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PANCREATIC CANCER

Spotlight on BRG1

Matthias Hebrok and colleagues have found that expression of BRG1 (also known as SMARCA4), an ATPase subunit of SWI/SNF complexes, can suppress the formation of intraductal papillary mucinous neoplasm (IPMN; a pre-cancerous lesion of pancreatic adenocarcinoma (PDA)) in mice.

Loss of *Brg1* in the acinar cells and some of the ductal cells of the pancreas in a mouse model of oncogenic $Kras^{G12D}$-driven PDA mostly resulted in the development of cystic lesions at 9 weeks of age rather than the pancreatic intraepithelial neoplasia (PanIN) precancerous lesions that commonly develop in $Kras^{G12D}$-expressing mice. The cystic lesions contained dysplastic ductal cells in which BRG1 expression was lost; they were similar to human IPMN and rapidly progressed to PDA. A comparison of $Kras^{G12D}$; $Brg1^{-/-}$- generated IPMN–PDA with $Kras^{G12D}$; $Trp53^{-/+}$-mediated PanIN–PDA revealed distinct transcriptional profiles that included a difference in the expression of genes associated with invasion and metastasis. This, along with a reduced proliferation rate, might explain why IPMN–PDA was less lethal in the mice than PanIN–PDA (and this finding mirrors that for human patients with these subsets of pancreatic cancer). Interestingly, loss of *Brg1* from adult acinar cells that expressed $Kras^{G12D}$ in mice resulted in no IPMN lesions and the suppression of PanIN development. However, loss of *Brg1* in adult ductal cells that expressed oncogenic *Kras* resulted in atypical ductal cells and in some cases IPMN-like lesions.

These findings suggest that BRG1 is required for PanIN formation in acinar cells and inhibits the KRAS-driven transformation of ductal cells. These data also indicate that the SWI/SNF complexes influence the route towards PDA development.

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> “BRG1 is required for PanIN formation in acinar cells”

ORIGINAL RESEARCH PAPER von Figura, G. *et al.* The chromatin regulator Brg1 suppresses formation of intraductal papillary mucinous neoplasm and pancreatic ductal adenocarcinoma. *Nature Cell Biol.* **16**, 255–267 (2014)

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