Cancer stem cells (CSC) present a formidable clinical challenge by escaping therapeutic intervention and seeding tumors through processes that remain incompletely understood. Here, we describe small subpopulations of pancreatic cancer cells with high intrinsic Wnt activity (Wnt(high)) that possess properties indicative of CSCs, including drug resistance and tumor-initiating capacity, whereas cell populations with negligible Wnt activity (Wnt(low)) preferentially express markers of differentiation. Spontaneous response to extrinsic Wnt signals induces signaling networks comprising ERK1/2 and epithelial-mesenchymal transition that subsequently confer cancer stemness traits to susceptible cells. Wnt enhancer R-Spondin 2 (RSPO2) seems to play a prominent upstream role in regulating this interplay. In this context, Wnt(high) cells were more likely to give rise to Wnt(high) progeny, tended to be more metastatic, and revealed higher levels of RSPO2 expression. Our studies reveal adaptive aspects of pancreatic cancer stemness arising from driver populations of CSCs that misappropriate functional and responsive elements of archetypical self-renewal pathways. Blocking such stemness-promoting pathways in conjunction with established chemotherapy could provide means to
disrupt dynamic CSC process and present novel therapeutic targets and strategies.