Study reveals gene 'switched off' in early stages of pancreatic cancer allows rapid tumor growth and spread

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HNF4A is methylated and suppressed in pancreatic cancer. Credit: Gastro Hep Advances (2024). DOI: 10.1016/j.gastha.2024.04.005

Scientists at Nottingham Trent University, the University of Nottingham,
Stanford University and the University of California and Cedars-Sinai Medical Center, Los Angeles, have found that the molecule "HNF4A" suppresses pancreatic cancers, regulating their growth and aggressiveness.

Importantly, they observed that HNF4A was significantly shut down in the very early stages of the cancer, declining further as the disease spread. The study is published in the journal *Gastro Hep Advances*.

Part of the digestive system, the pancreas is a gland that produces digestive juices and hormones such as insulin.

On average, there are more than 10,400 new cases of pancreatic cancer in the UK each year and more than 9,500 people will die from the disease.

Fewer than 7% of patients will survive pancreatic cancer beyond five years and there are challenges around screening, diagnosis and treatment.

Pancreatic cancer is typically diagnosed at an advanced stage when the optimal treatments are no longer suitable for the majority of patients and there can be significant resistance to radiotherapy and chemotherapy.

As part of the study, the researchers analyzed pancreatic cancer and healthy tissues to reveal the exact mechanism that tumors use to switch off the expression and beneficial function of HNF4A.

Previous research has looked at the beneficial role of HNF4A in human physiology, especially in tissues of the gastrointestinal tract including the pancreas, liver and intestine.

Disturbance or loss of HNF4A activity is known to lead to various types of disease including cancer, diabetes and inflammatory bowel diseases.
By integrating the patient data with different pharmacological and genetic approaches, the researchers uncovered the tumor-suppressive role of the molecule.

When correlating the molecule's expression alongside the patient data, they found that low expression of HNF4A was linked to poor patient survival.

While several studies have examined the way in which cells behave in pancreatic cancer, the exact underlying mechanisms have remained largely unknown.

The researchers argue that this new understanding will help with the potential development of new standalone or combined treatments for pancreatic cancer.

"Not only have we uncovered the tumor-suppressive role of HNF4A, but also how it is switched off from the very early stage of the disease," said lead researcher Dr. Maria Hatziapostolou, a scientist in Nottingham Trent University's John van Geest Cancer Research Center.

She said, "We found that certain modifications, called DNA methylation, are added on the specific gene to shut it down. Loss of HNF4A drives pancreatic cancer development and aggressiveness and we now know correlates with poor patient survival.

"We hope that this new understanding of the mechanism through which this occurs will help to pave the way for new therapeutics to help fight the disease."

Dr. Chris Macdonald, Head of Research at Pancreatic Cancer UK said, "We desperately need kinder and more effective treatment options for pancreatic cancer. The majority of pancreatic cancers are diagnosed at a
late stage, with 80% not being detected until after the disease has spread and is no longer operable. This is reflected in its poor survival rate; over half of people with the disease die within three months of diagnosis.

"Improving our fundamental understanding of what makes pancreatic cancer grow and spread so rapidly is vital if we are to make much needed breakthroughs. This project gives us new information on how pancreatic cancer is able to suppress certain molecules to help it spread aggressively around the body which, in turn, could lead to the development of more effective treatment options in the future."


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