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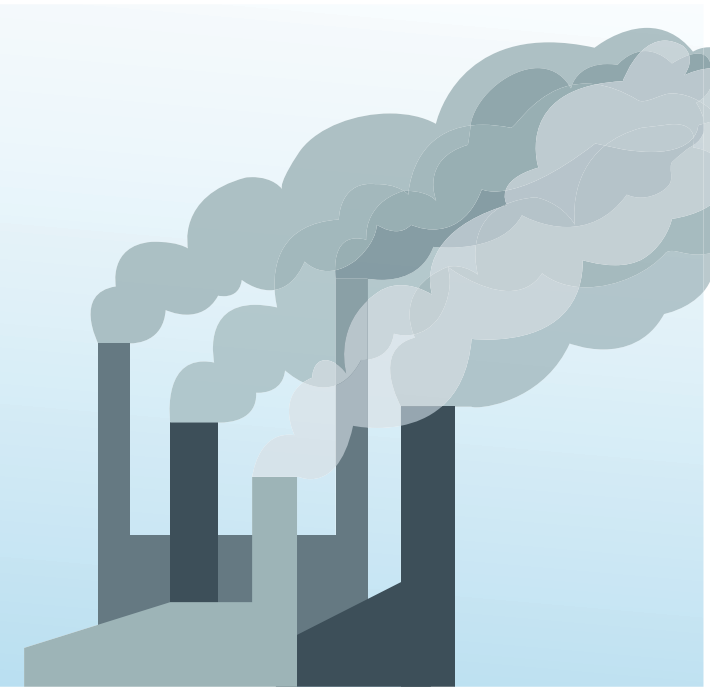
METABOLISM

Choose your carbon source

Glucose and glutamine are the primary carbon sources for ATP production and biosynthesis in proliferating mammalian cells, but how their uptake and metabolism is coordinated according to supply is poorly understood. A recent report uncovers new mechanistic details of this regulation, indicating that flux through the hexosamine pathway is a crucial determinant of glutamine uptake.



Cellular uptake of glucose and amino acids (including glutamine) requires growth factor signalling. Craig Thompson and colleagues studied the metabolic consequences of glucose deprivation on human and mouse haematopoietic cells stimulated with the growth factor interleukin-3 (IL-3). Surprisingly, instead of a compensatory increase, glutamine consumption decreased in glucose-starved cells, leading to the depletion of metabolites in multiple metabolic pathways. This result indicates that cells place a unique importance on glucose as a carbon source, irreplaceable by glutamine, possibly owing to the wide range of metabolic pathways that it supplies. Indeed, resupply of labelled glucose fed carbons to the glycolytic, pentose phosphate and hexosamine pathways into which glutamine cannot feed.

Evidence that the hexosamine pathway of macromolecule glycosylation is a sensor of glucose supply came from the demonstration that providing *N*-acetyl-glucosamine (GlcNAc; a hexosamine pathway intermediate) rescues the defective glutamine uptake and growth of glucose-depleted cells, possibly by growth factor-dependent upregulation of the glutamine transporter SLC1A5. This is despite the inability of labelled GlcNAc to enter the glycolytic or TCA pathways and so provide cellular energy or support for biosynthetic reactions from its own metabolism.

The metabolic effects of glucose depletion were amplified by the observed concurrent downregulation of the receptor IL-3Rα, thus reducing the flux of growth factor signalling and contributing to the loss of cellular viability. IL-3Rα expression and signalling was also rescued by GlcNAc. Although the mechanistic details are incomplete, it is likely that GlcNAc enables glycosylation of IL-3Rα (a glycoprotein), thus facilitating its membrane expression.

It will be interesting to see whether this regulation of carbon sources occurs in the presence of growth factors other than IL-3. Additionally, it remains to be determined whether the reliance on glucose and glutamine to maintain oncogenic proliferation can be exploited as an anticancer therapeutic strategy and whether such inhibitors of metabolic processes will be sufficiently non-toxic to normal tissues.

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ORIGINAL RESEARCH PAPER Wellen, K. E. *et al.* The hexosamine biosynthetic pathway couples growth factor-induced glutamine uptake to glucose metabolism. *Genes Dev.* **24**, 2784–2799 (2010)