Friendly neighbours feed tumour cells

In pancreatic cancer, neighbouring non-cancerous cells degrade their own proteins through a process called autophagy and release amino acids that are then taken up and used by the cancer cells

JURRE J. KAMPHORST & EYAL GOTTLIEB

The cancer pancreatic ductal adenocarcinoma (PDAC) has a poor prognosis, and is an area of intense biomedical research. Previous studies[1,2] have shown that PDAC has a growth-promoting effect on pancreatic stellate cells in the surrounding connective tissue, and these cells reciprocate by supporting tumour growth and spread. On page 479, Sousa et al.[3] investigate the possibility that pancreatic stellate cells directly provide tumour cells with nutrients, in studies using mice and human pancreatic cells.

A key feature of PDAC is desmoplasia, in which the tumour becomes enmeshed and surrounded by dense, scar-like tissue[1,4]. As well as the tumour cells, desmoplasia involves other cell types, including pancreatic stellate cells, which are mainly responsible for the condition, and immune cells. Desmoplasia is a serious medical concern, because it forms a barrier to treatment with chemotherapeutic drugs as a result of poor blood perfusion into the tumour[5]. Paradoxically, desmoplasia is promoted by the release of signalling factors by the tumour, even though it also impedes the tumour's blood supply and hence its access to oxygen, glucose and other nutrients.

How can tumour cells obtain sufficient food and energy in the resulting nutrient poor conditions? Sousa et al. showed that when PDAC cells were grown in vitro with either pancreatic stellate cells or even in the solution in which the stellate cells had been previously grown, oxygen consumption by the PDAC cells increased. This indicates that factors from the stellate cells can stimulate the activity of energy-producing organelles called mitochondria. Sousa and colleagues found that the increased mitochondrial activity is due to tumour consumption of the amino acid alanine, which is released at a high rate by the stellate cells.

The authors used alanine labelled with heavy carbon isotopes to trace the fate of this imported amino acid in tumour cells. Surprisingly, they found that alanine had an unusual metabolic fate in PDAC cells beyond its normal role in protein synthesis. When taken up by the cells, alanine can be metabolized to pyruvate in the aqueous intracellular region known as the cytosol. However, the authors found that instead it went primarily into the mitochondrial pool of metabolite molecules (Fig. 1).

Pyruvate is a key molecule in the mitochondrial tricarboxylic acid cycle, which generates cellular energy and feeds into biosynthetic pathways such as lipid synthesis. It is usually generated by glucose metabolism in a process called glycolysis. Another potential source of pyruvate is alanine transamination, in which pyruvate is produced by the removal of nitrogen from alanine. Alanine transamination can occur in the cytosol or the mitochondria.

Sousa et al. found that the alanine supplied to pancreatic cancer cells undergoes transamination primarily in the mitochondria, producing pyruvate that enters the tricarboxylic acid cycle to provide the cells with energy and lipid molecules. Such selective channelling of alanine to these biosynthetic pathways frees up glucose in the cell for use in other roles, such as production of the amino acid serine, which is required for nucleic-acid biosynthesis and hence cell growth and division.

Although Sousa and colleagues' work documents the metabolic support that alanine from pancreatic stellate cells can offer PDAC cells, it is unclear how and why alanine is

channelled specifically to mitochondria. Alanine-derived pyruvate in the cytosol can also be transported to mitochondria for energy and biosynthesis purposes, and yet this takes place to a lesser degree. Direct transamination of alanine to pyruvate in the mitochondria seals its metabolic fate as a source of energy or biosynthetic molecules. One possible explanation for this compartmentalization of alanine transamination is the potentially higher availability of the nitrogen-acceptor molecule α-ketoglutarate in the mitochondria, which might enable fast and efficient production of pyruvate in response to the large supply of alanine from stellate cells.

Sousa et al. made a surprising finding — that a process called autophagy could affect a neighbouring cell. Autophagy is a survival mechanism used by cells to break down and metabolize their expendable proteins, lipids and other macromolecules when nutrients are scarce. It has been considered to be a process that acts only in the cell itself. However, Sousa and colleagues demonstrated that inhibiting autophagy in pancreatic stellate cells did not affect the cells' growth, but rather abolished alanine release and the resulting support of PDAC-cell growth both in vitro and in vivo (when PDAC cells and pancreatic stellate cells were transplanted together into mice).

The metabolic support of tumour cells by autophagy in pancreatic stellate cells provides a twist to the emerging tale of metabolic scavenging by PDAC cells. These latter cells have a high basal autophagy rate, helping them to survive metabolic hardship[6,7]. The previous observation[8] that PDAC-cell scavenging of extracellular proteins such as albumin can support PDAC metabolism and growth in nutrient-limited conditions highlights the tendency of these cancer cells to exploit diverse nutrient sources. Extracellular material is taken up by the cell through macropinocytosis, a cell-membrane-based transport system. These uptake and autophagy processes depend on organelles called lysosomes, and lysosomal activity was recently found[9] to be increased in PDAC.

Sousa and colleagues' work provides metabolic insight into the well-documented crosstalk between cancer cells and their neighbours. It has been demonstrated[10] that pancreatic cancer cells send signals to adjacent stellate cells that then reciprocate and alter the intracellular signalling and metabolism of the cancer cells. It will be interesting to learn which tumour-generated signals stimulate autophagy and alanine secretion from the pancreatic stellate cells.

Jurre J. Kamphorst and Eyal Gottlieb are in the Cancer Metabolism Research Unit, Cancer Research UK Beatson Institute, Glasgow G61 1BD, UK. e-mails:
jurre.kamphorst@glasgow.ac.uk
e.gottlieb@beatson.gla.ac.uk

1. Feig, C. et al. Clin. Cancer Res. 18, 4266–4276 (2012).
2. Vonlaufen, A. et al. Cancer Res. 68, 2085–2093 (2008).
3. Sousa, C. M. et al. Nature 536, 479–483 (2016).
4. Sherman, M. H., Downes, M. & Evans, R. M. Cancer Prevent. Res. 5, 3–10 (2012).
5. Olive, K. P. et al. Science 324, 1457–1461 (2009).
6. Guo, J. Y. et al. Genes Dev. 25, 460–470 (2011).
7. Yang, S. et al. Genes Dev. 25, 717–729 (2011).
8. Commisso, C. et al. Nature 497, 633–637 (2013).
9. Perera, R. M. et al. Nature 524, 361–365 (2015).
10. Tape, C. J. et al. Cell 165, 910–920 (2016).

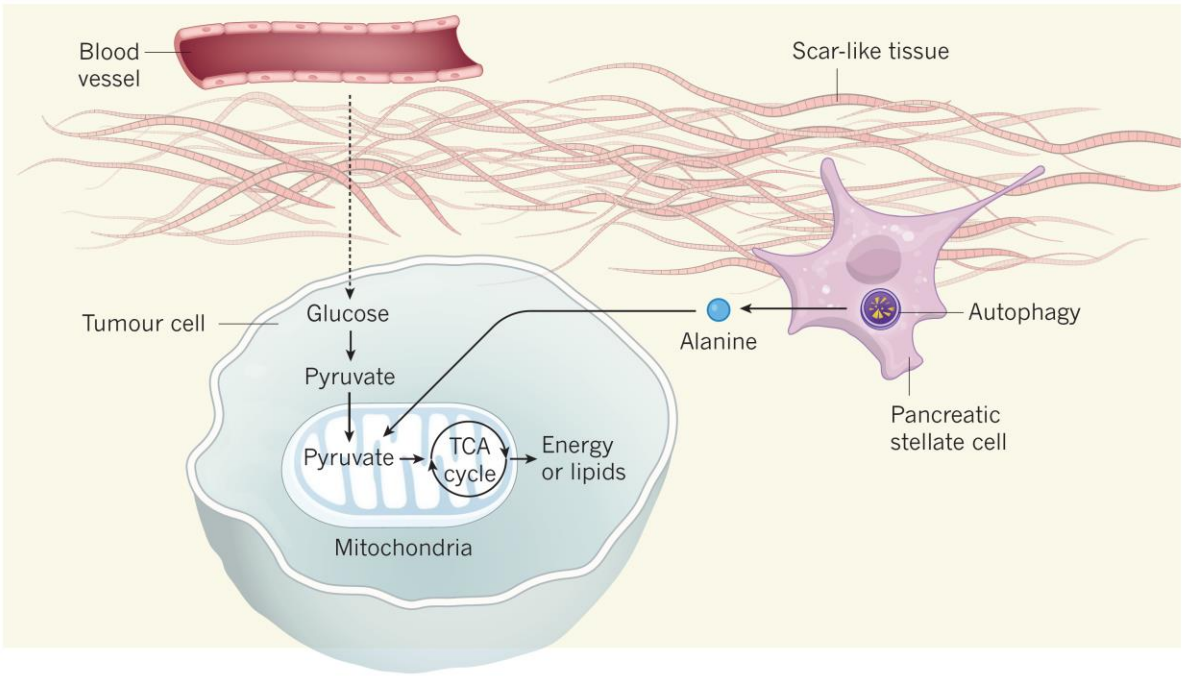

Figure 1 | Pancreatic stellate cells feed a tumour. Pancreatic ductal adenocarcinoma is a form of pancreatic cancer that is characterized by the build-up of dense, scar-like tissue pervading the tumour. This limits the delivery of oxygen and nutrients (including glucose) to the tumour cells by blood vessels. Sousa et al.[3] find that, near tumour cells, pancreatic stellate cells degrade their own proteins in a process called autophagy and release the resulting amino acids, most notably alanine, which are taken up and consumed by the tumour cells, facilitating cancer growth. In the tumour cell, alanine is metabolized to produce pyruvate in organelles called mitochondria, where pyruvate is used to produce energy and lipids through the tricarboxylic acid (TCA) cycle. The use of this pyruvate generated from alanine allows the limited glucose in the cell to be used for other metabolic purposes.