# Pancreatitis induces transcriptomic and epigenetic reprogramming of epithelial cells to elevate long-lasting cancer predisposition

S-04.3-1

**A. Carrer**[I,II]

[I]University of Padova, Padova, Italy, [II]Veneto Institute of Molecular Medicine, Padova, Italy

Acute pancreatitis (AP) is a relatively 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 after the episode. We speculated that pancreatitis could represent a paradigm of 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 vitroand 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.
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 pancreatitis. While immune-histological examination did not show any alteration post AP, granular analysis coupled with Bayesian modeling 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.
In detail, AP elevates cell-intrinsic unfolded protein response (UPR). In fact, 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 epigenome. Together, these alterations set a phenotypic state in post-mitotic epithelial cells that makes them more susceptible to oncogenic transformation.