Commentary

Collagen and fibronectin: threads linking obesity and breast cancer

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Evidence from epidemiological and clinical studies correlates obesity with an increased risk for postmenopausal breast cancer and a worse prognosis for breast cancer patients regardless of menopausal status (1). However, the cellular, molecular and structural mechanisms driving this process remain unclear. A potential structural mechanism is extracellular matrix (ECM) density, which is an independent risk factor for breast cancer (2,3). Myofibroblasts, the contractile, spindle-shaped, stress fiber-forming mesenchymal cells capable of producing copious amounts of ECM have emerged as a common hallmark of wound healing and tumor progression (4), leading to the generally held view that tumors are "wounds that do not heal".

Seo *et al*. (5) have proposed that obesity induced structural changes enhance interstitial ECM stiffness, stimulating cancer cell growth and motility, thus linking obesity and the ECM in breast cancer progression. They provide evidence that changes in the quantity and quality (increased linearity) of interstitial collagen as well as alterations in fibronectin conformation in both intact and ovariectomized obese female mammary adipose tissue promote mechanosignaling and the malignant potential of breast cancer cells.

To extend the relevance of their findings in mouse experiments to humans, Seo *et al*. (5) analyzed tumor-free breast tissue from normal, overweight and obese women, confirming that levels of α-smooth muscle actin (α-SMA), a myofibroblast marker, correlated with ECM remodeling and inflammation. In addition, they found that tumors from obese patients exhibited more severe desmoplasia relative to tumors from lean patients, with increases in collagen fiber thickness as well as aligned fiber length. Other studies have shown that ECM fibers play an important role in organizing and facilitating streaming migration of carcinoma cells and macrophages *in vivo*, with movement often found to occur along ECM fibers aligned perpendicular to nearby blood vessels, potentially promoting metastatic spread (6,7).

Obesity-associated inflammation has also been correlated with breast cancer progression (8,9) with macrophages having either positive or negative effects in the tumor microenvironment depending on their functional state (10,11). We have shown in a murine model of postmenopausal breast cancer that the anti-tumor effects of omega-3 polyunsaturated fatty acids (ω-3 PUFAs) do not occur through the GPR120 receptor which mediates some of their anti-inflammatory activity (12), suggesting that the TNF-α pathway is not a driver of luminal breast cancer in our model. Interestingly, nuclear accumulation of YAP/TAZ, the key nuclear relay of mechanical signals exerted by ECM rigidity and cell shape (13) is enhanced in tumors from obese patients (5). ω-3 PUFAs have recently been shown to ameliorate liver fibrosis by promoting YAP/TAZ degradation (14) and it is intriguing to speculate that beneficial effects of ω-3 PUFAs on breast cancers of obese individuals could be mediated via the inhibition of YAP/TAZ activity. This would be in keeping with results of a recent randomized clinical trial showing that ω-3 PUFAs decrease breast density in obese, but not overweight or normal weight postmenopausal women (15).

An inflammatory pathway that does appear to be causally related to obesity and breast cancer progression is the bacterially activated NLRC4 inflammasome and subsequent IL-1ß signaling, reported to act through adipocyte-mediated VEGFA expression and angiogenesis (16). The authors hypothesize that obesity-induced changes in the gut microbiome and endotoxaemia promote the NLRC4 inflammasome. Metformin inhibited obesity-associated tumor progression and was associated with a marked reduction in angiogenesis (16). An additional factor that was not considered, but could also play a role in these

studies is ECM remodeling, since VEGFA can stimulate fibrosis (17) and metformin has been shown to inhibit excessive ECM deposition in white adipose tissue of obese mice (18).

The interrelationship between breast fibrosis as measured by mammographic density and increased cancer risk has been known for decades (19). However, this increased tissue density is not typically associated with chronic inflammation in the normal breast. Rather breast tissue density is a heritable trait that is influenced by multiple factors including menopausal status, weight and number of live births (3). It has been noted that although obese postmenopausal women have approximately a 30% increased risk of developing breast cancer compared with normal weight women (1), obese women tend to have less dense breasts due to the abundance of adipose tissue (20). As Seo *et al*. (5) demonstrate, changes in the quantity and quality of the ECM in the presence of obesity-induced chronic inflammation may be a critical causative factor linking obesity with breast cancer progression.

In order to predict the cohort of obese women at increased risk for breast cancer and to develop new approaches for prevention and treatment, the molecular pathways underpinning key clinical observations need to be defined. To fill the many gaps in our knowledge, more attention should be focused on the temporal sequence of molecular events occurring during the initiation and progression of breast cancer in obese subjects. Seo *et al*. (5) have provided the impetus to include ECM signaling as a fundamental driver of obesity-induced breast cancer.

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Footnote

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