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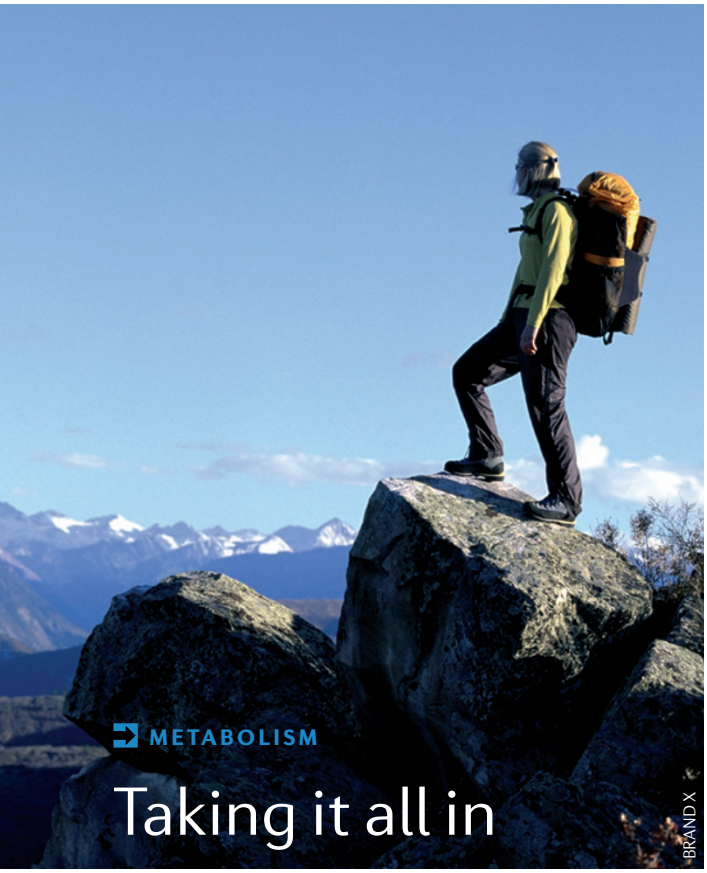

> tumour cells may use macropinocytosis to promote growth

Overexpression of oncogenic RAS has been shown to cause macropinocytosis, which is a type of endocytosis used by cells to take in extracellular fluid and its contents. Whether this process has any functional consequences or is involved in tumorigenesis is unclear.

Commisso *et al.* found that human pancreatic adenocarcinoma cells that endogenously express oncogenic $KRAS^{G12C}$ (MIA PaCa-2 cells) or bladder carcinoma cells that express $HRAS^{G12V}$ (T24 cells) had increased uptake of a labelled high molecular mass dextran (a marker of macropinocytosis) from the extracellular medium compared with cancer cell lines of the same tissue types that express wild-type RAS. Treatment of MIA PaCa-2 cells with an inhibitor that blocks macropinocytosis, but not other endocytic pathways, 5-(*N*-ethyl-*N*-isopropyl)amiloride (EIPA), blocked dextran uptake, and knockdown of KRAS also attenuated uptake. Macropinocytosis of dextran was also observed in xenograft tumours derived from MIA PaCa-2 cells and in an autochthonous mouse model of KRAS-driven pancreatic cancer.

Proteins, including serum albumin, make up approximately 70% of the soluble substances in extracellular fluid, so the authors asked whether macropinocytosis of these proteins could provide amino acids to drive metabolism and proliferation of transformed cells. They found that KRAS-transformed NIH3T3 cells, as well as MIA PaCa-2 and T24 cells, take up labelled bovine serum albumin (BSA) by macropinocytosis and then degrade it by proteolysis. The amino acid glutamine is an important carbon source to fuel the tricarboxylic acid (TCA) cycle in many cells, including those transformed by RAS. Therefore, the authors analysed intracellular concentrations of the glutamine-derived metabolites glutamate and α-ketoglutarate following incubation of the cells with albumin, and observed an increase in both metabolites that could be blocked by EIPA treatment. In addition, they found that ^{13}C-labelled yeast protein was taken up by macropinocytosis in KRAS-transformed NIH3T3 cells, and ^{13}C was incorporated into many intracellular amino acids and TCA cycle intermediates. Furthermore, the presence of albumin in the media allowed KRAS-transformed NIH3T3, MIA PaCa-2 and T24 cells to grow in conditions of glutamine deprivation, an effect that was blocked by EIPA.

To look at the effects of macropinocytosis *in vivo*, the authors treated mice bearing MIA PaCa-2 tumours with EIPA; this decreased tumour growth compared with controls. Interestingly, in preliminary experiments, the authors observed a depletion of glutamine in human pancreatic tumour tissue compared with adjacent normal tissue, suggesting that, in conditions of low glutamine, tumour cells may use macropinocytosis to promote growth, but this needs to be studied directly.

The authors also observed that NIH3T3 cells transformed by oncogenic SRC behaved similarly to those transformed by RAS, indicating that macropinocytosis may be a more general mechanism by which oncogenes promote cell growth.

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ORIGINAL RESEARCH PAPER Commisso, C. *et al.* Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. *Nature* 12 May 2013 (doi:10.1038/nature12138)