**Cell cycle arrest induces lipid droplet formation and confers ferroptosis resistance**

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**Presenter:** Chih-Ling Chen                 **Date/Time:** 2024/03/07, 15:00 -16:00

**Commentator:** Chi-Wu Chiang, Ph.D        **Location:** Room 601, Med College Building

**Background:**

Fatty acids are essential building blocks of cellular membranes and are important fuels for energy metabolism. When nutrients are abundant, cells store excess fatty acids in the form of triacylglycerols (TAG) in lipid droplets and play an important role in lipid storage. Diacylglycerol acyltransferases (DGATs) catalyze the last step in TAG synthesis. Lipid droplets have been shown to protect cells from lipotoxicity by sequestering TAGs containing polyunsaturated fatty acids (PUFAs).

PUFA-containing phospholipids (PUFAs-PLs) are particularly susceptible to peroxidation and render cells sensitive to ferroptosis, a type of regulated cell death that is triggered by uncontrolled PL peroxidation. In addition, previous studies demonstrated that inhibition of fatty acid synthesis alters lipid metabolism and affects ferroptosis sensitivity. Therefore, the cellular lipid composition plays a critical role in the regulation of ferroptosis. The role of lipid metabolism in the regulation of ferroptosis is well established; however, how different cell states affect the lipid composition and ferroptosis sensitivity remains incompletely understood.

**Objective/hypothesis:**

To investigate how cell cycling affects lipid composition and ferroptosis sensitivity and propose a ferroptosis-inducing approach to treat slow-cycling, therapy-resistant cancers.

**Results:**

The author treated cells with cell cycle inhibitors and ferroptosis inducers (RSL3 and erastin) and found that these arresting cells were remarkably resistant to RSL3-induced lipid peroxidation and ferroptosis. Considering the central role of lipid metabolism in regulating ferroptosis, the author next studied lipid compositional changes in cell cycle-arrested cells by conducting lipidomic analyses. The results showed that cell cycle arrest increased TAG levels and lipid droplet accumulation in a DGAT-dependent manner. DGAT inhibition orchestrates a reshuffling of PUFAs from TAGs to phospholipids (PLs). Furthermore, DGAT inhibition re-sensitized arresting cells to ferroptosis and lipid peroxidation. Therapy-resistant cells are often slow-cycling and less susceptible to antiproliferative drugs. Thus, the author found that 5-fluorouracil-resistant cells have an accumulation of lipid droplets and that combined treatment with ferroptosis inducers. In 5-FU-resistant xenograft tumor models, DGAT inhibitors effectively suppressed the growth of 5-fluorouracil-resistant tumors by inducing ferroptosis.

**Conclusion:**

Cell cycle arrest induces DGAT-dependent lipid droplet formation to sequester excessive PUFAs that accumulate in arrested cells in TAGs, resulting in ferroptosis suppression.