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Argininosuccinate Synthetase (ASS1) Expression in Pancreatic Ductal Adenocarcinoma and Response to Arginine Deprivation

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Some cancers lose expression of ASS1, the penultimate enzyme in arginine synthesis that converts aspartate and citrulline into argininosuccinate, resulting in dependence on exogenous arginine. Selective targeting of these cancers by arginine deprivation therapy (ADT) is currently in clinical trials, however biomarker development is needed to guide therapy more precisely. We aimed to investigate expression of ASS1 in human and murine pancreatic ductal adenocarcinoma (PDAC) cell lines and determine how this correlates to arginine dependence.

Using PDAC cell lines from a genetically engineered mouse model and human PDAC cell lines, MIAPaca2, BxPC3, PANC-1, ASS1 expression was assessed by immunoblotting. Cells were grown in arginine-free media supplemented with citrulline, arginine and argininosuccinate accordingly, and proliferation assays performed.

Differential ASS1 expression was seen in the murine PDAC cell lines; 6 out of 10 showed high expression. All murine cell lines exhibited dependence on exogenous arginine for normal proliferation, regardless of ASS1 status, and despite citrulline availability. Argininosuccinate supplementation rescued proliferation in all murine lines, indicating that the defect in ASS1-positive cells was not lack of argininosuccinate lyase activity, the final step in arginine synthesis. The human PDAC cell lines all expressed ASS1. As expected, BxPC3 was resistant to arginine deprivation and maintained normal proliferation in the presence of citrulline, suggesting functional ASS1. MIAPaca2 and PANC-1 retained dependence on exogenous arginine for proliferation, showing a similar phenotype to the mouse cells.

This is a surprising finding of sensitivity to arginine deprivation despite ASS1 expression in murine PDAC cells, and in a selection of human PDAC cell lines. We will establish whether ASS1 is mutated. By determining the basis of this metabolic defect, we may identify patients with ASS1-expressing pancreatic tumours as candidates for ADT.