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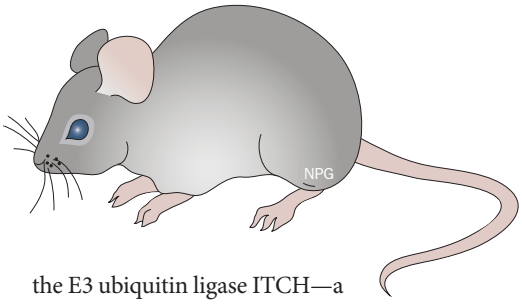
PANCREATIC CANCER

Mouse models link metabolism and deubiquitination with *Kras*



Pancreatic ductal adenocarcinoma (PDA) is one of the most lethal cancers; only 5% of patients are alive 5 years after diagnosis. With this bleak picture, it is crucial that researchers are undertaking the work to understand the biological mechanisms of this disease with the aim of improving therapy options. Now, two groups have used PDA mouse models to reveal novel mechanisms involving oncogenic $Kras^{G12D}$.

In the first study, led by Alec Kimmelman and Ron DePinho, a genetically engineered mouse model of PDA was created, which enabled the researchers to express oncogenic $Kras^{G12D}$ in the pancreas. This expression was doxycyline inducible and so the researchers could temporally control it by feeding doxycyline to the mice, or not. Kimmelman explained that this model allowed them to ask "whether $Kras^{G12D}$ was important for tumour maintenance."

Kimmelman went on to outline the main findings of the study: "first, we demonstrated that continued expression of oncogenic $Kras^{G12D}$ is required for tumour growth. Next, through an integrative approach of transcriptomic and metabolomic analysis, we showed that one of the key mechanisms of how $Kras^{G12D}$ promotes tumour maintenance is through rewiring of anabolic glucose metabolism."

Using genetic and pharmacological approaches, both the MAPK pathway and Myc-dependent transcription were shown to have key roles in the link between oncogenic $Kras^{G12D}$ and metabolism. In addition, several of the metabolic pathways that were identified as regulated by oncogenic $Kras^{G12D}$ were found to be functionally important for tumour growth. Kimmelman points out "given the difficulty in targeting the *KRAS* oncogene, these pathways may provide new entry points for therapeutic interventions."

The second study that assessed PDA in mouse models was led by David Tuveson and David Adams. Tuveson explained their elegant method: "'Sleeping Beauty' is the name used to describe the transposon mutagenesis method we used. The Sleeping Beauty system is comprised of a 'sleeping' transposable genetic element (the transposon) that lies dormant in the chromosomes, until an enzyme (the transposase or 'Prince Charming') kisses the transposon by cutting it out and allowing it to escape and 'hop' around the genome randomly. When the transposons hop into a gene that makes the cell turn into a pancreatic cancer quickly, we can simply identify the genes using modern molecular biology methods."

The surprise finding of the study was that loss of the deubiquitinase *Usp9x* cooperates with oncogenic $Kras^{G12D}$ to accelerate tumorigenesis and promote progression. After identifying this gene in mice, the team then assessed three independent groups of patients with PDA; loss of USP9X expression was a relevant event in human pancreatic cancer progression. This loss of expression is associated with loss of the E3 ubiquitin ligase ITCH—a target of USP9X that can be stabilized by deubiquitination.

Having established that USP9X is important in the progression of PDA, the work moved into cell lines. In most human cancer cell lines treated with a DNA methylase inhibitor or histone deacetylase inhibitor, USP9X mRNA and protein levels increased modestly, implying that *USP9X* is epigenetically regulated.

Clearly, we now know more than we did about the mechanisms behind $KRAS^{G12D}$ associated PDA, but there is still work to be done before this can change patient outlook. Tuveson says his and Adams' teams "will continue to investigate the molecular details of USP9X in pancreatic cancer. We will also investigate whether the gene can be 'awakened' with epigenome-modulating drugs in patients in whom the gene is silenced and see if this provides any therapeutic benefit."

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Original articles Ying, H. *et al*. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. *Cell* **149**, 656–670 (2012) | Pérez-Mancera, P. A. *et al*. The deubiquitinase USP9X suppresses pancreatic ductal adenocarcinoma. *Nature* doi:10.1038/nature11114