TUMORIGENESIS

Disruptive influence

A new mouse model of pancreatic cancer indicates that disruption of the transforming growth factor-β (TGFβ) signalling pathway leads to the development of premalignant lesions.

Pancreatic cancer has the worst prognosis of all gastrointestinal cancers, largely because of a lack of early clinical symptoms and effective treatments once the disease is diagnosed. So, good *in vivo* models of early pancreatic tumour development are needed to identify new diagnostic and treatment strategies.

Various genetic changes are known to contribute to the genesis of pancreatic cancer. In particular, more than 50% of human tumours have disrupted TGFβ signalling owing to the homozygous deletion of the signal transducer SMAD4. To investigate further, Chenzhong Kuang, Yan Chen and colleagues transgenically expressed rat *Smad7*, an inhibitor of the TGFβ signalling pathway, specifically in the pancreatic tissue of mice.

Having verified that SMAD7 was expressed at detectable levels, the authors analysed the histological changes within the pancreas. At 6 months of age these mice developed pancreatic intraepithelial neoplasia (PanIN), a precursor of invasive disease. Immunohistochemical analyses verified that the tumours arose from the pancreatic ductal epithelium and showed that these cells were actively proliferating.

The authors conclude that disruption of TGFβ signalling, which is known to be antiproliferative early on in tumorigenesis, promotes PanIN development and suggest that their mouse model should prove useful for identifying new treatments for this aggressive disease.

Nicola McCarthy

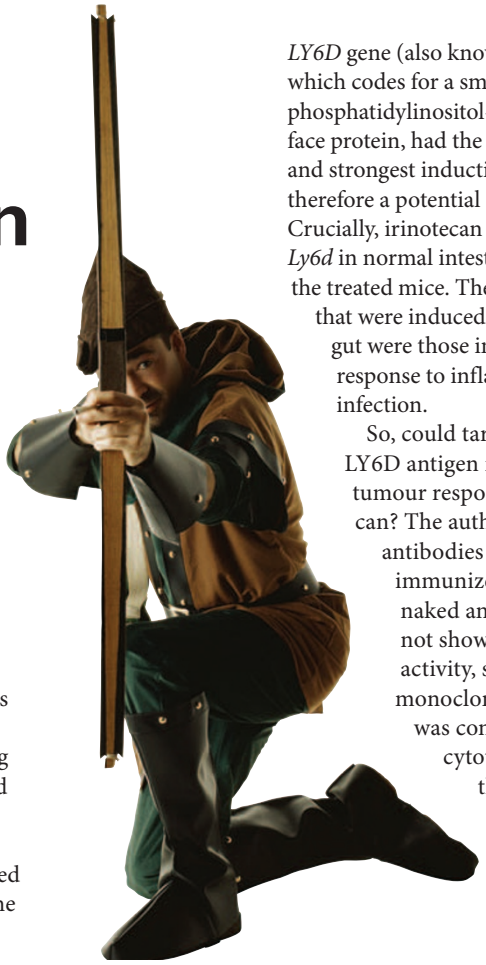
ORIGINAL RESEARCH PAPER Kuang, C. *et al.* *In vivo* disruption of TGF-β signalling by Smad7 leads to premalignant ductal lesions in the pancreas. *Proc. Natl Acad. Sci. USA* **103**, 1858–1863 (2006)

IMMUNOTHERAPY

Armed for action

When cancer cells are treated with chemotherapy, changes in gene transcription occur. Paul Polakis and colleagues investigated the possibility of exploiting this effect to target cancer cells. Using a cytotoxin-armed antibody, they targeted an antigen whose expression in cancer cells is induced by the topoisomerase-I inhibitor irinotecan.

The authors compared the expression of transcripts from human colorectal cancer xenografts grown in mice treated with either irinotecan or a saline control. Using expression profiling, they identified transcripts coding for cell-surface proteins that were significantly upregulated in the irinotecan-treated tumours relative to the controls. The *LY6D* gene (also known as *E48*), which codes for a small glycosyl-phosphatidylinositol-linked cell-surface protein, had the most consistent and strongest induction, and was therefore a potential antibody target. Crucially, irinotecan did not induce *Ly6d* in normal intestinal tissue from the treated mice. The only genes that were induced in the normal gut were those involved in a response to inflammation or infection.



So, could targeting the LY6D antigen improve on the tumour response to irinotecan? The authors obtained antibodies to LY6D from immunized mice. The naked antibody did not show any cytotoxic activity, so the LY6D monoclonal antibody was conjugated to the cytotoxin monomethyl auristatin E (MMAE). Tumour-bearing mice that were treated with irinotecan together with anti-interleukin-8 linked to the cytotoxin or with the vehicle alone as controls, showed attenuated tumour growth for 3 weeks before the tumours regrew. By contrast, treatment with irinotecan followed by the conjugated LY6D antibody led to complete responses in six of eight mice. Treatment with conjugated antibody alone did not have any anti-tumour activity.

LY6D has been used as a therapeutic target and diagnostic marker for head and neck cancer, and is expressed in stratified squamous and transitional cell epithelia. The effect of the LY6D antibody on these normal cells is not known, but Polakis and colleagues have shown that targeting a cell-surface antigen induced by chemotherapy is a worthwhile approach to pursue.

Ezzie Hutchinson

ORIGINAL RESEARCH PAPER Rubinfeld, B. *et al.* Identification and immunotherapeutic targeting of antigens induced by chemotherapy. *Nature Biotechnol.* **24**, 205–209 (2006)