IN BRIEF

PANCREATIC CANCER

Tracing origins

Studies of pancreatic ductal adenocarcinoma (PDA) have mostly used mouse models that express oncogenic KRAS in all cells of the pancreas. As such, not much is known about the PDA cell-of-origin. Kopp *et al.* have labelled and traced specific cell populations in the mouse pancreas following KRAS activation and discovered that acinar cells form PDA precursor lesions, whereas ductal and centroacinar cells do not. Lesion formation from acinar cells was dependent on the expression of the ductal fate determinant gene *Sox9*, indicating that a duct-like state is induced in these cells. Understanding this reprogramming pathway could aid the early detection of PDA and could provide new opportunities for therapies.

ORIGINAL RESEARCH PAPER Kopp, J. L. *et al.* Identification of Sox9-dependent acinar-to-ductal reprogramming as the principal mechanism for initiation of pancreatic ductal adenocarcinoma. *Cancer Cell* 27 Nov 2012 (doi:10.1016/j.ccr.2012.10.025)

METABOLISM

Nuclear functions

Pyruvate kinase M2 (PKM2) is a glycolytic enzyme that has also been shown to function in the nucleus as a transcriptional co-activator. Yang *et al.* found that PKM2, but not PKM1, is phosphorylated by ERK2 following epidermal growth factor receptor (EGFR) activation in glioblastoma cells. This allows *cis–trans* isomerization of PKM2 by the peptidyl-prolyl isomerase PIN1, which exposes a nuclear localization sequence on PKM2 that is then bound by importin α5, leading to nuclear translocation of PKM2 and the expression of glycolytic genes. Furthermore, expression of a mutant PKM2 that is unable to translocate to the nucleus prevents the growth of glioblastoma xenografts in mice.

ORIGINAL RESEARCH PAPER Yang, W. *et al.* ERK1/2-dependent phosphorylation and nuclear translocation of PKM2 promotes the Warburg effect. *Nature Cell Biol.* **14**, 1295–1304 (2012)

IMMUNOLOGY

A downside of chemotherapy

In addition to cytotoxic effects, chemotherapy has also been shown to have both positive and negative effects on antitumour immune responses. Bruchard *et al.* have shown that the chemotherapeutics gemcitabine and 5-fluorouracil activate the NOD-like receptor, pyrin-domain-containing 3 (NLRP3) inflammasome in myeloid-derived suppressor cells (MDSCs) to suppress antitumour immunity. Chemotherapy activated caspase 1 (CASP1) in MDSCs from tumour-bearing mice and cancer patients; this was dependent on NLRP3 and induced the secretion of interleukin-1β (IL-1β). This inflammasome activation in MDSCs was triggered by chemotherapy-induced lysosomal permeabilization and release of cathepsin B (which activates NLRP3). IL-1β did not affect the cytotoxicity of chemotherapy directly, but its release from MDSCs induced the secretion of IL-17 by pro-inflammatory $CD4^+$ T cells, which limited the effects of chemotherapy in mice. Tumours established in mice lacking *Nlrp3*, *Casp1* or *Il17a*, in wild-type mice treated with an IL-1 receptor antagonist, or in mice depleted for CD4 were more responsive to gemcitabine or 5-fluorouracil therapy, supporting the necessity of this pathway for the immunosuppressive effects of chemotherapy. Therefore, antagonists of this pathway might help to improve the efficacy of gemcitabine and 5-fluorouracil chemotherapy.

ORIGINAL RESEARCH PAPER Bruchard, M. *et al.* Chemotherapy-triggered cathepsin B release in myeloid-derived suppressor cells activates the Nlrp3 inflammasome and promotes tumor growth. *Nature Med.* 2 Dec 2012 (doi:10.1038/nm.2999)