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Poster Abstract Form

Targeting de novo lipogenesis improves gemcitabine-based chemotherapy efficacy in pancreatic ductal adenocarcinoma

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Introduction: Pancreatic ductal adenocarcinoma (PDAC) is highly chemoresistant, with poor survival outcomes. We investigated metabolic adaptations to gemcitabine (GEMC) and GEMC/paclitaxel (PTX) therapy to identify novel therapeutic targets.

Methods: PDAC cell lines (Panc1, MiaPaCa2) were adapted to GEMC or GEMC/PTX. Lipid metabolism was profiled using lipidomics, radiolabeled substrates, and LC-MS/MS. Key enzymes were targeted via siRNA knockdown.

Results: GEMC resistance upregulated de novo lipogenesis via acetyl-CoA carboxylase (ACC), fatty acid synthase, (FAS), and stearoyl-CoA desaturase (SCD1). Panc1 cells uniquely produced sapienic acid via FADS2, an alternate desaturation pathway that is compensatory for SCD1-mediated desaturation. Knockdown of FAS, SCD1, and FADS2 sensitised cells to GEMC, but Panc1 cells required dual desaturase knockdown to exhibit an effect. GEMC/PTX resistance further enhanced lipogenesis and selectively downregulated FADS2 in Panc1 cells, increasing their vulnerability to SCD1 inhibition. Further screening of patient-derived organoids and commercial cell lines led to the detection of sapienic acid in 2/3 patient-derived organoids and 2/4 commercial PDAC cell lines, suggesting that FADS2-mediated sapienate synthesis may be a common feature in PDAC.

Conclusion: Our findings support lipid metabolism as a promising and translatable therapeutic avenue in PDAC, with sapienic acid biosynthesis emerging as a potentially widespread and actionable target. Our data suggest that combining gemcitabine/paclitaxel with SCD1 inhibitors could result in improved chemotherapy efficacy in PDAC.