Metabolic and immunological interactions between adipose tissue and breast cancer
Implications of obesity in tumor progression

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Abstract
Triple-negative breast cancers have fewer treatment options than other breast cancers. The overall goal of this research is to identify new pharmaceutical targets for triple-negative breast cancer through studies of the tumor-promoting crosstalk between tumor and surrounding adipose tissue. In paper I, we established extracellular flux analyzer-based methodology to evaluate metabolic function of cultured cells, used in paper II and III. In paper II, we identified the C1q/TNF-related protein family member C1qtnf3 as one of the most upregulated secreted proteins in E0771 triple negative breast cancer-associated mouse adipose tissue – in particular in the obese setting. Antibody-mediated blockage of C1QTNF3 reduced macrophage infiltration in breast cancer-associated adipose tissue in mice. In cultured macrophages, C1QTNF3 decreased oxidative phosphorylation and enhanced M1-polarization. In paper III, we demonstrated that E0771 breast cancer tumors grew faster, associated with increased de novo lipogenesis from glucose, if transplanted orthotopically into adipose tissue than if transplanted outside adipose tissue. Based on our vitro data, we propose that adipose tissue-produced lactate triggers the observed increase in de novo lipogenesis in the tumor. In conclusion, paracrine interactions between adipose tissue and breast cancer involve both immunological and metabolic processes, associated with enhanced tumor progression. In the future, we hope that pharmaceutical targeting of these interactions, in combination with conventional therapy, will improve the survival of breast cancer patients.

Keywords: Breast cancer, Adipose tissue, Macrophage, Metabolism, Paracrine.