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Introduction to Immune Escape and Mechanistic Foundations

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Abstract: Breast cancer represents a biologically heterogeneous malignancy in which immune evasion plays a pivotal role in disease progression and therapeutic resistance. Among the diverse mechanisms underlying tumor immune escape, immune checkpoint pathways have emerged as central regulators of anti-tumor immunity. These checkpoints, including programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1), cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), lymphocyte activation gene-3 (LAG-3), T-cell immunoglobulin and mucin-domain containing-3 (TIM-3), and T cell immunoreceptor with Ig and ITIM domains (TIGIT), function physiologically to maintain immune homeostasis but are frequently co-opted by tumor cells to suppress immune surveillance. In breast cancer, particularly in aggressive subtypes such as triple-negative breast cancer, the upregulation of these inhibitory pathways contributes to T-cell exhaustion, impaired antigen presentation, and an immunosuppressive tumor microenvironment enriched with regulatory T cells, myeloid-derived suppressor cells, and tumor-associated macrophages. These factors collectively facilitate tumor progression, metastasis, and resistance to conventional therapies including chemotherapy, radiotherapy, and endocrine treatment. Recent advances in immunotherapy, especially immune checkpoint inhibitors, have provided new therapeutic opportunities by restoring anti-tumor immune responses. Clinical trials evaluating agents targeting PD-1/PD-L1 and CTLA-4 have demonstrated promising, albeit variable, outcomes in breast cancer patients. However, therapeutic efficacy remains limited by intrinsic and acquired resistance mechanisms, tumor heterogeneity, and immune-related toxicities. The identification of predictive biomarkers such as PD-L1 expression, tumor-infiltrating lymphocytes, and tumor mutational burden has improved patient stratification, yet their clinical utility is constrained by variability and lack of standardization. Emerging research focusing on novel checkpoint targets, combinatorial therapeutic strategies, and precision immunotherapy approaches offers potential avenues to overcome these challenges. This review comprehensively examines the role of immune checkpoints in breast cancer progression and treatment resistance, highlighting mechanistic insights, clinical developments, biomarker strategies, and future perspectives aimed at optimizing immunotherapeutic outcomes.

Keywords: Immune checkpoints; Breast cancer; PD-1/PD-L1; CTLA-4; Tumor microenvironment

1.0 Introduction – Epidemiology, Immune Surveillance, and Immune Checkpoints

Breast cancer remains the most frequently diagnosed malignancy among women worldwide and a leading cause of cancer-related mortality, reflecting its complex biological heterogeneity and evolving resistance mechanisms [1]. Despite significant advances in early detection and targeted therapies, a substantial proportion of patients develop recurrence or metastatic disease, often driven by immune evasion strategies. The concept of immune surveillance, originally proposed to explain the immune system's role in detecting and eliminating nascent tumor cells, has evolved into a more dynamic framework encompassing immunoediting, which includes elimination, equilibrium, and escape phases [2]. During the elimination phase, innate and adaptive immune cells recognize tumor-associated antigens and mediate cytotoxic responses. However, tumors that survive this phase enter equilibrium, where immune pressure selects for less immunogenic clones. Eventually, these clones acquire the capacity to evade immune detection and destruction, leading to clinical disease progression.

Central to this immune escape process are immune checkpoints, which are regulatory pathways that maintain self-tolerance and prevent excessive immune activation under physiological conditions. Tumors exploit these checkpoints to suppress anti-tumor immunity. Key inhibitory receptors such as programmed death-1 (PD-1) and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) are expressed on T cells and function as negative regulators of T-cell activation [3]. Their ligands, including PD-L1, are often overexpressed in tumor cells and stromal components, contributing to an immunosuppressive microenvironment. The upregulation of immune checkpoints in breast cancer is particularly evident in aggressive subtypes such as triple-negative breast cancer (TNBC), where immune evasion plays a dominant role in disease progression and therapeutic resistance [4].

The clinical relevance of immune checkpoints has been underscored by the success of immune checkpoint inhibitors (ICIs), which have transformed cancer therapy by restoring anti-tumor immunity. However, their efficacy in breast cancer has been variable, highlighting the need for a deeper understanding of tumor-immune interactions and resistance mechanisms. The interplay between tumor cells, immune cells, and the microenvironment forms a complex network that determines disease outcome. Understanding these interactions is critical for developing effective immunotherapeutic strategies.

2.0 Immunobiology – Innate and Adaptive Immune Responses in Breast Cancer

The immune response to breast cancer involves a coordinated interplay between innate and adaptive immune systems, each contributing distinct yet interconnected roles in tumor recognition and elimination. Innate immune cells, including natural killer (NK) cells, macrophages, and dendritic cells (DCs), serve as the first line of defense against tumor cells. NK cells are capable of recognizing and killing tumor cells in a non-major histocompatibility complex (MHC)-restricted manner, primarily through the detection of stress-induced ligands and the absence of self-MHC molecules [5]. However, tumor cells can evade NK cell-mediated cytotoxicity by downregulating activating ligands or secreting immunosuppressive cytokines such as transforming growth factor-beta (TGF-β).

Macrophages within the tumor microenvironment exhibit remarkable plasticity and can adopt either pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes. Tumor-associated macrophages (TAMs), which are predominantly M2-like, promote tumor progression by enhancing angiogenesis, suppressing immune responses, and facilitating metastasis [6]. Dendritic cells play a pivotal role in antigen presentation and the initiation of adaptive immune responses. However, in breast cancer, DCs often exhibit impaired maturation and reduced antigen-presenting capacity, limiting their ability to activate T cells effectively.

Adaptive immunity, mediated by T and B lymphocytes, is essential for sustained anti-tumor responses. Cytotoxic CD8+ T cells recognize tumor antigens presented by MHC class I molecules and induce apoptosis of cancer cells through the release of perforin and granzymes. Helper CD4+ T cells support this response by producing cytokines that enhance cytotoxic activity and promote immune memory. However, the activation and function of T cells are tightly regulated by immune checkpoints. Chronic antigen exposure in the tumor microenvironment leads to T-cell exhaustion, characterized by the upregulation of inhibitory receptors such as PD-1, LAG-3, and TIM-3, resulting in diminished effector function [7].

B cells also contribute to anti-tumor immunity through antibody production and antigen presentation, although their role in breast cancer remains complex and context-dependent. The presence of tumor-infiltrating lymphocytes (TILs), particularly CD8+ T cells, has been associated with improved prognosis and response to therapy in certain breast cancer subtypes, especially TNBC and HER2-positive tumors [8]. However, the immunosuppressive environment often limits their effectiveness.

3.0 Immune Checkpoint Pathways – Mechanistic Insights

Immune checkpoint pathways are critical regulators of immune homeostasis, but their dysregulation in cancer leads to immune suppression and tumor progression. Among the most extensively studied pathways are PD-1/PD-L1 and CTLA-4, along with emerging checkpoints such as LAG-3, TIM-3, and TIGIT.

The PD-1/PD-L1 pathway plays a central role in peripheral immune tolerance. PD-1 is expressed on activated T cells, while its ligand PD-L1 is expressed on tumor cells and immune cells within the tumor microenvironment. Binding of PD-L1 to PD-1 inhibits T-cell receptor signaling, reduces cytokine production, and induces T-cell exhaustion [9]. This pathway is frequently upregulated in breast cancer, particularly in TNBC, where it contributes to immune escape.

CTLA-4, another inhibitory receptor expressed on T cells, regulates early stages of T-cell activation in lymphoid organs. It competes with the co-stimulatory receptor CD28 for binding to B7 molecules on antigen-presenting cells. CTLA-4 engagement leads to reduced T-cell proliferation and activation, thereby limiting immune responses [10].

Emerging checkpoints such as LAG-3, TIM-3, and TIGIT further contribute to immune suppression. LAG-3 binds to MHC class II molecules and negatively regulates T-cell activation. TIM-3 interacts with ligands such as galectin-9, leading to T-cell exhaustion and apoptosis. TIGIT competes with the activating receptor CD226 for binding to CD155, inhibiting T-cell and NK cell function [11]. These pathways often co-express with PD-1, suggesting synergistic roles in immune suppression.

Table 1: Immune Checkpoint Molecules and Mechanisms

Checkpoint	Ligand	Mechanism of Action	Effect on Immunity
PD-1	PD-L1/PD-L2	Inhibits TCR signaling	T-cell exhaustion
CTLA-4	B7-1/B7-2	Blocks co-stimulation	Reduced T-cell activation
LAG-3	MHC-II	Suppresses T-cell proliferation	Immune inhibition
TIM-3	Galectin-9	Induces T-cell apoptosis	T-cell dysfunction
TIGIT	CD155	Inhibits NK and T cells	Immune suppression

4.0 Breast Cancer Subtypes – Immunological Differences

Breast cancer is a heterogeneous disease classified into distinct molecular subtypes based on hormone receptor (HR) status, HER2 expression, and gene expression profiles. These subtypes exhibit significant differences in their immunogenicity and response to immunotherapy. Hormone receptor-positive (HR+) breast cancers are generally considered “immune cold” tumors, characterized by low levels of TILs and limited immune activation. The tumor microenvironment in HR+ cancers is often dominated by immunosuppressive factors, making them less responsive to immune checkpoint blockade [12].

HER2-positive breast cancers display intermediate immunogenicity, with higher levels of TILs compared to HR+ tumors. HER2-targeted therapies, such as trastuzumab, can enhance immune responses through antibody-dependent cellular cytotoxicity (ADCC), highlighting the interplay between targeted therapy and immune mechanisms [13].

Triple-negative breast cancer (TNBC) is the most immunogenic subtype, characterized by high mutational burden, increased TILs, and elevated PD-L1 expression. These features make TNBC more responsive to immunotherapy, although resistance remains a significant challenge [14].

5.0 Tumour Microenvironment – Immunosuppressive Networks

The tumor microenvironment (TME) in breast cancer is a complex and dynamic ecosystem composed of tumor cells, immune cells, stromal cells, and extracellular matrix components. It plays a critical role in shaping immune responses and promoting tumor progression. Immunosuppressive cells such as regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and TAMs are key contributors to immune evasion.

Tregs suppress effector T-cell function through the secretion of inhibitory cytokines such as IL-10 and TGF-β, as well as through direct cell-cell interactions [15]. MDSCs inhibit T-cell activation by depleting essential nutrients and producing reactive oxygen species. TAMs promote tumor growth by enhancing angiogenesis and suppressing immune responses.

Hypoxia within the TME further exacerbates immune suppression by inducing the expression of PD-L1 and other inhibitory molecules. The interplay between these factors creates a hostile environment for anti-tumor immunity, facilitating immune escape and treatment resistance.

6.0 Immune Escape Mechanisms

Breast cancer cells employ multiple strategies to evade immune detection and destruction. One of the primary mechanisms is the upregulation of PD-L1, which inhibits T-cell activity. Tumors may also downregulate antigen presentation machinery, including MHC class I molecules, reducing their visibility to cytotoxic T cells [16]. Additionally, the secretion of immunosuppressive cytokines and the recruitment of inhibitory immune cells further contribute to immune escape.

7.0 Treatment Resistance

Immune checkpoints are intricately linked to resistance mechanisms against conventional therapies. Chemotherapy and radiotherapy can modulate immune responses, but chronic exposure may lead to adaptive resistance characterized by increased PD-L1 expression. Endocrine resistance in HR+ breast cancer has also been associated with immune suppression and altered checkpoint signaling [17].

8.0 Immunotherapy – Checkpoint Inhibitors and Combination Strategies

The emergence of immune checkpoint inhibitors (ICIs) has fundamentally reshaped the therapeutic landscape of oncology, including breast cancer, by targeting the inhibitory pathways that dampen anti-tumor immune responses. Among these, monoclonal antibodies directed against PD-1, PD-L1, and CTLA-4 have demonstrated clinical efficacy, particularly in immunogenic subtypes such as triple-negative breast cancer (TNBC). Agents such as Pembrolizumab, Nivolumab, Atezolizumab, and Ipilimumab function by disrupting inhibitory receptor–ligand interactions, thereby restoring T-cell activity and promoting tumor cell destruction [18].

Mechanistically, PD-1 blockade reinvigorates exhausted T cells within the tumor microenvironment, enhancing cytokine production and cytotoxicity. CTLA-4 inhibition, on the other hand, primarily acts at the priming phase of T-cell activation in lymphoid tissues, promoting the expansion of tumor-specific T cells [19]. However, monotherapy with ICIs has shown limited efficacy in certain breast cancer subtypes, necessitating the exploration of combination strategies.

Combination therapies aim to overcome resistance and enhance therapeutic efficacy by targeting multiple pathways simultaneously. For instance, ICIs are often combined with chemotherapy, which can induce immunogenic cell death and increase antigen presentation. The combination of Pembrolizumab with chemotherapy has demonstrated improved progression-free survival in patients with metastatic TNBC in clinical trials such as KEYNOTE-355 [20]. Similarly, the combination of Atezolizumab with nab-paclitaxel showed initial promise in the IMpassion130 trial, although subsequent studies have yielded mixed results [21].

Beyond chemotherapy, ICIs are being combined with targeted therapies such as HER2 inhibitors, PARP inhibitors, and anti-angiogenic agents. PARP inhibitors, for example, increase DNA damage and neoantigen formation, thereby enhancing tumor immunogenicity. Additionally, dual checkpoint blockade, such as PD-1 plus CTLA-4 inhibition, has shown synergistic effects in preclinical models, although toxicity remains a concern [22]. Emerging strategies also include combinations with vaccines, adoptive cell therapies, and oncolytic viruses, all aimed at amplifying anti-tumor immune responses.

Table 2: Approved Immune Checkpoint Inhibitors and Clinical Outcomes in Breast Cancer

Drug	Target	Indication	Clinical Outcome
Pembrolizumab	PD-1	TNBC (metastatic, PD-L1+)	Improved PFS and OS
Atezolizumab	PD-L1	TNBC (PD-L1+)	Increased PFS (variable OS)
Nivolumab	PD-1	Investigational	Modest activity
Ipilimumab	CTLA-4	Investigational	Limited monotherapy efficacy

9.0 Biomarkers – PD-L1, Tumor-Infiltrating Lymphocytes, and Tumor Mutational Burden

The identification of reliable biomarkers is critical for predicting response to immunotherapy and guiding treatment decisions in breast cancer. PD-L1 expression is the most widely used biomarker for selecting patients for PD-1/PD-L1 inhibitors. Immunohistochemical assays are employed to assess PD-L1 levels on tumor cells and immune cells, with higher expression generally correlating with improved response to ICIs [23]. However, variability in assay methodologies and cutoff thresholds has limited its predictive accuracy.

Tumor-infiltrating lymphocytes (TILs) represent another महत्वपूर्ण biomarker, reflecting the host immune response against the tumor. High levels of TILs, particularly CD8+ cytotoxic T cells, are associated with better prognosis and increased sensitivity to immunotherapy, especially in TNBC and

HER2-positive breast cancers [24]. TILs also serve as a surrogate marker of tumor immunogenicity and may predict response to chemotherapy.

Tumor mutational burden (TMB) is an emerging biomarker that quantifies the number of somatic mutations within a tumor genome. High TMB is associated with increased neoantigen formation, which enhances immune recognition. Although breast cancer generally exhibits lower TMB compared to other malignancies such as melanoma or lung cancer, subsets of TNBC and BRCA-mutated tumors demonstrate higher mutational loads and may benefit from ICIs [25].

Additional biomarkers under investigation include gene expression signatures, microsatellite instability (MSI), and circulating immune markers. The integration of multiple biomarkers into composite predictive models is likely to improve patient stratification and optimize therapeutic outcomes.

10.0 Challenges – Toxicity, Resistance, and Tumor Heterogeneity

Despite the promise of immunotherapy, several challenges limit its widespread efficacy in breast cancer. Immune-related adverse events (irAEs) are a significant concern, arising from the nonspecific activation of the immune system. These toxicities can affect multiple organ systems, including the skin, gastrointestinal tract, liver, and endocrine glands, and may require immunosuppressive treatment [26].

Primary and acquired resistance to ICIs represent major obstacles. Primary resistance occurs when tumors fail to respond to therapy, often due to low immunogenicity, absence of TILs, or defective antigen presentation. Acquired resistance develops after an initial response and may involve mechanisms such as upregulation of alternative immune checkpoints, loss of neoantigens, or alterations in signaling pathways such as JAK/STAT [27].

Tumor heterogeneity further complicates treatment, as different regions of the tumor may exhibit distinct molecular and immunological profiles. This spatial and temporal heterogeneity can lead to variable responses to therapy and the emergence of resistant clones. Additionally, the immunosuppressive tumor microenvironment continues to pose a barrier to effective immune activation.

11.0 Future Perspectives – Precision Immunotherapy

The future of immunotherapy in breast cancer lies in the development of precision medicine approaches that tailor treatment to individual patient characteristics. Advances in genomics, transcriptomics, and proteomics are enabling the identification of novel targets and predictive biomarkers. Personalized immunotherapy strategies, including neoantigen-based vaccines and adoptive T-cell therapies, hold significant promise for enhancing treatment efficacy [28].

Emerging checkpoint targets such as LAG-3, TIM-3, and TIGIT are being actively investigated in clinical trials, with the aim of overcoming resistance to existing therapies. Combination strategies that integrate immunotherapy with targeted agents, radiotherapy, and metabolic modulators are also being explored. Furthermore, the use of artificial intelligence and machine learning in analyzing complex biological data may facilitate the development of predictive models and optimize treatment selection.

12.0 Conclusion

Immune checkpoints play a central role in breast cancer progression and treatment resistance by enabling tumors to evade immune surveillance and suppress anti-tumor immunity. While significant progress has been made in understanding these pathways and developing targeted therapies, challenges such as resistance, toxicity, and heterogeneity remain. Continued research into the molecular mechanisms of immune regulation and the development of innovative therapeutic strategies will be essential for improving outcomes in breast cancer patients.

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