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METABOLISM

Haem is where the heart is

> inhibition of haem biosynthesis and degradation could be a valid therapeutic target for patients with HLRCC

Fumarate hydratase (FH), an enzyme in the tricarboxylic acid (TCA) cycle, is mutated in the germline of patients with hereditary leiomyomatosis and renal cell cancer (HLRCC). This mutation results in a non-functional TCA cycle, but kidney cells with this mutation can form aggressive tumours. Understanding how these cells survive in the face of this metabolic change is important for the treatment of this disease. Eyal Gottlieb and colleagues now show that flux through the haem oxygenase pathway is vital.

Gottlieb and colleagues generated immortalized mouse kidney cells that have floxed *Fh1* alleles. Infection of these cells with adenovirus expressing CRE recombinase resulted in homozygous *Fh1* deletion and a build up of succinate and fumarate, the two metabolites generated in the TCA cycle before the conversion of fumarate to malate by FH. To understand how these cells manage in the absence of FH, the cells were grown either in ^{13}C-labelled glucose or in ^{13}C-labelled glutamine, which are the two major sources of carbon for cancer cells. Exposure to ^{13}C-glucose did not result in substantial labelling of fumarate, but growth in ^{13}C-glutamine resulted in fumarate in which all four carbons were labelled; this indicated that, in *Fh1*-null cells, no accessory pathway exists to overcome the block that is imposed by FH loss, and that metabolism of glutamine feeds directly into the generation of succinate and fumarate. So, how do these cells generate NADH and maintain mitochondrial function? To assess this, the authors used a systematic computational approach based on flux balance analysis. These *in silico* data indicated that 24 metabolic reactions are synthetic lethal with FH loss (showing a dependence on these reactions), and 18 of these were reactions involving haem metabolism.

Haem can be generated using succinyl CoA, which can be produced through glutaminolysis to generate α-ketoglutarate and subsequently succinyl CoA (from which succinate and fumarate are generated) in the TCA cycle. Haem is also degraded to produce bilirubin. This linear pathway of glutamine metabolism through to bilirubin generation allows for some production of mitochondrial NADH. Consistent with these findings, *Fh1*-null cells have an increased expression of genes that are involved in heam catabolism and bilirubin excretion, including haem oxygenase 1 (*Hmox1*). Knockdown of *Hmox1* using short hairpin RNAs reduced the colony formation of *Fh1*-null cells, and similar results were evident using a HMOX1 inhibitor, zinc protoporphrin (ZnPP). Notably, neither of these treatments had a significant effect on wild-type cells.

Re-expression of FH in UOK262 cells, which are a recently established HLRCC human cell line, improved oxygen consumption, reduced the levels of fumarate and reduced bilirubin excretion. Moreover, these cells were less sensitive to inhibition of HMOX1.

These findings indicate that the inhibition of haem biosynthesis and degradation could be a valid therapeutic target for patients with HLRCC and that such treatments should have minimal side effects. They also illustrate how the use of computational models combined with experimental data can speed up the identification of select targets to treat specific tumour types.

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STOCKBYTE

ORIGINAL RESEARCH PAPER Frezza, C. *et al.* Haem oxygenase is synthetically lethal with the tumour suppressor fumarate hydratase. *Nature* 17 Aug 2011 (doi:10.1038/nature10363)
FURTHER READING Folger, O. *et al.* Predicting selective drug targets in cancer through metabolic networks. *Mol. Sys. Biol.* **7**, 501 (2011)