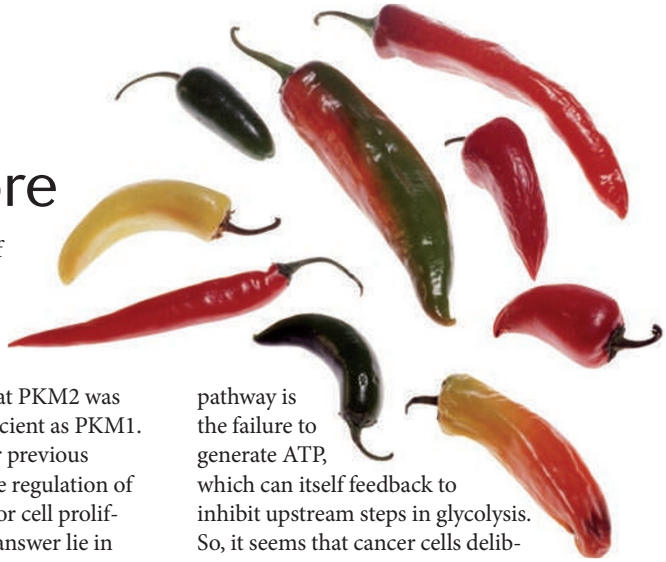

METABOLISM

Less is sometimes more

In 1924, Otto Warburg noticed changes in the way cancer cells metabolized glucose compared with the metabolism of their healthy counterparts. Not only did they show increased glucose uptake, but they also used less glucose for oxidative phosphorylation, opting instead for fermentation. Warburg surmised that this metabolic switch (known as the Warburg effect) was the cause of cancer: a proposal that was quickly rejected with the subsequent discovery of oncogenes and tumour suppressors. In recent years, however, Warburg's original observations have been enjoying a second wind, with researchers asking not only how cancer cells metabolize glucose differently, but also why this occurs. Glycolysis, after all, generates much less ATP than oxidative phosphorylation, so a team led by Lewis Cantley set out to determine its oncogenic appeal.

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Cantley's group had previously found that tumour cells exclusively expressed the embryonic form (M2) of the enzyme pyruvate kinase (PKM2), whereas expression of the M1 isoform (PKM1) was restricted to healthy, adult tissue. So why were cancer cells reverting to PKM2 for glycolysis? The group compared the catalytic activities of the two isoforms on their cellular substrate phosphoenolpyruvate (PEP) and found that PKM2 was less than 50% as efficient as PKM1. This paralleled their previous finding that negative regulation of PKM2 was crucial for cell proliferation. So, did the answer lie in what PKM2 was not doing? The authors suspected that unprocessed PEP might have another cellular function, so they radiolabelled PEP and noticed that a radioactive phosphate was being transferred to a 25 kDa protein. Further analyses by mass spectrometry showed that this protein was phosphoglycerate mutase 1 (PGAM1), a known glycolytic protein. Phosphorylation of PGAM1 occurred on the catalytic histidine 11 (H11) residue and increased the mutase activity of this enzyme. Efficient conversion of PEP to pyruvate, not involving pyruvate kinase, was found to be associated with the reaction, providing evidence of a feedforward loop. The authors also reported that PKM-expressing cells had less H11 phosphorylation of PGAM1. One advantage of using this pyruvate kinase-independent pathway is the failure to generate ATP, which can itself feedback to inhibit upstream steps in glycolysis. So, it seems that cancer cells deliberately use the less efficient PKM2 in order to activate this alternative pathway, thereby severing the ties between ATP production and the anabolic processes that are required for ruthless cell division.

A few questions still remain, such as how is the phosphate group being transferred from PEP to PGAM1? Given that neither enolase nor pyruvate kinase were required for this reaction, the identification of the enzyme responsible is a priority. For now, however, these results suggest that blocking this alternative pathway might represent an exciting new frontier in cancer therapeutics.

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ORIGINAL RESEARCH PAPER Vander Heiden, M. G. *et al.* Evidence for an alternative glycolytic pathway in rapidly proliferating cells. *Science* **329**, 1492–1499 (2010)