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### Let's not forget: Peptidases in Alzheimer's disease

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# GENERAL INTRODUCTION AND SCOPE OF THE THESIS

## INTRODUCTION

Alzheimer's disease (AD) is the most common form of dementia and is a devastating progressive neurodegenerative disorder currently affecting over 35 million people worldwide. This number is expected to raise because of the growing world population and increasing longevity. Symptoms of AD include impaired memory, personality changes, hallucinations and cognitive decline. Aging is an important risk factor to develop AD; 1 in 3 people over the age of 85 are affected by AD. Cure or disease-modifying therapies are not available and clinical diagnosis is based on impairment of memory and other cognitive functions.

AD is hallmarked by extracellular aggregates of A $\beta$  peptides (plaques) and accumulation of these peptides starts decades before the onset of the first symptoms. The A $\beta$  peptide is generated from the amyloid precursor protein (APP). Depending on the processing of APP, either the A $\beta$  peptide is produced (amyloidogenic pathway) or a different, non-toxic peptide (non-amyloidogenic pathway). Understanding of the underlying biological processes has been gained from studies investigating gene mutations in familial AD which is the rare, heritable form of the disease. These gene mutations lead to an increased production of the A $\beta$  peptide, resulting in the formation of plaques and associated symptoms. Knowledge about these gene mutations has also contributed to the generation of AD mouse models.

However, most cases of AD (over 95%) are not inherited and are termed 'sporadic'. It is likely that this form of AD is not caused by excessive production of the A $\beta$  peptide but rather a less efficient clearance. The final result is the same, the A $\beta$  peptide accumulates and leads to plaque formation as observed in the brains of AD patients.

The aim of this thesis is to investigate the role of peptidases in AD, as part of the cellular proteostasis network that degrades peptides. We have analyzed which peptidases are able to degrade the A $\beta$  peptide and how their levels and activity change during the development of AD. We have been particularly interested in changes that occur in early stages of AD before the onset of symptoms and whether these changes can be observed in AD mouse models. Understanding of processes that take place in the early stages of the disease is important to allow therapeutic intervention before AD becomes manifest. In addition, we have examined whether changes in peptidase activity can be used to diagnose AD in early stages.

## SCOPE OF THE THESIS

Production and secretion of the A $\beta$  peptide is affected by neuronal activity. In [chapter 2](#), we review

underlying molecular mechanisms and discuss the role of neuronal hyperactivity in the presymptomatic stages of AD.

Changes in the brains of presymptomatic AD patients are investigated in **chapter 3**. We designed a quenched fluorogenic A $\beta$ <sub>40</sub> peptide that becomes fluorescent upon degradation. By measuring degradation of the quenched A $\beta$ <sub>40</sub> peptide in human post mortem hippocampal tissue in different Braak stages of sporadic AD we showed less efficient A $\beta$  clearance by the peptidase insulin-degrading enzyme already in Braak stage I and II, before the onset of any symptoms. Furthermore, we demonstrated that, unlike in human hippocampal tissue, two commonly used AD mouse models did not show decreased A $\beta$  clearance during AD development. In **chapter 4**, we investigated whether the reduction in A $\beta$  degradation as observed in human post mortem hippocampal tissue can be observed in CSF or blood plasma of AD patients. We describe an assay of measuring the quenched A $\beta$ <sub>40</sub> peptide degradation as a diagnostic and prognostic tool for AD. In **chapter 5**, a filed patent is described for the application of quenched A $\beta$ <sub>40</sub> peptide degradation as a diagnostic and prognostic tool. In **chapter 6**, we describe in detail the method in which quenched fluorescent peptides are used to study peptide degradation in living cells and cell lysates.

In **chapter 7**, we examine early changes in human and mouse brains during the progression to AD. We describe a microarray screen to study gene expression changes in the prefrontal cortex of an AD mouse model during the development of AD. Mainly genes involved in the immune response showed altered expression. We compared this data to gene expression changes in the human prefrontal cortex during AD development and show that there is almost no overlap; in human prefrontal cortex mainly genes involved in synaptic activity have altered expression.

In **chapter 8**, we study the tripeptidyl peptidase II (TPP2) that is involved in many cellular processes including antigen presentation, cancer, cell proliferation and DNA repair. To identify (in)direct proteomic targets of TPP2, we performed a proteomic screen in SH-SY5Y cells with the use of the SILAC (stable isotope labeling by amino acids in cell culture) method. Diminished TPP2 activity resulted in decreased levels of phosphorylated ERK1 and ERK2 in the nucleus. Furthermore, we show for the first time the involvement of TPP2 in synaptic activity and its ability to alter cellular levels of APP. In **chapter 9**, we investigate the link between TPP2 and the amyloid precursor protein and show that TPP2 knock down led to accumulation of O-glycosylated APP in the Golgi complex and higher levels of C-terminal APP fragments that result from  $\alpha$ -secretase cleavage (CTF- $\alpha$ ) (the non-amyloidogenic pathway) in SH-SY5Y cells and organotypic hippocampal mouse brain slices.

In **chapter 10**, we summarize the results presented in the preceding chapters and formulate conclusions.