

Development of breast-adipose co-culture model to decipher the impact of lipid heterogeneity on triple-negative breast cancer

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Lipid composition has been associated with increased chemoresistance and mortality in triple-negative breast cancer (TNBC), a highly aggressive breast cancer subtype accounting for 10-15% of all breast cancer cases. Fatty acids in the tumor microenvironment (TME) promote TNBC progression by driving metabolic inflammation. Despite this, the unique impact of TNBC-associated lipids as a subsequent energy source is not fully understood. Deciphering the lipid heterogeneity in the TME will provide insight into TNBC progression to ultimately unveil novel therapeutic targets. Prior works have identified a heterogeneous distribution of lipids between primary TNBC tumors and matched breast tissue. Specifically, the lipid species linoleic acid (LA) and oleic acid (OA) were upregulated in TNBC tumors but not elevated in hormone positive breast tumors. We hypothesized that the distinct TNBC lipid composition enriched in LA and OA fuels TNBC progression. We developed a model of the TNBC TME that is enriched for LA and OA through the co-culture of adipogenic differentiated breast adipose-derived stem cells (BrASC) and TNBC spheroids to determine the impact of the TME lipid composition on TNBC. We constructed an adipocyte-TNBC co-culture model by treating BrASC with fatty acids distinct to TNBC during differentiation to adipogenic lineage. Fatty acid production and uptake were confirmed with quantitative BODIPY fluorescence microscopy and qRT-PCR. We also showed that fatty acids increased the total triglyceride profile in differentiated BrASC. Through quantitative fluorescence microscopy, we determined that up to 200 μ M of lipid can be added to the system while retaining cell viability. Further, BrASC incorporated exogenous lipids during adipogenic differentiation, and RNA sequencing data revealed differential gene expression in LA and OA when compared to controls, including upregulation of carbohydrate and lipid metabolism pathways. Further, fluorescence microscopy demonstrated lipid transfer occurred during the co-culture of BrASC with TNBC. Using this co-culture model, future studies are poised to evaluate the impact of an altered TME lipid profile on TNBC progression.