# SINGLE-NUCLEI MULTIOMIC APPROACH REVEALS PERMANENT REPROGRAMMING OF EXOCRINE CELLS AFTER PANCREATITIS

**All Authors**

Fantuz M.(1,2), Fontana G. (1,3), Liebig J.(4), Lukassen S.(4), Conrad C.(4), Carrer A.(1,2)

**Affiliation**

1. Veneto Institute of Molecular Medicine (VIMM), Padova, Italy.  
2. Department of Biology, University of Padova, Padova, Italy  
3. Department of Translational Medicine, University of Ferrara, Ferrara, Italy  
4. Center for Digital Health, Berlin Institute of Health (BIH), Berlin, Germany

**Motivation**

Acute pancreatitis (AP) is a common inflammation of the pancreatic parenchyma that typically resolves without clinical complications. However, epidemiological evidence shows that individuals who suffered AP are at elevated risk of developing pancreatic cancer for several decades. We speculated that pancreatitis could represent a long-lasting dyshomeostatic stress response that leads to the establishment of a pro-oncogenic memory of inflammation. Indeed, AP-primed epithelial cells show enhanced propensity to dysplasia in vitro and in vivo. We tested the hypothesis that AP events induce either permanent changes in the epigenome or skewing of sub-populations in the pancreatic ecosystem.

**Methods**

To dissect molecular and cellular dynamics that outlast AP events, we performed single-nuclei multiomic (RNA+ATAC) sequencing in mouse pancreata after induction of- and recovery from experimental pancreateatitis. While immune-histological examination did not show any alteration post AP, multiomic revealed extensive transcriptomic and epigenomic reprogramming in acinar cells, which are common cell-of-origin for pancreatic cancer. This is not linked to expansion of progenitor-like clones but is enforced on functionally-distinct (“idling”) acinar cells.

**Results**

In detail, AP elevates cell-intrinsic unfolded protein response (UPR); indeed, AP-primed acinar cells show augmented spliced Xbp1 and cleaved ATF6 levels. We also observed that UPR inducers promote acinar cell plasticity, linking UPR stress to pancreatic cancer initiation. Mechanistically, AP induces an irreversible increase of chromatin accessibility in acinar cells. This leads to hypertranscription and protein dyshomeostasis and to AP1-mediated poising of the genome. Together, these alterations set a phenotypic state in post-mitotic epithelial cells that makes them more susceptible to oncogenic transformation.

**Corresponding Author**

Name, Surname: Marco, Fantuz  
Email: marco.fantuz@vimm.it  
Submitted on: 10.04.2024