Nature Reviews Cancer | Published online 25 Jul 2016; doi:10.1038/nrc.2016.80

PANCREATIC CANCER

Dodging immunosuppression

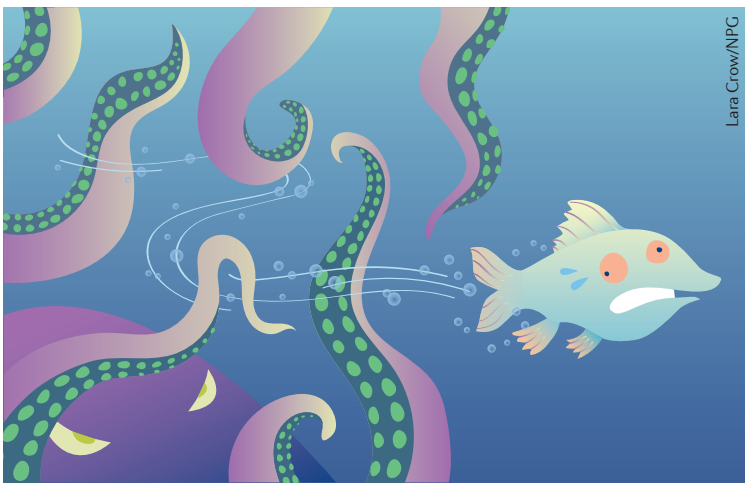
> checkpoint inhibitor therapy (in combination with gemcitabine)… improved with FAKi treatment

The microenvironment of most pancreatic ductal adenocarcinomas (PDACs) is highly fibrotic and immunosuppressive, which might explain the low efficacy of immunotherapy observed to date in these patients. Jiang *et al.* reasoned that focal adhesion kinase 1 (FAK1), which is connected to inflammation and fibrosis as well as tumour progression, might have a role in driving immunosuppression in PDAC.

The authors first showed that human PDAC tissues had high levels of both overall and phosphorylated FAK1 (pFAK1), specifically in the tumour cells as opposed to the stromal cells. High pFAK1 also correlated with low $CD8^+$ infiltrating cytotoxic T lymphocytes (CTLs), and together these markers indicated poor patient survival. Similar data were observed in PDAC from KPC mice (which express oncogenic *Kras* and lack one copy of *Trp53* in pancreatic cells). The FAK1 (and FAK2) inhibitor VS-4718 (FAKi) improved survival of both KPC and KPPC (which additionally lack the second copy of *Trp53*) mice compared with both untreated mice and mice treated with gemcitabine, a chemotherapy commonly used to treat PDAC.

FAKi-treated KPC and KPPC mice had decreased fibrosis and stromal cell proliferation. In contrast to previous studies that showed enhanced disease progression following stromal depletion in PDAC, these authors found that stromal depletion as a result of FAKi treatment did not accelerate PDAC; this might be due to the ability of the FAKi to also prevent tumour cell invasion. FAKi-treated PDACs also had significantly fewer immunosuppressive myeloid cells.

To confirm that the observed FAKi effect was a result of FAK inhibition in tumour cells and not cells of the microenvironment, FAK1 was knocked down in PDAC cells from KPC mice (KP cells). Although loss of FAK1 did not affect proliferation of KP cells *in vitro*, it did reduce tumour growth when they were implanted into immune-competent mice. Furthermore, these FAK1-knockdown tumours had reduced fibrosis, reduced levels of immunosuppressive myeloid cells and increased levels of $CD8^+$ CTLs compared with control tumours. FAKi treatment of PDAC cells also reduced the production of inflammatory and fibrotic cytokines, which the authors showed were responsible for promoting both myeloid cell migration and fibroblast proliferation *in vitro*.



Lara Crow/NPG

Both excessive stroma and infiltrating immunosuppressive cells may blunt responses to PDAC therapy. Given the role of FAK1 in these processes, the authors investigated whether FAKi treatment could improve therapeutic responses. Indeed, FAKi treatment in combination with gemcitabine improved median overall survival of KPPC mice. The efficacy of immunotherapy was also improved: in mice bearing tumours derived from KP cells, both adoptive T cell transfer therapy and programmed cell death protein 1 (PD1; also known as PDCD1) checkpoint inhibitor therapy (in combination with gemcitabine) were improved with FAKi treatment. Notably, in KPPC mice with established tumours, which most closely resemble human PDAC, treatment with gemcitabine, anti-PD1 and anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4) did not improve survival, but adding the FAKi to this regimen did, with 2 of 15 mice still alive after 6 months.

At least one trial testing a FAKi in combination with gemcitabine and anti-PD1 is ongoing (NCT02546531), and these preclinical data support further efforts in this area.

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ORIGINAL ARTICLE Jiang, H. *et al.* Targeting focal adhesion kinase renders pancreatic cancers responsive to checkpoint immunotherapy. *Nat. Med.* http://dx.doi.org/10.1038/nm.4123 (2016)