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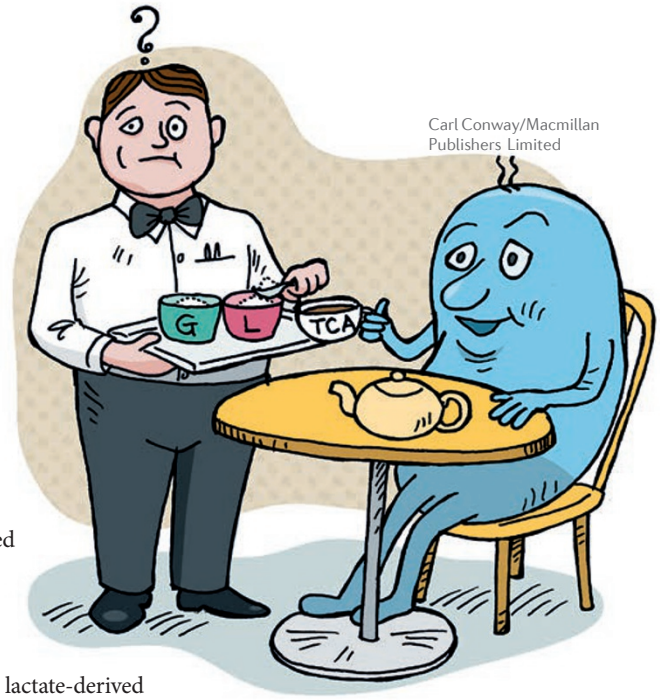
> the use of lactate as a respiratory fuel was dependent on the anatomical location

METABOLISM

# More lactate, please

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Traditionally, lactate, the end product of glycolysis, has been regarded more as a metabolic waste than a fuel in tumour cells. However, a recent study in *Cell* describes the metabolism of lactate in human lung tumours *in vivo*, showing that exogenous lactate is consumed and used, predominantly over glucose, as a respiratory fuel.

During glycolysis, glucose, a main metabolic fuel in many tumour cells, is converted into 3-phosphoglycerate (3PG) and then via pyruvate into lactate. The fate of glucose in tumours was studied by stable isotope labelling. Intra-operative infusions of glucose, labelled with heavy carbons ([$^{13}$C]glucose), into patients with non-small-cell lung cancer (NSCLC) was followed by subsequent analysis of the $^{13}$C content in 3PG and lactate from tumour tissue, and revealed two groups of patients with distinct labelling patterns. Compared with adjacent benign lung tissue, one group showed a similar level of labelling of lactate relative to 3PG, and the other group showed a higher level of labelling of lactate relative to 3PG (a high lactate-to-3PG ratio), which correlated with tumour progression. Metabolic flux analysis indicated that glucose-derived lactate in the plasma contributed to the high lactate-to-3PG ratio. This indication was confirmed by direct infusion of patients with [$^{13}$C]lactate, leading to the presence of $^{13}$C in tumour lactate, pyruvate and tricarboxylic acid (TCA) cycle intermediates, which was indicative of the ability of the tumours to take up lactate and use it as a respiratory fuel.

To corroborate the findings from patients, mice with NSCLC xenografts were infused with [$^{13}$C] lactate. The xenografts were either orthotopic lung or subcutaneous tumours derived from H460, HCC827 or HCC15 cell lines. In all mouse models, lactate-derived carbons were detected in tumour lactate and TCA cycle intermediates. The lactate-to-3PG ratio was higher in orthotopic lung tumours compared with subcutaneous tumours, demonstrating that the use of lactate as a respiratory fuel was dependent on the anatomical location.

The source of lactate in the tumour could be either direct uptake from the plasma or uptake of pyruvate or alanine and subsequent conversion. Formation of lactate from pyruvate, and indirectly from alanine, occurs in parallel with a transfer of hydrogen from NADH to newly formed lactate. This transfer is reversible, which enables exogenous lactate to be converted into pyruvate, and to enter the TCA cycle. To identify the source of lactate, mice were infused with lactate labelled with heavy hydrogen ([$^{2}$H]lactate). The researchers detected lactate in the tumour containing $^{2}$H label. Because lactate derived from pyruvate or alanine would have lost the $^{2}$H label, this observation showed that lactate was taken up from the plasma. Of note, deletion of monocarboxylate transporters (MCTs) in xenografts showed that the uptake and entry of lactate into the TCA cycle was dependent on MCT1 rather than MCT4. Finally, to distinguish the relative contribution of lactate and glucose to the TCA cycle, tumours were infused in parallel with [$^{13}$C] glucose and [$^{13}$C]lactate. Surprisingly, lactate, rather than glucose, was the predominant carbon source for TCA cycle intermediates in HCC15-derived and H460-derived tumours.

This research underlines the flexibility of tumours in using certain nutrients and metabolic pathways. Understanding this metabolic plasticity remains a challenge in cancer metabolism research.

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**ORIGINAL ARTICLE** Faubert, B. *et al.* Lactate metabolism in human lung tumors. *Cell* **171**, 358–371 (2017)
**FURTHER READING** Corbet, C. & Feron, O. Tumour acidosis: from the passenger to the driver's seat. *Nat. Rev. Cancer* **17**, 577–593 (2017) | Hui, S. *et al.* Glucose feeds the TCA cycle via circulating lactate. *Nature* http://dx.doi.org/10.1038/nature24057 (2017)