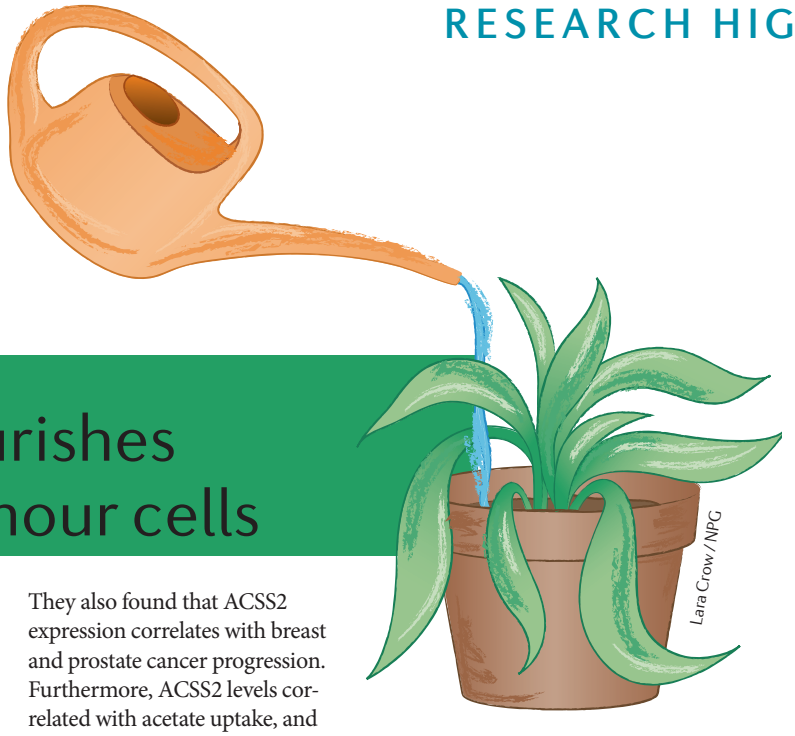

METABOLISM

Acetate nourishes stressed tumour cells

Acetate is ligated to coenzyme A (CoA) by acetyl-CoA synthetases (ACSSs) to form acetyl-CoA, which can be used in fatty acid synthesis (lipogenesis) and in histone acetylation. Lipogenesis is required for cell growth and survival, and three papers now characterize acetate metabolism in tumours under nutrient-poor conditions.

Schug and Peck *et al.* assessed the role of lipogenesis in hypoxia and nutrient-poor conditions (metabolic stress). They traced ^{13}C-labelled glucose in several cancer cell lines cultured using a customized serum that approximates physiological nutrient conditions. In normoxic conditions, glucose was mostly used in the tricarboxylic acid (TCA) cycle, as well as for fatty acid synthesis. In hypoxia, the ^{13}C labelling of fatty acids and TCA intermediates was considerably decreased, and further analyses of spheroids and xenograft tumours (which both have oxygen gradients that can induce metabolic stress) revealed high levels of acetyl-CoA and fatty acid precursors when fatty acid synthase or ACSS2 were inhibited. This suggests that hypoxia induces a dependence on acetate, rather than glucose, as a carbon source for fatty acid synthesis. Next, the authors traced ^{13}C-acetate and found that the pool of acetyl-CoA labelled with ^{13}C increased in hypoxic and nutrient-poor conditions. This and further experiments showed that acetate is the main source of acetyl-CoA in conditions of metabolic stress.

These authors found that ACSS2 knockdown was the top hit in a screen for inducing growth inhibition of several breast and prostate cancer cell lines cultured in hypoxia. They also found that ACSS2 expression correlates with breast and prostate cancer progression. Furthermore, ACSS2 levels correlated with acetate uptake, and hypoxia and lipid depletion induced the expression of ACSS2. ACSS2 knockdown in several cancer cell lines that were grown as xenografts decreased tumour growth, demonstrating that acetate is an important nutrient for tumour cells undergoing metabolic stress.

Mashimo and Pichumani *et al.* analysed patient-derived xenograft (PDX) tumours derived from patients with glioblastoma or brain metastases. Six glioblastoma PDX models received an infusion of ^{13}C-labelled acetate and glucose, and ^{13}C NMR analysis indicated a shift towards acetate oxidation. Accordingly, the proportion of acetyl-CoA that was labelled by ^{13}C-acetate was much higher in the tumours. They assessed five PDX models of brain metastases to see whether acetate is a common nutrient in the brain. Importantly, the primary tumours from which these metastases were derived do not usually show ^{11}C-acetate uptake via positron emission tomography (PET). However, ^{13}C NMR analysis revealed that acetate oxidation was significantly increased in the brain metastases.

ACSS2 levels were high in the PDX tumours, and ACSS2 expression was inversely correlated with survival of patients with glioma. To validate the importance of ACSS2 in patient tumours, they infused ^{13}C-labelled acetate in four patients with glioblastoma or brain metastases, prior to surgical resection. The ^{13}C NMR spectra again revealed a shift towards acetate oxidation, accompanied by high levels of ACSS2 expression.

Comerford and Huang *et al.* knocked down each of the three ACSS enzymes in HepG2 liver carcinoma cells and found that ACSS2 knockdown had the greatest suppression of ^{14}C-acetate labelling in lipids and histones. Using two genetically engineered mouse models of liver cancer in which *Acss2* was also ablated, the authors showed that tumour burden was significantly reduced compared with controls. They also found that ACSS2 expression was inversely correlated with survival in a cohort of 154 cases of triple-negative breast cancer. Finally, ^{11}C-acetate PET imaging of the two mouse models of liver cancer showed that acetate was taken up to a greater extent in ACSS2-expressing tumour-bearing liver than in non-tumour-bearing liver.

Together, these papers demonstrate the importance of acetate as a nutrient for a variety of tumour types, which potentially reflects a response to the poor growth conditions that are often experienced by tumour cells. Therefore, ACSS2 may be an effective anticancer target.

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> “these papers demonstrate the importance of acetate as a nutrient for a variety of tumour types”

ORIGINAL RESEARCH PAPERS Schug, Z. T. & Peck, B. *et al.* Acetyl-CoA synthetase 2 promotes acetate utilization and maintains cancer cell growth under metabolic stress. *Cancer Cell* **27**, 57–71 (2015) | Mashimo, T. & Pichumani, K. *et al.* Acetate is a bioenergetic substrate for human glioblastoma and brain metastases. *Cell* **159**, 1603–1614 (2014) | Comerford, S. A. & Huang, Z. *et al.* Acetate dependence of tumors. *Cell* **159**, 1591–1602 (2014)