IA-16 Metabolic adaptations in pancreatic cancer. Kathryn E. Wellen. University of Pennsylvania, Philadelphia, PA, USA.

Effective targeting of metabolism for cancer therapy is challenging in part because of extensive flexibility within metabolic pathways. For example, the enzyme ATP-citrate lyase (ACLY) has been of interest as a cancer therapeutic target because of its central role in generating nucleo-cytosolic acetyl-CoA for lipid synthesis and acetylation reactions. However, ACLY deficiency or inhibition triggers upregulation of the cytosolic acetyl-CoA synthetase ACSS2, enabling production of acetyl-CoA from acetate for the synthesis of fatty acids. In pancreatic cancer, tumor formation is suppressed in the absence of ACLY, but once tumors are established, ACSS2 is highly expressed and ACLY deficiency is tolerated. Despite this flexibility in acetyl-CoA generation, targeting of downstream processes that rely on acetyl-CoA, via combined BET inhibition and mevalonate pathway inhibition, suppresses tumor growth in mice. Analogously, it is possible that other metabolites whose abundance is tightly defended in cancer cells may point to targetable compensatory mechanisms or downstream processes on which tumor cells are reliant. Recent evidence suggests that the hexosamine biosynthesis pathway, which generates the glycosyl donor UDP-GlcNAc, holds promise for therapeutic targeting in pancreatic cancer, although its regulation in cancer cells remains poorly understood. In this presentation, I will discuss new data uncovering a key role for metabolic adaptation to nutrient deprivation in sustaining UDP-GlcNAc production and tumor growth.