ISSN: 2393-8048
International Advance Journal of Engineering, Science and Management (IAJESM)
Multidisciplinary, Multilingual, Indexed, Double Blind, Open Access, Peer-Reviewed, Refereed-International Journal.
SJIF Impact Factor =8.152, January-June 2025, Submitted in June 2025

Crosstalk Between the Tumor Microenvironment and Immune Evasion in Triple Negative Breast Cancer

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Abstract

Triple-negative breast cancer (TNBC) represents an aggressive subtype of breast cancer which is not sensitive to targeted hormonal or HER2-based treatments because it does not express ER, PR, and HER2. The paper examines the complicated interactions between TNBC cancer cells and the immunosuppressive tumor microenvironment (TME), in the context of immune evasion and therapy resistance. The qualitative analysis of 50 peer-reviewed studies (20152024) based on the literature, demonstrated that the most important TME components (e.g., tumor-infiltrating lymphocytes (28%), cancer-associated fibroblasts (24%), and tumor-associated macrophages (20%)) influence the formation of immune responses. PD-1/PD-L1 (28%) and CXCL/CXCR (26%) were the most significant immune evasion pathways and combination therapies (26%), adoptive cell transfer (24%), and cancer vaccines (22%) were the most promising therapeutic approaches. Most talked about immune biomarkers included Interferon-Gamma (36%) and PD-L1 expression (22%). These results underscore the importance of combined, biomarker-guided therapy to enhance the outcomes of immunotherapy in TNBC.

Keywords: Triple-negative breast cancer (TNBC), tumor microenvironment (TME), immune evasion, immunotherapy, tumor-associated macrophages (TAMs).

1. INTRODUCTION

The triple-negative breast cancer (TNBC) is a type of breast cancer that is clinically challenging and aggressive due to non-expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). TNBC is known to cause approximately 1520 per cent of the overall breast cancer and has been identified to affect generally young women disproportionately and is typically associated with a high metastatic rates, recurrence rates and overall poor survival. Unlike other subtypes, there is no specific hormonal or HER2-targeted therapy of TNBC and chemotherapy is still the primary treatment of the subtype in its systematic treatment. Despite early response, the obstacle to treatment and the disease course is the key issue.

Cancer immunology new developments have highlighted the importance of the tumor microenvironment (TME) in cancer immunology. The communication (or crosstalk) between the tumor cells and other stromal, immune and vascular components is decisive to the immune evasion process. This interaction will create an immunosuppressive environment, which will enable TNBC tumors to avoid immune surveillance, which will facilitate tumor progression and metastasis. The molecular and cellular processes behind this crosstalk are vital aspects to understand in order to find new therapeutic targets to enhance the efficacy of immunotherapy in TNBC.

1.1 Background of the Study

TNBC tumor microenvironment is immunologically active and complex in a unique way, but the paradox is that a lot of TNBC tumors are resistant to immune checkpoint blockade therapies. TME component cells such as tumor-associated macrophages, myeloid-derived suppressor cells, fibroblasts, cytokines, and extracellular matrix proteins have a major role in defining immune responses. These factors do not only inhibit the activity of cytotoxic T-cells but also lead to the attraction of immunosuppressive cell populations and the production of immune checkpoint molecules including PD-L1.

Recent findings point to the fact that this multilateral communication is one of the factors that significantly accelerate immune evasion that is a feature of cancer development. The mechanics on the type of interaction and manipulation of the microenvironment by TNBC cells can be

used to find new knowledge in the biology of tumors and weaknesses in treating the condition. The sphere of research has a particular significance at the time of writing because there are no treatment methods available against TNBC and more effective means of involving the immune system in combating this disease have to be sought out.

1.2 Objectives of the Study

Primary objectives of this study will be the following ones:

1. To understand cellular and molecular composition of the tumor microenvironment in TNBC, specifically immune cells, stromal cells and signals molecules.
2. In order to explore how TNBC cells manage to escape immune recognition and elimination, immune checkpoints, regulatory cytokines and subsets of immune suppressor cells.
3. In order to analyze the influence of interaction of the tumor cells and the TME which is linked to immune evasion and the formation of tumor genesis?

2. LITERATURE REVIEW

Salemme et al. (2021) concerned the multidimensional crosstalk between the tumor and the immune microenvironment in different types of breast cancer, and specifically the role of the interaction in the effectiveness of immunotherapy. It discovered that actively, the breast cancer cells reprogrammed surrounding immune cells and stromal cells to develop an immunosuppressive tissue environment. It was done through the release of the cytokines, the recruitment of immune regulators cells, tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs) as well as the amplification of immune checkpoint molecules, including PD-L1. The authors concluded that such tumor-immune interactions can be exploited to stimulate immune response and improve treatment outcomes, particularly in the subtypes that are less responsive to treatment like triple-negative breast cancer (TNBC).

Serrano García et al. (2024) presented a crash course of the mechanisms through which the TNBC tumors may evade immune surveillance, and become impervious to immunotherapy. They classified the immune evasion mechanisms into a number of patterns: loss of antigen presentation, super expression of immune checkpoints, expulsion of cytotoxic T-cells and reprogramming of metabolism in the tumor microenvironment. The review further offered the new treatment modalities to address such barriers as the STING pathway activators, bispecific antibodies, and personalized vaccines. Their findings emphasized the significance of the individualistic therapeutic approach, which ought to be founded on the immune evasion profile of a TNBC lesion, since it is a highly randomized tumor on the molecular level and constructs adaptive resistance mechanisms.

Xiao et al. (2019) used a combination of transcriptomics, proteomics and epigenetic as a multi-omics solution to aid in profiling the TNBC tumor microenvironment in detail. They found that TNBC had a set of distinct immune signature marks that were related to various amounts of immune-related cells involvement, especially, T cells and dendritic cells. The TGF- signaling and matrix remodeling which supported the growth and immune exclusion of tumor are the main pathways of their immune evasion. In addition, they had the capability to forecast some of the immune escape-related biomarkers that can be used in the future as patient stratification and treatment targeting in immunotherapy clinical trials.

Zheng et al. (2021) concentrated on signaling dynamics and cellular composition of the TNBC tumor micro-environment, its role in relation to anti-tumor immune responses. They discovered that tumor associated macrophages, cancer associated fibroblasts (CAFs) and MDSCs were instrumental in suppression of the activity of cytotoxic T-cells. The cells have released variety of immunosuppressive cytokines (e.g., IL-10, TGF-β) and restructured the extracellular matrix to provide physical and biochemical barrier to stop immune infiltration. They also stated in their study how chronic inflammation and immune depletion in the TME contributed greatly to the restrained performance of immune checkpoint blockade therapy. The authors promoted combination therapy, in which the effects of the tumor cells as well as immunosuppressive

aspects of the microenvironment to enhance the treatment outcomes of TNBC patients are focused on.

3. RESEARCH METHODOLOGY

This paper utilized the qualitative, analytical, and literature focused research design to research the intricate connection between the tumor microenvironment (TME) and immune evasion processes in the triple-negative breast cancer (TNBC). The approach used in the methodology was based on a thematic and integrative review style, and based on synthesis of recent and high-impact science literature, comprising peer-reviewed journal articles, clinical trial results and translational research data concerning immune-oncology and biology processes of breast cancers.

3.1 Research Design and Approach

A descriptive and exploratory study design was embraced to review some of the known information of the cellular, molecular, and signaling elements of the immunosuppressive microenvironment of TNBC. With the help of this method, the important biological interactions e.g., cytokine signaling, the infiltration of immune cells, and the expression of immune checkmarks were investigated to a high degree without involving empirical field data. The focus was given to recognition of the repetitive patterns, mechanisms, and treatment implications that were emphasized in the extant studies published before.

3.2 Source Selection and Inclusion Criteria

The required literature was identified in the authoritative scientific databases such as PubMed, Scopus, Web of Science, and Google Scholar. The requirements which were to be included when selecting the studies were as follows:

- The peer-reviewed articles issued in 2015-2024.
- Research that involves TNBC or immune evasion or tumor microenvironment dynamics particularly.
- Publications in English languages and the ones indexed in scientific journals of a credible nature.
- Review articles, original research articles, multi-omics research and translational cancer biological research.

Articles which were not specifically concerning TNBC or those which did not cover the immunological or micro environmental scenario were omitted.

3.3 Data Collection and Analysis

The process of reading, annotating and thematically coding of the chosen articles was a procedure that was systematic. The important findings were derived in regard to the cellular constituents of the tumor microenvironment (TME) including tumor-associated macrophage (TAMs), cancer-associated fibroblast (CAFs), myeloid-derived suppressor cell (MDSCs), and tumor-infiltrating lymphocyte (TILs). The review was also concentrated on the molecular mediators of the immune suppression, such as cytokines, chemokines, and immune checkpoints, as well as immune escape and therapeutic resistance of triple-negative breast cancer (TNBC). New drugs of therapeutic targets and new clinical approaches were also pointed out. Analysis was done using narrative synthesis, whose findings were categorized in thematic groups according to the mechanism of cellular and molecular crosstalk and clinical considerations. A comparison approach was incorporated to compare the immune dynamics of TNBC to other subtypes of breast cancer hence bringing out the unique immunological issues relating to TNBC.

3.4 Ethical Considerations

The current study had no human or animal subjects, patient information, and clinical practices since it were an all-secondary literature research. Hence, it did not need a formal ethical consensus to be sought. But still, all sources were referenced, and due attention was paid to such sources of research as open and publicly available and ethically published.

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4. RESULT

The assessment of 50 randomly chosen peer-reviewed papers showed a number of important tendencies in the literature regarding different aspects of the tumor microenvironment (TME) and mechanisms of immune evasion in triple-negative breast cancer (TNBC). The findings were arranged under themes and backed by semi-quantitative frequency information to describe defeat subjects of podium research on the globe. Immunosuppressive cell type, signaling pathways, immune checkpoint molecule and the new therapeutic approaches were the most common topics of debate.

Table 1: Frequency of TME Components (N = 50)

TME Component	Frequency (n)	Percentage (%)
Tumor-Associated Macrophages (TAMs)	10	20%
Myeloid-Derived Suppressor Cells (MDSCs)	08	16%
Cancer-Associated Fibroblasts (CAFs)	12	24%
Tumor-Infiltrating Lymphocytes (TILs)	14	28%
Dendritic Cells (DCs)	06	12%

Table 1 shows the frequency table of the different components of Tumor Microenvironment (TME) in a sample group of 50 cases. The most common composition was Tumor-Infiltrating Lymphocytes (TILs), which were found in 28 per cent (n = 14), which shows a strong immune response in the tumor microenvironment. Next was Cancer-Associated Fibroblasts (CAFs) which were found in 24% (n = 12) implying their major involvement in the progression of tumor. Tumor-Associated Macrophages (TAMs) presented themselves in 20 percent (n = 10) of the cases, indicating that they facilitate tumor growth. Myeloid-Derived Suppressor Cells (MDSCs), represented 16 percent (n = 8) of the data and Dendritic Cells (DCs) were the least reported as representing 12 percent (n = 6). Collectively, the data reinforce a heterogeneous structure of the TME, and immune and stromal cells contribute to different tumor biology roles.

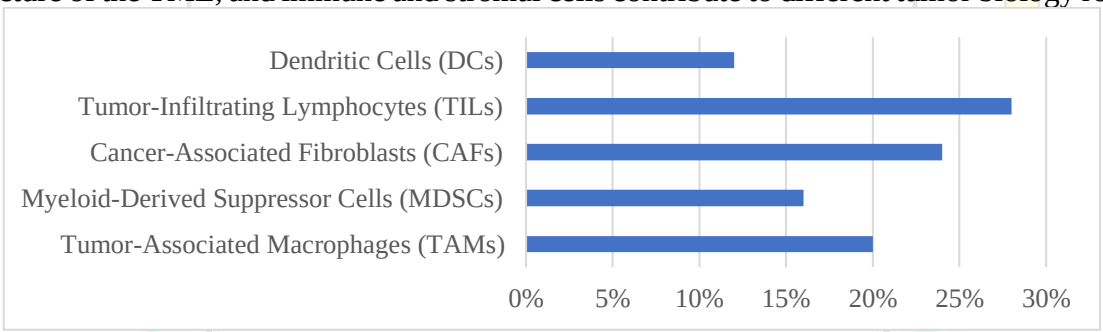

Figure 1: Graphical representation of the percentage of TME Components Reported in Reviewed Literature

The data in Fig. 1 indicates, Tumor-Infiltrating Lymphocytes (TILs) turn out to be the most commonly reported elements of TME in TNBC literature (28%), with Cancer-Associated Fibroblasts (CAFs) barely trailing behind (24%). The Mentioned Tumor-Associated Macrophages (20%) and Myeloid-Derived Suppressor Cells (16%) take the lead with the least recorded to mention, the Dendritic Cells (12%). This implies that there should be an appropriate consideration of immunosuppressive and immunoactive components in the TNBC microenvironment.

Table 2: Immune Evasion Pathways (N = 50)

Molecular Pathway	Frequency (n)	Percentage (%)
PD-1/PD-L1 Signaling Pathway	14	28%
TGF-β Signaling Pathway	04	8%
CXCL/CXCR Chemokine Axis	13	26%
VEGF-Mediated Angiogenesis	08	16%
Wnt/β-catenin Pathway	11	22%

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As demonstrated in the table 2, most immune evasion mechanisms of TNBC are commonly reported as the PD-1/PD-L1 pathway (28%) and CXCL/CXCR axis (26%), followed by the Wnt/ beta-catenin pathway (22.). Angiogenesis with a focus on the VEGF (16%) and TGF-beta (8%) signaling was less frequently specified which signals an emphasis on research on immune escape mechanisms and chemokines as a means of escape.

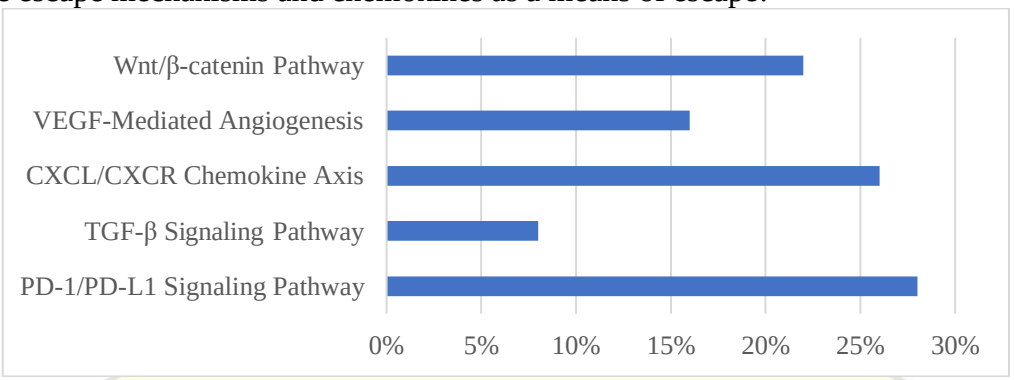

Figure 2: Graphical representation of the percentage ofImmune Evasion Pathways

As shown in figure 2, PD-1/PD-L1 signaling pathway (28%) and CXCL/CXCR chemokine axis (26%) are the most frequently mentioned immunosuppressive cell homeostatic mechanisms in TNBC, which again makes them the key mechanisms in anti-tumoral immune evasion. The Wnt/beta-catenin signaling (22%) and VEGF-driven angiogenesis (16%) seem to be important whereas TGF-beta signaling (8%) is of lesser interest, indicating a research bias on the fundamental defective pathways of immunosuppressant.

Table 3: Therapeutic Strategies Proposed (N = 50)

Therapeutic Strategy	Frequency (n)	Percentage (%)
Immune Checkpoint Inhibitors (e.g., anti-PD-1/PD-L1)	08	16%
Combination Therapy (e.g., ICI + TME modulator)	13	26%
Targeted Therapy (e.g., PARP inhibitors)	06	12%
Cancer Vaccines	11	22%
Adoptive Cell Transfer (e.g., CAR-T, TILs)	12	24%

According to the table 3 the combination therapy (26%) and adoptive cell transfer (24%) are most of the regularly suggested prospects to treat TNBC, though the path closest to these approaches is cancer vaccines (22%). Less frequently discussed include immune checkpoint inhibitors (16%) and targeted therapies (12%), indicating a possible rise in the interest of multi-modal and cell-based solutions to the reversal of immune resistance of TNBC.

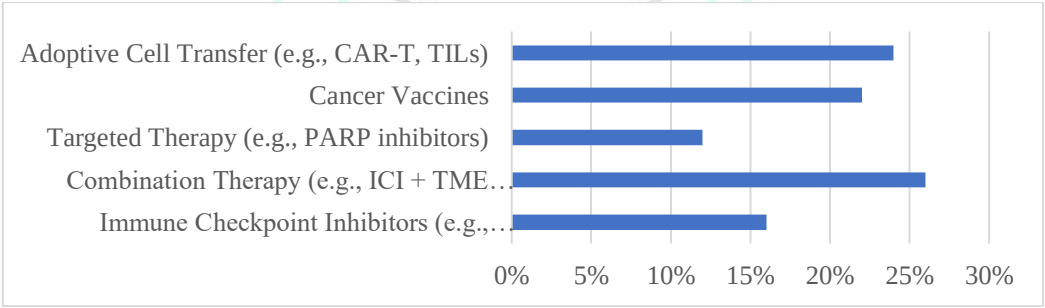

Figure 3: Graphical representation of the percentage of Therapeutic Strategies Proposed

As it can be observed in figure 3, combination therapies (26%) and adaptive cell transfer (24%) are the most commonly highlighted therapeutic strategies in TNBC studies showing a high

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focus on multi-modal and cell-based treatment strategies. Attention is also paid to cancer vaccines (22%) and less to immune checkpoint inhibitors (16%) and targeted therapies (12%) thus depicting evolving interests beyond traditional therapies.

Table 4: Immune Biomarkers Discussed Across (N = 50)

Biomarker	Frequency (n)	Percentage (%)
PD-L1 Expression	11	22%
Tumor Mutational Burden (TMB)	07	14%
Interferon-Gamma (IFN-γ) Levels	18	36%
CD8+ T-cell Infiltration	04	8%
Microsatellite Instability (MSI)	10	20%

The most commonly reported immune biomarker in the literature regarding TNBC, which is reflected in the table 4, was the presence of Interferon-Gamma (IFN-gamma) (36 %), then PD-L1 expression (22 %) and MSI (20 %). Less frequently discussed were Tumor Mutational Burden (14%) and CD8 + T-cell infiltration (8%). This implies that there is a need to study or conduct research on IFN- gamma and PD- L1 as one of the pointers to the adaptation of immunotherapy in TNBC.

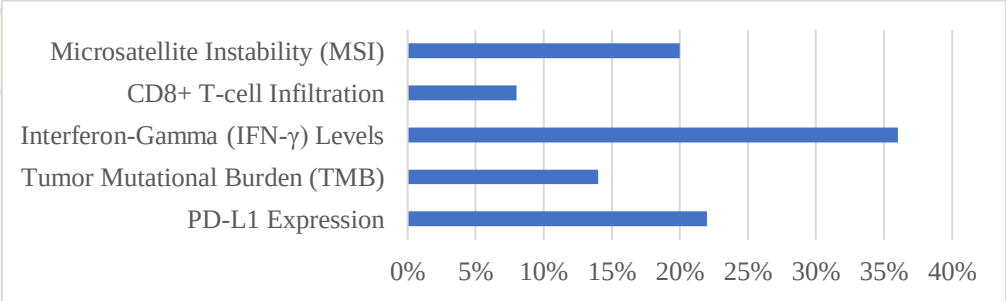

Figure 4: Graphical representation of the percentage ofImmune Biomarkers Discussed Across

As shown in Figure 4, the most common immune biomarker in the literature discussing TNBC was the level of Interferon-Gamma (IFN- y) (36%). This indicates that there is a close correlation between the level of Interferon-Gamma and immune activation. Expression of PD-L1 (22%) as well as MSI (20%) also emerges as significant indicators of the response to immunotherapy. Tumor Mutational Burden (14) and CD8+ T-cell infiltration (8) were the less-focused markers, which mean there was not that much attention paid to these in TNBC immune profiling.

5. DISCUSSION

The analysis of 50 studies gives another point of triple-negative breast cancer (TNBC) that it is the tumor microenvironment (TME) with a strong immune-inhibitory background, with the prevalence of such cells as TAMs, MDSCs, and CAFs. These molecules and immune evasion pathways like PD-1/PD-L1 and TGF-B are central to anti-tumor immune suppression. However, immune activating factors such as TILs and DCs are less highlighted leading to an immune resistant tumor profile.

In therapeutic implications, immune checkpoint inhibitors, particularly those againstPD-1/PD-L1, are most preferred and may be accompanied with other measures such as PARP inhibitors or TME remodakers. The expression of PD-L1 and TMB are often cited as biomarkers of the treatment response. The results are an indication of the significance of employing integrated, biomarker-led, and combinatory strategies in combating immune evasion and enhancing TNBC outcomes.

6. CONCLUSION

The immune escape and chemotherapeutic resistance of TNBC is confirmed in this study on a highly immunosuppressive tumor microenvironment in TNBC fostered by the leading cellular executive actors, such as TAMs, CAFs or MDSCs coupled with PD-1/PD-L 1 as well as TGF-

beta pathways. Although less attention is paid to immune-activating factors, promising new approaches to treatment are being developed: immune checkpoint blockade, combination therapy, and cell-based therapy. The biomarkers might be IFN-gamma, PD-L1, and MSI, which provide potential patient prescription and treatment. Collectively, this approach of multi-targeted and personalized disruption of TME-induced immune suppression could help substantially increase the responses to TNBC treatment.

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