

Study shows pancreatic cancer cells reverse to advance malignancy

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A Ludwig Cancer Research study has identified a previously unrecognized mechanism by which cancer cells of a relatively benign subtype of pancreatic tumors methodically revert—or 'de-differentiate'—to a progenitor, or immature, state of cellular development to spawn highly aggressive tumors that are capable of

metastasis to the liver and lymph nodes.

The study, led by Ludwig Lausanne's Douglas Hanahan and published in *Cancer Discovery*, a journal of the American Association for Cancer Research, also shows that engagement of the mechanism is associated with poorer outcomes in patients diagnosed with pancreatic neuroendocrine tumors (PanNETs). Further, its findings provide concrete evidence that such cellular de-differentiation, widely observed across cancer types, is a not merely a random consequence of cancer [cells'](#) other aberrations.

"Our study provides a clear example in a single tumor type that de-differentiation is an independently regulated and separable step in multi-step tumorigenesis," said Hanahan, distinguished scholar at the Ludwig Lausanne Branch. "Moreover, this is not nonspecific de-differentiation, but rather, the result of a precise reversion of a developmental pathway that generated the mature cell type from which the cancer arose."

PanNET tumors originate from the islet beta-cells of the pancreas, which produce the hormone insulin. Hanahan and his colleagues had previously reported that these tumors can be divided into two subtypes: a relatively benign, 'well-differentiated' subtype that maintains many features of insulin producing beta-cells, and a more aggressive and poorly-differentiated subtype that lacks those features.

Using a PanNET mouse model, they showed in the current study that the 'poorly differentiated' cancer cells have many characteristics of normal islet progenitor cells, and that the progression from benign to aggressive PanNET tumors requires cancer cells to retrace the pathway of beta cell differentiation and maturation to assume the progenitor state.

The researchers also uncovered a molecular circuit in [cancer cells](#) that governs this de-differentiation. They report that [tumor](#) cells poised to de-

differentiate step up their production of a type of RNA molecule that regulates gene expression known as microRNA18. This ultimately causes the activation of Hmgb3, a protein that controls the expression of a suite of genes that pushes the cells into a progenitor state.

The results of this study provide new insights on de-differentiation as part of the puzzle of [cancer](#) and furnish preliminary evidence supporting its inclusion as a distinct and separable step, or perhaps sub-step, in the deadly progression toward malignancy.

More information: Sadegh Saghafinia et al. Cancer cells retrace a stepwise differentiation program during malignant progression, *Cancer Discovery* (2021). [DOI: 10.1158/2159-8290.CD-20-1637](https://doi.org/10.1158/2159-8290.CD-20-1637)

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