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Topic Category: 4034-ASIP Extracellular matrix – inflammation and immunopathology

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Presentation Preference: Oral

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Sponsor's Society: Pathology - American Society for Investigative Pathology (ASIP) - Host Society

Keywords: 1. obesity 2. interstitial fibrosis 3. macrophage

Obesity-associated extracellular matrix remodeling promotes a tumor-associated macrophage phenotype in tumor-free breast adipose tissue

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Background: Obesity is associated with an increased risk for breast cancer development in postmenopausal women and a worse prognosis in women with breast cancer regardless of menopausal status. Historically this association has been attributed to altered estrogen biosynthesis mediated in part by inflammation of obese adipose tissue. Adipose tissue inflammation is histologically evident by the accumulation of pro-inflammatory macrophages surrounding adipocytes. However, recent evidence from mouse models suggests that a second population of macrophages residing diffusely throughout the stromal vascular fraction of adipose tissue is also increased in obesity. Little is known about this specific population of macrophages in breast tissue and whether the physicochemical alterations to adipose tissue that occur during obesity, such as extracellular matrix remodeling, alter macrophage biological behavior to a tumor-promoting phenotype.

Objectives: To evaluate the spatial distribution of pro- and anti-inflammatory macrophages in lean versus obese breast tissue, to determine if structural and mechanical changes to breast adipose tissue during obesity play a role in macrophage activation, and to identify whether these changes promote a permissive microenvironment for future tumor development.

Methods and Results: Using tumor-free regions of mastectomized breast tissue, we found that CD206+ anti-inflammatory macrophages are the dominant macrophage population regardless of body mass index (BMI) but they are increased to a greater magnitude in obese breast adipose tissue based on CIBERSORT analysis of RNA transcripts. Furthermore, the phenotype of macrophages in breast tissue from obese women is significantly more similar to that of tumor-associated macrophages when evaluated by Gene Set Enrichment Analysis (GSEA) and compared to a previously published Tumor Associated Macrophage (TAM) gene expression data set. This increase in CD206+ macrophages positively correlates with interstitial fibrosis in vivo as determined by immunohistochemical and picrosirius red image analysis. The association is experimentally supported in vitro by increases in murine bone-marrow derived macrophage (BMDM) expression of arginase-1 and a macrophage morphology consistent with an anti-inflammatory phenotype when cells are cultured on an obese versus lean decellularized extracellular matrix model system. Finally, angiogenesis-related genes are differentially expressed in breast tissue between lean and obese women based on GSEA analysis. Immunohistochemistry studies illustrate a positive correlation between CD31+ positive vascular profiles and CD206+ macrophages in breast adipose tissue. In vitro studies confirm that BMDM cultured on obese versus lean decellularized ECM secrete factors that promote endothelial cell migration and tubulogenesis, experimental outcomes that suggest a functional impact on angiogenesis, a critical step in tumorigenesis.

Conclusions: Collectively, our data support a model where obesity-associated interstitial fibrosis promotes a macrophage phenotype similar to TAMs and this macrophage population might be an important contributor to the underlying pathophysiology linking obesity and breast cancer.

Support or Funding Information

This work was supported by NIH/NCI R01CA185293, NIH/NCI Center on the Physics of Cancer Metabolism 1U54CA210184-01NIH and NIH Office of the Director T32OD001100