Metabolism is essential for life and its alteration is implicated in multiple human diseases. The transformation from a normal cell to a cancerous one requires metabolic changes to fuel the high metabolic demands of the cancer cell, including but not limited to cell proliferation and cell migration. Our group investigates cancer metabolism from an evolutionary point of view. We hypothesise that given specific microenvironmental conditions and metabolic constraints, there is an optimal mode of cell metabolism to achieve a metabolic objective. This metabolic mode will offer an evolutionary advantage and therefore will be selected for during the time course of cancer development. First, we aim to uncover the metabolic objectives and metabolic constraints upon which natural selection is acting. Second, we aim to determine which known (and yet to be discovered) molecular alterations are driving the deterministic or stochastic occurrence of the optimal metabolic modes.

Serine one-carbon catabolism with formate overflow

Serine catabolism to glycine and a one-carbon unit has been linked to the anaerobic requirements of proliferating mammalian cells. However, previous genome-scale modeling from our group predicted a catabolic role for energy generation with one-carbon release as formate. We have now experimentally proven that in cultured cells the majority of serine derived one-carbon units is released from cells as formate, and that formate release is dependent on mitochondrial complex I and reverse 10-formyl-tetrahydrofolate synthetase activity. We have also demonstrated that in mice, 50% of plasma formate is derived from serine and that serine starvation or complex I inhibition reduces formate synthesis in vivo. These observations have significant implications to our understanding of one-carbon metabolism, energy metabolism and the use of complex I inhibitors to treat cancer.

Our work shows that cells run serine one-carbon catabolism in excess of the biosynthetic demand of one-carbon units. Most of the excess one-carbon units are released as formate in the conditions tested. For every formate molecule released from cells one ATP molecule is phosphorylated to form ATP via reverse mitochondrial 10-formyl-THF synthetase. The coupling of the mitochondrial NAD$^+$ dependent 5,10-methylene-THF dehydrogenase to mitochondrial oxidative phosphorylation can contribute with an additional 2.5 molecules of ATP per formate molecule released. In fact, the only cell autonomous phenotype we have observed in MTHFD1L knockdown cells is an increase in glycolysis, a canonical pathway for energy generation. While this evidence is not conclusive, it supports the idea that serine one-carbon catabolism with formate overflow can contribute to energy generation. Further work is required to investigate if this contribution is enhanced in certain cancers relative to normal tissues.

The phenomenon of serine one-carbon catabolism with formate overflow resembles the well-known phenotype of glucose catabolism with lactate overflow (the Warburg effect). Both phenotypes are characterised by the apparent ‘waste’ of carbon atoms and energy production. They are different with respect to localisation. The Warburg effect contributes to cytostatic and the serine one-carbon catabolism to mitochondrial energy generation. They also differ in the magnitude of the pathway rate, glucose catabolism being significantly higher than serine catabolism. However, this rate difference is not unexpected considering that mitochondria represent a low percentage of the biomass content of normal proliferating cells and cancer cells. Finally, similar to the re-synthesis of glucose from lactate in the liver via the Cori cycle, serine could be re-synthesised in the liver, contributing to the organism’s balance of energy, and one-carbon units.

The demonstration of serine catabolism with formate overflow has several implications to our understanding of mammalian metabolism in normal physiology and disease states. Of most importance is the use of metformin, a mitochondrial complex I inhibitor, for the treatment of cancer. A study in mice has shown that metformin treatment synergises with serine deprivation in the growth inhibition of mouse xenograft tumours. Our data suggest a reduction in plasma formate synthesis from serine as a consequence of treatment with complex I inhibitors. Taken together, this evidence indicates that both treatment strategies inhibit the serine one-carbon catabolism to formate, potentially contributing to the observed synergy.

Our future research will focus on uncovering the function of serine one-carbon metabolism with formate overflow and its relevance for cancer development and treatment.

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