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PANCREATIC CANCER

Mapping malignant tissue dynamics

New research has identified the molecular networks underlying pancreatic regeneration and early carcinogenesis, revealing distinct dynamic patterns of proliferation between different pancreatic cell types.

The development of pancreatic ductal adenocarcinoma (PDAC) is poorly understood but oncogenic *KRAS* mutations are critical. However, mature pancreatic acinar cells are refractory to neoplastic transformation following activation of oncogenic KRAS, but not in the presence of pancreatitis. "These data led us to hypothesize that the inflammatory insult might alter the dynamics in tissue homeostasis and therefore render the adult cells more susceptible to oncogenic KRAS," explains author Christoph Michalski.

To determine if locally altered tissue dynamics are the underlying driving force in PDAC, the researchers analysed and compared pancreatic tissue at multiple time points in pancreatitis-induced wild-type mice and a mouse model of pancreatitis-accelerated, mutant *Kras*-driven PDAC. Histological and transcription data were collected for specific cell types, leading to molecular network models for regeneration or early carcinogenesis.

In wild-type mice with pancreatitis, the investigators defined three distinct phases of inflammation, regeneration and refinement that corresponded to proliferative waves of mesenchymal, progenitor-like and acinar cells. During regeneration, a coordinated proliferation transition between the three cell types was found. Conversely, in *Kras*-mutated mice, carcinogenesis was characterized by an extended inflammatory phase with persistent and parallel proliferation of all cell types.

Mathematical modelling of transcriptional data revealed that, under inflammatory conditions, the complexity of the molecular network mediating the proliferative transition of progenitor-like to acinar cells during regeneration was greater than that maintaining the proliferation of progenitor-like cells in early carcinogenesis. The simplified network in early carcinogenesis was associated with increased susceptibility of acinar cells to form KRAS-induced preneoplastic lesions, indicating a key initiating event in PDAC.

> "…locally altered tissue dynamics are the underlying driving force in PDAC…"

"We introduce a concept of molecular tissue dynamics in early pancreatic carcinogenesis that extends beyond descriptive morphology," concludes author Bo Kong. "We would like to further clarify how the complex network needed for acinar cell proliferation neutralizes the transforming effect of oncogenic KRAS in the absence of inflammation." The researchers also plan to determine if this work can facilitate the development of so-called liquid biopsies and biomarker targets for early PDAC detection in risk groups.

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