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The identification and functional evaluation of novel cancer-associated fibroblast subtypes and matrisome proteins in pancreatic cancer

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Akademisk avhandling

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Abstract
Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy characterized by an extensive desmoplastic stroma. The stroma is the site of intricate communication between malignant cells and their surrounding environment. This tissue microenvironment (TME) is populated by a heterogenous mixture of cell types and extracellular matrix proteins. Distinct stromal elements confer tumour-restraining or tumour-promoting influences on tumorigenesis. Characterizing stromal composition therefore represents an opportunity to identify candidates for therapeutic intervention to facilitate improved clinical outcomes. In this thesis we identify galectin-4 as an extracellular matrix protein which is upregulated in PDAC. We find that galectin-4 exerts a pro-tumorigenic influence in PDAC through promoting immune suppression, highlighting its potential as a novel therapeutic target. We subsequently provide a comprehensive characterization of mesenchymal cell diversity in PDAC including cancer-associated fibroblasts (CAFs) which represent one of the dominant stromal cellular components. We identify inflammatory CAF (iCAF) and myofibroblastic CAF (myCAF) subtypes in addition to defining a novel interferon-response CAF (ifCAF) subtype. In addition, we demonstrate that pancreatic stellate cells (PSCs) are capable of forming iCAFs, myCAFs and ifCAFs in response to tumour-derived signals using an organoid-based co-culture model and define biological pathways regulating CAF subtype formation. We then perform a high-throughput drug-screen using this co-culture model to identify compounds which can suppress tumour growth indirectly through modifying CAFs. One such compound is GNF-5 which we show can suppress cancer cell proliferation indirectly through manipulating CAF phenotype. Taken together, this thesis augments our understanding of the composition of the PDAC stroma and identifies potential therapeutic targets as well as developing an approach to discover drugs which yield a therapeutic benefit through targeting the PDAC stroma.

Keywords
Cancer-associated fibroblast (CAF), heterogeneity, pancreatic ductal adenocarcinoma (PDAC), myofibroblastic CAF (myCAF), inflammatory CAF (iCAF), interferon response CAF (ifCAF), single-cell RNA sequencing (scRNAseq), pancreatic stellate cells (PSCs), organoid-based co-culture model, matrisome, extracellular matrix (ECM).

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