A gene that increases the risk of pancreatic cancer controls inflammation in normal tissue

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Inflammation is a defensive response of the body to pathogens, but when it persists, it can be harmful, even leading to cancer. Hence, it is crucial to understand the relationship between inflammation and cancer. A group of researchers at the Spanish National Cancer Research Centre (CNIO) has now discovered an unexpected link between the two processes. In the pancreas, one of the genes that increases the risk of developing pancreatic cancer also controls inflammation. This finding offers "a major conceptual change," says Paco Real from the CNIO. As well as helping to understand the origin of tumours, the finding suggests new strategies for the prevention of pancreatic cancer. The research is published in *Nature*.

Inflammation is generally considered a defensive mechanism organised by the cell in response to an external pathogen. But CNIO researchers see it now as a defensive mechanism that the cell keeps suppressed unless it is required. The new findings show the specific control mechanisms that suppress inflammation in normal pancreas.

Starting with this conceptual change, the CNIO group also discovered that, at least in the pancreas, molecular mechanisms involved in the normal functions of healthy tissue, such as cellular differentiation, also suppress inflammation. In other words, the normal functioning of the cell involves keeping inflammation under lock and key.

These results clarify previous findings by the same researchers showing that in mice without the mechanism that inhibits inflammation, the pancreas is prone to develop a cancer induced by mutations in the KRAS gene, a key gene in pancreatic cancer. "We see that when cells are not correctly differentiated, a state of pre-inflammation occurs, and we know that in this context, cells are more sensitive to mutations in the KRAS; it's as if the cells move to the starting grid, ready for inflammation and cancer," explains Real. The mechanism that controls inflammation is a gene called NR5A2. Researchers have studied its function in depth in mice and have verified that the results can be extrapolated to humans.

Real says, "In mice, when there are normal levels of NR5A2, inflammatory phenomena are suppressed, whereas when levels of NR5A2 fall, inflammatory programmes are activated and the risk of developing pancreatic cancer increases. In humans, individuals with low levels of this same gene in the pancreas display a very similar state of pre-inflammation to that detected in mice."

NR5A2 is the switch that activates inflammation. In humans, variants in this gene have been identified that increase the risk of pancreatic cancer. These variants are common in the population—having these variants is not sufficient to cause pancreatic cancer, but researhcers now know that they are associated with a trigger of the initial stages of inflammation and an increased risk if they also

occur alongside other circumstances, such as KRAS mutations.

This fits in very well with clinical observations. Pancreatic cancer frequently occurs in patients with a genetic predisposition, mutations in the KRAS gene, and in those with pancreatitis, inflammation of the pancreas.

Now researchers are faced with two new strategies to make further progress. One is to determine whether the existence of a genetic link between inflammation and cancer is also found in other organs; the other is to try and apply the new knowledge to the prevention of pancreatic cancer, which currently has one of the worst prognoses, partly due to its late diagnosis.

The researchers think that detecting initial states of inflammation would also provide useful warning signs. But they need to be able to detect those signs using a simple blood test: "The pancreas cannot be biopsied, as other more easily accessible tissues can. We are going to try and detect this pre-inflammatory state in the blood, first in mice and then in humans," says Real.

More information: Isidoro Cobo et al, Transcriptional regulation by NR5A2 links differentiation and inflammation in the pancreas, *Nature* (2018). DOI: 10.1038/nature25751

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