Targeting the Retromer Protein Trafficking Pathway: A New Therapeutic Approach for Alzheimer’s and Parkinson’s Diseases

GREGORY A. PETSKO, D. PHIL.
ARTHUR J. MAHON PROFESSOR OF NEUROLOGY AND NEUROSCIENCE
FEIL FAMILY BRAIN AND MIND RESEARCH INSTITUTE
WEILL CORNELL MEDICAL COLLEGE

Retromer is a multi-protein complex that traffics endosomal cargo back to the Golgi. Implicated in both sporadic and familial Alzheimer’s disease (AD), and more recently in familial Parkinson’s disease (PD), retromer has been shown to traffic the Amyloid Precursor Protein (APP) away from the endosome, where the beta-secretase is optimally active, thereby regulating Aβ peptide accumulation. We have identified pharmacological chaperones that enhance retromer stability and function, with the goal of redirecting APP away from those compartments in which it is proteolized. First, we relied on the crystal structures of retromer proteins to identify the ‘weak link’ of the complex, and to complete an in silico screen of small molecules predicted to enhance retromer stability (the Figure below shows the docked complex). Among the hits, an in vitro assay identified one molecule that stabilized retromer against thermal denaturation by more than 10 degrees C. Second, we turned to cultured hippocampal neurons, showing that the small molecule increases the levels of retromer proteins, shifts APP away from the endosome, and decreases Aβ accumulation dramatically, in a dose-dependent manner. Together, these findings clarify mechanisms of retromer stability, and identify a pharmacological chaperone that has therapeutic potential for AD and other neurodegenerative disorders.

Publications:
