International Journal of Immunology Research
www.immunologyjournal.in
Online ISSN: 2664-8873, Print ISSN: 2664-8865
Received: 15-09-2022, Accepted: 14-10-2022, Published: 18-10-2022
Volume 4, Issue 1, 2022, Page No. 14-16

The impact of breast cancer on systemic immunity

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DOI: https://doi.org/10.33545/26648865.2022.v4.i1a.22

Abstract
Breast cancer significantly influences systemic immunity, presenting challenges and opportunities for therapeutic intervention. This review explores the multifaceted interactions between breast cancer and the immune system, highlighting mechanisms of immune suppression, evasion, and modulation employed by cancer cells. We discuss the role of chronic inflammation in cancer progression, the alterations in the tumor microenvironment that favor tumor growth while inhibiting effective immune responses, and the impact of conventional treatments on immune function. Special attention is given to the exploitation of immune checkpoint pathways by breast cancer cells, which leads to the development of immune checkpoint inhibitors as a promising treatment strategy. Furthermore, we examine the complex process of metastasis and its implications for immune surveillance and response. Understanding these interactions is crucial for advancing the development of immunotherapies that aim to enhance the immune system's ability to combat breast cancer, thereby opening new avenues for improving patient outcomes.

Keywords: Systemic immunity, immune suppression, immune evasion, chronic inflammation, tumor microenvironment, immune checkpoint inhibitors, metastasis, immunotherapy

Introduction
Breast cancer stands as a formidable adversary in the realm of oncology, posing significant challenges not just through its local tumor effects but also its systemic impact on the body's immune defense mechanisms. The intricate dance between breast cancer and the immune system is characterized by a dual nature: while the immune system endeavors to recognize and eliminate cancer cells, breast cancer cells develop sophisticated strategies to evade immune surveillance and foster an immunosuppressive environment. This dynamic interaction significantly influences disease progression, metastasis, and patient outcomes.
The systemic impact of breast cancer on immunity encompasses a broad spectrum of effects, including the modulation of immune cell populations, alteration of cytokine and chemokine profiles, and dysregulation of immune checkpoints. These effects can lead to a diminished immune response, not only against the tumor itself but also against other pathogens, reflecting the profound implications of breast cancer on the overall immune health of patients.
Understanding the systemic effects of breast cancer on immunity is not only critical for grasping the disease's complexity but also for guiding the development of new therapeutic strategies. In recent years, the field of cancer immunotherapy has emerged as a promising frontier, offering novel approaches to harness the power of the immune system in combating cancer. However, the success of these.

Objective of study
The main objective of this study is to investigate the impact of breast cancer on systemic immunity.

Literature Reviews
Research indicates significant changes in the systemic immunity of breast cancer patients, characterized by alterations in both the numbers and functions of various immune cells. Studies have shown an increase in regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) in the blood of breast cancer patients, which are associated with immunosuppression and poor prognosis (Mozaffari F *et al*., 2009) [1]. These cells inhibit the activity of effector immune cells, such as cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells, crucial for tumor surveillance and elimination.
Conversely, there is evidence of decreased functionality and numbers of NK cells and CTLs in breast cancer patients, contributing to reduced tumor immunosurveillance and increased susceptibility to metastasis (Shakhar K *et al*., 2017) [2]. This imbalance between effector and regulatory immune cells highlights a critical aspect of how breast cancer can modulate systemic immunity to favor tumor progression.

Breast cancer also influences the systemic immune response through the dysregulation of cytokine and chemokine production. The tumor and its microenvironment can secrete various cytokines and chemokines that promote an immunosuppressive state, such as interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), while simultaneously reducing the levels of pro-inflammatory cytokines critical for effective anti-tumor immunity (Sun Y *et al*., 2019) [3]. This cytokine imbalance can facilitate tumor evasion from immune surveillance and contribute to the progression and metastasis of breast cancer.

The systemic effects of breast cancer on immunity also extend to the impairment of immune surveillance mechanisms. Tumor cells can evade detection by expressing immune checkpoint molecules like PD-L1, which bind to PD-1 on T cells, leading to their exhaustion and inability to attack tumor cells (Edechi *et al*., 2019) [5]. Additionally, breast cancer cells can undergo phenotypic changes that reduce their immunogenicity, a process known as immune editing, further complicating the immune system's ability to target and eliminate these cells effectively.

The systemic impact of breast cancer on immunity has significant implications for treatment strategies. The understanding of how breast cancer modulates the immune system has led to the development of immunotherapies aimed at reactivating the immune response against tumor cells. Treatments such as immune checkpoint inhibitors, which block PD-1/PD-L1 interactions, have shown promise in some breast cancer patients, particularly those with triple-negative breast cancer (TNBC) (Spitzer MH *et al*., 2017) [6].

Tumor Immunoediting and Immune Evasion

Tumor immunoediting is a process that describes the dual role of the immune system in both controlling and shaping the immunogenicity of tumors. This process can be divided into three phases: elimination, equilibrium, and escape. Initially, the immune system can recognize and eliminate nascent tumor cells through mechanisms involving cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells. However, some tumor cells may survive these attacks due to inherent or acquired mutations that make them less visible or more resistant to immune responses. During the equilibrium phase, a state of dormancy is achieved where the immune system suppresses tumor growth without completely eradicating it. This phase can select for tumor cells that are more adept at evading immune detection, leading to the escape phase. In the escape phase, tumor cells proliferate and spread due to their ability to avoid immune recognition and destruction, often through the expression of immune checkpoint molecules like PD-L1, which bind to PD-1 on T cells and induce their inactivation.

Immunosuppressive Tumor Microenvironment

The tumor microenvironment (TME) of breast cancer plays a pivotal role in mediating the interactions between cancer cells and the immune system. The TME is characterized by a complex mix of tumor cells, immune cells, stromal cells, and extracellular matrix components, all of which can influence tumor progression and metastasis.

One key feature of the breast cancer TME is its ability to create an immunosuppressive milieu that hampers effective anti-tumor immunity. This is achieved through various mechanisms, including:

- **Recruitment of Regulatory T Cells (Tregs) and Myeloid-Derived Suppressor Cells (MDSCs):** These cells can inhibit the activity of effector immune cells, such as CTLs and NK cells, through the secretion of immunosuppressive cytokines (e.g., TGF-β, IL-10) and other mechanisms.
- **Expression of Immune Checkpoint Molecules:** Tumor cells and certain immune cells within the TME can express molecules like PD-L1, which interact with PD-1 on T cells to induce their exhaustion and dysfunction.
- **Metabolic Competition:** Tumor cells can alter the metabolic landscape of the TME to deprive effector immune cells of essential nutrients, impairing their function.
- **Induction of an Inflammatory Environment:** Chronic inflammation within the TME can promote tumor growth and immune evasion by fostering an environment conducive to cancer cell survival and proliferation.

Systemic Effects of Breast Cancer on Immunity

Alterations in Immune Cell Populations

Breast cancer can significantly alter the composition and function of various immune cells in the bloodstream and peripheral tissues. One of the hallmark changes is the increase in regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), both of which play crucial roles in maintaining immune tolerance and suppressing anti-tumor immunity. Tregs, in particular, are known to inhibit the activity of effector T cells and natural killer (NK) cells, reducing the immune system's ability to target and eliminate cancer cells. Similarly, MDSCs suppress T cell activation and proliferate in response to tumor-derived factors, further contributing to an immunosuppressive environment conducive to cancer progression.

Conversely, the numbers and activity of effector immune cells, such as cytotoxic T lymphocytes (CTLs) and NK cells, may be diminished in breast cancer patients. These cells are essential for identifying and destroying cancerous and virally infected cells. Their reduced functionality not only hampers the body's ability to fight the tumor but also weakens its overall infectious disease defense.

Impact on Immune Surveillance

The immune system's surveillance mechanism is designed to detect and eliminate nascent tumor cells. However, breast cancer can impair this process through several strategies, including the expression of immune checkpoint

molecules like PD-L1, which bind to PD-1 receptors on T cells, leading to their exhaustion and ineffective tumor cell targeting. Additionally, breast cancer cells can undergo immune editing, altering their antigenic profile to become less recognizable to the immune system, a process facilitated by mutations and epigenetic changes driven by the tumor microenvironment.

Cytokine and Chemokine Dysregulation

Cytokines and chemokines, signaling molecules critical for initiating and directing immune responses, are often dysregulated in breast cancer. Tumors can produce immunosuppressive cytokines such as TGF-β and IL-10, which inhibit the activation and proliferation of immune effector cells and promote the expansion of Tregs and MDSCs. Conversely, pro-inflammatory cytokines like TNF-α and IL-6, which are also elevated in breast cancer, can contribute to chronic inflammation, another risk factor for cancer progression. The altered cytokine and chemokine milieu not only supports tumor growth and spread but also disrupts systemic immune regulation, affecting the body's response to infections and other diseases.

Conclusion

The review of current literature on the impact of breast cancer on systemic immunity underscores the profound influence that breast cancer exerts beyond the primary tumor site, affecting the body's immune response in complex and multifaceted ways. This influence manifests through alterations in immune cell populations, with an increase in immunosuppressive cells like regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), alongside a decrease in cytotoxic cells such as natural killer (NK) cells and cytotoxic T lymphocytes (CTLs). These changes contribute to an environment that not only favors tumor growth and metastasis but also diminishes the immune system's capacity to surveil and respond to malignancies effectively.

Furthermore, breast cancer induces significant cytokine and chemokine dysregulation, promoting a systemic immunosuppressive state that facilitates tumor evasion and progression. The disease's ability to evade immune detection through mechanisms like immune checkpoint expression and immune editing underscores the sophistication of its interaction with the immune system, representing a critical challenge for effective treatment.

This complex interplay between breast cancer and systemic immunity opens new avenues for therapeutic intervention, particularly through immunotherapy. The potential of treatments such as checkpoint inhibitors, vaccines, and adoptive cell therapies is considerable, yet their efficacy varies widely among individuals and cancer subtypes, highlighting the necessity for personalized treatment approaches.

The need for further research is pressing, both to elucidate the detailed mechanisms through which breast cancer affects systemic immunity and to identify biomarkers that can predict responses to immune-based therapies. Additionally, exploring combinations of immunotherapy with traditional treatments could yield more effective, multimodal therapeutic strategies. In conclusion, understanding the systemic impact of breast cancer on the immune system is crucial for the development of targeted, effective, and personalized treatments, promising a future where the power of the immune system is harnessed to combat this pervasive disease more effectively.

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