

Cancer

Metabolic vulnerability in tumours illuminated

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A tracer molecule has been used to analyse tumours *in vivo* in mice and to group cancers according to their metabolic characteristics. Such information could have implications for determining how different malignancies are treated. **See p.380**

Altered energy metabolism is a hallmark of malignancy that can be harnessed to detect and treat cancer¹. But tumours are metabolically diverse, so, for treatments to be targeted effectively, non-invasive methods are needed that can observe metabolic characteristics *in vivo*. Momcilovic and colleagues² report on page 380 that an imaging agent called 4-¹⁸F]fluorobenzyl triphenylphosphonium (¹⁸FbNTP) can be used to identify tumours in mice that could be targeted by inhibitors of oxidative phosphorylation, one of the cellular pathways involved in energy production.

Mitochondria are cellular organelles that integrate essential metabolic functions in the cell, including energy production, the

synthesis of biological molecules and signal transduction. These organelles use oxidative phosphorylation to produce the molecule adenosine triphosphate (ATP), the major energy currency of the cell. Oxidative phosphorylation capitalizes on an electrochemical gradient, known as the membrane potential ($\Delta\Psi_m$), that is established by the oxidation of glucose- or nutrient-derived ‘fuel’ molecules in mitochondria (Fig. 1a). Mitochondrial metabolism supports cell proliferation and cancer progression in some malignancies^{3–5}. However, tools have been lacking to observe oxidative phosphorylation directly in tumours, or to predict which tumours rely on this pathway as opposed to other energy-generating

pathways – such as glycolysis, which occurs outside mitochondria, in the cytoplasm.

Momcilovic *et al.* used ¹⁸FbNTP to study oxidative phosphorylation in mouse models of lung cancer. This tracer is a positively charged ion that localizes to the negatively charged inner membrane of mitochondria, where oxidative phosphorylation occurs⁶ (Fig. 1a). The inclusion of fluorine-18 atoms in the molecule provides a radioactive signal that allows accumulation of the tracer to be observed with positron emission tomography (PET), an imaging technique that is commonly used to monitor cancer in the clinic.

In mice genetically engineered to develop non-small cell lung cancer (NSCLC), Momcilovic *et al.* observed ¹⁸FbNTP retention in a subset of tumours. They validated the specificity of the probe by showing that drugs that increase or decrease $\Delta\Psi_m$ had the expected effect on the ¹⁸FbNTP signal monitored by PET.

The authors found that ¹⁸FbNTP uptake by the various tumour subsets differed, even though they contained the same cancer-promoting ‘drivers’ (mutations in genes encoding the cancer-promoting protein KRas and the tumour-suppressor protein Lkb1). As in human NSCLC, tumour subsets in this mouse model are histologically diverse; that is, they have different tissue architectures when viewed under the microscope. One tumour subtype, called adenocarcinoma, tended to take up ¹⁸FbNTP, whereas another subtype, squamous cell carcinoma, did not (Fig. 1b). This was true even for adenocarcinomas and squamous cell carcinomas in the same mouse. Further evidence of the metabolic variability of these tumours came from studies using [¹⁸F]fluoro-2-deoxyglucose (¹⁸F-FDG) – a PET tracer that is commonly used in the clinic to detect glucose uptake in tumours. Squamous cell carcinomas that were exposed to both ¹⁸F-FDG and ¹⁸FbNTP took up ¹⁸F-FDG but not ¹⁸FbNTP, whereas for adenocarcinomas exposed to both tracers, some took up just ¹⁸FbNTP and others took up both tracers. Together, the findings reveal that lung tumours have diverse metabolic ‘personalities’ that are amenable to non-invasive monitoring.

Can the metabolic characteristics monitored by these probes be used to predict whether a tumour will respond to treatment? This question is timely because many metabolic inhibitors – including the oxidative-phosphorylation inhibitor IACS-010759 – are undergoing evaluation in clinical trials⁷. Most of these trials do not have the benefit of being able to non-invasively assess the activity of the pathway targeted by the drug. Momcilovic *et al.* found that, when mouse tumours were grouped according to their ¹⁸FbNTP signal, only those with a high uptake of ¹⁸FbNTP (generally adenocarcinomas) showed marked growth suppression

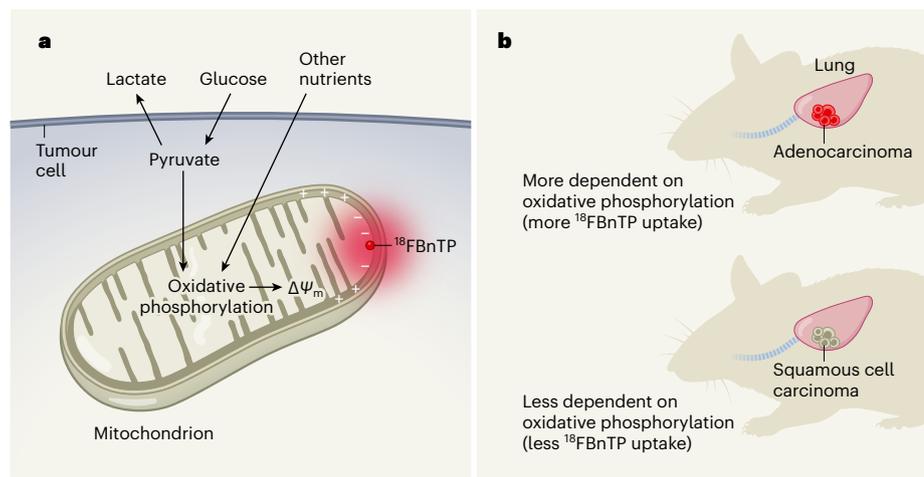


Figure 1 | A non-invasive way to identify tumours susceptible to targeting by a metabolic inhibitor.

a, During cellular metabolism, glucose and other nutrients are taken up into cells. Glucose is converted to the molecule pyruvate, which is either converted to lactate and secreted from the cell (in a process termed glycolysis) or used to fuel a process called oxidative phosphorylation, which is necessary for energy generation in organelles called mitochondria. Both processes produce energy, but tumours vary in the pathway that they prefer. The metabolism of ‘fuel’ in mitochondria through oxidative phosphorylation establishes an electrochemical gradient called the mitochondrial membrane potential ($\Delta\Psi_m$). This generates negative charges on the organelle’s inner membrane, to which the molecule 4-¹⁸F]fluorobenzyl triphenylphosphonium (¹⁸FbNTP) binds; ¹⁸FbNTP can then be imaged using a technique called positron emission tomography (PET). **b**, Momcilovic *et al.*² report that the level of ¹⁸FbNTP uptake can be used to group mouse lung tumours according to whether they are more dependent on oxidative phosphorylation (generally a subset of lung cancers called adenocarcinomas) or less so (usually a subset called squamous cell carcinomas). This difference can be used to predict a tumour’s response to inhibitors of oxidative phosphorylation.

when treated with IACS-010759. Inhibiting oxidative phosphorylation rapidly suppressed ^{18}F BnTP uptake, even before the onset of tumour-cell death, indicating that monitoring the tracer provides a way of predicting whether the tumour will respond to the drug. These findings speak to the potential of ^{18}F BnTP to group tumours according to whether or not they are likely to respond to such inhibitors, and to detect early therapeutic responses non-invasively.

The authors' findings resonate with emerging themes in cancer-metabolism research. Previous studies have generally focused on glycolysis – specifically, the rapid, non-mitochondrial conversion of glucose to the molecule lactate – as a major energy source for cancer cells grown *in vitro*. By contrast, the role of oxidative phosphorylation has been under-appreciated. But studies of human NSCLC *in vivo* have revealed metabolic heterogeneity and prominent metabolism using pathways linked to oxidative phosphorylation (such human studies lacked the tools to monitor oxidative phosphorylation directly)^{8,9}.

Metabolic reprogramming in cancer has commonly been considered to involve a 'switch' from oxidative phosphorylation to glucose uptake, leading instead to glycolysis, but the findings reported by Momcilovic *et al.* support

the idea that this is an oversimplification. In their models, some of the adenocarcinomas take up both ^{18}F -FDG and ^{18}F BnTP, and glucose uptake as revealed by ^{18}F -FDG with PET neither rules out oxidative phosphorylation nor predicts whether tumours will respond to or resist oxidative-phosphorylation inhibitors. The use of ^{18}F BnTP instead provides a more direct assessment of oxidative phosphorylation by providing a way of monitoring $\Delta\psi_m$, and might help to interpret the metabolic significance of other tracers.

With respect to the particular utility of ^{18}F BnTP in NSCLC, it is notable that histological classification of these tumours in humans so far requires invasive tissue sampling, usually from a single site that might not reflect the complexity across the entire tumour. This is important, because the distinction between adenocarcinoma and squamous cell carcinoma influences the choice of chemotherapy¹⁰. An imaging technique such as the one proposed by Momcilovic and colleagues might therefore help to guide therapeutic decision-making.

The challenges of assessing disease-associated metabolic perturbations *in vivo* have hampered our ability to translate mechanistic insights into therapies. Imaging agents such as ^{18}F BnTP might help by enabling key aspects of tissue metabolism

to be observed non-invasively. Altered mitochondrial function, including enhanced or suppressed $\Delta\psi_m$, has been observed in diverse human diseases, including cancer, neurodegeneration and heart dysfunction, not to mention normal ageing¹¹. It will be fascinating to see whether ^{18}F BnTP can help us to understand such conditions in experimental organisms, and eventually in humans.

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This article was published online on 30 October 2019.

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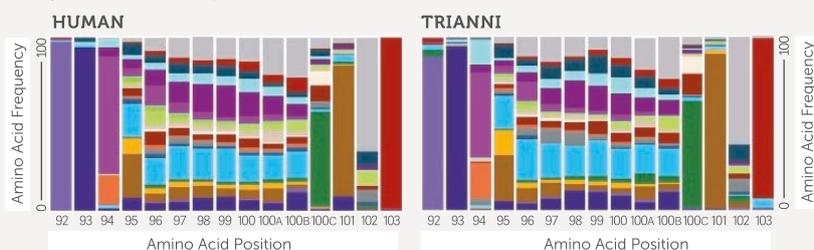
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