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Kras and Lkb1 mutations synergistically induce intraductal papillary mucinous neoplasm derived from pancreatic duct cells

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Abstract

Objective: Pancreatic cancer can arise from precursor lesions called intraductal papillary mucinous neoplasms (IPMN), which are characterised by cysts containing papillae and mucus-producing cells. The high frequency of KRAS mutations in IPMN and histological analyses suggest that oncogenic KRAS drives IPMN development from pancreatic duct cells. However, induction of Kras mutation in ductal cells is not sufficient to generate IPMN, and formal proof of a ductal origin of IPMN is still missing. Here we explore whether combining oncogenic Kras G12D mutation with an additional gene mutation known to occur in human IPMN can induce IPMN from pancreatic duct cells.

Design: We created and phenotyped mouse models in which mutations in Kras and in the tumour suppressor gene liver kinase B1 (Lkb1/Stk11) are conditionally induced in pancreatic ducts using Cre-mediated gene recombination. We also tested the effect of β-catenin inhibition during formation of the lesions.

Results: Activating Kras G12D mutation and Lkb1 inactivation synergised to induce IPMN, mainly of gastric type and with malignant potential. The mouse lesions shared several features with human IPMN. Time course analysis suggested that IPMN developed from intraductal papillae and glandular neoplasms, which both derived from the epithelium lining large pancreatic ducts. β-catenin was required for the development of glandular neoplasms and subsequent development of the mucinous cells in IPMN. Instead, the lack of β-catenin did not impede formation of intraductal papillae and their progression to papillary lesions in IPMN.

Conclusion: Our work demonstrates that IPMN can result from synergy between Kras G12D mutation and inactivation of a tumour suppressor gene. The ductal epithelium can give rise to glandular neoplasms and papillary lesions, which probably both contribute to IPMN formation.

Keywords: IPMN; mucinous neoplasm; pancreatic ductal adenocarcinoma; pancreatic tumorigenesis.

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