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Physiological roles of amyloid precursor protein *in vivo* - zebrafish as a model

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i **Europa**, Konferenscentrum Wallenberg, Medicinaregatan 20A, den 19 November 2021, klockan 09:00

av **Jasmine Chebli**

Fakultetsopponent:
Michael Lardelli, Associate Professor
The University of Adelaide, Australia

Avhandlingen baseras på följande delarbeten

I. Banote RK, **Chebli J**, Şatır TM, Varshney GK, Camacho R, Ledin J, Burgess SM, Abramsson A, and Zetterberg H. *Amyloid precursor protein-b facilitates cell adhesion during early development in zebrafish*. 2020. Sci Rep 10(1): 10127

II. **Chebli J**, Rahmati M, Banote RK, Abramsson A, and Zetterberg H. *Amyloid precursor protein-b coordinates the assembly of the trigeminal ganglia in zebrafish*. Manuscript

III. **Chebli J**, Rahmati M,. Lashley T, Edeman B, Oldfors A, Zetterberg H, and Abramsson A. *The localization of amyloid precursor protein to ependymal cilia in vertebrates and its role in ciliogenesis and brain development in zebrafish.* 2021. Scientific Reports 11(1): 19115

IV. Abramsson A, **Chebli J**, Banote RK, Sauer M, Hansson KT, Blennow K, Gobom J and Zetterberg H. *Proteomic analysis of amyloid precursor protein-b mutant zebrafish (Danio rerio) larvae reveals changes in proteins involved in neural development, cell adhesion and gene regulation*. Manuscript

V. Rahmati M, **Chebli J**, Banote RK, Roselli S, Agholme L, Zetterberg H and Abramsson A. *Transcriptional adaptation between zebrafish amyloid precursor protein gene family members*. Manuscript

SAHLGRENSKA AKADEMIN
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Physiological roles of amyloid precursor protein *in vivo* - zebrafish as a model

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Abstract

Amyloid-beta precursor protein (APP) is an evolutionarily conserved transmembrane protein expressed in many different tissues. APP belongs to a gene family consisting of two other APP-like proteins (APLP1 and APLP2). APP has been shown to be involved in biological processes such as neurite outgrowth, neuronal migration, synapse formation and plasticity, and cell-cell interactions. APP also plays a central role in the development of Alzheimer's disease (AD). APP's physiological role has been difficult to understand and despite all research is not yet completely understood. The purpose of this thesis was to study the role of APP during early development with zebrafish as the main model system.

We have focused on the zebrafish's Apps and have tried to understand their function with the help of genetic knockout models created using the CRISPR / Cas9 method. We report that *appb* mutants have weakened cell adhesions that give rise to changes in cell organization. We also report that the *appb* mutants are smaller but develop into fertile and healthy adult individuals. We also found defects in the formation of the trigeminal ganglia (TG) and that Appb seems to have a role in cell-cell interaction. The more widespread TG also consisted of fewer nerve cells, indicating that Appb promotes nerve cell formation. Furthermore, our studies demonstrate APP expression in cilia on sensory nerve cells and ependymal cells covering the brain chambers. The conserved expression of APP in ependymal cilia in mice and humans suggest an important and preserved function. Zebrafish with mutated App were found to have defects in the formation of both cilia and cerebral ventricles. To identify new signalling pathways through which Appb controls these functions, we studied protein changes in *appb* mutants using mass spectrometry. These studies highlight changes that both confirm known and suggest new regulations by *appb*, especially in neural development, cell adhesion and in gene regulation. Finally, we tried to answer the underlying mechanisms behind compensation within the App family. We found that mutations in the *app* genes activate expression of homologous genes *via* so-called transcriptional adaptation.

In conclusion, the findings reported in this thesis showed that App is implicated already in early cellular adhesion and sensory neuronal differentiation processes and is located to several sensory cilia *in vivo*. The use of zebrafish as a model organism allowed us to gain valuable knowledge on the physiological roles of App.

Keywords: Amyloid-beta precursor protein, amyloid precursor protein-b, zebrafish, physiological functions, development, trigeminal ganglia, ependyma, cilia, proteomics, translational adaptation

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