Mechanisms regulating lipid storage in breast cancer cells

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Alteration of lipid metabolism is a hallmark of breast cancer (BC). However, the underlying mechanisms are still largely elusive. We performed screenings for metabolic modifiers in BC cells focusing on a gene family encoding forty-five membrane trafficking proteins. In parallel, the prognostic value of these genes in BC was assessed by interrogating the Metabric dataset. Among the genes identified in the screenings, whose upregulation also predicted worse prognosis in BC, we selected TBC1D7 for high resolution studies.
TBC1D7 is highly expressed in glucose-avid Triple-negative tumors (TNBC) and correlates with reduced patient survival in univariate and multivariate analyses in the TNBC patient subpopulation. The best characterized function of TBC1D17 is to bind and to stabilize the TSC1/TSC2 complex, which negatively regulates mTORC1. However, additional TSC-independent functions have also been proposed. By performing metabolic flux analyses we found that cells overexpressing TBC1D7, or a TBC1D7 point mutant that is impaired in its binding to TSC1, elevate glucose metabolism to generate fatty acids, while glutamine is mostly employed to sustain the Tricarboxylic Acid cycle. Accordingly, in the overexpressing cells the size of lipid droplets is increased and inhibition of the
lipid enzymes ACSL3 and SCD1 impairs their formation suggesting that TBC1D7 promotes de novo lipogenesis. Moreover, overexpression of TBC1D7, or of its mutant, stimulates the growth of tumor cell spheroids, when cultured in 3D Matrigel, a pro-neoplastic feature that is blocked by treatment with an SCD1 inhibitor. Finally, we found that TBC1D7 inhibits lipophagy further contributing to the accumulation of intracellular lipids. Taken together, these data suggest a novel mechanism that integrates lipogenesis and lipid consumption in BC cells.