BT11

Exploration and Targeting of Neuroendocrine Cancer Tumorigenic Signal Transduction

Karine Pozo[1,2*]; Angela Carter[1,2*]; Florian Plattner[1,2]; Gabriel Mettlach[1,2]; Tanvir Singh[1,2], Hans Ghayee[2,3]; Herb Chen[4]; Fiemu Nwariaku[2,5]; James A. Bibb[1,2,6]

[1]Department of Psychiatry, The University of Texas Southwestern Medical Center, Dallas TX 75390, USA
[2]Harold C. Simmons Comprehensive Cancer Center, The University of Texas Southwestern Medical Center, Dallas TX 75390, USA
[3]Department of Endocrinology, The University of Texas Southwestern Medical Center, Dallas TX 75390, USA
[4]Endocrine Surgery Research Laboratory, University of Wisconsin Carbone Cancer Center, Madison, WI 53792, USA
[5]Department of Surgery, The University of Texas Southwestern Medical Center, Dallas TX 75390, USA
[6]Department of Neurology and Neurotherapeutics, The University of Texas Southwestern Medical Center, Dallas TX 75390, USA
*Equal contributors

Background: Neuroendocrine (NE) and neuronal cells both arise from neural tube ectodermal progenitors. They share common mechanisms of calcium-dependent exocytosis, neurotransmitter/hormone synthesis, and signal transduction. The protein kinase, Cdk5 mediates these overlapping functions. Excitotoxic dysregulation of Cdk5 is a critical contributor to neuronal injury and death during ischemia or brain injury. In contrast, in NE cells, Cdk5 dysregulation and invocation of pathways overlapping with those mediating brain injury results in neoplasia and tumorigenesis.

Methods: Here we employ a multidisciplinary approach including human tissue histopathology and immunohistology, advanced mouse modeling transgenics, in vivo imaging, electron microscopy, pharmacology, biochemistry, mass spectroscopy, cell biology, high through put screening, and phosphorylation state-specific antibody technology, and DNA array analysis to explore the mechanisms of NE cancer tumorigenesis.

Results: We demonstrated Cdk5 expression and aberrant activity in thyroid C cells and medullary thyroid carcinoma. Cdk5 inhibition arrested MTC cell growth. Transgenic induction of aberrant Cdk5 caused robust and lethal MTC in mice. We now find Cdk5 and p35 expression in many other NE tumor types and growth of neoplastic cells derived from a variety of NETs are Cdk5-dependent. We derived a tumorigenic signal transduction mechanism library consisting of protein phosphorylation sites up-regulated in growing versus arrested mouse MTC tumors. High-throughput screening of these mechanisms yielded anti-neoplasia SIPs with specific cytotoxicity toward neoplastic MTC cells, but not normal human cell controls.

Conclusion: We believe that different forms of NE cancer share common or overlapping tumorigenic mechanisms. We aim to develop a personalized diagnostic panel based on phosphorylation state-specific antibodies to these pathways and couple it to targeted therapies to more effectively treat NE cancer.