Brg1 promotes both tumor-suppressive and oncogenic activities at distinct stages of pancreatic cancer formation.

Pancreatic ductal adenocarcinoma (PDA) develops predominantly through pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) precursor lesions. Pancreatic acinar cells are reprogrammed to a "ductal-like" state during PanIN-PDA formation. Here, we demonstrate a parallel mechanism operative in mature duct cells during which functional cells undergo "ductal retrogression" to form IPMN-PDA. We further identify critical antagonistic roles for Brahma-related gene 1 (Brg1), a catalytic subunit of the SWI/SNF complexes, during IPMN-PDA development. In mature duct cells, Brg1 inhibits the dedifferentiation that precedes neoplastic transformation, thus attenuating tumor initiation. In contrast, Brg1 promotes tumorigenesis in full-blown PDA by supporting a mesenchymal-like transcriptional landscape. We further show that JQ1, a drug that is currently being tested in clinical trials for hematological malignancies, impairs PDA tumorigenesis by both mimicking some and inhibiting other Brg1-mediated functions. In summary, our study demonstrates the context-dependent roles of Brg1 and points to potential therapeutic treatment options based on epigenetic regulation in PDA.