Targeting familial Alzheimer’s disease

Statement of the Problem: More than 200 genetic mutations in presenilins (PSENs) are associated with autosomal-dominant, early-onset, familial Alzheimer’s disease (FAD). An estimated 1-2% of all Alzheimer’s patients have this rare genetic disorder, with disease onset invariably occurring in midlife, in many cases as early as in the mutation carrier’s 30s. PSENs encode for the catalytic component of γ-secretase, a membrane-embedded protease complex that cleaves within the transmembrane domain of the amyloid precursor protein (APP) to produce the amyloid β-peptide (Aβ) that deposits in the Alzheimer’s brain. Decades of research have failed to clearly identify the pathogenic form of Aβ, and γ-secretase inhibitors have failed in Alzheimer’s clinical trials, actually making subjects cognitively worse. We, therefore, set out to determine the specific biochemical alterations in γ-secretase that result from FAD mutations in PSEN.

Methodology: As γ-secretase has multiple proteolytic functions and produces a range of Aβ peptides that vary in length at their C-termini, we determined the effects of FAD PSEN mutations on specific functions of the protease and on the range of produced Aβ peptides.

Findings: We found that these mutations decrease a carboxypeptidase activity that trims initially formed long Aβ peptides to shorter forms. We further elucidated determinants of APP processing by γ-secretase that dictate where proteolysis occurs and the general mechanism of carboxypeptidase trimming of Aβ peptides.

Conclusion & Significance: FAD apparently results from deficient carboxypeptidase activity in the mutant γ-secretase complexes, resulting in increased proportions of longer Aβ peptides. Thus, small molecules that rescue this specific deficient function of mutant γ-secretase complexes, rather than general inhibitors of protease activity, would be worthwhile as potential therapeutics to prevent or delay FAD. Molecular tools are in development to allow high-throughput screening for such compounds.

Biography

Michael S Wolfe received his BS in chemistry from the Philadelphia College of Pharmacy and Science and PhD in medicinal chemistry from the University of Kansas. After postdoctoral stints at the University of Kansas and the NIH, he joined the faculty of the University of Tennessee in Memphis. In 1999, he moved to Harvard Medical School and Brigham and Women’s Hospital, where his work focused on understanding the molecular basis of Alzheimer’s and related disorders and identifying effective approaches for pharmacological intervention, becoming Professor of Neurology in 2008. He returned to the University of Kansas in October of 2016 as the Mathias P Mertes Professor of Medicinal Chemistry. Awards for his work include the Sato Memorial International Award in Bioorganic and medicinal chemistry from the Pharmaceutical Society of Japan, the MetLife Award for Biomedical Research, a Zenith Fellows Award from the Alzheimer’s Association, and the Potamkin Prize from the American Academy of Neurology.

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