Education

1968-1969 — University of Vermont, College of Medicine, Medical Education
1973-1976 — University of Vermont College of Medicine, Medical Education
1973-1976 — University of Vermont, College of Medicine, Medical Education
1976-1977 — Massachusetts General Hospital, Internship
1976-1979 — Massachusetts General Hospital, Residency Training
1976-1979 — Massachusetts General Hospital, Residency Training
1976-1979 — Salem Hospital-Massachusetts General Hospital, Internship
1979-1980 — McLean Hospital, Residency Training
1979-1980 — Mclean Hospital, Residency Training

Research Summary

In major neurodegenerative diseases, such as Alzheimer's and Parkinson's, the abnormal accumulation of one or more polypeptides within or around neurons is central to pathogenesis. Our research focuses on two aspects of neurobiology that govern the fate of normal and pathogenic proteins: the regulation of proteolytic processing and the control of protein export into axons and synapses. We have identified dysfunction of the endosomal-lysosomal system, involving altered endocytosis and mistrafficking of proteases to endosomes, as the earliest known pathological response of neurons in Alzheimer's disease. Our cell modeling studies show early endosomes to be major generators of the toxic beta-amyloid peptide and implicate dysfunction of endosomes in the mechanism of ?-amyloid accumulation in 'sporadic' Alzheimer's, the most common form of the disease. Genetic manipulations of proteolytic systems in mice are being used, together with cell culture models, to determine the consequences of endosomal-lysosomal and calpain system dysfunction on processing of Alzheimer-related proteins, receptor-mediated signal transduction, and neuronal cell death pathways. To maintain neural circuitry, neurons transport a large proportion of their newly synthesized proteins into axons. The perikaryal accumulation of specific cytoskeletal proteins - a pathological hallmark of Alzheimer's, ALS, and other neurologic diseases - is believed to arise in part from impaired axonal transport. A second interest of our research is to identify the molecular determinants of cytoskeletal protein transport and assembly in neurons. For example, we are defining the minimum structural requirements for neurofilament translocation by studying axonal transport and axon ultrastructure in mice after targeted deletion or mutagenesis of each of the three neurofilament subunit genes. Neurofilament transport is also regulated by sequential protein phosphorylation, triggered in part by signals from oligodendroglial cells. We have been determining the signaling pathways, phosphorylation sites, and functional implications of these post-translational modifications. Disease relevance is also being explored in several behavioral and psychiatric settings.

Research Interests

Major Research Interests: Regulation of protein structure and function by proteolysis and phosphorylation, Cell and molecular biology of the neuronal cytoskeleton, Molecular mechanisms of brain aging and cell death, Pathogenesis and treatment of Alzheimer's disease.