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Review

Fat Biology in Triple-Negative Breast Cancer: Immune Regulation, Fibrosis, and Senescence

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Obesity, now officially recognized as a disease requiring intervention, has emerged as a significant health concern due to its strong association with elevated susceptibility to diverse diseases and various types of cancer, including breast cancer. The link between obesity and cancer is intricate, with obesity exerting a significant impact on cancer recurrence and elevated mortality rates. Among the various subtypes of breast cancer, triple-negative breast cancer (TNBC) is the most aggressive, accounting for 15% to 20% of all cases. TNBC is characterized by low expression of estrogen receptors and progesterone receptors as well as the human epidermal growth factor 2 receptor protein. This subtype poses distinct challenges in terms of treatment response and exhibits strong invasiveness. Furthermore, TNBC has garnered attention because of its association with obesity, in which excess body fat and reduced physical activity have been identified as contributing factors to the increased incidence of this aggressive form of breast cancer. In this comprehensive review, the impact of obesity on TNBC was explored. Specifically, we focused on the three key mechanisms by which obesity affects TNBC development and progression: modification of the immune profile, facilitation of fibrosis, and initiation of senescence. By comprehensively examining these mechanisms, we illuminated the complex interplay between TNBC and obesity, facilitating the development of novel approaches for prevention, early detection, and effective management of this challenging disease.

Key words: Triple-negative breast cancer, Obesity, Tumor microenvironment, Immunity, Fibrosis, Senescence

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INTRODUCTION

Obesity, which is becoming increasingly prevalent, has gained official recognition as a 'disease' requiring intervention. According to the World Health Organization, obesity is defined as a body mass index equal to or greater than 30 kg/m^2.[1] This condition is closely linked to susceptibility to metabolic diseases, cardiovascular diseases, musculoskeletal diseases, depression, Alzheimer's disease, and various types of cancer, including breast cancer.[2-8] The link between obesity and cancer is complex, with obesity being associated with increased risk of cancer.[9] Furthermore, obesity is associated with increased risk of cancer recurrence and higher mortality rates.[10] Therefore, management of obesity is important for improving cancer outcomes, emphasizing the need for early intervention in patients with early-stage cancer.

Triple-negative breast cancer (TNBC) has low expression of estrogen receptor and progesterone receptor as well as the human epidermal growth factor 2 receptor protein, and it accounts for 10% to 15% of breast cancer cases.[11,12] It is the most aggressive type of breast cancer and is characterized by a low response to treatment and strong invasive properties; few studies have been performed in this type breast cancer.[13] While there are many complexities yet to be uncovered, current research has revealed a multitude of factors influencing the development of TNBC. Age, race, genetic variations, family history, oral contraceptive use, and weight, including obesity or overweight, have emerged as notable contributors.[14-18]

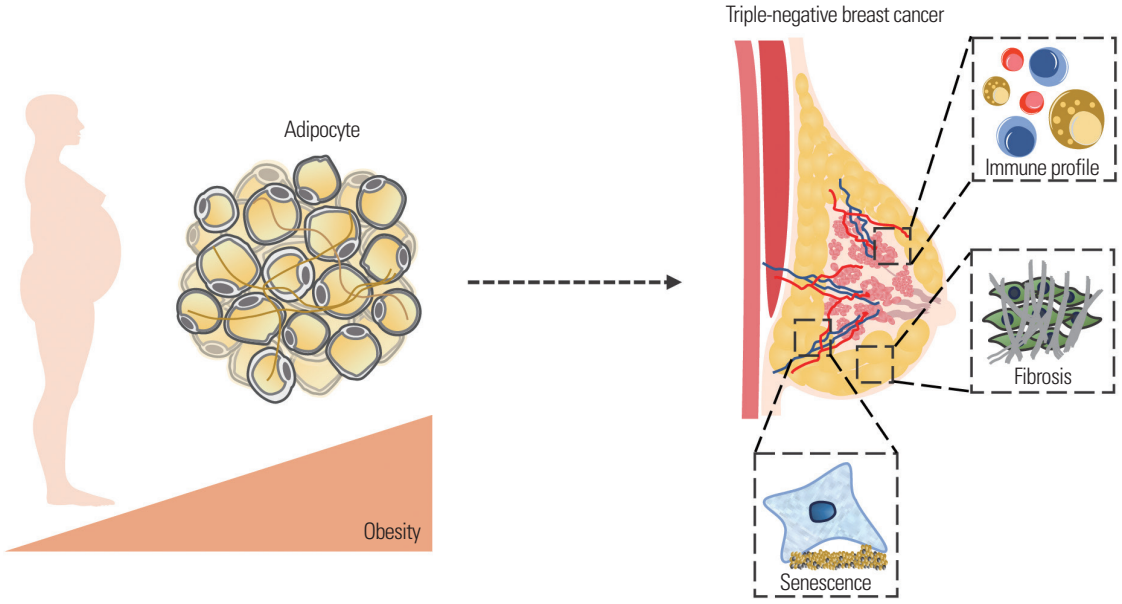

Figure 1. The immune profile, fibrosis, and senescence in adipocytes and triple-negative breast cancer (TNBC). The similarities between the tumor microenvironment in TNBC and obesity and their effects on the development of cancer. Natural killer (NK), natural killer T (NKT) cells, and lymphocytes indicate modification of the immune network, fibroblast and collagen participate in the facilitation of fibrosis, and senescent cells and senescence-associated secretory phenotype are related to initiation of senescence.

An abundance of research has delved into the intricate correlations between obesity and TNBC. It has been firmly established that a TNBC diagnosis is notably more prevalent among individuals classified as obese, as opposed to those who are not obese. Recent investigations have studied distinct clinical disparities within TNBC that are intimately linked to obesity.[19,20] Notably, obese TNBC patients frequently present with more substantial tumor dimensions and elevated T-stage categorizations and exhibit a propensity for higher tumor grades.[21] Nevertheless, the exact influence of metabolic changes in adipose tissue on the progression of TNBC remains a mystery, underscoring the need for additional research.

Therefore, we aimed to investigate the influence of obesity on TNBC based on existing research. We focused on how obesity impacts TNBC development through three mechanisms: modification of the immune profile, facilitation of fibrosis, and initiation of senescence (Fig. 1).

IMPACT OF CANCER-ASSOCIATED ADIPOCYTES AND TNBC PROGRESSION

Recent studies have revealed that obese animals exhibit a state of hypoxia in adipose tissue.[22,23] This hypoxia leads to interactions between adipose cells and stromal vascular cells, driving tumor initiation and progression.[24] Within adipose tissue, hypoxia triggers increased insulin resistance; decreased adiponectin; and elevated leptin, adipocyte apoptosis, and endoplasmic reticulum (ER) stress.[25-28] Ultimately, these changes result in favorable microenvironment alterations for tumor development, such as enhanced vascularization and extracellular matrix (ECM) remodeling.

In summary, the impact of obesity on tumorigenesis can be summarized in three main facets. First, there is an increase in inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6). This cytokine upregulation leads to chronic inflammation, primarily associated with breast cancer and colorectal cancer.[29,30] Second, the elevated level of leptin activates oncogenic transcription factors, linked to breast cancer and prostate cancer.[31,32] Last, the reduction in adiponectin interferes with proliferation and mutagenesis, potentially leading to breast cancer and lung cancer.[33] As a result of these characteristics, adipose tissue has emerged as a crucial component in the tumor microenvironment (TME).

Through these insights, it has become evident that obesity significantly influences various cancers, with a pronounced impact on breast cancer. In TNBC with obesity, these insights are aligned with the previously mentioned effects of obesity on tumor development.

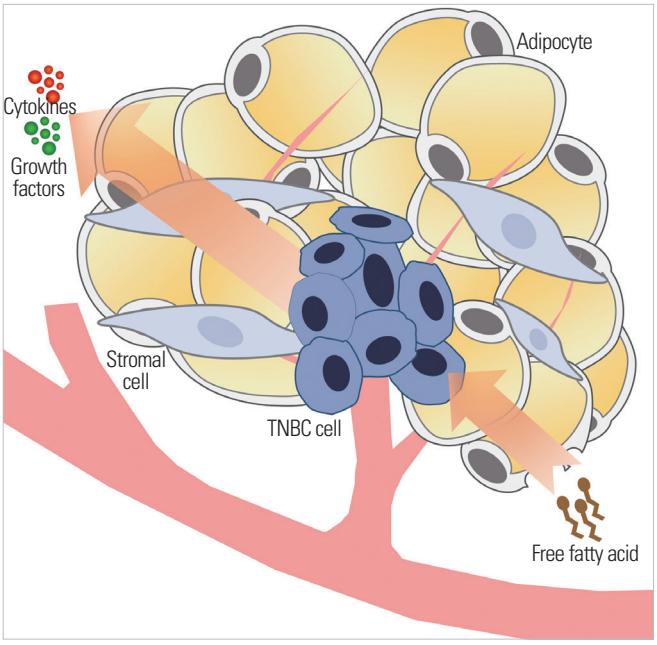

Figure 2. The impact of obesity on triple-negative breast cancer (TNBC) tumor development. Adipocytes secrete free fatty acids (FFA) toward TNBC cells, and both TNBC cells and stromal cells are influenced by FFA. TNBC cells respond to these signals by releasing cytokines and growth factors, acting in tandem with stromal cells to promote TNBC tumor progression.

These cancer-associated adipocytes release free fatty acids into breast cancer cells,[34] triggering the secretion of pro-inflammatory cytokines and growth factors, including interferon-gamma, insulin-like growth factor (IGF)-1, IL-6, IL-8, leptin, and TNF-α (Fig. 2).[35-37] These insights are consistent with research indicating that obese TNBC patients have elevated levels of inflammatory cytokines TNF-α and IL-6 and lower level of adiponectin compared to that in non-obese patients.[20] Remarkably, these inflammatory cytokines accelerate tissue inflammation and activate signaling pathways, contributing to the aggressive nature of TNBC.

In TNBC, adipose tissue stem cells play a significant role in facilitating tumor growth, epithelial-mesenchymal transition (EMT), and invasion of breast cancer cells, which ultimately lead to changes in the composition of the ECM. Specifically, obesity contributes to increased secretion of leptin into TNBC cells. This mechanism converts adipose stem cells and triggers EMT in cancer cells,[38] modifying the TNBC microenvironment and amplifying metastatic potential through the leptin-mediated pathway. Research has shown that when leptin is combined with cyclic adenosine monophosphate-elevating agents, it has the capability of inducing apoptosis in TNBC.[39]

Conversely, adiponectin exerts a negative influence on breast tumor formation.[20] Adiponectin expression is notably lower in breast cancer tissue from obese individuals than in individuals that are not obese. The impact of adiponectin varies based on estrogen receptor status, with an elevated leptin-to-adiponectin ratio showing a more pronounced association with TNBC than human epidermal growth factor 2 receptor -positive breast cancer.[40] Furthermore, adiponectin hinders cell proliferation, invasion, and migration, while also triggering apoptosis and autophagic cell death in estrogen receptor and progesterone receptor-negative breast cancer.[41]

In conclusion, adipose tissue impacts TNBC in multiple ways. Cytokines derived from adipose tissue promote the migration and proliferation of TNBC cells, disrupting normal adipokine and hormone levels. This disruption fosters the promotion of mitogenic and mutagenic pathways, advancing tumor progression in obese TNBC patients.

MODIFICATION OF THE IMMUNE PROFILE OF TNBC WITH OBESITY

Numerous studies have emphasized the impact of obesity on the immune landscape, often referred to as "meta-inflammation."[42,43] With the development of obesity, there is an increase in immune infiltration and angiogenesis, leading to increased inflammation.[42] These findings have been emphasized in multiple studies, highlighting the significance of this phenomenon in the context of obesity-related pathophysiology. Therefore, there should be a focus on the influence of obesity on the heterogeneity of the immune system in TNBC.

The expression of the immune checkpoint ligand programmed death ligand-1 (PD-L1) in obesity is associated with immune suppression, and the expression of the programmed death-1 receptor (PD-1) and PD-L1 in TNBC shows an intermediate level of variability.[44,45] In TNBC tumors, PD-L1 expression inhibits the interaction between PD-L1 and the PD-1 receptor, restoring T-cell activation and supporting antitumor immunity.[46] Interestingly, several studies have indicated that TNBC patients with obesity, characterized by an exhausted immune response, may have impaired checkpoint function.[47,48]

Moreover, insulin signaling plays a critical role in the development

of obesity-related cancers, including TNBC. The IGF system is closely associated with tumorigenesis and the development and progression of tumor cells.[49] Leptin directly affects the activation of the IGF-1 receptor, creating mutual activation between leptin and the IGF-1 receptor.[50] This phenomenon leads to migration and proliferation of TNBC cells, as higher level of IGF-1 receptors is observed in TNBC. In addition, TNBC exhibits rapid growth that is dependent on glucose utilization and aerobic glycolysis.[51] This rapid glycolytic growth and increased glucose uptake create an environment rich in anabolic precursors, promoting accelerated growth and contributing to mitochondrial dysfunction which, in turn, enhances resistance to cancer cell apoptosis.[52]

Furthermore, obesity has a significant impact on both the activity and numbers of natural killer (NK) and natural killer T (NKT) cells.[53] Obesity induces alterations in the phenotype and functionality of NK cells. These changes, along with obesity-induced shifts in the function and number of T-cells, collectively contribute to increased cancer susceptibility in obese individuals.[54] In addition, there is an increase in immature, non-cytotoxic NK cells and a decrease in mature, cytotoxic NK cells in obese patients with TNBC.[55,56] These findings suggest that a reduction in both the number and function of NK cells can be anticipated in TNBC patients who are obese.

In summary, TNBC is characterized by enhanced fatty acid synthase and glycolysis,[51] whereas obesity is associated with immune paralysis of NK cells. Specifically, obesity exerts an inhibitory effect on NK cell function, which normally contributes to the control of tumor cell growth and metastasis. However, in the presence of breast cancer cells, NK cell function is impaired, resulting in reduced antitumor activity.[57] Collectively, the interplay between obesity and TNBC triggers a complex immune response that promotes cancer cell proliferation.

FACILITATION OF FIBROSIS OF OBESE TNBC

ECM proteins serve a dual role in regulating the mechanical properties of adipose tissue and influencing adipogenesis.[58] When obesity leads to an increase in adipocyte volume and tissue mass, it disrupts the normal functioning of adipose tissue. This disruption triggers inflammation and eventually results in adipose tissue fibrosis.[59] In addition, homeostasis and organization of the epithelial tissue are affected by the ECM in adipocytes.[60] This process highlights the critical role of ECM proteins in adipose tissue homeostasis and the pathogenesis of adipose tissue fibrosis associated with obesity. Stiff and increased ECM contributes to the local and systemic pathologies associated with obesity, promoting collagen formation around adipocytes, which leads to fibrosis.[61] In addition, high ECM stiffness leads to EMT in cancer cells, ultimately resulting in local migration, invasion, metastasis, and the loss of epithelial polarity.[62-65] These conditions are particularly notable in mammary tissue, where collagen deposition and alignment increase around mammary ducts and pre-neoplastic lesions.[66] Specific changes are characterized by increased expression of collagen VI and reduced elastin in subcutaneous fat, signifying alterations in ECM properties.[67] These changes affect tissue ability to retain secreted molecules, with transforming growth factor beta 1 (TGFβ1) expression being a notable example. TGFβ1 is known to induce EMT in tumor cells and to foster the growth of cancer-associated fibroblasts (CAFs) within the TME.[68] In obese adipose tissue, TGFβ1 expression is upregulated.[69] Initially, it is produced in an inactive or latent form, requiring extracellular activation before it can bind to receptors. Consequently, latent TGFβ1 present in the ECM binds to latent TGFβ1 proteins and matrix components, including decorin, which sequesters inactive TGFβ1 until activation. Within the mammary ECM of obese patients, decorin becomes enriched and forms a complex with latent TGFβ1, resulting in increased TGFβ1 storage.[70] This influences both tumor cell proliferation and CAF development. Specifically, ECM components participate in TNBC progression by influencing the activation of the signaling pathways that govern the properties of TNBC cells.[67] An interesting observation is the increased presence of collagen VI in both TNBC and obese ECM. This increase is mediated through ECM, growth factors, and mitogen-activated protein kinase (MAPK) signaling pathway interactions. Specifically, collagen VI has been found to impact TNBC cell adhesion, two-dimensional migration, and three-dimensional invasion.[71] In simpler terms, obesity can profoundly alter the composition of ECM in TNBC tissue, potentially enhancing its local invasiveness and metastatic potential.

Hypoxia, characterized by insufficient tissue oxygenation due to reduced blood supply, has been extensively studied as a major con-

tributor to fibrosis in obese adipose tissue.[72] In adipose tissue, there is a notable increase in the expression of hypoxia-induced factor-1 alpha (HIF-1α).[73] Furthermore, the growth of tumors triggers intra-tumoral hypoxia, leading to concurrent activation of the HIF-1α pathway within the TME.[74] Elevated HIF-1α in breast tumors, including TNBC, can cause metabolic changes in tumor cells and promote metastasis.[75,76] These findings suggest that upregulation of HIF-1α stimulates tumor formation and contributes to aggressive tumor growth.

SENESCENCE IN THE MICROENVIRONMENT OF TNBC PATIENTS WITH OBESITY

The impact of aging in the microenvironment on obese TNBC patients has not yet been clearly elucidated. However, the influence of obesity and breast cancer, especially TNBC, on cellular aging has been well-established. Therefore, we were focused on the effects of obesity and TNBC on cellular aging.

The increase in inflammatory markers in obese patients might be due to certain cell populations undergoing senescence.[77] Several studies have inferred that adipose tissue serves as a primary reservoir of senescent cells.[78,79] Cellular senescence can be induced by multiple factors, such as DNA damage, telomere attrition, oxidative damage, mitotic stress, mitochondrial dysfunction, ER stress, and oncogene activation.[80-86] DNA damage, which is frequently induced by telomere shortening and early onset cellular senescence, is the key factor in triggering senescence among these factors. Similarly, activation of oncogenes, such as DNA replication stress, can lead to DNA damage in TNBC. Consequently, there is a significant increase in the expression of DNA damage markers, dysregulated checkpoints, and suppressed DNA repair pathways in TNBC.[87]

Senescent cells also release a set of molecules known as senescence-associated secretory phenotype (SASP). This group of molecules is comprised of inflammatory factors, proteases, and growth factors, all of which foster an inflammatory environment and contribute to tumor development and progression.[88,89] SASP factors are classified into three groups: soluble signaling factors (chemokines, growth factors, and interleukins), secreted proteases, and secreted insoluble protein and ECM components.[90] The most important element here is the ECM. According to the results of these studies, obesity in TNBC promotes the expression of cancer stem cell and MET genes through leptin.[91] Concomitantly, senescent cells exhibit an increased adenosine monophosphate:adenosine triphosphate ratio.[92] adenosine monophosphate-activated protein kinase (AMPK), a key regulator of growth and cellular processes such as autophagy and cell polarity, is activated by the reduced intracellular adenosine triphosphate level.[93]

Furthermore, senescent cells impact ER stress and the unfolded protein response, leading to activation of these pathways, increasing the demand for SASP production.[94] This activation triggers a heightened demand for SASP production and results in alterations in cell morphology through increased activity of the mammalian target of rapamycin (mTOR) in senescent cells.[95] The composition of the SASP is influenced by various signaling pathways, including the mTOR pathway. Secretion by senescent cells plays a significant role in SASP.[96] In obesity, the expression levels of ER stress and SASP increase, and these increases are associated with senescence. Furthermore, there is a noticeable connection between the functional aspects of invasion, migration, and ER stress in TNBC.[97,98] Evidence is emerging to suggest that various cellular stresses associated with obesity and tumors play a role in cellular senescence, resulting in accumulation of senescent cells in adipose tissue and various types of cancer.

CONCLUSION

Overall, we sought to clarify how obesity affects the growth and advancement of this aggressive type of cancer. We explored three main mechanisms: changes in the immune system, promotion of fibrosis, and onset of senescence. Each of these mechanisms significantly impacts the challenging clinical landscape of TNBC in individuals dealing with obesity.

Considering the complexity of these interactions, a multidisciplinary approach is essential when devising personalized treatment strategies. These strategies should address not only tumor-related factors, but also the metabolic effects of obesity. Such a comprehensive approach holds promise for improving outcomes and prognoses in TNBC patients who are dealing with obesity.

Subsequent research should concentrate on specific intervention

points within the intricate interplay of obesity and TNBC. Targeting these points could disrupt the cancer-promoting effects of obesity, potentially leading to more refined treatment strategies and ultimately better outcomes for those with obesity and TNBC.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

Study concept and design: CML and SF; drafting of the manuscript: CML and SF; critical revision of the manuscript: CML and SF; obtained funding: SF; and study supervision: SF.

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