TUMOUR METABOLISM

Energy exchange

Tumour cells have long been known to have an increased metabolic rate, a property that is clinically exploitable. But how crucial is this for the maintenance of the tumour *in vivo*?

Normal cells produce their ATP in the mitochondria through oxidative phosphorylation, unless oxygen is limiting, in which case glucose is converted to lactate to produce ATP. Many tumour cells opt for the second pathway even in the presence of oxygen — known as the 'Warburg effect'. Changes in the mitochondria are also evident in tumour cells (such as an increased mitochondrial membrane potential), so Valeria Fantin and colleagues investigated the growth of tumour cells and examined the function of the mitochondria when lactate production is compromised.

One of the enzymes involved in lactate production is lactate dehydrogenase A (LDHA). Most of the mouse tumour cell lines that the authors examined were reliant on lactate production for their survival. However, two mouse mammary cell lines that express the oncogene *Neu* (also known as *Erbb2*) did not undergo apoptosis on treatment with *Ldha* short hairpin RNAs, and so were used to produce stable cell lines with reduced LDHA expression. These cells proliferated less than the parental cell lines under normoxic conditions, and this difference was exacerbated in hypoxic conditions. The LDHA-deficient cells were reliant on oxidative phosphorylation, and so produced much less ATP than the parental cells, possibly explaining their reduced proliferation *in vitro*. In addition, the NEU-expressing LDHA-deficient cells had a reduced mitochondrial membrane potential compared with the parental cells, and were less sensitive to a small molecule, F16, that is toxic to carcinoma cells with higher than normal mitochondrial membrane potential. Therefore, there is a link between mitochondrial membrane potential and the use of lactate to produce ATP.

So, does the reliance of NEU-expressing LDHA-deficient cells on oxidative phosphorylation compromise their growth *in vivo*? The NEU-expressing parental cell lines and the LDHA-deficient cells were transplanted into the mammary gland fat pads of syngeneic mice. The survival of mice with the parental cell lines was 58 days on average, whereas mice transplanted with LDHA-deficient cells survived for 162 days on average. So, cells without LDHA were able to survive and grow *in vivo*, but their growth was severely compromised.

Humans can survive in the absence of LDHA with relatively minor clinical effects, so targeting LDHA in tumour cells looks to be a promising avenue in cells that rely heavily on the Warburg effect for tumour survival.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Fantin, V. R., St-Pierre, J. & Leder, P. Attenuation of LDH-A expression uncovers a link between glycolysis, mitochondrial physiology and tumour maintenance. *Cancer Cell* **9**, 425–434 (2006)
FURTHER READING Gatenby, R. A. & Gillies, R. J. Why do cancers have high aerobic glycolysis? *Nature Rev. Cancer* **4**, 891–899 (2004)

IN BRIEF

AUTOPHAGY

Autophagic and tumour suppressor activity of a novel Beclin1-binding protein UVRAG

Liang, C. *et al. Nature Cell Biology* **8**, 688–698 (2006)

Autophagy, is involved in cellular responses to stress and starvation and in tumorigenesis. The tumour suppressor Beclin1 (BECN1) induces autophagy as part of the phosphatidylinositol 3 kinase class III (PI3KC3) complex. Liang *et al.* identify the candidate tumour suppressor UVRAG as part of the BECN1–PI3KC3 complex. UVRAG promotes autophagy and suppresses the tumorigenicity of HCT116 human colon cancer cells in mice. Furthermore, like BECN1, UVRAG is mono-allelically mutated in various human cancers.

BREAST CANCER

Leptin signaling promotes the growth of mammary tumors and increases the expression of vascular endothelial growth factor (VEGF) and its receptor type two (VEGFR2)

Gonzalez, R. R. *et al. J. Biol. Chem.* 6 July 2006 (doi: 10.1074/jbc.M601991200)

Increased serum leptin levels correlate with obesity and increased risk of breast cancer, and levels of leptin and its receptor are increased in breast tumour tissue. Gonzalez *et al.* show that leptin increases the expression of VEGF, VEGFR2 and cyclin D1, which leads to increased proliferation in 4T1 mouse mammary tumour cells. Pretreatment of syngeneic mice with a small-peptide leptin receptor antagonist (LPrA2) slowed the growth of injected 4T1 cells and decreased tumour burden, indicating that leptin inhibitors might be useful breast cancer therapeutics.

TUMOUR IMMUNOLOGY

High numbers of tumor infiltrating FOXP3-positive regulatory T-cells are associated with improved overall survival in follicular lymphoma

Carreras, J. *et al. Blood* 6 July 2006 (doi: 10.1182/blood-2006-04-018218)

Most patients with follicular lymphoma (FL, a subtype of adult B-cell non-Hodgkin lymphoma), have incurable disease that frequently develops resistance to therapy or transforms to aggressive diffuse large B-cell lymphoma (DLBCL). Carreras et al. examined samples from 97 patients at diagnosis and 37 at first relapse using an antibody to the regulatory-T-cell (T_{reg}) marker FOXP3. Increased T_{reg} numbers predicted improved survival, and T_{reg} numbers were reduced on transformation of FL to DLBCL, which indicates that T_{regs} might modulate the host immune response and biological behaviour of FL.

TUMOUR CLASSIFICATION

A molecular correlate to the Gleason grading system for prostate adenocarcinoma

True, L. *et al. Proc. Natl Acad. Sci.* USA **103**, 10881–10996 (2006)

The Gleason scoring system is based on the histological grade of tumours, dividing them into those that show well-differentiated or poorly differentiated features. Leroy Hood, Peter Nelson and colleagues have identified an 86-gene signature that distinguishes low-grade from high-grade prostate adenocarcinomas. Characterizing the molecular phenotype of histological grade is of potential clinical importance.