Chaperonnes en de aggregatie van Tau. Chaperonnes and the aggregation of Tau

https://neurodegenerationresearch.eu/survey/chaperonnes-en-de-aggregatie-van-tau-chaperonnes-and-the-aggregation-of-tau/

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Country

Netherlands

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Chaperonnes en de aggregatie van Tau. Chaperonnes and the aggregation of Tau

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alzheimer nederland (ISAO)

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€ 100,000

Start date of award

01/10/2014

Total duration of award in years

2

Keywords
Research Abstract
General objective: Testing the hypothesis that the Hsp90 chaperone can counter Tau aggregation. We will address this by answering three key questions:
1. Can Hsp90 influence Tau aggregation?
2. Hsp90 is an ATP-dependent chaperone system – does ATP influence Tau aggregation?
3. Hsp90’s ATPase cycle is controlled by a range of co-chaperones and can be inhibited – can co-chaperones and inhibitors modulate Hsp90’s effect on tau aggregates, positively or negatively?

The Hsp90 chaperone interacts in vivo and in vitro with the Tau protein, the aggregation of which is a molecular cause for Alzheimer Disease. We have recently described a structural model of an Hsp90-Tau complex, showing the Tau protein behaves as a bona fide client of the Hsp90 chaperone. We found Hsp90 to bind to the Tau's microtubule-binding repeat region, which forms the toxic aggregates. Molecular chaperones such as Hsp90 are the first line of the cellular defence system against protein damage and aggregation. Together this suggests a direct role for Hsp90 in dealing with Tau aggregation. We hypothesize that Hsp90 can counter aggregation of Tau. The aim of this grant application is to test the hypothesis.

We answered question 1: Hsp90 influences Tau aggregation – yes, Hsp90 does reduce the aggregation rate of Tau in vitro. We created ATPase mutants of Hsp90 and are currently investigating the effect on Tau aggregation. We purified all relevant components needed to run the ATPase cycle of Hsp90, so that we now can investigate their role in the interaction of Hsp90 with Tau.

Furthermore, we made significant technical progress relevant to address our key questions. (i) We characterised the Tau interactome in neuronal extracts. We identified aggregation-dependent Tau interactors, some of which are depending on chaperone levels. This opens new avenues to identify the molecular origin of the toxicity of Tau aggregates in Alzheimer. (ii) We established native gels and sucrose gradient as methods to characterise and monitor Tau aggregation. These assays will increase our tools to monitor chaperone interaction with distinct aggregation states of Tau. It offers us new possibilities to isolate the different aggregation stages of Tau, which improves our potential to meet our objectives.

Further information available at:

https://www.alzheimer.nl/onderzoek/onderzoeksprojecten/project/chaperonnes-en-de-aggregatie-van-tau

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