

Review Article



Obesity and Breast Cancer: The Role of Crown-Like Structures in Breast Adipose Tissue in Tumor Progression, Prognosis, and Therapy

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Conflict of Interest

The authors declare that they have no competing interests.

ABSTRACT

Obesity is associated with increased risk and aggressiveness of many types of cancer. Women with obesity and breast cancer are more likely to be diagnosed with larger and higher-grade tumors and have higher incidence of metastases than lean individuals. Increasing evidence indicates that obesity includes systemic, chronic low-grade inflammation, and that adipose tissue can act as an important endocrine site, secreting a variety of substances that may regulate inflammation, immune response, and cancer predisposition. Obesity-associated inflammation appears to be initially mediated by macrophage infiltration into adipose tissue. Macrophages can surround damaged or necrotic adipocytes, forming “crown-like” structures (CLS). CLS are increased in breast adipose tissue from breast cancer patients and are more abundant in patients with obesity conditions. Moreover, the CLS index-ratio from individuals with obesity seems to influence breast cancer recurrence rates and survival. In this review, we discuss the most recent cellular and molecular mechanisms involved in CLS establishment in the white adipose tissue of women with obesity and their implications for breast cancer biology. We also explain how CLS influence the tumor microenvironment and affect breast cancer behavior. Targeting breast adipose tissue CLS can be a crucial therapeutic tool in cancer treatment, especially in patients with obesity.

Keywords: Adipocytes; Adipose tissue; Breast neoplasms; Macrophages; Obesity

INTRODUCTION

Overweight and obesity are major risk factors for cancer and chronic diseases such as diabetes, insulin resistance, and cardiovascular disease [1]. These conditions are currently on the rise in low- and middle-income countries. Obesity is characterized by an excessive accumulation of adipose tissue accompanied by systemic chronic inflammation, and it is associated with several types of cancer: breast, ovarian, liver, and pancreatic cancers, among others [2,3]. Overweight and obesity are defined by body mass index (BMI), the ratio between an individual's weight (in kilograms) and the square of their height (in meters). A person with

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a BMI of 25 or more is considered overweight, and a BMI of 30 or more is considered obese, according to the World Health Organization (WHO) classification [4]. However, BMI is an imprecise tool to determine obesity status, since it does not provide a quantitative analysis of the adiposity directly. Instead, it correlates with a few direct measures of body fat content [5]. In contrast, computed tomography is capable of providing an estimate of the amount of fat stored in different adipose tissue compartments. However, this technique is not routinely used in the diagnosis of obesity [6].

Adipose tissue is an endocrine and immune organ [7,8] composed of an intricate network of heterogeneous cell types, including infiltrating immune cells, such as lymphocytes (T and B cells), mast cells, and antigen-presenting leukocytes (macrophages and dendritic cells). Granulocytes, fibroblasts, endothelial cells, extracellular matrix (ECM), and other stromal components are also present [9,10]. This complex network may have a dramatic impact on carcinogenesis and tumor promotion [8,9,11,12]. Obesity has been associated with a higher risk of developing breast cancer, particularly in postmenopausal women, as well as with a worse disease outcome for women of all ages [13].

Breast cancer is the most common cancer in women worldwide [14-16]. Several risk factors for breast cancer are well-established by epidemiologic studies and include exogenous hormones, family history of cancer, genetic traits, race, ethnicity, and physical inactivity [16]. There are three surface receptors commonly used to characterize breast cancer: the estrogen receptor (ER), the progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2). According to their presence or absence, breast cancer can be classified into ER+/-, PR+/-, and HER2+/- . Triple negative breast cancer (TNBC) is characterized by the absence of ER-/PR-/HER2- receptors [17]. TNBC is considered more aggressive with a poorer prognosis than other types of breast cancer, mainly because there are fewer targeted medicines that treat triple-negative breast cancer [18]. Systemic effects of adiposity are believed to be implicated in breast cancer development and aggressiveness, and may involve breast fat [19].

Adipocytes secrete many paracrine and endocrine hormones, as well as adipokines, and are classified into four types: white, brown, beige, and pink [8,20]. These regulate local and systemic metabolism and inflammation [8,9,11,21]. In mammary tumors, white adipocytes are the major component of the stromal microenvironment, and they can accelerate cancer progression by releasing free fatty acids and producing several inflammatory cytokines [22], inducing tumor proliferation and angiogenesis [8,9,11,23].

Expansion of white adipose tissue, characterized by white adipocyte hyperplasia (an increase in adipocyte number) and/or hypertrophy (an increase in adipocyte size), promotes inflammation mediated by macrophage infiltration, activation, and polarization [24]. Adipose tissue macrophages (ATMs) are highly inflammatory and can secrete proinflammatory cytokines such as tumor necrosis factor α (TNF- α). ATMs likely contribute to propagation of the recruitment of additional macrophages by releasing chemokines such as monocyte chemoattractant protein-1 and chemokine (C-C motif) ligand 2 (MCP1/CCL2). An increase of ATMs can result in the formation of crown-like structures (CLS) that surround dead adipocytes [25-27]. During obesity, ATM infiltration positively correlates with adipocyte size and CLS density [27,28].

CLS formation in the breast adipose tissue is related to the production of several immunomodulatory molecules which may favor breast cancer cell proliferation and progression. Here, we provide an overview of the mechanisms involved in CLS formation and

their correlation with breast cancer. Moreover, we discuss the role of CLS in breast cancer prognosis, clinical-pathological parameters, and therapeutic approaches.

ADIPOSE TISSUE-ASSOCIATED MACROPHAGES AND CROWN-LIKE STRUCTURES

Adipose tissue is heterogeneous and contains a diversified pattern of immune cells and adipocytes depending on the anatomical localization. During weight gain, adipose deposits expand beyond the tissue capacity, resulting in white adipose tissue dysfunction and secretion of a greater number of inflammatory cytokines [29]. This moves the tissue toward a phenotype with more pro-inflammatory immune cells inducing a higher inflammatory response [30].

Adipose tissue can increase in size (hypertrophy) and in number of adipocytes (hyperplasia), accompanied by structural and cellular changes in the tissue in response to excess energy. These changes include fibrosis, local inflammation, infiltration of immune cells, polarization of macrophages from an anti-inflammatory to a pro-inflammatory phenotype, adipocyte death, hypoxia, and mechanical stress in the ECM [31,32].

Excessively hypertrophied adipocytes can induce secretion of chemotactic factors and promote recruitment of immune cells to the adipose tissue. Elevated expression of monocyte chemoattractant protein-1 (MCP-1) and chemokine (C-C motif) ligand 2 (CCL2) in the white adipose tissue (WAT) of subjects with obesity can prompt an increased influx of monocytes that will differentiate into macrophages to migrate and infiltrate into WAT, setting up a feed-forward inflammatory process [33].

The newly recruited monocytes then become polarized, turning into either proinflammatory M1 macrophages (or classically activated macrophages) or into anti-inflammatory M2 macrophages (alternatively activated macrophages) [34]. Macrophage populations can be distinguished based on the expression of surface markers and their location; for example, CD206, CD163, arginase-1, Mg11, and IL-10 characterize the M2 macrophage population, which is involved in adipocyte tissue remodeling. M1 macrophages can be distinguished based on iNOS, CD86, and CD80 markers, while also expressing genes such as interleukin-6 (IL-6) and TNF- α [35]. Adipose tissue from lean individuals presents more M2 than M1 macrophages, while adipose tissue from obese individuals present more abundant M1 compared to M2 macrophages [36]. Macrophages in lean adipose tissue play an important role in maintaining the function and homeostasis of the tissue through phagocytosis of dead adipocytes, secretion of anti-inflammatory cytokines, and regulation of iron flux, which plays an important role in adipogenesis [37,38].

In conditions of obesity and overweight, M1 macrophages can accumulate and upregulate CD11c and F4/80 [39], producing proinflammatory factors that potentiate inflammation and insulin resistance [40]. M1 macrophages can deregulate adipocyte signaling processes, increase the production of reactive oxygen species, and secrete proinflammatory cytokines associated with oxidative stress and tissue destruction [40]. M1 macrophages in adipose tissue can form a characteristic “crown-like structure (CLS)” around the necrotic, hypertrophied, and dying adipocytes that need to be resorbed [27,28,41,42]. Electron microscopic analysis of human and mouse adipose tissue in conditions of obesity showed

ruptured adipocyte membranes and the presence of cellular debris, dilated endoplasmic reticulum, and cytoplasmic lipid droplets, suggesting necrosis [43]. CLS is considered a hallmark of the proinflammatory process in adipose tissue, characterized by adipocyte cell death and intense release of free fatty acids, and infiltration of other immune cells such as lymphocytes, neutrophils, and mast cells, promoting and maintaining the exacerbated inflammatory state [44]. Moreover, adipose tissue macrophages are an important source of the proinflammatory cytokines TNF- α and IL-6, which can block the insulin receptors, leading to insulin resistance [45].

However, a deeper characterization is needed of the adipocyte cell death type that occurs during obesity; how this influences the polarization of macrophages is not yet clear. Even though CLS is a proinflammatory microenvironment, debate about the M1 or M2 profiles of macrophages in obesity is ongoing. Recent work indicates that a complex mixture of M1 and M2 macrophage phenotypes can be observed in white adipose tissue during obesity [46], indicating that macrophages cannot be classified using the simple dual M1/M2 model. Importantly, excess accumulation of adipose tissue produces a proinflammatory “metabolically activated” macrophage (MMe) phenotype, mechanistically distinct from M1 or M2 activation [47,48]. It was demonstrated that MMe accumulation in mammary adipose tissue promotes the establishment of TNBC during obesity, indicating that the metabolic status of these macrophages under conditions of weight gain may be crucial to cancer progression [49].

CROWN-LIKE STRUCTURES AND BREAST CANCER: CLINICAL-PATHOLOGICAL PARAMETERS AND PROGNOSIS

CLS are related to free fatty acid release in adipose tissue, NF- κ B activation, and generation of a pro-inflammatory microenvironment [50]. For these reasons, CLS are often used as a biomarker of adipose tissue inflammation [51]. Adipose tissue inflammation associated with metabolic syndrome may favor breast cancer development and progression [52]. Given the important biological function of CLS, methods have been developed to measure these structures by light microscopy, and an index has been created to quantify CLS severity on a scale ranging from 0 to 1.0 [30]. CLS were found to be related to several stages of cancer formation and progression in different types of cancer, including breast cancer in women [53] and men [54], squamous cell carcinoma [55], endometrial cancer [56], prostate cancer [57], and hepatocellular cancer [58].

Consistent with clinical and experimental observations, the prognostic value of CLS in breast cancer may vary according to race/ethnicity [59], menopausal status [60,61], tumor subtype [62], presence of fibrosis [63], increased mammary tumor vascular density [64], resistance to therapy [65], and treatment responsiveness [66]. The breast cancer microenvironment is highly heterogeneous, composed of several immune cell types and molecules that are reprogrammed to sustain tumor growth and spread. The most abundant immune cells are macrophages, and more than 50% of macrophages are tumor-associated macrophages (TAMs) [67].

During carcinogenesis, circulating monocytes are recruited by tumor-derived chemoattractants including CCL2 (MCP-1) and CSF-1, and also differentiate into TAM. An

enhanced understanding of how obesity modulates M1 and M2 macrophage density and function in human breast tissue is important, since most of TAM are composed of M2 macrophages [68] and could play a role in tumorigenesis by suppressing anti-tumor immune responses [69,70]. TAM are found along the tumor-stroma border, an area characterized by improved fibrotic ECM remodeling [71], allowing macrophages with an M1 profile to polarize to M2 through contact with molecules that mimic biochemical and biophysical alterations of ECM [72], thus contributing to worse cancer clinical outcomes [73].

The TAM with an M1 profile exhibit antitumor properties that identify and destroy cancer cells via phagocytosis and cytotoxicity. However, experimental data suggest that during tumor initiation, proinflammatory macrophages might promote malignant transformation through mutagenic reactive species of oxygen and nitrogen [74]. Additionally, the presence of inflammatory configurations is related to NF- κ B activation and enhanced levels of proinflammatory mediators, including TNF- α , IL-6, and cyclooxygenase-2 (COX-2)-derived prostaglandin E₂ (PGE₂) [30]. These mediators can act to upregulate the transcription of the *CYP19* gene encoding aromatase, leading to estrogen production [75] and worse breast cancer prognosis.

The presence of more CD68 and CD163 macrophage markers in breast adipose tissue is correlated with increased numbers of cancer-associated adipocytes in the breast cancer microenvironment [76,77], and these events are related to decreased survival in breast cancer patients [62,76,78]. These findings indicate that CLS can affect cancer development and impact breast cancer patients' overall survival (**Figure 1**).

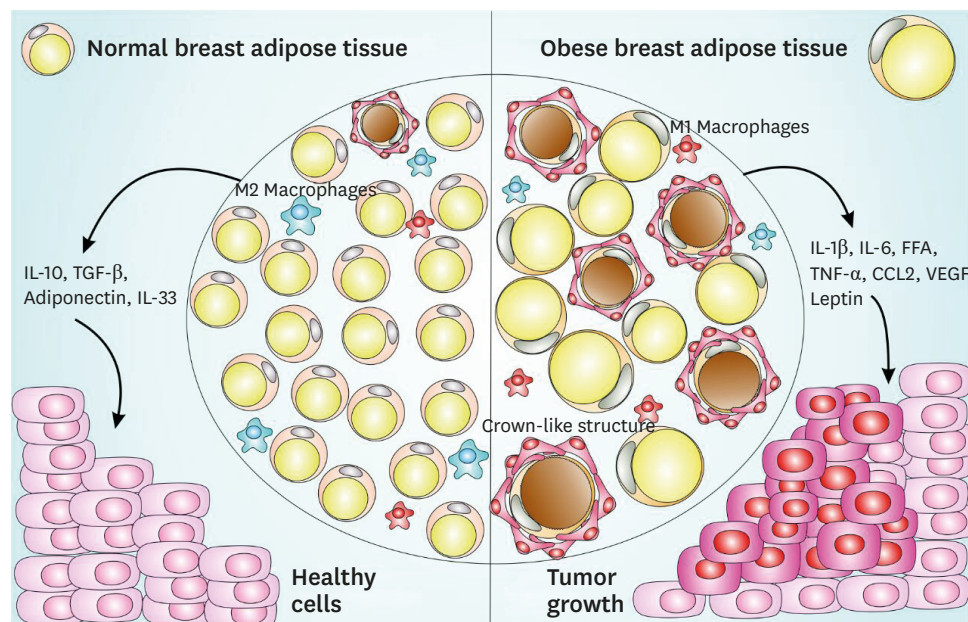


Figure 1. CLS-mediated signaling pathway in normal and obese adipose tissue and impact on breast cancer. Normal breast adipose tissue is characterized by the presence of smaller and less numerous white adipocytes, fewer crown-like structures, a prevalent M2 macrophages subset, with the secretion of anti-inflammatory cytokines such as IL-10, TGF- β , IL-33, and adiponectin. Obese breast adipose tissue is characterized by larger size and more abundant white adipocytes, with the secretion of pro-inflammatory cytokines such as IL-1 β , IL-6, FFA, TNF- α , macrophages-chemoattractant CCL-2 chemokine, angiogenesis inducers such as VEGF, a prevalent M1 macrophages subset and an increased production of leptin, a negative feedback signal in the regulation of energy balance. This obese breast adipose tissue provides a favorable microenvironment to cancer establishment and progression.

CLS = crown-like structures; IL = interleukin; TGF = transforming growth factor; FFA = free fatty acid; TNF = tumor necrosis factor; CCL = chemokine (C-C motif) ligand; VEGF = vascular endothelial growth factor.

Table 1. Clinical and experimental studies in breast cancer and crown-like structures

Reference	Model	Target	Results
Morris et al., 2011 [53]	Human	Aromatase activity; adipocyte size; serum inflammation marker; CLS-B index	CLS-B correlated with BMI and adipocyte size
Subbaramaiah et al., 2011 [91]	Animals	NF- κ B Activation; TNF- α , IL-1 β , and COX-2 levels; aromatase activity; CLS	Obesity-inflammation-aromatase axis in the mammary gland and WAT, and its association with CLS, increased risk of ER breast cancer
Subbaramaiah et al., 2012 [75]	Human	Aromatase activity; CLS-B index	CLS-B index as an improved correlation marker of breast cancer and obesity
Iyengar et al., 2015 [60]	Human	CLS-B presence; Circulating inflammatory mediators	CLS-B is associated with metabolic syndrome and worse breast cancer prognosis
Cowen et al., 2015 [64]	Animal	Effect of a high-fat/high-calorie diet on mammary carcinogenesis	Breast adipose tissue inflammation induced by diet increases tumor vascular density
Seo et al., 2015 [63]	Animal; <i>in vitro</i> and human	Role of obesity in interstitial fibrosis in mammary fat	α -SMA levels correlated with CLS-B contribute to increased levels of matrix extracellular remodeling in obesity
Koru-Sengul et al., 2016 [62]	Human	Association between the number of TAM and/or CLS and ethnicities	Race is associated with the numbers of TAM and CLS in breast cancer
Mullooly et al., 2017 [89]	Human	CLS-B and sex steroid hormones in breast adipose tissue	CLS were not related to hormone levels or tumor characteristics, but were associated with hormone ratios
Vaysse et al., 2017 [90]	Human	CLS-B associated with mammary adipocyte size, body composition, and serum biomarkers	CLS was associated with systemic markers
Brown et al., 2017 [61]	Human	Effect of menopause on breast aromatase expression in relation to BMI, CLS and systemic markers of metabolic dysfunction	Postmenopausal women had higher BMI and presence of CLS than did premenopausal women
Cha et al., 2018 [76]	Human	Macrophage infiltration and identification of CLS status	CD68+ and/or CD163+ macrophages and CLS are present in adipose tissue near the breast cancer lesion
Iyengar et al., 2018 [59]	Human	CLS compared in Taiwanese vs Caucasian women	Compared with Caucasians, Taiwanese women had larger breast adipocytes despite lower BMI after adjusting for BMI and menopausal status
Greenlee et al., 2019 [79]	Human	Inflammation and BMI in Hispanic/Latina breast cancer patients	Prevalence of CLS-B was associated with Hispanic/Latina patients
Springer et al., 2019 [73]	Human and mice	Extracellular matrix affects macrophage phenotype	Fibrotic extracellular matrix remodeling promotes a TAM phenotype of macrophages in CLS

CLS-B = crown-like structures in breast; BMI = body mass index; TNF- α = tumor necrosis factor α ; IL = interleukin; COX-2 = cyclooxygenase-2; WAT = white adipose tissue; ER = estrogen receptor; α -SMA = α -smooth muscle actin; TAM = tumor-associated macrophage.

CLS are also correlated with race with regard to breast cancer prognosis. Iyengar et al. [59] reported that menopausal Taiwanese women had pathologically enlarged adipocytes and increased presence of CLS in breast tissue, despite having a lower BMI than Caucasian women in the United States. In contrast, in Hispanic/Latin breast cancer survivors who underwent mastectomy, CLS were absent in 35% of patients with grade II and III obesity [79], indicating that a subset of patients with normal BMI and breast cancer can also present signs of inflammation and metabolic abnormalities (Table 1).

This healthier phenotype presented by some individuals with obesity is called metabolically healthy obesity, characterized by a lower degree of systemic inflammation, favorable inflammatory and hormonal profiles, normal adipokine secretion patterns, and reduced levels of ectopic and visceral fat storage [80,81]. A subgroup of normal-weight individuals with abnormal metabolic parameters (those exhibiting metabolically unhealthy non-obesity or metabolically obese normal weight) has also been described [82]. However, metabolically healthy obese people may be more prone to the risk of obesity-associated cancer mortality [83,84].

CROWN-LIKE STRUCTURES AND BREAST CANCER TREATMENT

Since the presence of CLS in breast adipose tissue involves the modulation of several components such as proinflammatory immunological cells, proinflammatory cytokines,

adipocyte cell death, release of free fatty acids, and different hormones, it is important to note that any anti-cancer therapy targeting CLS can be potentially mediated by all these parameters. Endocrine therapy is one treatment tool for breast cancer, as it blocks estrogenic activity and suppress adipose tissue aromatization of androgens to estrogens [85]. Although aromatase inhibitors reduce circulating estrogens in most cases, conditions of overweight and obesity in patients with breast cancer (premenopausal and postmenopausal) make patients more prone to a higher risk of recurrence and resistance to therapy [86]. Estrogen replacement therapy in ovariectomized mice with obesity revealed that treatment with 17 β -estradiol is enough to attenuate weight gain, reduce production of inflammatory markers and number of CLS [87], and reduce the expression of genes related to inflammation (*Cd68*, *Mcp1*, and *Tnf*) [88].

The presence of CLS and inflammatory mediators in breast adipose tissue in women with both breast cancer and obesity is associated with changes in intracellular signaling and significant changes in cell dysfunction [30]. The CLS are implicated not only in inflammation, rather than in obesity alone, but also as drivers of aromatase activity in the breast via a complex and dynamic system of paracrine interactions between macrophages and other cells [53,75], a process also associated with increased estrogen-to-androgen ratios [89]. These findings underscore the role of CLS as a potential booster of estrogenic signaling and may be crucial for endocrine therapy selection during breast cancer treatment [90]. *In vitro* experiments further defined the pathways mediating this effect, showing that macrophage COX-2 expression and PGE₂ production promote estrogen receptor (ER α) target gene expression [91]. Based on these results, post-menopausal patients with obesity and breast cancer may benefit from an aromatase inhibitor/COX-2 inhibitor combination treatment during breast cancer [92].

Supplementation of breast cancer patients with omega-3 fatty acids can also modulate CLS in breast cancer tissue and serve as an important adjuvant in the treatment of this cancer. There are multiple preclinical and epidemiologic studies suggesting that eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) attenuate inflammation and reduce risks for breast cancer [93,94]. *In vitro* studies also corroborate the anti-tumor effects of omega-3 against human breast cancer cells [95,96]. In a study using rodents, omega-3 supplementation significantly decreased the number and size of CLS and F4/80+ macrophages and decreased expression of proinflammatory mediators including *Ptgs2*, IL-6, CCL2, TNF- α , NF- κ B, and interferon- γ proteins in the mammary fat pad [97].

CLS can be also modulated by other compounds such as polyphenols (resveratrol) decreasing inflammation in breast tissue and potentially affecting breast cancer. Supplementation with resveratrol in the diet of mice with obesity and breast cancer resulted in lower numbers of CLS and decreased proinflammatory cytokine gene expression [66].

Since CLS can be also be identified in a significant proportion of normal-BMI women undergoing mastectomy for breast cancer risk reduction or therapy, CLS may be also important in breast cancer treatment in normal weight women [98], not only in obese breast cancer patients.

To date, at least three clinical trials have advanced in the investigation of adiposity and inflammation to evaluate the risk factors associated with metabolic profile and tumor growth, which influence disease-free survival, overall mortality, and breast-cancer-specific

mortality (NCT02240836; NCT03091842; NCT02598557). The forthcoming results of these studies should elucidate the relationship of CLS function to prognosis in different subtypes of breast cancer, providing new therapeutic approaches.

CONCLUSION

CLS are increased in breast adipose tissue from breast cancer patients and are particularly abundant in patients with conditions of obesity. Breast cancer associated with chronic obesity is most common in postmenopausal women. In this review, we discussed how CLS are related to the inflammation status of breast adipose tissue, and how these events can be decisive for breast cancer development and treatment, especially in obese women.

To improve interventions to prevent and treat breast cancer, a better understanding of the physiological and molecular mechanisms involved in breast tissue inflammation is crucial. It is important to understand that breast adipose tissue CLS are important keys to breast tissue inflammation and, consequently, may directly influence the development and treatment of breast cancer.

Targeting breast adipose tissue CLS can be a prominent therapeutic tool during cancer treatment, especially in patients with obesity. Therefore, tests based on body adipose tissue composition and inflammation in daily medical practice could be very effective to better stratify patients and direct combinatorial approaches in clinically relevant ways toward breast cancer treatment.

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