Lucía Chávez Gutiérrez

Center for human genetics

Laboratory for the Research of Neurodegenerative Diseases

University of Leuven

MSc in Sciences, University of Morelos, Mexico, 1999
MD in Physiology (Neurosciences), University Pablo de Olavide, Spain, 2002
PhD in Science, National University of México (UNAM), 2005

Staff scientist at the University of Leuven, since 2005

E-mail: Lucia.ChavezGutierrez@cme.vib-kuleuven.be

Phone: +32 (16) 34 72 35

Keywords

Alzheimer's Disease - γ-secretase - Aph1

Science

One of the hallmarks of Alzheimer's disease is the accumulation of amyloid plaques in the brain. Amyloid plaques are composed of Abeta peptide, which is generated from the amyloid precursor protein (APP) by sequential cleavages of the beta and the γ-secretases. Most therapeutic strategies aim to reduce the accumulation of Abeta peptide in the brain by either inhibiting its production or by enhancing its degradation. Therefore, both beta and γ-secretases has been considered as potential drug targets in AD.

γ-Secretase complex is an intramembrane protease composed by presenilin, the catalytic subunit; nicastrin, the anterior pharynx defective and presenilin enhancer-2 as essential cofactors. The catalytic subunit exists in the active γ-secretase complex as a heterodimer of the N- and C-terminal fragments resulting from endoproteolysis; they present the two Asp residues involved in the catalysis. Nicastrin is a type 1 membrane protein with a large and highly glycosylated ectodomain involved in the maturation and stability of the complex. There are two Aph1 genes in humans (Aph1a and Aph1b) and a duplication of the Aph1b generated a third gene, (Aph1c) in rodents. Recently it was shown that inactivation of the Aph1b gene in an Alzheimer's disease mouse model leads to improvements in the AD specific phenotype without Notch side effects [7], suggesting that APH-1b is a potential pharmacological target. The PEN-2 subunit, a hairpin like protein, plays a role in the activation of the protease complex.

The clinical application of candidate drugs against the gamma secretase has failed due to fact that this enzyme has a broad specificity. Apart from APP, γ-secretase is involved in

the process of many other type 1/ single-span membrane proteins, including the Notch receptor. Therefore, an effective and safe therapy targeting γ-secretase implies the use of inhibitors that selectively decrease Aβ levels without affecting any of the other cellular functions in which this enzyme is involved. In order to develop such inhibitors, we need to understand much better how this enzyme works.

Our approach aims to evaluate functional and structural aspects of the γ-secretase complex in order to advance our knowledge of the catalytic mechanism, its modulation and inhibition. In particular, the project intents to evaluate the potential of the substrate binding site as a pharmacological target in AD, results that could profoundly affect strategies to cure AD by targeting γ-secretase processing of APP in a more specific way at the level of initial substrate binding.

Selected publications

Chávez-Gutiérrez L, Tolia A, Maes E, Li T, Wong PC, De Strooper B (2008) Glu(332) in the Nicastrin ectodomain is essential for gamma-secretase complex maturation but not for its activity. J. Biol Chem. 283(29): 20096-20105.