Alzheimer´s amyloid degradation by secreted lysosomal enzymes

https://neurodegenerationresearch.eu/survey/alzheimers-amyloid-degradation-by-secreted-lysosomal-enzymes/

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Sweden

Title of project/programme

Alzheimer´s amyloid degradation by secreted lysosomal enzymes

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01-07-2013

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3.0

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

amyloid degradation | microglia lysosomes | lysosomal acidity | brain imaging | lysosomal synapse

Research Abstract
Alzheimer disease (AD) is the most common form of dementia, affecting 25 million individuals worldwide. Some degenerating brain areas present increased amyloid-beta (Ab) production, leading to Ab plaque formation. It is unclear how microglia, the main immune cells of the brain, degrade plaques that are significantly larger than the cells themselves. Our hypothesis is that microglia can secrete lysosomal enzymes upon contact with Ab and create an extracellular digestive compartment, the lysosomal synapse, that helps to break down the Ab plaque, as we

have previously seen in macrophages encountering large aggregated LDL deposits. In order to visualize the lysosomal synapse in vitro and in vivo and determine its acidic properties, novel pH probes selectively uptaken by microglia lysosomes will be tested in cell cultures and in AD model mice, and visualized using confocal and live imaging multiphoton microscopy. Next, we will investigate the mechanisms that regulate lysosomal activity in macrophages and microglia using molecular biology and siRNA techniques, as our previous work demonstrated that acidification of microglia lysosomes enhances Ab degradation. The main aim of this project is to obtain data about the mechanisms of microglia lysosomal secretion and the role of extracellular hydrolysis of Ab by lysosomal enzymes, with the long term goal of developing non-inflammatory therapies aiming at enhancing brain Ab degradation in AD patients as an alternative to Ab immunization

Types:
Fellowships

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