Probing what fuels cancer

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Cancer is often described as a genetic disease, after all the transition a cell goes through in becoming cancerous tends to be driven by changes to the cell's DNA.

But genes, though hugely important, might not be the whole story. Researchers at Oxford University are interested in understanding how changes in cells' metabolism – the chemical processes through which cells get the energy they need – could also prime them to become cancerous.

They have just started collaborating with a lab at Keio University in Japan to bring large-scale techniques to the study of metabolic processes going on in cancer cells, much as gene technologies have given such insight into DNA changes involved in cancers.

'Altered cellular metabolism is a hallmark of cancer,' says Dr Patrick

Pollard, who is leading this effort in the Nuffield Department of Clinical Medicine at Oxford.

This is not a new finding - it is something that has been known for a long time. The biochemist and Nobel laureate Otto Warburg pointed it out in the early 1900s. He observed that most cancer cells get the energy they need predominantly through a high rate of glycolysis (the metabolic process that breaks down glucose to release energy). It helps the cancer cells deal with the low oxygen levels that tend to be present in a tumour.

But whether dysfunctional metabolism causes cancer, as Warburg believed, or is something that happens afterwards is a different question.

In the meantime, gene studies rapidly progressed and gave us a picture of how genetic changes lead to cancer.

It goes something like this: DNA mutations spring up all the time in the body's cells, but most are quickly repaired. Alternatively the cell might shut down or be killed off before any damage is caused. However, the repair machinery is not perfect. If changes occur that bypass parts of the repair machinery or sabotage it, the cell can escape the body's normal controls on growth and further DNA changes can begin to accumulate as the cell switches to become cancerous.

So what has metabolism got to do with this? We get the energy we need from food of course, and we talk about our metabolism in the way our bodies make use of that food as a fuel for everything we do during the day. Our cells are the same. They have whole series of chemical reactions going on simultaneously to keep them working, wherever and whatever they are doing in the body – from heart cells to neurons in the brain and liver or pancreatic cells. Cellular metabolism is a constant process with thousands of metabolic reactions happening at the same time, all of which need to be regulated to keep our cells ticking over

healthily.

It's what happens when the regulation of cellular metabolic processes goes wrong that could be of interest. And it's only a lot more recently that techniques to probe the entirety of metabolic processes in the cell have advanced. The result is something of a return to vogue for studies to understand how altered cellular metabolism and cancer are linked.

Studies of the genetic basis of cancer and dysfunctional metabolism in cancer cells are complementary, Patrick believes. 'Genomic data is very important, but certain changes in cells can’t always be accounted for by genetics.'

He is now collaborating with Professor Tomoyoshi Soga's large lab at Keio University in Japan, which has been at the forefront of developing the technology for metabolomics research over the past couple of decades (metabolomics being the ugly-sounding term used describe research that studies all metabolic processes at once, like genomics is the study of the entire genome).

The Japanese lab's ability to screen samples for thousands of compounds and metabolites at once, coupled with the access to tumour material and cell and animal models of disease in Oxford, should give great power to probe the metabolic changes that occur in cancer.

There is reason to believe that dysfunctional cell metabolism is important in cancer. Some genes with metabolic functions are associated with some cancers, and changes in the function of a metabolic enzyme have been implicated in the development of gliomas.

These results have led to the idea that some metabolic compounds, or metabolites, when they accumulate in cells, can cause changes to metabolic processes and set cells off on a path towards cancer.

Patrick Pollard and colleagues have now published a perspective article in the journal *Frontiers in Molecular and Cellular Oncology that proposes fumarate as such an 'oncometabolite'. Fumarate is a standard compound involved in cellular metabolism.*

In that article, the researchers summarise evidence (often from their own lab) that shows how accumulation of fumarate when an enzyme goes wrong affects various biological pathways in the cell. It shifts the balance of metabolic processes and disrupts the cell in ways that could favour development of cancer.

This work on metabolic pathways involving fumarate has already led to a cheap and reliable diagnostic test for a rare form of cancer caused by accumulation of fumarate within cells. Their test for hereditary leiomyomatosis and renal cell cancer (HLRCC) involves screening tumour samples for a particular molecular fingerprint unique to this type of cancer. The Oxford researchers are now hoping to develop their test for clinical use, largely to help with genetic counselling for families as the condition can be inherited.

While HLRCC is a rare type of cancer, Patrick Pollard says: 'Metabolic changes are observed in most cancers, so there could be wider implications. Lots of findings about pathways that are important in cancer come from studying rare cancers.'

This is where the collaboration with Keio University comes in. The Keio group is able to label glucose or glutamine, basic biological sources of fuel for cells, and track the pathways cells use to burn up the fuel. It allows the scientists to work out the metabolic pathways that are being used preferentially by different cell types including cancer-derived cell lines.

Patrick gives an example of how the research might progress: they could profile the metabolites in a cohort of tumour samples and matched normal

tissue. This would produce a dataset of the concentrations of hundreds of different metabolites in each group. Statistical approaches could suggest which metabolic pathways were abnormal. These would then be the subject of experiments targeting the pathways to confirm the relationship between changed metabolism and uncontrolled growth of the cancer cells.

Patrick and colleagues write in their latest article that the shift in focus of cancer research to include cancer cell metabolism 'has highlighted how woefully ignorant we are about the complexities and interrelationships of cellular metabolic pathways'.

Hopefully, research efforts like this large-scale approach to understanding cell metabolism can give insight into how cells respond to shifted metabolic processes and how this is associated with the development of some cancers.

Provided by Oxford University