In adaptation to oncogenic signals, pancreatic ductal adenocarcinoma (PDAC) cells undergo epithelial-mesenchymal transition (EMT), a process combining tumor cell dedifferentiation with acquisition of stemness features. However, the mechanisms linking oncogene-induced signaling pathways with EMT and stemness remain largely elusive. Here, we uncover the inflammation-induced transcription factor NFATc1 as a central regulator of pancreatic cancer cell plasticity. In particular, we show that NFATc1 drives EMT reprogramming and maintains pancreatic cancer cells in a stem cell-like state through Sox2-dependent transcription of EMT and stemness factors. Intriguingly, NFATc1-Sox2 complex-mediated PDAC dedifferentiation and progression is opposed by antithetical p53-miR200c signaling, and inactivation of the tumor suppressor pathway is essential for tumor dedifferentiation and dissemination both in genetically engineered mouse models (GEMM).
and human PDAC. Based on these findings, we propose the existence of a hierarchical signaling network regulating PDAC cell plasticity and suggest that the molecular decision between epithelial cell preservation and conversion into a dedifferentiated cancer stem cell-like phenotype depends on opposing levels of p53 and NFATc1 signaling activities.