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Immunopathological Mechanisms Observed in the Intratumoral Microenvironment and Their Relationship with Worse Prognosis in Triple-Negative Breast Cancer

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ABSTRACT

Background: In the 21st century, the main cause of death in both sexes worldwide is cardiovascular disease, followed by neoplasms. In women, the main cause of morbidity and mortality is breast cancer. Therefore, understanding the immunological mechanisms associated breast cancer and its correlation with poor prognosis is very important.

Methods: In this study, a search was done on PubMed and Google Scholar, using the following medical subject headings (MeSH) in the search engine: “triple negative breast cancer”, “breast cancer microenvironment”, “immune cells”, “prognosis”, “regulatory t reg”, “T cells” and “tumor-associated neutrophils”. Thus, a total of 81 articles were found and reviewed, published between 2002 and 2023.

Results and conclusions: It is essential to understand the immunological mechanisms associated with the tumor microenvironment, to create new targeted treatment schemes for each variant of breast cancer, for example triple negative in order to reduce the mortality rate and increase disease-free survival.

INTRODUCTION

Breast cancer (BC) is the most common cancer in women worldwide, affecting approximately 11.6% during their lifetimes, with a prevalence of 30.3% and a mortality of 18.4% in 2018, in all ages, in the world.[1] This type of cancer has been divided into different classifications depending on histological, molecular, immunological[2,3], and genetic characteristics. One of the most important classifications is based on the presence of hormonal receptors, such as estrogen and progesterone receptors, and human epidermal growth factor receptor 2 (HER2) expression, defined as 3+ protein expression by immunohistochemistry (IHC) and/or HER2/neu gene amplification greater than or equal to 2.0 by fluorescence in situ hybridization (FISH). The absence of hormone receptor expression (defined by a percentage ≤1% of estrogen and progesterone receptors by IHC) and HER2 negatively (0 to 1+ determined by IHC or lack of gene amplification (FISH <2.0)) is known as Triple-Negative Breast Cancer (TNBC).[2,3] TNBC is the most aggressive subtype of breast cancer, accounting for approximately 12-20% of all breast cancer cases; however, TNBC is now classified depending on its

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molecular characteristics. This molecular subclassification subdivides it into six subtypes: basal-like 1 (BL1), basal-like 2 (BL2), immunomodulatory (IM), mesenchymal (M), mesenchymal stem-like (MSL), and luminal androgen receptor (LAR) subtype.[4] Although this classification is of great clinical importance in the subdivision of TNBC, in this review those subtypes with better prognosis (as some metaplastic carcinomas) will not be considered, and the TNBC will be considered as a bad prognosis in general.

The tumor microenvironment (TME) refers to the interaction between tumor cells, immune cells, stromal cells, extracellular matrix (ECM), and other non-cancerous cells. TNBC cells interact with the TME to survive and grow.[5] The most important microenvironment cell components are immunological cells, which include regulatory T cells, tumor-associated macrophages (TAMs), tumor-associated neutrophils (TANs), B cells, and plasma cells; stromal cells, such as cancer-associated fibroblasts (CAFs), and cancer-associated adipocytes (CAAs); and the extracellular matrix.[6] The interaction between BC cells and their TME provides them with unique characteristics, including resistance to cell death, deregulation of cellular metabolism, sustaining proliferative signaling, evading growth suppressors, avoiding immune destruction, enabling replicative immortality, unlocking phenotypic plasticity, and senescence, which are known as "hallmarks of cancer". [7]

The traditional treatment guidelines are based on surgery and postoperative adjuvant chemotherapy in early-stage TNBC; however, if the patient has inoperable locally advanced BC, the neoadjuvant chemotherapy is a major part of treatment to reduce the tumor size and, if possible, a breast-conserving surgery. In metastatic and recurrent TNBC, the systemic therapy is the main component of TNBC treatment, which includes immunotherapy and targeted therapies. Currently, research into the tumor microenvironment and its function in cancer pathogenesis is still ongoing to create new TNBC therapeutic strategies.

This paper mainly introduces the immune cells and related factors in the TNBC microenvironment, discusses the current TNBC treatment, and summarizes the characteristics of the TNBC microenvironment and its role in prognosis, in order to: (I) understand the immunological components of the TNBC microenvironment; (II) summarize the current therapeutic strategies of TNBC; and (III) introduce the consequences of TNBC microenvironment after using different systemic therapies.

In the present study, a search was performed on PubMed and Google Scholar platforms, using the following medical subject headings (MeSH) in the search engine: "triple negative breast cancer", "breast cancer microenvironment", "immune cells", "prognosis", "regulatory t lymphocytes", "T cells" and "tumor-associated neutrophils". A total of 100 articles published between 2002 and 2023 were found and reviewed.

TNBC microenvironment

Most tumors, such as BC, are highly immunogenic; therefore, their TME has a high concentration of infiltrating immune cells, but most of them, are inhibitory immune populations, including regulatory T cells, and myeloid-derived immunosuppressive cells (MDSCs), such as TAMs, TANs, and CAFs.[6] The microenvironment has high levels of PD-1 and PDL-1. The most frequent inflammatory cells are CD163+ histiocytes, CD3+ T lymphocytes, CD68+ histiocytes, cytotoxic CD8+ T lymphocytes, CD4+ cells, and CD20+ B lymphocytes.[8,9]

BC can manipulate immune defenses via intrinsic and extrinsic pathways. The immune system efficiently recognizes tumor cells by presenting BC antigens to T cells, which can expand and become effector-specific T cells.[10] There are two immune checkpoints that can upregulate or downregulate the immune stimulation: cytotoxic T lymphocyte antigen 4 (CTLA-4), a co-inhibitory molecule on T cells that inhibits cells activation by ligation with CD86 and CD80; programmed death 1 (PD-1) is another immune checkpoint, that can be inhibited by programmed death ligand 1 (PD-L1) expressed in tumor cells.[11,12] TNBC has the strongest tumor immunogenicity of all BC subtypes.[13] Liu *et al.* demonstrated this by analyzing the high expression levels of immune-related genes in their inflammatory infiltrates.[14] High PD-L1 expression has a worse clinical outcome in BC, but high levels of PD-L1 are necessary for immunotherapy by the immune checkpoint inhibitors.[15,16]

Tumor-infiltrating lymphocytes (TILs)

Tumor-infiltrating lymphocytes (TILs) comprise a mixture of B lymphocytes, cytotoxic T lymphocytes (CTLs), CD4 T cells, NK cells, and plasma cells. TILs are the immunological anti-tumor response and are associated with prognosis in BC.[6,17] CTLs are the first line of adaptive anti-tumor response and can be recognized as positive CD2, CD3, CD5, CD7, and CD8 by IHC. They recognize and kill neoplastic cells through cell cycle inhibition, apoptosis induction, and activation of macrophage.[6,18,19] CTLs are activated by the interaction with activated CD4+ T lymphocytes,

promoting antitumor activity, but if the immune reaction and the interleukins secretion of BC leads to an immunosuppressive state, the CD4+ T lymphocytes will transform into T reg cells, inhibiting the antitumor CD8+ response.[12,20,21] Immune cells can contribute by homing to distant organs to establish pre-metastatic niches.[22,23]

T regs (CD4+ and CD25+ by IHC) are key mediators of immunotolerance, which suppress CD8+ T cell functions, promote tumor invasion and metastasis by downregulating the host immune response, and promote active secretion of chemokines through the C-C chemokine receptor type 5 (CCR5)-associated and CCR5 axis. They promote immune escape by expressing T cell markers, such as IFNγ, PD-L1, and FOXP3+. [24–26] In addition, the high concentrations of interleukins promote tumor growth.[24,27,28]

High levels of TILs are associated with the best prognosis by increasing the tumor response to neoadjuvant chemotherapy and anthracycline-based chemotherapy. He *et al.* concluded found that each 10% increment of TILs and high-level TILs (≥50%) in BC predicts improved overall survival (OS) and pathological complete response (pCR), specifically in the HER-2 overexpression and TNBC.[29–31] In one meta-analysis that included 2,987 patients with early-stage BC over a median follow-up of 113 months, it was found that TILs were associated with a reduction in recurrence, and death. [32] MDSCs such as TAMs are implicated in the induction of CTL tolerance. [33] In addition, an increase in TILs was associated with longer overall survival in TNBC but not in HER2+ and luminal BC. [34]

Natural killer (NK) cells (CD56+) are part of the native immune system and can induce tumor cell death. When activated by the contact with tumor cells, they can release perforins and granzymes, inducing cell apoptosis. [35] TILs have prognostic utility in early stage, but they can be useful as a prognostic marker during neoadjuvant treatment because they have been associated with higher rates of pCR. In addition, the presence of TILs in residual disease at the time of surgery in patients with TNBC after neoadjuvant chemotherapy indicates a favorable prognosis. [36]

After antigenic exposure, B cells can be differentiated into plasma cells that express CD38 by IHC as characteristic cell surface markers (CD138+ has been proposed to be another characteristic plasma cell surface marker, but it can be expressed in many cancers, such as BC) [37,38], with the capacity of antibody secretion. [39,40] It has been proven that these types of cells can contribute to BC tumorigenesis. In one study, they demonstrated that intratumorally CD38+ plasma cell density was an independent prognostic marker, and the higher expression of IgG genes also predicted better outcome in TNBC. [8,39,41–44] The relationship between better prognosis and high levels of CD38+ plasma cells infiltrating TNBC may be related to antigen spreading, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity. [45,46]

In summary, multiple authors conclude that the high levels of intratumorally CD8+ T cells, NK cells, and CD20+ B cells represent better prognosis than low levels of these immune cells, as shown in Figure 1. [20,47–49]

Myeloid-derived immunosuppressive cells (MDSCs)

- *Tumor-associated macrophages (TAMs)*

One of the most studied immune cell populations is TAMs. [60] These immune cells come from blood circulating monocytes that migrate to the BC niche due to an antitumor response and are then transformed into activated macrophages. Previously, macrophages were divided into two subtypes (M1 and M2) depending on the type of interleukins predominance (pro-inflammatory or anti-inflammatory, respectively). [60,61] Currently, this classification does not allow all the subgrouping of macrophages, especially TAMs, but TAMs share characteristics similar to M2 macrophages (M2-type genes, such as CD276, CD163, MS4A6A, and TGFβ1). [62–65] In order to discriminate these new macrophage populations, Eleanor *et al.* performed a systematic review of trials from 1900 to 2020 reporting OS or progression-free survival (PFS), TAM phenotype, and density. They included 22 studies with 8446 patients, concluding that CD163+ TAMs which express similar phenotype to M2 macrophages are a better predictor of poor survival outcomes in BC. [60] In addition, these immune cells express PD-L1 and PD-L2 for immunoregulation [66–68], and they can induce PD-L1 expression by secreting IFN-γ and activating the JAK/STAT signaling pathway in TNBC. [74,75]

- *Tumor-associated neutrophils (TANs)*

Neutrophils are myeloid cells that play multiple roles; however, the most important is to protect against microorganisms. [76] Currently, there is evidence that neutrophils play a role in the intratumor microenvironment in BC because they have been immersed in the inflammatory infiltrate. [22] TANs express several immunosuppressive pathways, including STAT3, TGFβ, and ROS. In addition, accumulation of immunosuppressive TANs is associated with acquired immune checkpoint blockade (ICB). [77] TANs can be divided into circulating neutrophils and tumor-infiltrating neutrophils (TINs), the latter of which are closely related to BC cells. TINs induce migration, invasion, and epithelial to mesenchymal transition (EMT) of

BC. [78] As macrophages, TANs can be polarized depending on the predominance of inflammatory interleukins and their function in N1 (anti-tumor) and N2 (pro-tumor). [79] Neutrophil polarization and neutrophil extracellular trap (NET) secretion contribute to pre-metastatic niche formation as shown in Figure 2. [69]

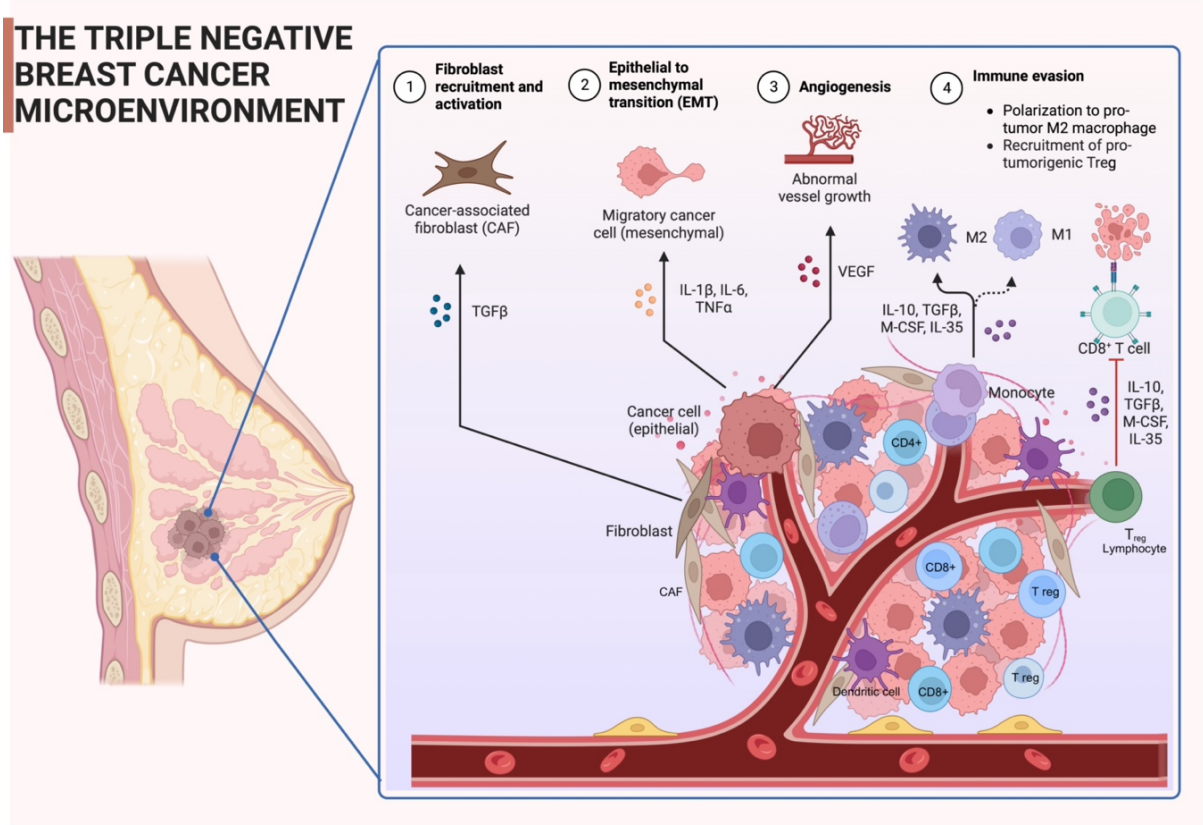

Figure 1. The TNBC Microenvironment. Several immunological characteristics are associated with tumorigenesis. 1) Fibroblast recruitment and activation may lead to CAFs, which can induce ECM remodeling, 2) Cancer cells transform into mesenchymal-like cells with the capacity to migrate, 3) Angiogenesis by the active secretion of VEGF by cancer cells, 4) Immune evasion by the creation of an immunosuppressive state. TNBC (Triple-Negative Breast Cancer); CAFs (Cancer-Associated Fibroblasts); ECM (Extracellular Matrix); EMT (Epithelial to Mesenchymal Transition); VEGF (Vascular Endothelial Growth Factor); TGFβ (Transforming Growth Factor Betha); TNFα (Tumor Necrosis Factor α); M-CSF (Macrophage Colony-Stimulating Factor); IL (Interleukin). [8–12,14–16,20–31,33,35,36,39,41–73] Created with Biorender.com

- *Cancer-associated fibroblasts (CAFs)*

CAFs (defined as positive vimentin and α-smooth muscle actin (αSMA) by IHC [80]) play an important role in the BC microenvironment. They participate in the regulation of cancer cell proliferation and invasion by promoting neoangiogenesis and extracellular matrix (ECM) remodeling. [81] However, Costa *et al.* discovered the existence of four subgroups of CAFs depending on their molecular profile and immunological activity. They identified that CAF-S1 was associated with an immunosuppressive state by increasing the survival of CD4+ CD25+ T lymphocytes, and promoting differentiation of CD25+ FOXP3+ cells, known classically as T reg cells, through B7H3, CD73, and DPP4. [81–85] The importance of CAFs can be used as a prognostic marker post-neoadjuvant chemotherapy and immunotherapy, as can be seen in the mouse model reported by Takai *et al.* [70]

- *Cancer-associated adipocytes (CAAs).*

Adipose cells in the microenvironment of mammary glands are composed of adipocytes and adipose-derived stem cells (ADSCs). They are known as CAAs when they are adjacent to BC cells. [72] CAAs are aberrant adipocytes that exhibit an aberrant phenotype, a decrease in late adipocyte differentiation markers, and overexpression of inflammatory cytokines and proteases. They mediate a complex crosstalk network between adipocytes and BC cells, which plays a role in the growth of cancer cells by inducing lipolysis, creating a rich free fatty acid environment, and promoting their proliferation, viability, migration, and invasion by secreting paracrine adipokines, including leptin, adiponectin, IL-6, and C-C motif chemokine ligand 2/5 (CCL2, and CCL5). In addition, cancer cells can regulate the ECM remodeling by secreting pro-inflammatory interleukins, such as interleukin-6 (IL-6) that

activates β catenin signaling pathway in adipocytes to form fibroblasts [71–73] However, the highly complex interactions between CAAs and BC cells are not yet fully understood. Table 1 summarizes the immunological cells associated with TNBC.

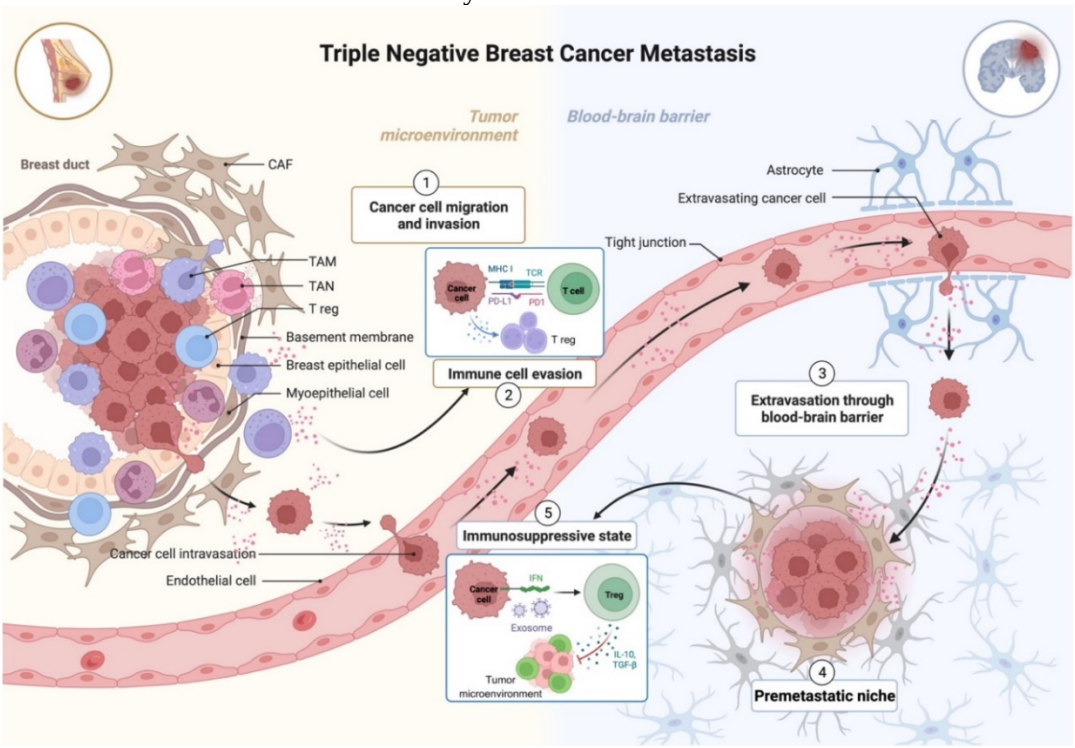

Figure 2. TNBC microenvironment and its mechanisms of invasion and metastasis. 1) Cancer cell migration and invasion through the interaction between tumor cells and tumor microenvironment cells, 2) Immune cell evasion, 3) Extravasation through the blood-brain barrier and other organs by the interaction with endothelial receptors, 4) At this time, in distant organs, there are immune cells influenced by interleukins secreted by tumor cells and the interaction with the extracellular matrix making a premetastatic niche, necessary for cancer cells, 5) Immunosuppressive state is necessary for the survival of malignant cells. CAFs (Cancer-Associated Fibroblasts); TAM (Tumor-Associated Macrophages); TAN (Tumor-Associated Neutrophils); PD-1 (Programmed Death-1); PD-L1 (Programmed Death Ligand-1); MHC-I (Major Histocompatibility Complex-I); TCR (T Cell Receptor); IFN (Interferon); TGFβ (Transforming Growth Factor Betha). [8–12,14–16,20–31,33,35,36,39,41–73] Created with Biorender.com

Table 1. Characteristics of the immunosuppressive state in the TNBC microenvironment

Microenvironment components	Mechanism of pathogenesis	Effect on Prognosis	References
Breast cancer cells	Secretion of interleukins, invasion, and angiogenesis.	Negative.	(8,9,14–16,50,52)
CD4+ T lymphocytes	Inducing antitumor response.	Positive.	(6,12,18–21)
CD8+ T/NK lymphocytes.	Promoting cancer cell death by inducing apoptosis signaling pathways.	Positive.	(35,53)
T reg lymphocytes.	Creating an immunosuppressive state by secreting anti-inflammatory interleukins, such as IL-10 and TGF-β.	Negative.	(24,27,28)
CD20+ B/CD38+ plasma cells	Antigen spreading, complement-dependent cytotoxicity, and antibody-dependent cellular cytotoxicity.	Positive.	(45,46,59)
Tumor-associated macrophages.	Creating an immunosuppressive state by secreting anti-inflammatory interleukins, such as IL-10 and TGF-β.	Negative.	(60,61,66–68,75)
Tumor-associated neutrophils.	Neutrophil polarization and NET secretion contributing to pre-metastatic niche formation.	Negative.	(69,76–79)
Cancer-associated fibroblasts.	ECM remodeling and angiogenesis.	Negative.	(70,81–85)
Cancer-associated adipocytes.	Release of free fatty acids, which are used by cancer cells.	Negative.	(71–73)

Endothelial cells

Endothelial cells are an important component of the TME, which can regulate the adhesion of tumor cells and their invasion into the endothelial monolayer. Vascular endothelial growth factor (VEGF) is the most important pro-angiogenic factor and is actively secreted by TNBC cells, promoting its growth and invasion. In addition, TNBC cells produce plasminogen activator inhibitor-1 (PAI-1) and stimulate the secretion of chemokines, such as CCL5, which interact with other TNBC cells to enhance their migration, invasion, and metastasis. [86]

Extracellular matrix (ECM)

The ECM is a complex network of different proteins whose composition and functions are necessary for the maintenance of breast tissue and TME homeostasis. [87] There are three subtypes of proteins that make up the ECM: structural proteins, such as collagen and elastin, whose function is to provide tissue strength and resilience; specialized glycoproteins, such as fibronectin, whose function is to regulate the ECM-cell adhesion; and proteoglycans, which control the passage of many growth factors and cytokines. [88] TNBC has more fibroblasts, which are necessary for ECM remodeling. ECM rigidity contributes to mechanosignaling, vascular distribution, and pro-tumorigenic immune infiltration. In addition, many ECM proteins are deregulated in TNBC, which promote invasion and metastasis [89]; however, further investigations are necessary to clarify their role in TNBC pathogenesis.

Recent advances in immune targeted therapy in patients with TNBC

The traditional treatment guidelines are based on surgery and postoperative adjuvant chemotherapy in early-stage BC; however, if the patient has inoperable locally advanced BC, the neoadjuvant chemotherapy is considered as the main component of treatment guidelines to reduce the tumor size and, if possible, a breast-conserving surgery. Systemic chemotherapy, in addition to immune checkpoint inhibitors and poly (ADP-ribose) polymerase (PARP) inhibitors, is considered in metastatic BC; however, it could be administered in early-stage TNBC as adjuvant and neoadjuvant therapy. [90]

TNBC cells express PD-L1 on their membrane surfaces, and the interaction of CTLA-4 with T cell membrane surfaces results in T cell anergy. These two immune checkpoints are important for an effective immune response. There are two types of immune checkpoint inhibitors, PD-1 inhibitors (pembrolizumab) and CTLA-4 antibody inhibitors (ipilimumab). The inhibition of these two immune checkpoints helps the immune system to recognize cancer cells by suppressing the TNBC immune evasion system. [91] In 2021, the United States Food and Drug Administration (FDA) approved pembrolizumab in combination with chemotherapy as neoadjuvant therapy for locally recurrent unresectable and metastatic TNBC that expressing PD-L1 with a combined positive score (CPS) ≥10, which is defined as the number of PD-L1-stained cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100. [92]

PARP inhibitors are the first clinically approved drugs that show promising activity in patients with BC affected by harmful mutations in breast cancer susceptibility genes 1 or 2 (BRCA1/2), which are key components in the homologous recombination repair (HRR) pathway. The mechanism of action of PARP inhibitors is the competing binding of PARP1 and PARP2 catalytic domains, which displaces nicotinamide adenine ribonucleotide (NAD+) from its active site, thus preventing the recruitment of single-strand DNA repair effectors. [93]

Nowadays, these new treatment strategies are considered the backbone of systemic therapy as neoadjuvant therapy in early-stage and advanced TNBC in contrast with alternative neoadjuvant therapies because they confer benefits in response and survival outcomes. [94]

Antitumor therapies induce TME remodeling

As mentioned above, the conventional treatment for TNBC is a combination of immune checkpoint inhibitors and chemotherapy. It is currently known that anticancer therapies play an important role in the TME remodeling. Chemotherapy induces abnormal blood vessels that lead to high interstitial pressure and poor blood perfusion in tumor tissues. [95] In one study, they characterized the TME post-treatment of patients with non-small-cell lung cancer (NSCLC) who received neoadjuvant PD-1 blockade with chemotherapy. They demonstrated that TME was completely different between pre. and post-neoadjuvant treatment. The post-neoadjuvant TME had more CTLs and NK cells, reduced immunosuppressive T regs, and expanded TAMs with anti-tumor phenotype. [96]

Radiotherapy as a therapeutic modality in BC is associated with high levels of immune infiltration because tumor cell death releases an increased concentration of damage-associated molecular patterns (DAMPs), which include ATP, calreticulin, heat shock protein, and high mobility group box 1 (HMGB1). [97] These DAMPs activate toll-like receptors on the dendritic cell membrane surface, leading to CTL activation. In addition, radiation

activates the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway, which results in an increased secretion of type I interferons (IFN), leading to the infiltration of CD8+ and CD4+ T cells and migration of MDSCs. [98] On the other hand, radiotherapy induces senescence-like fibroblasts that favor tumor growth. CAFs secrete a high concentration of CXCL12, whose function is tumor cell stemness and radiotherapy resistance. [99] In addition, radiation induces endothelial cell damage, which, despite increasing hypoxia and therefore cancer cell death, also induces NF-kB activity, resulting in IL-6, CCL1, and CCL5 production, which attracts T reg lymphocytes and promotes a pro-tumor microenvironment. [99]

As with radiotherapy, chemotherapy is another therapeutic modality in BC that increases the concentration of DAMPs by tumor cell death. Even though high TIL concentrations are associated with better prognosis, it has been shown that post-treatment TIL concentrations decrease considerably due to lymphodepletion secondary to chemotherapy. [100] Chemotherapy transforms fibroblasts into CAF-like senescent phenotype, which have pro-tumor effects by secreting growth factors. [100] In addition, chemotherapy induces IL-6 and TNF-α secretion by dysfunctional endothelial cells, promoting a proinflammatory environment. [100]

CONCLUSION

Breast cancer is the most common type of cancer in women worldwide. Triple-negative breast cancer is the most aggressive subtype of this type of cancer because it has the strongest tumor immunogenicity of all BC subtypes and represents between 12% and 20% of all breast cancer cases. Therefore, over time, new research questions have arisen to better understand the TNBC physiopathogenesis and, in this way, create new treatment strategies.

This article aimed to analyze, through an exhaustive review of the literature, the immunopathological mechanisms associated with the TME reported by various authors over time and its relationship with a worse or better prognosis of this type of cancer. The intratumor microenvironment in TNBC is a complex mechanism that ranges from any type of cell in the white series to adipose cells. Understanding the TME in TNBC will allow health professionals to establish appropriate treatment and prognosis lines for this type of cancer according to its different immunopathological characteristics, with the aim of reducing mortality in women with TNBC and increasing the survival rate.

ETHICAL CONSIDERATIONS

Not applicable.

CONFLICT OF INTERESTS

None to declare.

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