GUEST LECTURE SERIES

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Lipid Droplets Control the Generation of Mitogenic Lipid Mediators and Ferroptotic Death Signals

Lipid droplets (LDs) integrate fatty acid metabolism and signaling with cellular stress response mechanisms. However, our understanding of their contribution to the intracellular trafficking of various types of fatty acids across different cellular states remains limited. Here, we demonstrate that LDs control the entry of PUFAs into lipid oxygenation pathways, thereby impacting the biosynthesis of lipid signaling molecules and regulating ferroptosis sensitivity. On the one hand, we observe that the incorporation of PUFAs into triglycerides stored within LDs, and their subsequent release through lipolysis mediated by adipose triglyceride lipase (ATGL), is essential for the conversion of PUFAs into lipid mediators derived from cyclooxygenase and lipoxygenase. In triple-negative breast cancer cells, ATGL can regulate these biosynthetic pathways independently of the group IVA cytosolic phospholipase A_2 (cPLA$_2$α), yet ATGL also facilitates the incorporation of LD-derived PUFAs into membrane phospholipids, which are substrates for cPLA$_2$α. On the other hand, when cellular antioxidant defenses are compromised, the turnover of LDs emerges as a critical factor in determining cell survival. We find that inhibition of glutathione peroxidase 4 (GPX4) triggers the redistribution of PUFAs from membrane phospholipids to LDs through diacylglycerol acyltransferase (DGAT)-mediated triglyceride synthesis. This, in turn, diminishes lipid peroxidation, acting as a protective mechanism against ferroptotic cell death. However, the concurrent LD breakdown via ATGL-mediated lipolysis promotes lipid peroxidation over time, suggesting that maintaining a delicate balance between LD biogenesis and breakdown is essential for safeguarding cells against ferroptosis. Finally, our findings demonstrate that inhibiting DGAT-mediated LD biogenesis is sufficient to enhance cancer cell sensitivity to ferroptosis, suppress lipid mediator production and inhibit cancer cell proliferation both *in vitro* and *in vivo*. Thus, the biogenesis and breakdown of LDs control the entry of PUFAs into lipid oxygenation pathways that drive the generation of both mitogenic and lethal lipid peroxidation signals.