A highly plastic immune mimicking stem-like population drives resistance to chemotherapy and targeted therapies in pancreatic cancer models

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Introduction: Inflammation is essential for tissue repair, yet in the pancreas it can synergize with oncogenic mutations to drive malignant transformation. Only specific acinar subpopulations with stem like properties expand during acinar to ductal metaplasia (ADM), revealing early epithelial heterogeneity in tumor initiation. Across tumor types, cancer stem cells (CSCs) exploit immune mimicry programs to evade surveillance and sustain progression. How early inflammatory cues initiate immune mimicry in pancreatic epithelial cells and shape therapy response remains unclear.
Results: Employing single cell RNA sequencing across pancreatic tumorigenesis, together with mouse models, we showed that some acinar cells undergoing ADM activate a transcriptional program linked to plasticity and immune restricted genes, including the immune cannonical marker CD45. An equivalent immune mimicking state also arises after KRAS/p53 mutations without ADM, indicating a shared induced program. This phenotype persists throughout murine and human tumor development and is detectable in tumor cell lines. Transcriptomic profiling of CD45+ tumor cells reveals enrichment for the classical PDAC subtype, OXPHOS, stemness, and invasive programs. 3D culture and OXPHOS promoting conditions expand this immune mimicking CD45+ CSC compartment, as does gemcitabine. Interestingly, acute RAS inhibitor treatment enriches this population and induces a reprogrammed, drug tolerant state.
Conclusion: In this work, we identify an immune like epithelial population arising during early inflammation that persists as a CSC compartment with functional consequences for immune evasion and therapy resistance. Under RAS inhibition, CSCs retain intrinsic tolerance, revealing a plasticity driven layer of drug resistance in pancreatic cancer.