

Identification of Tumorigenic Cells and Therapeutic Targets in Pancreatic Neuroendocrine Cancers

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Background: Pancreatic neuroendocrine tumors (PanNETs) are a type of pancreatic cancer with limited therapeutic options. Consequently, most patients with advanced disease die from tumor progression. Current evidence indicates that a subset of cancer cells are responsible for tumor development, metastasis, and recurrence, and targeting these tumor initiating cells is necessary to eradicate tumors. However, tumor initiating cells and the biological processes that promote pathogenesis remain largely uncharacterized in PanNETs.

Methods: We used 39 human tissue specimens, developed a novel cell line (APL1) from a well-differentiated patient PanNET, created xenograft models using primary tumors transplanted into NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ (NSG) mice, and utilized a RIP-Cre Rb/p53/p130 genetic model of PanNETs to characterize tumorigenic cells in PanNETs and identify and validate potential therapeutic targets.

Results: Here we profile primary and metastatic well-differentiated tumors from a patient and identify MET as an important growth factor receptor for PanNET growth. Furthermore, we identify a highly tumorigenic cell population within primary patient, well-differentiated, low or intermediate grade PanNETs characterized by increased CD90 expression and ALDHA1 activity. We identify phenotypically distinct cellular subsets in well-differentiated PanNETs and provide evidence for the stem-like properties of the CD90hi cell fraction. All PanNETs analyzed express CD47, a “don’t eat me” signal co-opted by cancers to evade innate immune surveillance. Furthermore, we demonstrate that blocking CD47 signaling promotes engulfment of tumor cells by macrophages in vitro and inhibits tumor growth and prevents metastases in vivo.

Conclusions: Our findings provide a foundation for developing therapeutic strategies that eliminate tumor initiating cells in PanNETs and show how deep examination of individual cases can lead to potential therapies.