Genetics Day Poster Submission

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Title: DRUG-INDUCED P53 ACTIVATION INHIBITS PRECANCEROUS TRANSFORMATION

Abstract: Pancreatitis is an inflammatory disease characterized by fibrosis and acinar cell death. Surviving acinar cells undergo acinar-to-ductal metaplasia (ADM), a regenerative process in which cells dedifferentiate, proliferate, and then redifferentiate into acinar cells. Patients with recurrent pancreatic injury exhibit sustained ADM, exocrine insufficiency, Kras upregulation and mutations, and the formation of preneoplastic lesions. The lack of treatment options for pancreatitis patients reinforces the need for strategies that could resolve pancreatic damage and stop disease progression. Mouse models of pancreatic ductal adenocarcinoma (PDAC) harboring a hyperactive p53 variant exhibit reduced Mdm2 binding and are resistant to transformation (Mello et al. 2023). Here, we show that treatment with the Mdm2 inhibitor Nutlin-3a phenocopies this resistance, enabling the redifferentiation of metaplastic acinar cells following induction of acute pancreatitis. Restoration is lost in p53 null mice, indicating that the effects of Nutlin-3a are dependent on p53 expression. We hypothesize that p53 activation can signal for the differentiation of acinar cells, and will utilize lineage tracing models to follow the fate of metaplastic cells.