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Mechanisms and Models for Cdk5 dependent Neuroendocrine Tumors

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BACKGROUND

Neuroendocrine tumors (NETs) occur in various forms: sporadically and as a consequence of causally-linked mutations. They are generally characterized by their indolent course, debilitating symptoms, and untreatable lethality. Advances that have improved outcomes for these cancers have been limited. Following the discovery that mechanisms that cause neurodegeneration in the central nervous system can also cause NET tumorigenesis, we have been studying various types of NETs to understand the mechanistic causes, create novel clinically accurate models, and identify diagnostic biomarkers. Our hypothesis is that diverse genomic variations converge upon common pro-neoplastic signaling mechanisms such as the aberrant activation of the protein kinase, Cdk5, to drive progression of most Neuroendocrine tumors.

METHODS

Experimental models including human tumors, cell lines, and organ-specific inducible bitransgenic animal models were utilized for the characterization of NETs. Whole exome sequencing, bulk transcriptomics, phosphoproteomics, and immunohistochemistry tissue microarray profiling were performed. Biomarker directed anti-Cdk5 targeted therapies will be tested in vivo using inducible autologous bi-transgenic tetracycline response element mouse models of PNETs, PCs, and GINETs. Cdk5 inhibitors with broad therapeutic windows will be used as the biomarker-directed therapy.

RESULTS

We will summarize some of the most notable advances made in our NET research program based on the understanding that aberrant Cdk5 activation plays a pivotal role in oncogenesis. The models demonstrate that pancreatic NETs (PNETs) and pheochromocytomas (PCs) exhibit markedly elevated expression of p25, the cleaved activator of Cdk5, resulting in persistent and mis-localized kinase activity that drives tumor progression. Immunohistochemical analyses of human NET tissues and genetically engineered mouse models confirmed high p25 levels and aberrant Cdk5 activity across all NET tumor types including GI, pulmonary, and pituitary forms. Notably, this oncogenic signaling axis appears independent of initiating genomic lesions, suggesting that Cdk5/p25 activation represents a convergent downstream mechanism in NET pathogenesis. The transgenic mouse models with neuroendocrine cell type-specific inducible p25 expression recapitulate key features of human NETs, including chromogranin A positivity and elevated proliferation indices. We will present selected findings on the potential of experimental and preclinical treatment approaches for Cdk5 dependent NETs.

CONCLUSIONS

The inducible mouse models provide a useful preclinical tool for testing new therapies. The downstream effectors of Cdk5 can serve as predictive molecular signatures for the early detection of tumors in NET patients. The next step involves developing a clinically relevant multiplex assay system that could allow quantitation of biomarker levels from the core biopsies of patient tumors.

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