MILESTONE 6

Not a simple switch

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Cells respire—they consume oxygen and glucose to produce energy in the form of ATP. When oxygen is not available, cells in differentiated tissues break glucose down into lactate (through glycolysis) for energy production. The 'Warburg effect' describes Otto Warburg's observations in the 1920s that malignant tumour cells mainly perform glycolysis even in the presence of oxygen (aerobic glycolysis), thus resulting in high lactate secretion. These observations led him to believe that during malignant transformation, initial irreversible damage in respiration was followed by upregulation of glycolysis to replace the loss of respiration energy. According to Warburg, the origin of cancer was purely based on metabolic alterations. We know today that Warburg was not quite right: oncogenic signalling fundamentally contributes to malignant transformation, partly by regulating metabolism.

By the 1990s, the presence of aerobic glycolysis in some tumours had been clinically exploited for cancer detection through fluorodeoxyglucose–PET imaging. Yet the molecular basis of the Warburg effect remained ill-defined. In 1997, Chi V. Dang and colleagues reported that the glycolytic enzyme lactate dehydrogenase A (LDHA), which catalyses the final step of glycolysis, is a transcriptional target of the oncoprotein MYC. They showed that overexpression of MYC or LDHA resulted in greater aerobic lactate production in cultured fibroblasts. LDHA was also necessary for MYC-induced anchorage-independent cell growth. These findings provided a molecular basis for the Warburg effect, which, contrary to Warburg's hypothesis, involved an oncogene frequently altered in cancer.

The link of cancer-driving gene mutations to the Warburg effect was corroborated on the level of tumour suppressors. Cellular respiration relies on the tricarboxylic acid (TCA) cycle as well as the electron-transport chain (ETC) coupled to oxidative phosphorylation (OXPHOS) in the mitochondria. Indeed, the tumour-suppressor protein p53 was found to participate in controlling the balance between glycolysis and OXPHOS, as reported by Paul M. Hwang's and Karen Vousden's groups in 2006 (See *Mitochondrial complex II mutations found in tumours* on the interactive timeline).

The TCA cycle also generates molecules needed for biomass production. Considering that glycolysis is a relatively inefficient way to produce energy, Craig B. Thompson's group, in one of the first cancer metabolism studies to use carbon-13 isotope tracing, explored the metabolic underpinnings of the Warburg effect. They found that cancer cells use glucose-derived TCA-cycle intermediates in synthetic pathways (particularly fatty acid synthesis). Cells also require continuous replenishment of the TCA cycle with a non-glucose carbon source—a process achieved through uptake and metabolism of the amino acid glutamine. These and other data led Matt G. Vander Heiden, Lewis C. Cantley and Thompson to propose a model in which metabolism in cancer cells is adapted to optimize access to nutrients and their incorporation into biomass, thereby generating a growth advantage.

Further shaking Warburg's hypothesis of irreversibly damaged mitochondria in cancer, Navdeep S. Chandel's group showed that mitochondrial metabolism and ETC function are required for cancer cell growth induced by the oncoprotein KRAS in vitro and in vivo. Moreover, glucose metabolism in the pentose-phosphate pathway (PPP) was found to be crucial for oncogenic KRAS-induced growth, through generating nucleotide precursors as well as NADPH. PPP-derived antioxidants are also linked to promoting cancer cell survival, as shown by Joan Brugge's group, thus highlighting the importance of antioxidant defence in cancer growth.

Research in the 2010s led the field further away from Warburg's path, showing substantial heterogeneity in cancer metabolism, and highlighting the oncogenotype and tissue environment as key determinants. Eileen White's and Alec Kimmelman's groups revealed that oncogenic KRAS-driven cancer cells depend on autophagy, a catabolic pathway that degrades intracellular organelles and macromolecules. Autophagy maintains mitochondrial metabolism and redox control, and allows cancer cells to maintain growth in nutrient-scarce environments. David M. Sabatini's and Cantley's groups have reported amplification of the gene encoding the rate-limiting enzyme in the serine synthesis pathway in certain cancer types, thus making the growth of these cancers dependent on serine and glycine metabolism. Crucially, J. Michael Bishop's group has shown in mice that metabolism in MYC-driven liver cancer not only differs from metabolism in MYC-driven lung cancer, but also differs from metabolism in liver cancer driven by the oncoprotein MET. In humans, Ralph J. DeBerardinis and colleagues have observed metabolic heterogeneity among tumours across patients and within the same patient as well as among regions within the same tumour.

This complexity signifies that the cancer metabolism field has long outgrown the confines of the hypothesis that Warburg proposed nearly a century ago. Since then, seminal findings have been reported by many groups. Although research in the past two decades has largely focused on primary tumours, insights into metabolism during metastasis, in the tumour microenvironment, and in the systemic context, are rapidly advancing. To date, only a limited number of agents targeting cancer metabolism have been successfully applied in the clinic (See *IDH1 mutations lead to the generation of 2-hydroxyglutarate* and *FDA approval of enasidenib for acute myeloid leukaemia* on the interactive timeline), but this is likely to change in the future.

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ORIGINAL ARTICLES Shim, H. et al. c-Myc transactivation of *LDH-A*: implications for tumor metabolism and growth. *Proc. Natl Acad. Sci. USA* **94**, 6658–6636 (1997) | Matoba, S. et al. p53 regulates mitochondrial respiration. *Science* **312**, 1650–1653 (2006) | Bensaad, K. et al. TIGAR, a p53-inducible regulator of glycolysis and apoptosis. *Cell* **126**, 107–120 (2006).
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