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The role of microglia in Alzheimer's disease
Investigating mechanisms regulating amyloid-β clearance

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i salen Ivan Östholm, Medicinaregatan 13, onsdagen den 15 juni 2016, klockan 09:00

av Carl-Henrik Andersson

Fakultetsopponent:
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Avhandlingen baseras på följande delarbeten

I. Kettunen, P, **Andersson, C-H,** Sundell, J, Offenbartl, M I, Ahmadniaye, G, Olsson, M, Abramsson, A and Zetterberg, H. 2016. *Amyloid-β disrupts sensitization of the touch-evoked startle response in larval zebrafish.* Submitted.

II. **Andersson, C-H,** Strand, S and Kettunen, P. 2016. *The purinergic receptor p2y12 mediates amyloid-beta clearance by microglia.* Manuscript.

III. **Andersson, C-H,** Hansson, O, Minthon, L, Wallin, A, Zetterberg, H, Blennow, K, Skoog, I, Andreasen, N, Nilsson, S and Kettunen, P. 2016. *A haplotype of the purinergic P2Y12 gene is associated with increased risk of Alzheimer's disease.* Submitted.

IV. **Andersson, C-H,** Hansson, O, Minthon, L, Wallin, A, Zetterberg, H, Blennow, K, Skoog, I, Andreasen, N, Nilsson, S and Kettunen, P. 2016. *A genetic variant of the sortilin 1 gene is associated with reduced risk of Alzheimer's disease.* Accepted for publication in Journal of Alzheimer's disease.

V. Rosén, C, **Andersson, C-H,** Andreasson, U, Molinuevo, JL, Bjerke, M, Rami, L, Lladó, A, Blennow, K and Zetterberg, H. 2014. *Increased levels of chitotriosidase and YKL-40 in cerebrospinal fluid from patients with Alzheimer's disease.* Dementia and Geriatric Cognitive Disorders EXTRA. 4(2):297-304

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR NEUROVETENSKAP OCH FYSIOLOGI

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The role of microglia in Alzheimer's disease
Investigating mechanisms regulating amyloid-β clearance

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Abstract

Alzheimer's disease (AD) is the most common form of dementia today. The disease is characterized by the presence of amyloid plaques and neurofibrillary tangles in the brain, accompanied by a progressive neurodegeneration leading to memory loss. The underlying cause of the disease is largely unknown, but most evidence suggests that altered amyloid-β (Aβ) production is the putative cause of the disease. AD is also characterized by an inflammatory status in the CNS, although it is unclear whether the inflammation is the cause or the consequence of the disease. The aim of this thesis was to examine the role of microglia, the main immune cell in the brain, with regard to AD pathogenesis. This was carried out by experimental studies using the zebrafish as a model system in a combination with clinical analyses investigating biochemical differences and genetic variation in AD patients compared to controls. In paper I, we developed a novel zebrafish larvae model to study Aβ toxicity. The results indicated that injection with Aβ in animals leads to increased neurodegeneration and memory impairments, results similar to the pathological picture of AD. We also observed that oligomerization of the Aβ peptides was crucial for the neurotoxicity and that Aβ-induced neurodegeneration and memory impairments were mediated by separate pathways. In paper II, we used the newly developed zebrafish model to investigate how microglia interacts with injected Aβ. Confocal imaging revealed that microglia engulfs Aβ rapidly and that microglia is protective against Aβ-induced toxicity. Animals with reduced expression of microglia showed elevated levels of Aβ in the brain together with an increased neurodegeneration compared to controls. We also investigated the role of the p2y12 receptor and found that it plays a key role in the microglia-mediated clearance of Aβ in the brain. In paper III, we investigated genetic variation in the purinergic *P2Y12* gene in a case-control study and found a haplotype to be associated with increased risk of AD. In paper IV, we performed a genetic analysis of *SORT1*, encoding sortilin 1, a receptor expressed on microglia, and identified a genetic variant strongly associated with a reduced risk of AD. In paper V, we identified two markers, chitotriosidase and YKL-40, both representing inflammation, to be upregulated in cerebrospinal fluid (CSF) of AD patients. In summary, we developed a new zebrafish model that can be used to study Aβ-induced pathology, where p2y12 was found to be protective against Aβ toxicity. Our data also suggest that AD patients have increased inflammation in the CNS and that *P2Y12* together with *SORT1* are possible risk genes for AD. This indicates that the zebrafish and humans share molecular mechanisms of neuroinflammation and our new model can in the future be used to explore new target genes for AD diagnosis and development of therapeutics.

Keywords: microglia, neuroinflammation, amyloid-beta, Alzheimer's disease, genetic association, biomarker, cerebrospinal fluid, zebrafish, clearance, *in vivo* imaging

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