

Pancreatic cancer's killer trick offers treatment hope

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PANCREATIC cancer's deadliest trick could be its undoing. Despite each person's tumours having very different genetic mutations, they all cause the same metabolic changes that help it grow. What's more, drugs already exist that can block the process.

Pancreatic cancer is the most lethal of all common cancers – 95 per cent of people die within five years of diagnosis. One reason it is so deadly is that no two cases are genetically the same. That means the tumour is more likely to evolve resistance to drugs, and that genomic studies aiming to find common mutations that could be targeted by treatment have fallen flat.

So [Darren Saunders](#) and colleagues at the Garvan Institute of Medical Research in Sydney, Australia, tried a different approach. As well as looking for variations in the genome of different people's tumours, they also looked at the biological processes at work in the cells.

To do this, they switched from using dead tumour cell samples to patient-derived tumour cell lines, in which fresh samples of a person's tumour are grafted onto mice and grown to the required volumes. Growing them in animals makes for more lifelike tumours, and can produce large quantities of tissue for study.

This bank of living tumour cells allowed the team to study not only the genetics of the cells, but also how genetic mutations in the mitochondria – which drive energy production in the cell – caused changes in the cell's metabolism.

To analyse the tumour cells' metabolism, they used a technique called "[metabolomics](#)". This involves crushing live tumour cells and measuring the metabolites they contain using a mass spectrometer.

"You can think of it like lines on a train map," says Saunders. "Metabolomics allows us to map those pathways and see which ones are switched on and switched off [in a cell]."

Putting together their analyses of the mitochondrial DNA in each tumour cell line and the metabolic pathways at work, the team were able to deduce how each cell line's genetics [directly affected its ability to multiply](#).

They found that pancreatic cancer cells consume not only glucose, as normal cells do, but also glutamine. This leads to the production of fatty acids – the building blocks of new cells – thereby allowing the tumours to proliferate wildly. "Instead of using fuel for energy, they switch to using fuel to build new cells," Saunders says. The team presented its results at the [Lorne Cancer Conference](#) in Australia last month.

This process has been [seen before in other cancers](#), but this is the first time it has been shown to be involved in all pancreatic tumours, and that each tumour evolved different genetic mechanisms to do this.

The team was also able to see exactly how the cancers pulled off this trick. Each tumour they studied switched off the electron transport chain, which is involved in energy production. "The cells in each tumour are finding a different way to do that," Saunders says. Since this happened in all 12 cell lines studied so far, each originating from a different tumour, Saunders suspects it's the key change that makes pancreatic cancer so aggressive. The team now plan to genetically engineer healthy cells to produce the same metabolic behaviour. If those become cancerous, it will further prove the hypothesis.

The find offers enormous hope for treatment, says Saunders. There are drugs already [known to target this chain](#). So it doesn't matter that each person's tumour might find different ways to switch the chain off, drugs ought to be able to reverse the process.

The team is already testing the drugs in the tumour cell lines it created. If all goes well, animal testing could start within six months, says Saunders.

Finding these similarities between the tumours offers new hope for treating a cancer which seemed too varied to target effectively, says Claudio Santos at [University College London](#). "So perhaps in this age of cancer genomics showing how diverse and heterogenous human cancer is, we should be focusing on the common effects that different mutations lead to," he says.

This article appeared in print under the headline "Pancreatic cancer's weak spot found"

Personal treatment

When [Andrew Biankin](#) walked into the Garvan Institute of Medical Research in Sydney, Australia, in 1998 and said he wanted to study pancreatic cancer, the head of the department was unimpressed. "We have a problem," said Rob Sutherland. "You don't know anything about research, and I don't know anything about pancreatic cancer."

Sutherland couldn't know that he would be diagnosed with pancreatic cancer almost a decade later. By then Biankin, now at the University of Glasgow, UK, had sequenced the genomes of 100 tumours and found they were all different. So he created a way to graft tumours onto mice to test out treatments (see main story).

Biankin's team did this with Sutherland's tumour, "and hit it with about a dozen drugs to see which ones it would respond to". The drugs didn't work, and Sutherland died in 2012. But the finding that all these genetic differences trigger the same cellular pathway provides hope for others. Catherine de Lange