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BSc Biomedical Science, University of Leuven, 2009
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Keywords
Alzheimer Disease – Gamma-Secretase – APP Processing

Science
As γ-secretase is the final protease involved in the production of Aβ peptides which accumulate in the brain of Alzheimer patients, it has become one of the more attractive drug targets in AD. In addition to APP, γ-secretases cleave a number of type I transmembrane proteins, such as Notch, Neuregulin, ERBB4 and other important signaling molecules. γ-Secretases are therefore involved in various physiological processes and appear to have pathological significance not only for neurodegenerative disorders, but also for cancer, and likely psychiatric disease.

Gamma-secretase consists of four essential subunits: presenilin (PSEN), nicastrin, anterior pharynx defective (APH1) and presenilin enhancer 2, which probably assemble in a 1:1:1:1 ratio in cells. Because two PSEN and two APH1 homologues exist, at least four different γ-secretase complexes can theoretically be present in cells. This opens the possibility that drugs specific for one of these γ-secretases could act beneficially with regard to Aβ processing, while affecting less the processing of other substrates. This concept was recently proven in experiments that genetically inactivated the Aph1B-containing γ-secretase complexes in a murine AD model. In the current project we want to explore this hypothesis in more detail by defining better the function and the substrates of the different γ-secretases.

Our goal is to investigate the following questions: How do different complexes process APP_{C99}? Do they show different Aβ profiles? What is the substrate specificity of the different complexes? What is their expression pattern in adult brain? Could selective inhibition of certain complexes offer a therapeutic strategy to ameliorate AD symptoms?

Fellowships

Selected Publications
Acx, H., Chávez-Gutiérrez, L., Serneels, L., Lismont, S., Benurwar, M., Elad, N., De Strooper, B. (2014) Signature Amyloid β Profiles Are Produced by Different γ-Secretase Complexes. *Journal of Biological Chemistry* **289**, 4346-4355 (PMID: 24338474)