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Commentary
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Breast Cancer: Unraveling a Multifactorial Process

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Abstract

Significant improvements in breast cancer treatment and care have been made over the past decades, increasing the overall survival of such patients. However, many years of experimental and clinical research have shown that our knowledge of the altered genes that are expressed in breast cancer cells is insufficient to combat this disease. Breast cancer must be considered a complex tissue that engages in constant crosstalk with the host. The relevance of this interplay in influencing the development and outcome of the disease has provided new approaches for shaping the tumor microenvironment and host lifestyle in preventing and curing this type of tumor.

Commentary

Initially, researchers described cancer as a progression of genetic mutations in a deranged tumor mass and subsequently identified and characterized many of the tumor suppressor genes and oncogenes that are involved in the susceptibility to cancer [1]. For many years, breast cancer research has focused solely on tumor cell genes that are expressed or altered in breast cancer to understand the initiation, progression, and response to therapy of these tumors. As a result, successful achievements came from the identification of Estrogen (ER) and Progesterone (PgR) receptors and the amplification of the HER2 oncogene. With the aid of high-throughput technologies, myriad experimental and clinical data have led to the clinical use of these markers in predicting tumor aggressiveness and curing breast cancer patients. Targeted therapies against ER and HER2, in combination with chemotherapy, have improved patient survival [2]. Despite the rise in the incidence of breast cancer, survival rates have increased significantly due to the ability to make earlier diagnoses and administer more precise therapies. However, researchers have quickly realized that these findings have been insufficient to combat this disease.

Although breast cancer develops when cells in the breast begin to grow uncontrollably, they become malignant if they invade the surrounding tissues or spread to distant areas of the body. Thus, based on the initial belief that the intrinsic properties of cancer cells are the only determinant in cancer development and progression, researchers are examining the molecular complexity and heterogeneity that underlie these clinical outcomes in transformed cells and other cell types and non-cell components that sustain the growth and invasiveness of cancer cells. The current view of breast cancer as a complex tissue has revealed the dynamic interplay between tumor cells and the stroma, comprising fibroblasts, adipose cells, the vasculature, immune cells, an insoluble Extracellular Matrix (ECM), and the milieu of cytokines and growth factors. The interaction between cancer cells and the surrounding microenvironment has been investigated in many studies, which have demonstrated the importance of each stromal component in the dynamic development and progression of breast cancer. For example, during the onset of breast cancer, fibroblasts that lie adjacent to tumor cells become activated and acquire a drastically different phenotype with regard to morphology, immunophenotype, proliferation rate, cytokine profile, deposition of ECM proteins, and gene expression pattern. Such acquired characteristics render them able to sustain tumor progression and affect the response to treatment [3].

The levels and organization of ECM molecules are altered abnormally during the development of breast carcinoma. These changes effect the modification of the ECM architecture, favoring tumor development by nursing carcinoma cells and the surrounding stromal cells, including endothelial and immune cells [4]. The interplay between breast cancer cells and ECM components can also affect the recruitment of immune cells. Sangaletti et al. [5] recently demonstrated that elevated levels of the matricellular protein SPARC in the ECM results in the formation of a highly immunosuppressive micro-environment composed of infiltrating regulatory T cells, mast cells, and myeloid-derived suppressor cells (MDSCs).

In the presence of cancer cells, adipocytes alter their phenotype to downregulate differentiation

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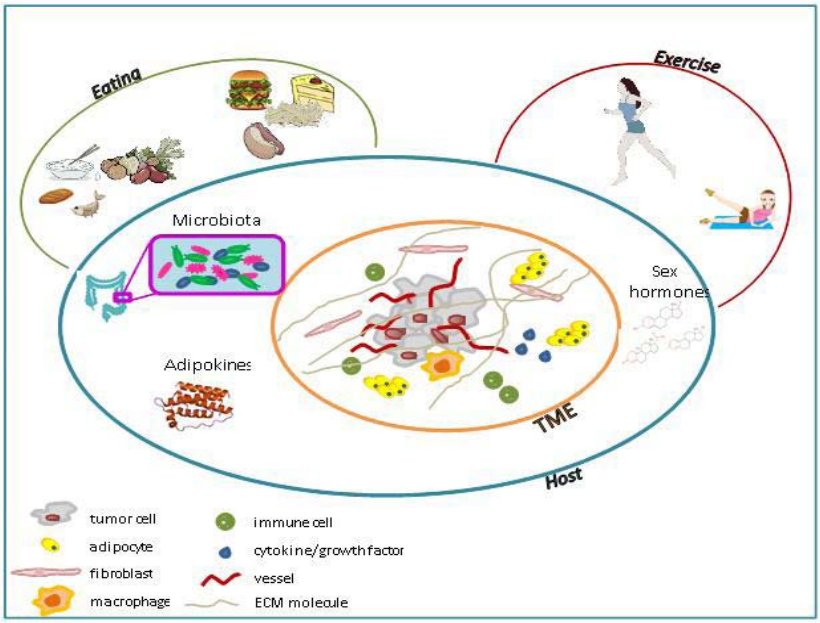

Figure 1: Breast cancer: A multifactorial process. Breast cancer develops and progresses through the interplay between molecularly altered breast epithelial cells and the surrounding Tumor Microenvironment (TME). Host characteristics, influenced by lifestyle, significantly contribute to the tumor/stroma interplay, disease progression, and response to therapy.

markers and lipid content and, analogous to Cancer-Associated Fibroblasts (CAFs), become cancer-associated adipocytes, undergoing molecular changes that are similar to those in adipocytes of persons with obesity and metabolic disorders [6], who have a higher cancer risk and poorer prognosis in various tumors, including breast cancer [7,8]. The mechanisms by which obesity contributes to breast cancer are complex and are not completely understood.

In a cross-sectional study of 1,779 patients with primary invasive breast cancer who were treated at a single institution in which we correlated markers of dysmetabolism and inflammation with immunohistochemically defined breast cancer subtypes [9], overweightedness/obesity and large waist circumference were significantly associated with the aggressive triple-negative and luminal B (HER2-negative and positive) subtypes, respectively, in premenopausal women. Obesity and metabolic syndrome were significantly linked to postmenopausal hormone receptor-positive tumors. Recently, higher baseline Body Mass Index (BMI) and greater increases in BMI were found to negatively affect outcomes in pre-, peri-, and early postmenopausal patients who were treated with adjuvant systemic therapy, except in those who were given trastuzumab [10].

Adipokines, small-peptide hormonal growth factors, are secreted primarily by adipocytes of white adipose tissue, which constitutes nearly 90% of normal breast tissue. Oversecretion of deleterious proinflammatory adipokines (e.g.: leptin), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) and hyposecretion of beneficial adipokines, such as adiponectin, have been reported in obese subjects [11]. Leptin upregulates aromatase, an enzyme that mediates a key step in the biosynthesis of estrogens, and transactivates ERα in the absence of its ligand; it promotes EMT and breast cancer stem cell phenotype; and also shapes the tumor microenvironment in the mammary gland by inducing the migration of endothelial cells, angiogenesis, and the recruitment of macrophages, monocytes, and neutrophils [12]. These actions contribute significantly to neoplastic transformation and breast cancer cell growth. A chronic inflammatory status, such as in obesity, can cause oxidative damage and inactivate proteins that are involved in DNA repair and apoptotic control, thus promoting cancer cell initiation and growth [13].

Increased infiltration by immunosuppressive macrophages has been observed in breast carcinoma lesions in obese women. White adipose depots, in breast tissue of overweight women, present many inflammatory foci that comprise dead adipocytes bordered by macrophages. Lipids in adipocytes undergo high turnover by nearby macrophages to sustain inflammation, supporting neoplastic transformation. Lipolysis-derived saturated fatty acids activate macrophages through Toll-Like Receptor (TLR) 4, stimulating NF-κB signaling, which in turn facilitates tumor outgrowth through the transcription of proinflammatory genes that govern immune cell recruitment and activity [14].

Although it initially suppresses tumor growth by destroying cancer cells, the immune system promotes tumor progression by establishing conditions in the tumor microenvironment that facilitate tumor outgrowth [15]. Preclinical and clinical studies have shown that breast cancer progression is under immunosurveillance and that chemotherapy and radiotherapy are particularly efficient if they elicit a robust tumor-targeting immune response. Thus, adipocyte-induced protumor inflammatory responses might also counteract the effects of therapies.

Body weight and adiposity are associated with the composition of the gut Microbiota [16]. The human gut, containing a least 10^{13} microorganisms, is a metabolic "organ" that processes otherwise indigestible components of our diet and regulates energy storage in the host. Dietary alterations, such as overeating in obesity, affect the gut microbiota composition and gut integrity, leading to the penetration of gut microbes and their products and the activation of TLRs on adipocytes. Given that obesity is a risk factor for tumor development and recurrence and overall mortality in breast cancer patients, areas of research have expanded to include lifestyle modifications that are

directed toward healthy gut microbiota and weight management.

In addition to the increase in cancer risk due to overnutrition, qualitative food composition is likely to be linked to the risk of developing breast cancer. A dietary inflammatory index that is based on nutrients that improve C - reactive protein (CRP) levels in serum correlates significantly with the risk of developing breast cancer in postmenopausal women [17]. Diets that are rich in fruits and vegetables and specific nutrients, such as (n-3) fatty acids, fibers, and vitamins E and C, have been associated with lower levels of CRP and inflammation. Moreover, engaging in even minimal amounts of exercise protects against breast cancer and improves the side effects of the treatment, quality of life, and overall survival in patients. These benefits share several mechanisms, including the depletion of adipose tissue, preservation of bone and muscle mass, reduction of insulin resistance, and improvements in immune and cardiovascular function [18].

Because only 5% to 10% BCs are related to inherited genetic alterations, breast cancer risk is considered to be largely attributable to environmental and lifestyle factors. The western obesogenic diet also increases the risk for breast cancer by inducing early menarche and delaying menopause [19], thus offering opportunities for early nutritional protection to prevent tumor development. Among genetically based breast cancer cases, the incidence of those that are caused by inherited mutations in BRCA1 or BRCA2 in early life has risen over the past several decades, implicating lifestyle risk factors, including diet, overweightedness, and low physical activity. In this regard, randomized controlled trials on diet and physical activity in BRCA mutation carriers are ongoing [20] and the COS study [21] to determine whether moderate improvements in nutrition, BMI, and physical fitness influence the incidence and progression of breast cancer in women with a genetic susceptibility.

Considering that breast cancer development and progression depend on stochastic mutational events and environmental factors (Figure 1), lifestyle modifications that provide a healthful diet, nutritional supplements, and regular exercise or a combination of these components could successfully mitigate the hazardous mutations that arise due to bad luck.

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