oxidative respiration occurs downstream of glycolysis, and so does not compete with glycolysis for carbon equivalents and would not interfere with a high glycolytic flux. Moreover, unlike respiring cells, which shuffle pyruvate from the cytoplasm into the mitochondria — the organelles within which oxidative respiration occurs — cancer cells actively excrete the lactate they generate from pyruvate. This contradicts the proposal that cancer cells shut down respiration to save carbon equivalents for biosynthesis. Finally, even some non-cancerous cells that do not make use of lactate (including yeast, T cells and induced pluripotent stem cells) undergo a Warburg-like metabolic restructuring during rapid growth.

Anastasiou and colleagues' results[4] bring the redox balance centre stage to explain this metabolic reconfiguration. They show that the glycolytic enzyme pyruvate kinase — a main regulator of the Warburg effect — facilitates tumour growth by preventing accumulation of ROS, and so avoiding oxidative damage.

In all living cells, ROS leak from the chain of reactions that constitute oxidative respiration, or are generated as by-products of both fatty-acid metabolism and biosynthetic redox reactions. Under normal physiological conditions this is not a problem, because ROS levels are kept low and in equilibrium with reducing molecules. In fact, a certain amount of ROS is necessary for normal physiology. But if the normal redox balance is disrupted, or ROS accumulate, oxidation and disturbed biochemical reactions damage macromolecules, ultimately leading to cell death. Therefore, cancer cells rely on a complex anti-oxidative machinery that can dynamically supply reducing equivalents and clear ROS when required[3].

Pyruvate kinase is a regulator of cellular anti-oxidative metabolism. Of the four human isoforms of this enzyme, PKM2 plays a crucial part in cancer metabolism. Like other metabolic enzymes, PKM2 levels increase in tumours[5]. However, this protein has a unique regulatory role in that its decreased catalytic activity is associated with tumour progression and the development of the Warburg effect[6,7].

When pyruvate kinase activity is low — as in cancer cells or in respiring yeast — its substrate, phosphoenol pyruvate, accumulates[8,9]. This inhibits the glycolytic enzyme triose phosphate isomerase and leads to activation of a pathway alternative to glycolysis — the pentose phosphate pathway[9]. Increased activity of this pathway protects against ROS in at least two ways. First, it provides NADPH, a reducing factor that is required for the activity of antioxidant enzymes and for the recycling of the anti-oxidant peptide glutathione. NADPH also compensates for the redox imbalance caused by increased nucleotide and fatty-acid synthesis[3]. Second, the pentose phosphate pathway regulates gene expression in favour of adaptation to oxidative stress[10].

Anastasiou and co-workers[4] establish that activation of the pentose phosphate pathway and its anti-oxidative activity are essential for cancer-cell growth (Fig. 1). They report that, in lung cancer cells, oxidation of PKM2 on the cysteine amino-acid residue 358 (Cys358) keeps its activity low. This increases both the concentration of glucose-6-phosphate — the metabolite that connects glycolysis to the oxidative, $NADP^+$-reducing branch of the pentose phosphate pathway — and flux through the pentose phosphate pathway.

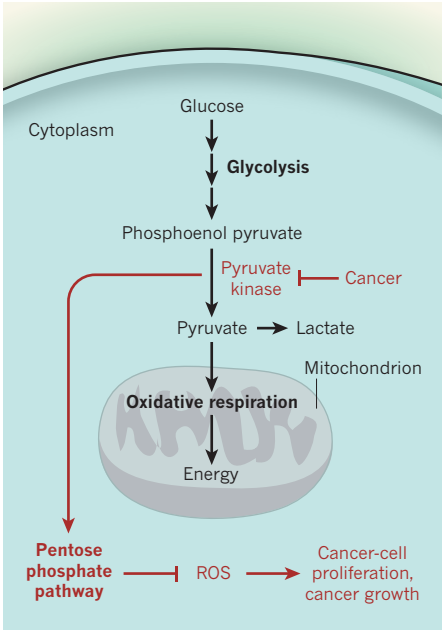

Figure 1 | Restructuring cellular metabolism. Glucose is converted to pyruvate by the cytoplasmic process of glycolysis, generating energy. When oxygen is present, pyruvate enters mitochondria, where it generates more energy through the process of oxidative respiration. But, in proliferating cells — and under anaerobic conditions — pyruvate is converted to lactate. In cancer and respiring yeast, reduced activity of pyruvate kinase, the enzyme that catalyses the final step of glycolysis, mediates redox balance by activating the pentose phosphate pathway[9]. Anastasiou *et al.*[4] show that activation of this pathway is crucial for cancer cells, and facilitates tumour growth by limiting ROS accumulation and, therefore, oxidative stress.

The authors interfered with the pyruvate-kinase-triggered activation of the pentose phosphate pathway by increasing PKM2 activity in the presence of oxidants. To do this, they mutated the enzyme's Cys358 to a serine residue or used small-molecule activators. This treatment had remarkable effects on cancer-cell growth. Accumulation of ROS caused oxidative damage and slowed the proliferation of cancer cells both in tissue culture and in tumours grafted into immunocompromised mice.

These data suggest that inducing the Warburg effect promotes cancer growth by activating the pentose phosphate pathway, maintaining the balance of redox equivalents, providing NADPH and activating antioxidant defence systems. The findings have notable implications for understanding the energetic balance during cancer development: blocking pyruvate kinase to redirect the metabolic flux is energetically costly under conditions of low respiratory activity because it diminishes the step that is responsible for the net yield of the cellular energy molecule ATP by glycolysis. This indicates that maintenance of the redox balance is more limiting for tumour growth than are energy levels or biosynthetic metabolism.

Could this metabolic reconfiguration be exploited for therapeutic purposes? Potentially, yes. But targeting a fundamental redox-balancing process must be cancer-cell specific, otherwise it would heavily damage other metabolically active cell types, including liver cells, immune cells and neurons. Yet, PKM2, triose phosphate isomerase, the pentose phosphate pathway and its associated metabolites are not cancer-cell specific. Nevertheless, a promising strategy might be to induce ROS overload in cancer cells, thereby making them vulnerable to oxidative damage by neutralizing the protective effects of the Warburg effect. To develop such strategies it will be essential to pursue comprehensive quantitative and qualitative investigations to understand all the ROS-producing biochemical reactions in the cancer cell. ■

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CORRECTION

In the News & Views article 'Ageing: Generations of longevity' by Susan E. Mango (*Nature* **479,** 302–303; 2011), it was stated that transient exposure of rats to a high-sugar/low-protein diet leads to glucose intolerance. This should have read "transient exposure of rats to a high-sugar/high-fat diet leads to glucose intolerance".