Met Activation Confers Increased Aggressiveness and Corresponds with Hypoenhancement on Contrast Enhanced Computed Tomography in Pancreatic Neuroendocrine Tumors

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Background: Pancreatic neuroendocrine tumors (PanNETs) are a type of pancreatic cancer with variable biological behavior. Previously, we showed that increased tumor aggressiveness was associated with hypo-enhancement on preoperative contrast enhanced computed tomography (CT). However, the molecular rationale for pathogenesis in this cohort of PanNETs is unknown.

Methods: We used snap-frozen tissue from patient PanNETs with either hypo- or hyper-enhancing imaging characteristics on preoperative CT. Using quantitative polymerase chain reaction, mRNA expression for MET, HIF1A, HGF, KDR, SNAI1, CDH2, VIM, CDH1, PECAM1, TEK, FLT4, and LYVE1 was determined and correlated to preoperative imaging characteristics and overall survival. Protein expression of the above genes and activated MET was confirmed by immunofluorescence. For treatment studies, PanNET cell line APL1 cells, previously transduced using lentivirus containing a green fluorescent protein (GFP) and luciferase constructs, were orthotopically injected into NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ (NSG) mice and treated with MET inhibitor MET-MAb antibody (Genentech).

Results: PanNETs that were hypo-enhancing on preoperative CT had increased expression of MET, HIF, HGF, SNAI1, CDH2, VIM, FLT4, and LYVE1 and decreased expression of CDH1, PECAM1, and TEK compared to hyper-enhancing tumors. Furthermore, blocking MET activation inhibits xenograft tumor growth, prevents metastases, and prolongs survival in vivo.
Conclusion: Our results demonstrate that PanNETs that are hypo-enhancing on contrast enhanced CT imaging studies and are associated with decreased overall survival have increased tumor hypoxia, increased mesenchymal characteristics, decreased epithelial features, diminished vascularity, and enhanced lymphatics compared to hyper-enhancing tumors. Furthermore, we show the efficacy of anti-MET therapy on PanNETs in animal treatment models.

Conclusion: Our findings suggest a molecular mechanism for increased tumor aggressiveness seen in hypo-enhancing tumors compared to hyper-enhancing tumors, and provide a strong preclinical justification for testing blocking anti-MET antibodies in patients with PanNETs

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