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Searching for novel connections in cancer metabolism

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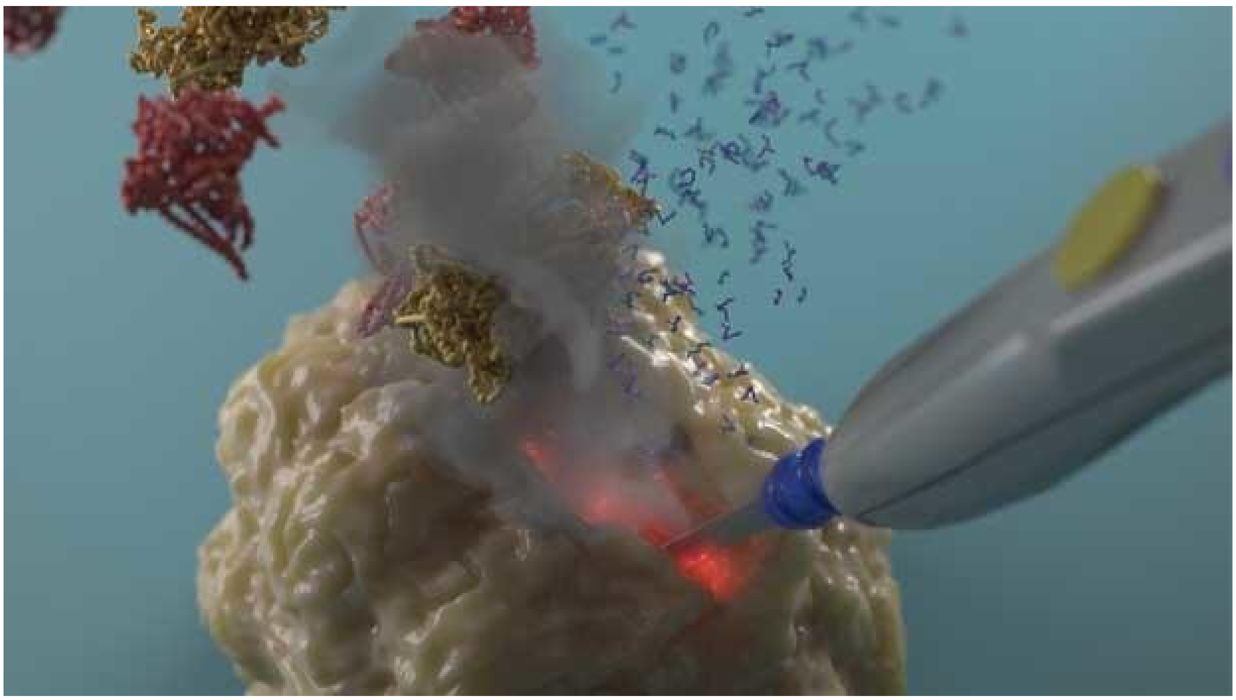

The iKnife has been used to hunt for patterns that could reveals clues about metabolism and cancer. Credit: Jeroen Claus (Phospho Biomedical Animation)

Imagine a line of dominoes. When one is lightly tapped and falls, the rest tumble.

The same is true of cancer. When a cell becomes cancerous, important cellular pathways are altered. And like a chain reaction, when one point in a pathway is mutated, the effects can be felt downstream—just like dominoes.

Some of the pathways that are disrupted in cancer regulate how cells acquire and process energy—their cellular metabolism.

But while a lot is known about the errors that disrupt metabolic pathways in cancer, not much has been done to link these mutations to how the cells behave. Until now.

Dr. George Poulogiannis is one of our scientists investigating the relationship between cellular metabolism, cancer and diet as part of our Rosetta Cancer Grand Challenges team, who are creating a "Google Earth of cancer."

Poulogiannis explained that by completing one part of this complex puzzle—finding novel connections in cancer metabolism—scientists can open the door to a better understanding of individual cancers and, in turn, pave the road to more tailored treatments.

And for a puzzle this complex, they needed a rather unique tool.

The iKnife

To assess the metabolic changes that occur in cancer cells, the team acquired an ingenious piece of equipment known as the Intelligent Knife (or iKnife).

The iKnife was invented by Professor Zoltan Takats at Imperial College London, who works with Poulogiannis on the Rosetta team and was a researcher in this latest study.

This electrosurgical device—designed to sniff out cancer during surgery—has so far been put to the test in breast cancer, and is starting to be trialled in ovarian cancer too.

"A few years ago, a technology was introduced which was based on a very simple idea, to connect the electro surgical device with a mass spectrometer and measure the ionisation profile of the smoke that is being generated," Poulogiannis explains.

Using this technique, the iKnife can precisely differentiate cancer from non-cancerous tissue in real-time. This means that surgeons know if they're cutting through healthy tissue or cancer only a few seconds after their first cut.

"We wanted to explore if using this technology could gather even more detailed information about the biology of the cancer and the key drivers of the disease."

Hunting for clues

Poulogiannis and his team were entering unchartered waters.

The team didn't know exactly what they were looking for, but they began hunting for patterns that could reveals clues about metabolism and cancer, screening a number of breast cancer cell lines, tumour samples and mouse models.

"When we did that, we observed something which at the beginning was quite strange," says Poulogiannis.

Their analysis revealed that the breast cancer samples could be split up into two distinct groups, based on the presence of particular fats sniffed out by the iKnife. And this split did not correlate with any of the features doctors currently use to group the disease—like hormone receptor status.

The team investigated further and discovered that the differences in fats could be explained by an error (mutation) in a gene that's part of an important metabolic pathway, the PIK3CA pathway.

Pieces of the puzzle

One of the fats found at particularly high levels in the samples was arachidonic acid. It's a fatty acid predominantly found in animal fats in our diet but can also be produced by cancer cells.

Significantly, this same fat plays a major role in the inflammatory response in cancer.

"We then tried to find what was the mechanism behind it [the stratification of the samples] and we found that some signalling pathways downstream of oncogenic PIK3CA regulate this overproduction of lipids. And the biomarker fatty acid that caught our attention was arachidonic acid, because this serves as the major hub of pro-inflammatory response in cancer. And this is a fatty acid we get both from the diet, and also PIK3CA mutant cancer cells have a unique ability to increase its production"

Using the iKnife, the team had slowly started to gather together the pieces from various studies and line them up like dominoes, making connections that hadn't been there before.

The team found that drugs that interfered with the PIK3CA pathway were far more effective at slowing tumour growth in mice with breast tumours when the mice were also fed a diet without fatty acids.

Poulogiannis explains how scientists had known for a while that the error in the PIK3CA pathway acted as a marker for a lack of response to certain inhibitors, "but no one quite understood why". Now, with the help of the iKnife, this research has revealed that this lack of response could be because of the overproduction of arachidonic acid.

The complete picture

As the dominoes fell one by one, Poulogiannis and his team followed the clues along the PIK3CA pathway to draw connections between diet, metabolism and cancer, "I think this is one of the first few studies, or maybe even the first, that shows a dietary fat restriction plays a major role in therapy response."

It's been a project filled with unexpected twists and turns, but Poulogiannis is happy with where they've ended up—uncovering new features of breast cancer biology and a new and exciting use for the iKnife.

Although it's early days, Poulogiannis is excited by the potential of these techniques to change the way we look for novel connections in cancer metabolism, and guide how we treat cancer in the future, which was a key part of the Rosetta project.

The Rosetta Cancer Grand Challenges team, led by Professor Josephine Bunch, are continuing to map different tumours in unprecedented detail, in order to develop new ways to diagnose and treat the disease.

"In this study we really managed to capture how metabolic phenotyping, using high-throughput technology, can really help us explain the biology and ultimately identify a novel metabolic vulnerability, a new way to target these tumours which was the whole, I think one of the major goals of this Grand Challenge."

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