The focus of our lab is to better understand how pancreatic cancer develops and progresses and use this knowledge to identify and test new clinically relevant therapies and combinations. To do this, we use mouse models of pancreatic cancer that recapitulate human tumours in terms of both the genetic alterations and the dense fibrotic and immuno-suppressive stroma. These models, therefore provide a clinically relevant platform, in which to test and validate or de-validate novel tumour cell and microenvironment targeted therapies.

Pancreatic cancer, or pancreatic ductal adenocarcinoma (PDAC), kills over 430,000 people every year. It is one of the deadliest epithelial malignancies, and both incidence and mortality are rising. In the UK alone, there are around 10,000 new cases every year, equivalent to about 30 new cases every day. Less than 1% of these patients will survive their disease for five years, and only 1% are likely to survive beyond ten years. Indeed, despite improvements in surgical management and significant investment in clinical trials, cure rates have only marginally increased over the last 50 years.

Many years of research have improved our understanding of disease evolution, genetic alterations, transcriptional subtypes, and the tumour microenvironment (TME). Activating mutations in KRAS are the most prevalent driver mutations, accompanied by loss of function of tumour suppressor genes. Some mutations found in subsets of patients may confer sensitivity to targeted therapies. For that reason, part of our work involves modelling mutations in the genes that are mutated in smaller subsets of human pancreatic cancer with a view to understanding the biological consequences of those mutations. Another feature characteristic of PDAC is the dense fibrotic stroma that surrounds and supports the tumour cells and can account for up to 90% of the tumour volume in the human disease. This microenvironment consists of fibroblasts and extracellular matrix proteins as well as significant inflammation with prominent myofibroblast infiltration and a dearth of effector T cells. Each component plays an important role in pancreatic cancer progression, able to influence tumour cell proliferation, survival, metabolism, migration, immune surveillance, and response to chemotherapy. Therefore, it is essential to investigate pancreatic tumour biology in vivo, in spontaneous tumours with a physiological microenvironment and immune response.

Modelling genetic subsets of patients

With regard to the recurring mutations in patients that may be actionable, we have developed several models to mimic these patients and identify therapeutic targets. Our suite of models covers the majority of genes/pathways identified in the patient tumours. For example, mice harbouring a Rnf43 deletion and found that Rnf43 deletion is a clinically-relevant porcupine inhibitor in these models. Mutations in DNA damage repair genes have also been shown to be mutated in 10-15% of cases as a back bone (Rax1-Cre, Kas1lox-lox). Using microdissection and single cell sequencing studies revealed that both the tumour and stromal microenvironment and immune response.

Figure 1

Figure 2

For tumour-targeted radiotherapy in GEM models of pancreatic cancer (Figure 1), which we are applying to these models. The use of radiotherapy in pancreatic cancer treatment has been limited thus far, however, this may be due to a lack of understanding of the effect of radiation on the pancreatic TME. Irradiation results in tumour cell death and release of tumour-associated antigens that can elicit a cytotoxic T cell response against the tumour. However, this is impeded by the release of inflammatory cytokines and chemokines which can result in altered fibroblast secretory output, ECM remodelling, macrophage polarisation and an even more immunosuppressive microenvironment. Thus, we are using our models to investigate responses in individual cells in the TME to determine the mechanisms controlling pro-tumorigenic immune and fibrotic responses with the aim of identifying rationale therapeutic combinations to promote anti-tumorigenic immune responses while inhibiting pro-tumorigenic immune and fibrotic responses.

Tumour heterogeneity

Microdissection and single cell sequencing studies in human pancreatic cancer have recently revealed that both the tumour and stromal compartments display significant heterogeneity in terms of gene expression and function. For example, antibody-based single cell analysis (Cytob) has highlighted two stable populations of cancer-associated fibroblasts with distinct expression profiles and immune cell interactions and defined by differential expression of CD105. CD105+ fibroblasts are tumour-permissive, whilst CD105- fibroblasts exhibit tumour restrictive behaviour which is dependent on the adaptive immune system.

The level of heterogeneity in mouse models has been the subject of some debate, both in terms of in vitro and in vivo tumour heterogeneity. We have now shown that these models do exhibit significant transcriptional heterogeneity, particularly between animals, despite identical initialisations (Figure 2). We now want to investigate the spatially resolved transcriptional landscape of tumours in these models, to monitor and understand the multi-level heterogeneity during tumour progression and in response to therapeutic intervention. This understanding is vital for the development of novel therapeutic strategies to improve the dismal statistics associated with this disease.

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