Formate metabolism in cancer

In his 1956 landmark paper, Otto Warburg hypothesised that cancer is caused by mitochondrial defects that result in increased rates of glycolysis with lactate overflow. Today, increased glycolysis is an established hallmark of cancer metabolism and forms the scientific basis for Positron Emission Tomography (PET) scans. In contrast, the Warburg hypothesis that cancers harbour defective mitochondria has remained controversial. Recent evidence indicates that some tumours have rates of glucose oxidation comparable to those observed in normal tissues, challenging the assumption that cancer cells are characterised by defective mitochondrial metabolism. A pathway that relies on functional mitochondria is the oxidation of the third carbon of serine to formate. Formate produced in the mitochondria is released into the cytosol, where it supplies the one-carbon demand for nucleotide synthesis. Work from our laboratory has shown that cancer cells produce formate at rates that exceed the biosynthetic demand of one-carbon units, resulting in formate overflow from cells (Meiser et al., Sci Adv 2016; 2: e1601273 and Meiser et al. Nat Commun 2018; 9: 1368). However, the selective advantage of this phenotype remains to be elucidated.

In 2018 we had a major breakthrough. We discovered that high rates of mitochondrial formate production, together with energy homeostasis mechanisms, induce glycolysis. Specifically, mitochondrial one-carbon metabolism oxidises the third carbon of serine to formate. Excess formate production induces an increase in the rate of purine synthesis resulting in higher AMP levels. Due to energy homeostasis mechanisms, the increase in AMP induces an increase in the levels of ADP and to a lesser extent of ATP, overall resulting in an increase of ADP. The increase in ADP thermodynamically pushes glycolysis, which in turn induces an increase in proliferation and cell migration. In the absence of mitochondrial formate production, all these effects can be recapitulated by formate supplementation.

The proposed biochemical mechanism has a number of implications for and beyond cancer metabolism. Previous work at the Institute, from the laboratory of Karen Vousden, has shown that some cancer cells are dependent on mitochondrial metabolism of serine to formate for their growth and survival. The homozygous deletion of enzymes in mitochondrial serine-to-formate metabolism is embryonic lethal in mice and the phenotype can be rescued by formate supplementation. Mitochondrial serine metabolism is also essential for T-cell activation. It remains to be elucidated whether mitochondrial formate production is inducing glycolysis in those contexts and to what extent the requirement of mitochondrial serine metabolism is determined by this mechanism. Finally, since excess formate production results in formate overflow from cells, the link between formate and glycolysis could act in a cell non-autonomous manner as well.

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