Researchers find potential new treatment approach for pancreatic cancer

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Scientists from The University of Manchester – part of Manchester Cancer Research Centre believe they have discovered a new way to make chemotherapy treatment more effective for pancreatic cancer patients.

Pancreatic cancer is an aggressive cancer with poor prognosis and limited treatment options and is highly resistant to chemotherapy and radiotherapy.

But researchers believe they have found an effective strategy for selectively killing pancreatic cancer while sparing healthy cells which could make treatment more effective.

Dr Jason Bruce, from the Physiological Systems and Disease Research Group, who led the research, said: "Pancreatic cancer is one of the most aggressive and deadly cancers. Most patients develop symptoms after the tumour has spread to other organs. To make things worse, pancreatic cancer is highly resistant to chemotherapy and radiotherapy. Clearly a radical new approach to treatment is urgently required. We wanted to understand how the switch in energy supply in cancer cells might help them survive."

The research, published in The *Journal of Biological Chemistry* this month, found pancreatic cancer cells may have their own specialised energy supply that maintains calcium levels and keeps cancer cells alive.

Maintaining a low concentration of calcium within cells is vital to their survival and this is achieved by calcium pumps on the plasma membrane.

This calcium pump, known as PMCA, is fuelled using ATP – the key energy currency for many cellular processes.

All cells generate energy from nutrients using two major biochemical energy "factories", mitochondria and glycolysis. Mitochondria generate approximately 90% of the cells' energy in normal healthy cells. However, in pancreatic cancer cells there is a shift towards glycolysis as the major energy source. It is thought that the calcium pump may have its own supply of glycolytic ATP, and it is this fuel supply that gives cancer cells a survival advantage over normal cells.

Scientists used cells taken from human tumours and looked at the effect of blocking each of these two energy sources in turn.

Their study, funded by the Biotechnology and Biological Sciences Research Council (BBSRC), Central Manchester University Hospitals NHS Foundation Trust (CMFT)/National Institute of Health Research (NIHR) Manchester Biomedical Research Centre and AstraZeneca, shows that blocking mitochondrial metabolism had no effect. However, when they blocked glycolysis, they saw a reduced supply of ATP which inhibited the calcium pump, resulting in a toxic calcium overload and ultimately cell death.

Dr Bruce added: "It looks like glycolysis is the key process in providing ATP fuel for the calcium pump in pancreatic cancer cells. Although an important strategy for cell survival, it may also be their major weakness.

"Designing drugs to cut off this supply to the calcium pumps might be an effective strategy for selectively killing cancer cells while sparing normal

cells within the pancreas."

Maggie Blanks, CEO of the national charity, the Pancreatic Cancer Research Fund said: "These findings will certainly of great interest to the pancreatic cancer research community and we'd be keen to see how this approach progresses. Finding weaknesses that can be exploited in this highly aggressive cancer is paramount, so we want to congratulate the Manchester team for their discovery."

More information: Andrew D. James, Anthony Chan, Oihane Erice Azparren, Ajith K Siriwardena, and Jason IE Bruce. "Glycolytic ATP Fuels the Plasma Membrane Calcium Pump Critical for Pancreatic Cancer Cell Survival." *J. Biol. Chem*. First Published on October 24, 2013, DOI: 10.1074/jbc.M113.502948

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