms, including undergoing epithelial-mesenchymal transition to promote extracellular matrix alteration, secretion of cytokines, chemokines, and other effectors, generating immunosuppressive microenvironments by promoting M2-type TAM differentiation, facilitating tumor invasion, metastasis, and angiogenesis, creating a hypoxic environment, and driving tumor drug resistance.[22,28,29] The robust fibroblast-related score (FRS) developed by Gu et al,[30] suggests a positive

correlation between FRS and tumor purity, the abundance of M2 and M0-TAMs, and regulatory T cells (T-regs), while showing a negative correlation with immune checkpoint activities. Notably, low FRS is often indicative of a "hot tumor" type in breast cancer, characterized by robust anti-tumor immunity and cytotoxicity. External validation cohorts have demonstrated that low FRS is associated with increased sensitivity to PD-1 inhibitor therapy and prolonged survival compared to high FRS.[30] Additionally, CAFs in breast cancer are regulated by effectors such as INHBA, a member of the transforming growth factor-β superfamily, which positively correlates with CAF infiltration in the tumor microenvironment and influences immune cell infiltration. Hence, studying CAF-related genes holds promise for advancing prognosis and predicting immunotherapy outcomes in breast cancer.[31] Wang et al,[29] developed a prognostic model for CAF-related genes based on five genes (SLC16A6, HBA2, CAB39L, and DLGAP), revealing significant upregulation of immune checkpoints like CD200, CD40, CD244, and TNFRSF8 in the high-risk group, which correlated with a better response to ICIs treatment. This study accurately predicted breast cancer prognosis, with the low-risk group exhibiting longer overall survival (OS).[29]

TILs play a pivotal role in the immune microenvironment of breast cancer, serving as crucial prognostic markers and predictors of immunotherapy response.[32] However, the reliability of TILs as markers is somewhat limited. In 2023, a study focusing on the tumor microenvironment-associated models of TNBC addressed this limitation by conducting a comprehensive analysis of the TIME in TNBC. The study successfully identified three key immune-associated prognostic genes: CXCL13, CCL5, and GZMB. CXCL13 emerged as a valuable predictor for increased TILs and improved OS and DFS in early-stage TNBC. CCL5 was predictive of better PFS, while GZMB served as a biomarker for immune escape. Additionally, the research team developed a TNBC risk score comprising six immune checkpoint blockade-related genes, including CD274, PD-1, CTLA-4, HAVCR2, IDO 1, and LAG 3. This risk score model proved to be an independent prognostic factor, with patients in the low-risk group exhibiting heightened immune infiltration, improved efficacy of immunotherapy, and prolonged overall survival.[33]

α-Synuclein (SNCA), originally associated with Parkinson's disease, has also been implicated in cancer development and progression. Zhou et al,[34] demonstrated SNCA's ability to reverse the EMT process in breast cancer, with its expression significantly correlating with OS, DFS, PPS, and DMFS, indicating a favorable prognosis. Moreover, SNCA overexpression suppressed invasion and metastasis of breast cancer in MDA-MB-231 cells while enhancing immune cell infiltration. SNCA has also been shown to enhance the sensitivity of breast cancer drugs, including HER2, EGFR, and VEGF targeting drugs, as well as chemotherapeutic drugs like cisplatin, gemcitabine, doxorubicin, and vincristine. While there have been suggestions of an association between SNCA and breast cancer immunotherapy, further research is required to confirm this association and its potential predictive role in breast cancer immunotherapy response.[34] The research team from the Department of Nail and Breast Surgery at The Second Affiliated Hospital of Zhejiang University School of Medicine in China discovered that fibronectin 1 (FN1) is associated with immune checkpoint inhibitors and TILs. FN1 exhibited a negative correlation with overall survival (OS) and disease-free survival (DFS) in breast cancer patients, suggesting its potential as a prognostic marker in breast cancer. Due to its correlation with immune infiltration, FN1 may serve as a promising target for breast cancer immunotherapy. FN1 expression was statistically significantly correlated with[14] ICIs, including PDCD1, IDO1, CD274, IL10, CD276, and VEGFA, among others. Additionally, FN1 expression was associated with breast cancer molecular subtyping, while SNCA consistently played a role across various breast cancer phenotypes.[34,35] Wang et al,[36] conducted a series of studies on the Shc SH2-domain binding protein 1 (SHCBP1) and found its expression in various cancers, including lung adenocarcinomas, breast cancers, hepatocellular carcinomas, and others. SHCBP1 can create a tumor-suppressive immune microenvironment and facilitate immune escape by upregulating immune checkpoint genes and other pathways, serving as a prognostic marker for several tumors. However, progress in understanding its role in breast cancer remains limited.[36]

Metabolism-Related Prognostic Markers

Iron death, a form of regulated cell death dependent on iron, is intricately linked with various cellular metabolic pathways, including amino acid metabolism, glucose metabolism, and redox homeostasis. Moreover, it holds significant relevance to cancer. Cancer-related signal transduction pathways, oncoproteins, and tumor suppressors can influence iron death. While many aspects of iron death mechanisms remain to be elucidated, studies have revealed that transcription

factors such as the human oncogenic hypermethylation gene (HIC1) can confer sensitivity to iron death. These mechanisms are classified as either transcription-dependent or transcription-independent.[37,38] HIC1, a widely expressed oncogene in normal tissues, is notably reduced in breast cancer tissues. It has been demonstrated that HIC1 is inversely correlated with Tumor Mutation Burden(TMB) in breast cancer and is highly expressed in patients who do not respond to pan-cancer immunotherapy.[39] Conversely, the iron death regulator (SQLR) exerts a pro-cancer effect, with in vitro experiments indicating that SQLR promotes breast cancer cell proliferation and metastasis. Additionally, models based on FR-related genes, including SQLR, suggest that elevated FR levels not only influence the tumor microenvironment but also participate in the iron death process in cancer. These findings suggest that the FR risk profile could be utilized to evaluate breast cancer prognosis. However, there appears to be a weak correlation with the expression of immune checkpoints, and the FR risk model may not serve as a reliable marker for predicting the efficacy of ICB.[40] The AKR1C1 gene has been linked to immune checkpoints like PD-1, PD-L1, and CTLA4, suggesting a favorable prognosis for breast cancer and its involvement in the immune response against breast cancer. However, it remains to be explored whether the AKR1C1 gene, associated with iron death, can predict the response to breast cancer immunotherapy.[41] Previous research has highlighted the significance of lipid metabolism-associated genes (LAMGs) in breast cancer, indicating that high expression of LAMGs correlates with poor immune status and high tumor purity, which in turn suggests a poorer prognosis.[42] Lipid metabolism also plays a role in the regulation of cellular sensitivity to iron death through various pathways. Shen et al,[43] pioneered the development of a gene model related to lipid metabolism to predict the response to immunotherapy in estrogen receptor-positive (ER+) breast cancer patients. The low-risk group exhibited increased immune cell infiltration with anti-tumor effects and high expression of checkpoint genes such as CTLA-4, PDCD1 (PD-1), LAG3, IDO2, and CD276, while the opposite was observed in the high-risk group. This model proves valuable in predicting the prognosis of ER(+) breast cancer and guiding immunotherapy strategies.[43,44]

Hypoxia and apoptosis are pivotal in cancer pathogenesis. Hypoxia-inducible factor (HIF-1) promotes apoptosis under hypoxic conditions. However, prolonged or severe hypoxia prompts cells to adapt to the hypoxic milieu, leading to evasion of apoptosis, necrosis, and uncontrolled proliferation. This fosters increased invasiveness and resistance to treatment.[45] Furthermore, HIF-1 triggers metabolic reprogramming, resulting in significant lactate accumulation within tumors. This lactate accumulation is critical for breast cancer development and progression, contributing to tamoxifen resistance in patients. Additionally, it induces PD-L1 expression in tumor cells, facilitating immune evasion. The high-lactic acid environment may also enhance cancer stemness, closely correlating with breast cancer recurrence and metastasis.[46] Building upon this understanding, Li et al,[46] developed a panel of hypoxic lactate metabolism-related genes (HLMRGs) to prognosticate and predict the response to immunotherapy in breast cancer patients. The low-risk group exhibited enhanced responses to immune checkpoint inhibitors. Notably, chemokines and their receptors such as CCL5, CCR2, and CCR5 were upregulated in the low-risk group. Breast cancer cells secrete CCL5, a chemokine mediated by Mesenchymal Stem Cells (MSCs). Research indicates that a hypoxic environment augments CCL5 secretion, albeit inhibiting it by suppressing HIF-1α, HIF-2α, and HIF-1β.[47] Extensive investigations have delineated the role of the CCL5-CCR5 and CCL2-CCR2 axes in increasing the Treg/CD4+CCR5+ cell ratio, fostering immunosuppression, neovascularization, tumor invasion, and metastasis in breast cancer patients, ultimately leading to an unfavorable prognosis.[46,48,49]

Other Prognostic Markers

The association between breast cancer and protein tyrosine phosphatase receptor type O (PTPRO) has been extensively explored across basic and clinical research domains. Xie et al,[50] elucidated that PTPRO inhibits the expression of PD-L1 on tumor cells via the JAK2-STAT1 and JAK2/STAT3/c-MYC pathways. This involves the downregulation of surface PD-1 on tumor-associated macrophages (TAMs) and the upregulation of surface PD-1 on CD8+ T cells, thus impeding tumor immune evasion.[50] Another investigation focused on PTPRO's impact on CD8+ T cell infiltration, culminating in the development of a PTS score (PTPRO-associated CD8+ T cell signature score). This study revealed that PTPRO enhances the suppressive TIME, indicating favorable immune status and function. Most significantly, the PTS score accurately predicts the response of breast cancer patients to immune checkpoint therapy.[51]

MDA-MB-231 human breast cancer cells serve as a common model for studying tumor metastasis and invasiveness. Various investigations have explored the relationship between examined genes and the proliferation, invasion, and metastasis of breast cancer cells by modulating their expression levels. Overexpression of CHAF1A, NCAPD3 (mitochondrial methylation-associated prognostic genes), PCDHA1, and CDCA5 (Cell Division Cycle-associated Protein 5) has been observed to enhance the proliferation and invasion of MDA-MB-231 cells. Conversely, overexpression of m6A-related genes TMEM71 and KLRB1 significantly inhibits the proliferation, migration, invasion, and DNA replication ability of MDA-MB-231 cells. Notably, KLRB1 may exert its inhibitory effect on breast cancer proliferation by blocking the G1 phase division. These genes have been identified as prognostic markers for breast cancer, with CHAF1A and NCAPD3 showing potential for predicting immunotherapy response.[52–57]

Furthermore, there are promising potential prognostic markers. High expression of retinoic acid-inducible protein 14 (RAI-14) in triple-negative breast cancer (TNBC) is associated with worse OS, PFS, and DFS. RAI-14 can also mediate the expression of PD-L1 in TNBC, enhancing the anti-tumor immune response and predicting a poorer prognosis. Carboxypeptidase N1 (CPN-1) is suggested as a potential upstream regulator of RAI-14. Its overexpression correlates with high expression levels of RAI-14 and PD-L1. CPN-1 has been proposed as a biomarker for predicting chemotherapy efficacy and is associated with poorer OS and PFS in invasive breast cancer. However, its relationship with immunotherapy remains to be elucidated.[58,59]

Trends in Breast Cancer Immunotherapy

Breast cancer immunotherapy has demonstrated promising outcomes in various clinical trials. For instance, the inclusion of dulvarizumab in neoadjuvant chemotherapy significantly increased overall survival rates from 83.5% to 95.2% compared to chemotherapy combined with surgery.[60] In the I-SPY2 study, a combination of dulvarizumab with a PARP inhibitor and a paclitaxel treatment regimen increased the rate of complete pathological remission across molecular subtypes of breast cancer.[61] Another study revealed that atezolizmab improved progression-free survival in advanced or metastatic breast cancer. Atezolizmab in combination with albumin-paclitaxel prolonged progression-free survival from 5.5 to 7.2 months compared to the placebo group.[62] However, despite these advancements, there are currently no approved drugs specifically for treating breast cancer through immunotherapy. Further research is needed to identify new immunotherapeutic targets for breast cancer treatment. One potential target is the enzyme indoleamine 2.3-dioxygenase 1 (IDO1), which is involved in the rate-limiting step of the amino acid-KYN pathway. Although both IDO1 and tryptophan 2.3-dioxygenase (TDO2) mediate immunosuppressive effects in cancer, most studies have focused on IDO1. However, a Phase III clinical trial investigating IDO1 as an immunotherapeutic target did not yield satisfactory results. Additionally, TDO2 has been associated with breast cancer immunosuppression, immune cell infiltration, and an unfavorable prognosis. Furthermore, the product of IDO1/IDO2 in the first step of amino acid conversion is kynurenine (KYN), which indirectly promotes the immunosuppressive function of IDO1/TDO2. Therefore, targeting only one gene or enzyme may not be sufficient to achieve optimal results. Developing immunotherapeutic agents that target multiple enzymes simultaneously may have better clinical efficacy for breast cancer immunotherapy.[63–65]

Conclusion

The quest for biomarkers capable of predicting therapeutic response and prognosis in breast cancer treatment is indeed crucial. Various studies have explored new or potential predictors across immune, metabolic, and cellular pathways. These include markers such as TMB, MSI-H/dMMR, tumor-infiltrating immune cells (TILs), HIC1 (human tumor hypermethylation gene), SQLR (iron death regulator), AKR1C1 (iron death-related gene), SNCA (α-synuclein), PTPRO (protein tyrosine phosphatase receptor type O), RAI-14 (retinoic acid-inducible protein 14), and CPN-1 (carboxypeptidase N1). However, it's becoming increasingly evident that targeting a single pathway with immunotherapy may not be sufficient in terms of efficacy, side effects, and drug resistance. Therefore, future research efforts should focus on developing immunotherapeutic agents that target multiple enzymes simultaneously. Additionally, these therapies could be combined with other treatment modalities, such as chemotherapy, to enhance therapeutic efficacy and benefit more patients. While this journey presents challenges, it also offers hope for patients, clinicians, and researchers alike.

Data Sharing Statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Ethical Approval

This study did not involve human or animal subjects, and thus, no ethical approval was required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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