Clinical Utility of Genomic Profiling of Pancreatic Neuroendocrine Tumors

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Background: Rare cancers pose particular difficulties for therapeutic development. We assessed the manner in which genomic information gained from novel technologies could be used clinically to improve the care of patients with pancreatic neuroendocrine tumors (PNETs).

Methods: We applied a novel technique using flow-cytometry to sort clonal populations of tumors cell for genomic profiling with array-based comparative genomic hybridization. We profiled the copy number aberrations present in the genomes of tumor cell populations from 7 PNETs.

Results: Of the 3 insulinomas studied, 2 had very simple genomes lacking significant aberrations at the genomic level predicting a benign phenotype. A third 8 mm low-grade insulinoma harbored numerous aberrations predicting malignant behavior including a focal amplicon within chromosome 11 containing GAB2, a known activator of the AKT pathway. A second PNET harbored a homozygous deletion of DISC1 at 1q42.1 that would also predict for activation of AKT. These tumors could be targeted with an AKT/PI3K inhibitor. In one PNET, we detected a focal deletion in 11p targeting 3 genes: IMMP1L an activator of the proapoptotic DIABLO, ELP4 a component of histone acetyltransferase, and PAX6, a key regulator of pancreatic islet hormone gene transcription necessary for normal islet cell development and an activator of c-MET, an oncogene. A glucagonoma harbored a deletion in CDX2. The CDX2 and CDX3complex with PAX6 and binds to the glucagon promoter. The same tumor harbored a deletion in CDKN2, a tumor suppressor gene that enhances p53-dependent apoptosis.
Conclusions: We have identified 3 potential ways in which clonal genomic profiling of PNETs by array CGH can assist in the clinical care of patients: 1) better definition of histopathology and determination of malignant phenotype, 2) provide insight into pathophysiology of excess hormone production, 3) expose therapeutic targets to guide decisions regarding selection of chemotherapy in patients with unresectable malignant PNETs.