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Physiological role of amyloid precursor protein during neural development

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i salen Hjärtats Aula, Sahlgrenska Universitetssjukhuset, fredagen den 16 juni 2017, klockan 09:00

av Rakesh Kumar Banote

Fakultetsopponent:
Arminda Suli, Assistant Professor, PhD
Brigham Young University, Utah, USA

Avhandlingen baseras på följande delarbeten

I. Abramsson A, Kettunen P, **Banote RK**, Lott E, Li M, Arner A, Zetterberg H. The zebrafish amyloid precursor protein-b is required for motor neuron guidance and synapse formation. Dev Biol. 2013; 15;381(2):377-88.

II. **Banote RK**, Edling M, Eliassen F, Kettunen P, Zetterberg H, Abramsson A. β-Amyloid precursor protein-b is essential for Mauthner cell development in the zebrafish in a Notch-dependent manner. Dev Biol. 2016; 1;413(1):26-38.

III. **Banote RK**, Edling M, Şatır TM, Burgess SM, Chebli J, Abramsson A, Zetterberg H. Characterization of β-amyloid precursor protein-b zebrafish mutants during early development. Manuscript, 2017.

IV. Abramsson A, **Banote RK**, Gobom J, Hansson KT, Blennow K, Zetterberg H. Quantitative proteomics analysis of amyloid precursor protein hypomorphic zebrafish (*Danio rerio*) embryos using TMT 10-plex isobaric labeling. Manuscript, 2017.

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Physiological role of amyloid precursor protein during neural development

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Abstract

Amyloid precursor protein (APP) is a type-one membrane-spanning protein with a large extracellular N-terminal domain and a small intracellular C-terminal domain. APP first gained interest due to its involvement in the pathogenesis of Alzheimer's disease (AD). Its proteolytic processing liberates the neurotoxic amyloid-beta (Aβ) peptide that accumulates in the amyloid plaques, characteristic of AD. Thus, APP has been intensively studied for its amyloidogenic properties with less focus on its normal cell biological roles. APP is an evolutionarily conserved protein involved in biological processes including neuronal migration, synaptogenesis, synaptic function and plasticity. Still, it is unclear what role APP plays in the development of specific neuronal cell types in the central nervous system. The aim of this thesis was to examine the physiological functions of the zebrafish Appb, a highly conserved homologue of human APP, during neural development. Through a knockdown approach, we found that Appb is required for the patterning and outgrowth of motor neurons in the spinal cord as well as for the synapse formation at the neuromuscular junction (NMJ), thus essential for the formation of normal locomotor behavior. We also show the cell-specific utility of Appb in the hindbrain-specific Mauthner cell (M-cell) development that our data indicate is mediated through a Notch1a-dependent mechanism. To confirm the function of Appb we generated an *appb* mutant carrying a homozygous non-sense mutation in exon 2. Although the smaller size of mutants was similar to morphants, mutants appeared morphologically normal after 48 hours post-fertilization (hpf), suggesting that the genetic deficit is compensated for, potentially by other App family members or by modifications of other genes, such as Notch. Lastly, to get a deeper insight into molecular pathways regulated by Appb, we determined the proteomic consequence of Appb down-regulation and provided crucial information on proteins and pathways that are differently expressed when the expression of Appb is modulated. In summary, we report on an essential role of Appb during neural development in the spinal cord and hindbrain and provide a link between Appb and other proteins and pathways. We believe that the zebrafish model used here provided appreciable knowledge in gaining insights into APP function and that the described studies above will significantly contribute to our understanding of this complex protein during neural development.

Keywords: Amyloid precursor protein-b, zebrafish, spinal cord, motor neuron, hindbrain, Mauthner cell, development, mass spectrometry, proteomics

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