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PANCREATIC CANCER

Between ROCK and a hard place

Priming pancreatic cancer tissue by inhibiting Rho-associated protein kinase (ROCK) to affect tumour tissue tension improves chemotherapy efficacy and reduces metastasis in experimental models, according to new research. This approach could lead to improved therapeutic strategies for this aggressive disease.

ROCK, via its effects on the cytoskeleton, maintains the shape and movement of cells, but also has roles in tumour progression, invasion and remodelling of the extracellular matrix (ECM). "Evidence suggests that manipulating ECM crosslinking and tumour stiffness could be an approach in [treating] multiple cancers," explains author Paul Timpson, but little is known about targeting tissue tension prior to chemotherapy.

Using *in vitro* and *in vivo* models of pancreatic cancer, live imaging of tumours and the surrounding stroma, as well as a biosensor to monitor therapeutic efficacy, the investigators assessed how transient tissue priming with the ROCK inhibitor, fasudil, affected the response of pancreatic cancer to chemotherapeutics. This approach led to substantial

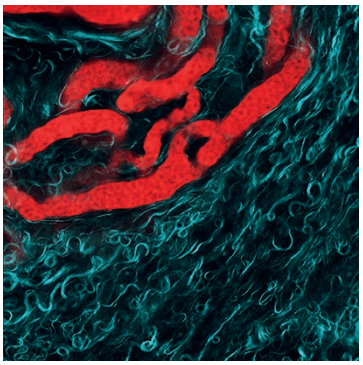

Image showing quantum dots marking the tumour vasculature (red) and the dense, desmoplastic extracellular matrix of the stroma (blue) typically found in pancreatic cancer. Image coutesy of P. Timpson.

therapeutic benefit, reducing primary tumour growth and cancer invasion in each of the models tested. "ROCK inhibition was also shown to relax blood vasculature and allow for more effective delivery of chemotherapy to the tumour," reports Timpson.

The researchers also used second harmonic generation imaging to assess fibrosis levels in patient pancreatic tumour samples from the Australian Pancreatic Genome Initiative cohort. A graded response to priming with fasudil was then observed in patient-derived xenografts, which correlated to the level of crosslinked collagen in the sample, with high crosslinked pancreatic cancers responding best to the priming.

Furthermore, fasudil impaired colonization efficiency and fibrotic niche remodelling in the liver, and sensitized tumour cells to shear stress, reducing their survival in the blood system. Thus, tissue priming before chemotherapy might be beneficial in both primary and metastatic pancreatic cancer. "This global benefit we observed from primary to secondary sites is critical, as pancreatic cancer is a highly aggressive disease," explains Timpson.

A key advantage of the latest work is that fasudil is currently approved for human use in Japan to treat cerebral vasospasm. "We envisage rapidly repurposing this off-patent cheap drug to be combined with chemotherapy in pancreatic cancer treatment," concludes Timpson.

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ORIGINAL ARTICLE Vennin, C. *et al.* Transient tissue priming via ROCK inhibition uncouples pancreatic cancer progression, sensitivity to chemotherapy, and metastasis. *Sci. Transl. Med.* **9**, eaai8504 (2017)