

Mitochondrial function in transgenic mice overexpressing human APP with the Arctic mutation

Project description for master thesis (30-45 credits)

Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common form of dementia in elderly people. Accumulation of amyloid β -peptide ($A\beta$) in the brain has been suggested to be an important event in the pathogenesis of AD. $A\beta$ is formed by proteolytic cleavage of the amyloid precursor protein (APP) resulting in peptides of different lengths, with $A\beta$ 1–40 and $A\beta$ 1–42 being the most abundant. Mutations in the *APP* gene are a known cause of early-onset familial AD, and the mechanism is believed to be mediated through altered $A\beta$ metabolism. One of the described mutations in the *APP* gene is the so called Arctic mutation (E693G) which results in familial dementia with clinical symptoms similar to AD but little is known about the mitochondrial function of this mutation in brain tissues. We have generated a transgenic mouse-model (TgAPP_{Arctic} mice) with brain-specific expression of human APP carrying the Arctic mutation. Dysfunctional mitochondria have been implicated in various neurodegenerative disorders including AD. A key question is: Does the Arctic APP mutation affect mitochondrial function in our transgenic APP_{Arctic} mouse model?

Aim: To study mitochondrial status in APP_{Arctic} transgenic mice brain tissues and determine whether this correlates with $A\beta$ deposition in different brain regions as we published/showed previously.

Materials and Methods: Brain tissues from either APP_{Arctic} homozygous, heterozygous and wild-type mice, will be used to measure ROS production, mitochondrial membrane potential, distribution and fragmentation (fis1, Drp1) of mitochondria. Proteins related to mitochondrial function such as SOD1, Bcl-2 and Bax, will be analyzed by western blot and the intensity of the protein levels will be quantified using CCD camera. The oxygen consumption of mitochondria prepared from brain homogenates will be measured and analyzed in collaboration with Stockholm University.

- The student will get the practical supervision from the supervisors and the student will get help from other people in the laboratory.
- It is not necessary to perform all suggested experiments (above) and suitable experiments will be selected based on the students' previous experiences.

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