METABOLISM

The importance of polarity

LKB1 is a serine/threonine kinase that is associated with the regulation of energy homeostasis and cell polarity. Somatic loss-of-function mutations in *STK11* (which encodes LKB1) account for Peutz–Jeghers syndrome (PJS), which is associated with an increased risk of developing gastrointestinal neoplasms and pancreatic cancer. Nabeel Bardeesy, Ronald DePinho and colleagues provide evidence for a link between cell polarity and, when deregulated, the development of pancreatic cancer.

Apical–basal polarity of acinar cells within the pancreas is important for the structure of the tissue and the secretion of factors involved in digestion and the regulation of glucose uptake. Bardeesy, DePinho and colleagues generated pancreas-specific *Stk11* knockout mice to determine the function of LKB1 in these processes. Although the mice were initially viable, fatality ensued 10–30 weeks later and this was associated with the replacement of normal pancreatic tissue with benign cystic tumours known as serous cystadenomas (which also occur in patients with PJS). This indicates that LKB1 has an essential role in the maintenance of pancreatic tissue structure and physiology.

To further characterize the role of LKB1, the authors assessed the development of the pancreas from birth. The LKB1-deficient pancreas was smaller than controls at postnatal day 1 (PD1), but ductal acinar structures were mostly intact, although less dense. From PD2 to PD8 they observed rapid loss of acinar cells and increased abnormal ductal structures, which is indicative of ductal metaplasia. Consistently, acinar cell death rate was increased 18-fold and there was evidence of activated Notch and STAT (signal transducer and activator of transcription) signalling — characteristic of ductal metaplasia. To assess whether the role of LKB1 in cell polarity regulation might be associated with these phenotypes, the authors analysed the organization of the cytoskeleton and showed that acinar cell polarity and the formation of tight junctions and adherens junctions was abrogated. Furthermore, the apical distribution of E-cadherin was lost and downstream substrates of LKB1, belonging to the AMP-activated protein kinase (AMPK), MAP/microtubule affinity-regulating kinase (MARK) and SAD protein families that establish tight junctions and regulate tubulin dynamics, were also deregulated by the loss of LKB1.

Therefore, the failure to maintain acinar cell polarity and thus tissue morphology appears to be a cause of serous cystadenoma that is associated with loss of LKB1 activity. In addition, these data demonstrate that LKB1 is not required for the development and differentiation of cells in the pancreas, but that LKB1 is crucial for the regulation and maintenance of epithelial cell polarity and survival *in vivo*. Presumably, LKB1 is not required prenatally because the secretory function of acinar cells is not active during this time. However, post-natally, defective acinar cell polarity in the pancreas — as a result of LKB1 ablation — probably results in acinar damage triggering acinar cell death and ductal metaplasia, which could explain the increased pancreatic cancer incidence among patients with PJS.

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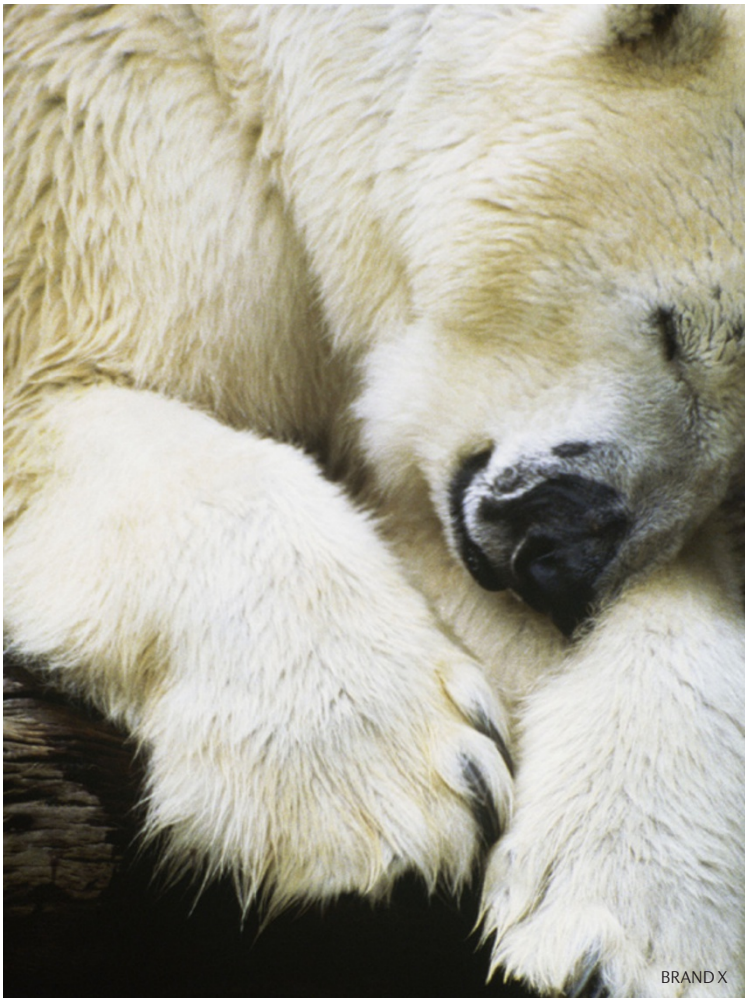
ORIGINAL RESEARCH PAPER Hezel, A. F. *et al.* Pancreatic Lkb1 deletion leads to acinar polarity defects and cystic neoplams. *Mol. Cell. Biol.* 28 Jan 2008 (doi 10.1128/MCB.00980-07)



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