Published in final edited form as:

Nat Rev Endocrinol. 2019 February ; 15(2): 71–72. doi:10.1038/s41574-018-0146-6.

Fuelling cancer cells

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Abstract

Cancer cells consume and utilize glucose at a higher rate than normal cells. However, some microenvironments limit the availability of nutrients and glucose. In 2018, researchers found that tumours depend on a variety of different nutrient sources, both locally and systemically, to overcome metabolic limitations and promote tumour progression and metastasis.

Oncogenic drivers in cancer cells elicit uncontrollable cell division and cell growth, which is coupled to an increase in the activity of anabolic pathways involved in biosynthesis. The anabolic demands are met by the acceleration of intracellular metabolism. It was assumed that in both normal and cancer cells, glucose fed the tricarboxylic acid (TCA) cycle directly via pyruvate, and overflow of this pathway led to excretion of lactate as waste. By using metabolic tracing in vivo, in 2017 it was shown that a large number of normal tissues consume lactate as a major fuel for the TCA cycle^{1,2} (FIG. 1). A key paper from the past 12 months demonstrated that among all tissues tested, only the brain exclusively utilizes pyruvate directly derived from glucose as a carbon source for the TCA cycle¹. While this finding might seem to oppose many ¹³C-labelled glucose-tracing experiments, most TCA-labelling from glucose is actually derived from lactate. Indeed, this phenomenon was also demonstrated in genetically engineered mouse models of lung and pancreatic cancer¹, as well as in human patients with lung cancer². Thus, in addition to glutamine, lactate is the predominant carbon source for the TCA cycle in many tissues. The extent to which glutamine and lactate fuel the TCA cycle in tumours seems to mirror the tissue of origin.

Why tumour cells excrete glucose-derived lactate and then import extracellular lactate to feed the TCA cycle remains to be determined. One suggested possibility is that the cells excreting lactate are not the cells that consume extracellular lactate. Within a heterogeneous tumour, the hypoxic cells depend on glycolysis and secrete high quantities of lactate. This lactate can then be taken up by the more oxygenated cells in the tumour to support respiration. However, this cannot explain the consumption of circulating lactate by both normal and tumour tissues. Interestingly, inhibition of the mitochondrial pyruvate carrier (MPC) inhibits lactate-mediated TCA cycle fuelling³. This finding was explained by the

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Competing interests

The authors declare no competing interests.

pyruvate derived from exogenous lactate being unable to enter mitochondria. Alternatively and intriguingly, MPC inhibition might prevent lactate entry into the mitochondria, where it can be converted to pyruvate by a putative mitochondrial L-lactate dehydrogenase (LDH), thereby conserving cytosolic NAD⁺ (FIG. 1). This idea is supported by the finding that LDHB can localize to the mitochondria⁴. While surprising, this landmark discovery does not diminish the importance of glucose metabolism during oncogenesis.

In fact, tumour cells compete with other organs and tissues, such as brain and insulin-responsive tissues, for glucose to support their growth. In a paper published in 2018, it was shown that leukaemic cells use a variety of methods to limit the consumption of glucose by normal tissues, increasing its availability for cancer cell utilization⁵. The authors demonstrate that cancer cells induce insulin-like growth factor-binding protein 1 (IGFBP1) secretion from adipose tissue to decrease the insulin sensitivity of healthy tissue. Furthermore, the tumour cells increase levels of DPP4, which inactivates GLP1 (an incretin that promotes insulin secretion). Finally, they demonstrate that the leukaemic cells induce gut dysbiosis to decrease systemic serotonin levels, further decreasing insulin secretion. Indeed, all of these mechanisms decrease insulin levels or insulin sensitivity in healthy tissues, which increases glucose availability for the cancer cells. Despite the decreased utilization by other tissues, the blood levels of glucose in mice with leukaemia were lower than those of control mice, indicating massive consumption of glucose by leukaemic cells. While this study demonstrates that blood-borne cancers can compete for systemic nutrients in the blood stream, solid tumours experience metabolic limitations due to local nutrient supply.

As solid tumours outgrow their vasculature, nutrient levels become limiting and 5'-AMP-activated protein kinase (AMPK) activation leads to tumour frugality as a means for survival. One method that cells use, macropinocytosis, is a nutrient scavenging programme where cells consume and degrade nearby macromolecules for fuel. In prostate cancer, for example, a key paper from 2018 demonstrated that the combination of AKT hyperactivation due to phosphatase and tensin homologue (PTEN) loss and AMPK activation leads to induction of macropinocytosis⁶. The centres of solid tumours are well known to be necrotic as a result of poor nutrient perfusion and hypoxia. However, it was not appreciated that the surviving tumour cells consume necrotic cells, via macropinocytosis, as nutrients to fuel survival. Indeed, the authors of this 2018 study show that PTEN-deficient prostate cancer cells directly consume necrotic debris. Under nutrient-depleted conditions, cancer cells utilized necrotic debris as a source for 35–71% of their biomass. Surprisingly, in nutrient-replete conditions, 14–25% of cellular biomass came from necrotic debris. This study demonstrates that prostate cancer cells not only consume necrotic debris during times of stress but also basally utilize macropinocytosis for nutrient uptake.

While macropinocytosis is one method of tumour cell survival in the harsh core of solid tumours, it was demonstrated this year that aspartate becomes limiting in these conditions for many tumour types⁷. To find out what metabolites are required for proliferation of tumour cells under hypoxia, the investigators treated a panel of cell lines with electron transport chain (ETC) inhibitors and found that resistant cell lines had increased levels of aspartate. Consistently, these cell lines had robust expression of SLC1A3, a glutamate–

aspartate transporter, and ectopic expression of SLC1A3 in ETC-sensitive cell lines rescued their growth. Indeed, ectopic expression of SLC1A3 increased tumour growth of cell lines that were sensitive to ETC inhibition using competitive xenograft models. Finally, the authors showed that aspartate contributes to purine synthesis in hypoxic cells. To further support the notion that aspartate is limiting for many tumour cells, in 2018, another group demonstrated that heterologous expression of guinea pig asparaginase, an enzyme that deamidates asparagine to aspartate (human cells do not have functional asparaginase activity), was sufficient to increase intracellular aspartate levels, rescue proliferation in response to ETC inhibition and hypoxia and robustly increase tumour growth in xenografts of many cancer cells⁸.

This year, another group also demonstrated that asparagine is essential for driving protein synthesis and proliferation when glutamine is depleted⁹. Glutamine is known to feed the TCA cycle and support nucleotide and protein biosynthesis. Mechanistically, asparagine increased protein stability of glutamine synthetase (GLUL), the rate-limiting enzyme in glutamine synthesis that converts glutamate to glutamine. This asparagine-dependent glutamine production restored protein synthesis and proliferation in glutamine-deprived cells. Consistent with asparagine's role in promoting protein synthesis during tumorigenesis, a key paper from 2018 showed that asparagine is required for metastasis in breast cancer¹⁰. In the absence of asparagine synthetase or when asparagine was depleted in the serum by diet restriction or systemic asparaginase treatment, fewer metastases occurred. Conversely, an asparagine-rich diet promoted metastasis. Mechanistically, asparagine-deprived cells showed decreased protein synthesis, particularly in proteins rich in asparagine. Intriguingly, epithelial–mesenchymal transition-related proteins are extremely rich in asparagine. As a result, when asparagine is limited, breast cancer cells had an epithelial morphology and their invasiveness was reduced in vitro. These data suggest that systemic asparaginase could be a useful adjuvant treatment for advanced breast cancer.

In summary, the studies highlighted here illustrate that cancer metabolism research is increasingly discovering new and unexpected mechanisms by which cancer cells derive fuel, gradually shifting from the classic fuelling by glucose. Some works provide immediate insight into patient care. For example, the realization that leukaemias induce and depend on systemic insulin resistance gives oncologists an entire arsenal of therapies used by endocrinologists treating millions of patients with diabetes mellitus. In addition, the realization that lactate is the main fuel for the TCA cycle in tumours is ground-breaking, but, as the same is also true for healthy cells, more work is required to parse out therapeutic opportunities that selectively target cancer cells.

Acknowledgements

The authors' research is supported by NIH grants R01AG016927, R01CA090764 and R01CA206167 (N.H.), by VA grant BX000733 (N.H.) and by F30CA225058 NIH award (A.R.T.).

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Key advances

- Lactate, not glucose, is a main carbon source for tricarboxylic acid (TCA) cycle oxidation in tumour cells^{1,2}.
- Leukaemic cells induce whole-body insulin resistance to increase glucose availability for their growth⁵.
- Prostate cancer cells consume necrotic cell debris under both nutrient-replete and nutrient-depleted conditions⁶.
- Many tumours become dependent on aspartate for continued growth in hypoxic environments^{7,8}.
- Asparagine is required for protein synthesis in glutamine-deprived conditions⁹ and promotes metastasis via epithelial–mesenchymal transition protein synthesis¹⁰.

Fig. 1 l. Metabolic fuelling of cancer.

Tumour cells preferentially utilize extracellular or circulating lactate as a carbon source for the tricarboxylic acid (TCA) cycle. α KG, α -ketoglutarate; GLUT, glucose transporter; LDH, L-lactate dehydrogenase; MCT, monocarboxylate transporter; MPC, mitochondrial pyruvate carrier.