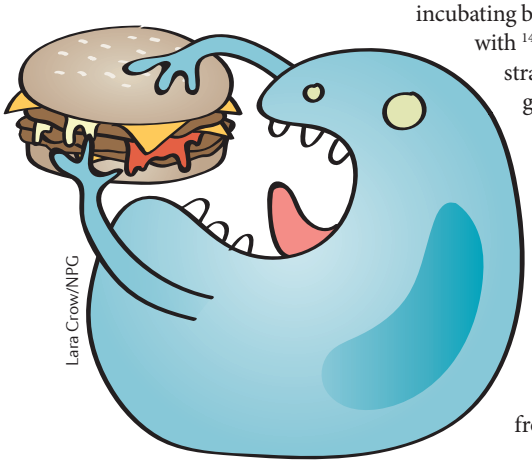
Nature Reviews Cancer | Published online 12 Sep 2016; doi:10.1038/nrc.2016.99

TUMOUR METABOLISM

The sugar-free, full-fat diet

> the authors investigated the possibility of altering regulation of fatty acid metabolism to impair tumour metabolic adaptation to acidosis.



Lara Crow/NPG

The increased proliferation of tumour cells is achieved partly by the ability of tumours to readjust their glycolytic-based metabolism, which promotes an acidic microenvironment. Acidosis, in turn, leads to reduction in glycolysis and in the glucose-derived biosynthetic intermediate acetyl-acetyl-CoA. Corbet *et al.* have now shown that under chronic acidosis tumour cells survive by obtaining acetyl-CoA from fatty acids rather than from glucose and that targeting key players of the fatty acid metabolism may impair tumour growth.

First, the authors investigated the influence of chronic acidic pH on patterns of acetylation in pH 6.5-adapted tumour cells, and observed hyperacetylation of mitochondrial proteins, which was mainly mediated by an increase in the mitochondrial acetyl-CoA pool. They then investigated which metabolic pathways known to generate acetyl-CoA contributed to the increased mitochondrial protein acetylation by incubating both types of cell with ^{14}C-labelled substrates (glucose, glutamine and the fatty acid palmitate). Acidic pH-adapted tumour cells showed an increase in acetylated mitochondrial proteins from palmitate compared with parental cells, whereas acetylated proteins from glucose were dramatically reduced, highlighting the contribution of fatty acid oxidation (FAO) to the pool of acetyl-CoA in the presence of chronic acidosis.

On the basis of previous results that had described increased glutamine metabolism in tumour cells under chronic acidic conditions, the authors also evaluated the contribution of glutamine to fatty acid synthesis (FAS). Both parental and pH 6.5-adapted tumour cells produced fatty acids *de novo* (although to a lower extent for the latter cell type), and lipids derived from pH 6.5-adapted tumour cells were enriched in ^{14}C from glutamine compared with parental cells, indicating a switch in the nature of the nutrients supplying lipogenesis.

Corbet *et al.* analysed the status of acetyl-CoA carboxylases ACC1 and ACC2 — encoded by *ACACA* and *ACACB*, respectively — the two enzymes that generate malonyl-CoA, which is involved in FAS but also negatively regulates FAO. They found that expression of both ACC2 protein and *ACACB* transcript were significantly decreased in acidic pH-adapted tumour cell lines from different tissues (such as cervix, pharynx and colon). The authors then hypothesized that this repression could be mediated by an epigenetic mechanism related to the histone deacetylation observed in the initial analysis of acetylation patterns, which had revealed that acetylation of histones H3 and H4 was strongly decreased in acidic pH-adapted cells. Further experiments showed that histone deacetylation in these cells was prevented when the deacetylases sirtuin 1 (SIRT1) and SIRT6 were silenced, whereas knocking down sirtuins did not affect H3 and H4 deacetylation in parental cells.

Finally, the authors investigated the possibility of altering regulation of fatty acid metabolism to impair tumour metabolic adaptation to acidosis. Re-expressing ACC2 in acidic pH-adapted cells prevented palmitate uptake and inhibited proliferation of these cells but did not affect parental cell growth. The authors also investigated the effect of silencing two other major enzymes involved in FAO — carnitine *O*-palmitoyltransferase 1 (CPT1A) and long-chain-fatty-acid-CoA ligase 1 (ACSL1) — which significantly reduced the growth of acidic pH-adapted cells without affecting parental cell growth. This effect was also achieved by the pharmacological CPT1 inhibitor etomoxir. Inhibiting FAO with etomoxir or FAS with the glutaminase inhibitor BPTES rapidly reduced the growth of tumours in mice carrying xenografts from pH 6.5-adapted tumour cells. Moreover, combination of both inhibitors showed additive inhibitory effects.

This study provides new insight into the acetylation-dependent regulation of the metabolism of tumour cells in the presence of acidosis as well as highlighting attractive targets to perturb lipogenesis and tumour cell growth in these acidic environments.

M. Teresa Villanueva

ORIGINAL ARTICLE Corbet, C. *et al.* Acidosis drives the reprogramming of fatty acid metabolism in cancer cells through changes in mitochondrial and histone acetylation. *Cell Metab.* **24**, 311–323 (2016)