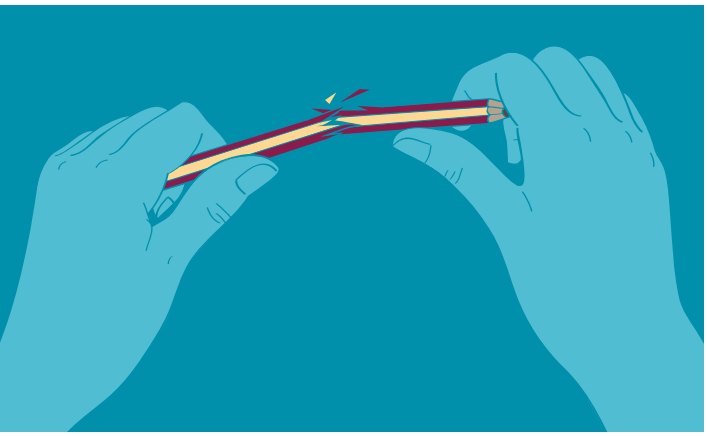
TUMOUR MICROENVIRONMENT

Genotype puts tension on a tumour

The success of chemotherapeutic treatments of pancreatic ductal adenocarcinoma (PDAC) is often inversely correlated with the extent of fibrosis around tumours; moreover, therapies that target components of the stroma have had mixed outcomes in patients with PDAC. Using a combination of biopsy samples from patients with PDAC and experimental mouse models, Laklai *et al.* have demonstrated for the first time that genetically induced tumour cell tension can shape the fibrotic nature of pancreatic tissue to promote tumour progression.

In illustrating a link between tumour epithelial tension and patient survival, the authors observed that the diameter of collagen fibres neighbouring PDACs correlated with poor prognosis. Interestingly, atomic force microscopy revealed that these specific collagen bundles were stiffer in patients expressing mutant SMAD4, implying that a decrease in transforming growth factor-β (TGFβ) signalling within the PDACs could influence the stromal phenotype.

> “genetically induced tumour cell tension can shape the fibrotic nature of pancreatic tissue”



Lara Crow/NPG

Complementing these patient tissue studies, $Kras^{G12D}$ mutant-driven PDAC mouse models with or without one allele of TGFβ receptor 2 ($Tgfbr2^{fl/+}$) confirmed that upon reduction of TGFβ signalling, PDAC lesions had thicker collagen fibres and increased extracellular matrix (ECM) stiffness. Furthermore, the stiffer ECM-enriched fibrosis of PDAC lesions upon loss of *Tgfbr2* was accompanied by a more contractile epithelium and upregulated mechanosignalling, as indicated by increased levels of phosphorylated myosin light chain 2 (MLC2) and yes-associated protein 1 (YAP1), respectively. These observations implied that it is intrinsically the genotype of the PDAC tumour cells that ultimately determines the extent of the fibrosis and the mechanophenotype of the carcinoma.

In establishing a mechanistic basis for elevated tumour cell tension upon impaired TGFβ signalling, Laklai *et al.* identified higher levels of phosphorylated signal transducer and activator of transcription 3 (STAT3), a transcription factor previously implicated in PDAC progression, in the pancreatic epithelium of $Kras^{G12D}Tgfbr2^{fl/+}$ mice. Moreover, inhibition of Janus kinase (JAK), the upstream activator of STAT3, blocked the ability of tumour cells derived from $Kras^{G12D}Tgfbr2^{fl/+}$ mice to contract and remodel collagen gels, implicating a JAK–Rho-associated protein kinase (ROCK)–STAT3 signalling pathway that is activated in PDAC tumour cells to control ECM stiffness in PDAC-associated fibrosis.

A pancreas-specific mouse model expressing a conditional β1 integrin-V737N mutant that recapitulates tension-dependent integrin clustering, enhanced contractility and increased focal adhesion signalling, enabled the authors to highlight that epithelial tension itself can directly drive STAT3 activation in pancreatic epithelial cells, even without an activating KRAS mutation.

This study went on to emphasize the importance of STAT3 activation in the development of a contractile, fibrotic epithelium in PDAC by showing that $Kras^{G12D}$ mice in which STAT3 is constitutively active induced cytoskeletal contractility and inflammation in pancreatic tissues, as indicated by elevated levels of phosphorylated MLC2 and increased immune cell infiltration, respectively. Conversely, pancreas-specific *Stat3* knockout in $Kras^{G12D}Tgfbr2^{fl/+}$ mice led to prolonged survival concomitant with reduced ECM stiffness and mechanosignalling.

Finally, the authors returned to clinical PDAC specimens to demonstrate that tumours from patients with SMAD4 mutations, and hence impaired TGFβ signalling, had elevated levels of activated STAT3 and increased mechanosignalling, as well as molecular correlates of ECM-enriched fibrosis. Furthermore, these SMAD4-mutant PDAC tissues exhibited a quasi-mesenchymal phenotype consistent with a more aggressive disease status and reduced survival.

This elegant study establishes that a causal relationship exists between specific genotypes, such as those leading to compromised TGFβ signalling and the degree of associated fibrosis, thus underscoring the idea that PDAC tumours should not be treated equally. Crucially, this work also highlights an underappreciated role of tumour cells, as opposed to the expected role of stromal fibroblasts, in creating tension in the pathology of PDAC. Perhaps tumours associated with SMAD4 mutations are more likely to be responsive to therapies that directly target fibrosis and more specifically, that target STAT3 activation and signalling.

Anna Dart

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