**Acidosis Forces Fatty Acid Uptake and Metabolism in Cancer Cells Regardless of Genotype**

Ibanez, Sébastien, et al. *Advanced Science* 12.40 (2025)

**Presenter:** Yu Han, Wang
**Advisor:** Prof. Shih Chieh, Lin
**Date/Time:** 2025/12/04, 16:20 -17:10
**Location:** Room 601, Med College Building

**Background:**

Tumor microenvironments are characteristically acidic due to high glycolytic activity.Although acidosis is known to reshape cancer metabolism, its impact on fatty acid uptake and lipid handling remains unclear. This study asks whether acidosis itself drives enhanced PUFA uptake and creates a targetable metabolic vulnerability.

**Objective:**

This study is tried to investigate the effect of acidosis on fatty acid delivery and metabolism in cancer cells.

**Results:**

Acidic extracellular pH universally increased PUFA uptake across multiple cancer cell lines by protonating PUFAs and promoting rapid flip–flop membrane entry, resulting in marked intracellular PUFA accumulation. This PUFA overload induced oxidative and ER stress, driving a strong reliance on ACOX1-mediated peroxisomal β-oxidation for survival. Genetic ACOX1 knockdown or pharmacologic inhibition with thioridazine selectively triggered apoptosis under acidic or PUFA-rich conditions, confirming ACOX1 as a stress-induced metabolic bottleneck.In 3D tumor spheroids and patient-derived organoids, acidosis similarly enhanced PUFA uptake and sensitized tumors to ACOX1 inhibition, demonstrating that this phenotype is preserved in more physiological models. In xenograft studies, an ω-3 PUFA–enriched diet significantly elevated tumor PUFA content and markedly amplified the anti-tumor efficacy of ACOX1 blockade. Conversely, MPC inhibition lowered tumor pH in vivo and reproduced the same PUFA-driven vulnerability. Taken together, these findings establish a microenvironment-driven metabolic dependency on ACOX1 that emerges specifically under acidosis-induced PUFA accumulation.

**Conclusion:**

This study shows that acidosis dictates PUFA uptake and forces a reliance on ACOX1, revealing a microenvironment-driven metabolic vulnerability in cancer. These principles extend beyond oncology, offering new therapeutic opportunities in diseases characterized by acidosis and altered lipid handling.