Opposing roles of DGAT-mediated lipid droplet biogenesis in the regulation of ferroptosis sensitivity

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Abstract

Lipid droplets (LDs) are dynamic fat storage organelles involved in fatty acid metabolism, signaling, and trafficking. By storing polyunsaturated fatty acids (PUFAs) in the form of neutral lipids, LDs can either mitigate or exacerbate lipotoxic damage. However, their role in regulating cellular fatty acid distribution, membrane unsaturation, and ferroptosis susceptibility remains poorly understood. Here, we show that inhibition of diacylglycerol acyltransferase (DGAT)-mediated LD biogenesis in PUFA-supplemented triple-negative breast cancer cells triggers widespread lipidome reorganization and membrane phospholipid acyl-chain remodeling, promoting lipid peroxidation and ferroptosis sensitivity. Lipidomic analyses reveal that LDs efficiently sequester exogenous PUFAs within triacylglycerols and cholesteryl esters, significantly altering neutral lipid unsaturation profiles. When LD formation is impaired by DGAT inhibition, PUFAs are redistributed into membrane ester and ether glycerophospholipids, enhancing overall membrane unsaturation, lipid peroxidation, and increasing ferroptosis susceptibility, even in the absence of additional ferroptosis inducers. In contrast, in human lung adenocarcinoma cells, LDs exhibit a dual, context-dependent role in ferroptosis regulation, whereby exogenous PUFA levels and the extent of ferroptosis protection determine whether DGAT inhibition promotes or protects against cell death. The pro-ferroptotic function of LDs predominates in these cells and is strongly enhanced by ferroptosis suppressor protein 1 (FSP1) deficiency, which amplifies lipid peroxidation within LDs and promotes its propagation to other cellular compartments. This study highlights LDs as multifaceted regulators of ferroptosis, interlinking metabolic and redox quality control mechanisms.