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Researchers slow pancreatic cancer growth by blocking key enzyme

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A research team from Imperial College London has shown that blocking the function of an enzyme known as Hhat slows the growth and spread of pancreatic cancer, by preventing a protein called Hedgehog from stimulating nearby normal cells to help the cancer.

The study, funded by the UK research charity Pancreatic Cancer Research Fund, examined the role of Hedgehog, whose usual job is to send signals to cells in embryos to divide and grow into the correct body parts. But while Hedgehog usually switches off when the embryo is formed, in many cancers, including pancreatic, it becomes abnormally reactivated.

Hedgehog cannot function without the help of the Hhat enzyme, which attaches a fatty molecule to its surface, enabling it to stick to other cells and start sending messages. In cancer, Hedgehog influences nearby healthy cells in an intricate sequence of signals, or 'signalling pathway', instructing them to secrete nutrients to feed the cancer cells and create the perfect environment for them to grow and spread.

Says lead researcher Professor Tony Magee: "Signalling pathways are complex. They're like a flow diagram, with a multitude of arrows travelling along and splitting off at many points along the way, each initiating a new chain reaction of activity. Whilst you could potentially stop the Hedgehog signal at many points along its journey, we wanted to see if we could simply prevent the process from starting in the first place. This meant stopping Hhat from attaching the fatty molecule to

Hedgehog, which is needed for the signalling."

Using genetic techniques, the Imperial team knocked out the Hhat function in pancreatic cancer cells and, as they hoped, the cancer cells showed substantially reduced growth and ability to spread in a test-tube assay. The findings are published in the latest issue of the journal *PLOS ONE*.

The Hedgehog signalling pathway is a good target for cancer researchers because it mainly switches back on in cancer cells and so blocking its function does not overly affect signalling in healthy cells.

However, the genetic techniques used to block Hhat in the laboratory are not possible with animal models or humans. For this, the research team needs to find chemical compounds which could be developed into a new drug to replicate this effect.

Professor Magee is confident that this is possible and, with his collaborator Dr Ed Tate, is planning to screen a huge library of molecules to select those whose properties look most likely to inhibit Hhat's function. They will test the best candidate molecules in mice to see if they can replicate their study findings, before moving on to human clinical trials.

Maggie Blanks, CEO of the Pancreatic Cancer Research Fund, said: "Professor Magee's findings add further weight to a growing body of evidence which points to Hedgehog signalling as an important driver of pancreatic cancer. To prevent this signalling pathway at its starting point is both a simple and ingenious approach that could herald the development of a new treatment. As developing new treatments and early detection methods are the core focus of the Pancreatic Cancer Research Fund, we await further announcements with great anticipation."

More information: The paper, Attenuation of Hedgehog acyltransferase-catalyzed Sonic hedgehog palmitoylation causes reduced signaling, proliferation and invasiveness of human carcinoma cells, is available at dx.plos.org/10.1371/journal.pone.0089899

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