Structural analysis of the conformational transitions of the K18 fragment of human tau driven by Hsp70 action

https://neurodegenerationresearch.eu/survey/structural-analysis-of-the-conformational-transitions-of-the-k18-fragment-of-human-tau-driven-by-hsp70-action/

Name of Fellow
Institution
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Contact information of fellow
Country

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Structural analysis of the conformational transitions of the K18 fragment of human tau driven by Hsp70 action

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Neurodegenerative disease in general

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Research Abstract
The proteins Tau and ?-synuclein are causative agents of several neurodegenerative diseases including Alzheimer’s and Parkinson’s disease. In physiological conditions these neurotoxic proteins adopt a disordered conformation but undergo conformational transitions leading to their aggregation and amyloid fibril formation under neuronal stress. ATP-driven molecular chaperones of the heat-shock protein (Hsp) family have been postulated to play a critical role in inhibiting the gain-of-toxic function of these proteins. However, little is known about the binding and activation mechanism of neurotoxic proteins, and of disordered proteins in general, induced by Hsps. Given the dynamic and unstable nature of these interactions and activation cycles, NMR spectroscopy is ideally suited to obtain insight into the nature of these interactions. In the attached application I propose to obtain – by means of novel artful NMR experimental designs, complemented with extensive biochemical and biophysical characterization – a detailed model of the aggregation-prone fragment of Tau bound to the two different allosteric conformations of Hsp70. This will for the first time shed light onto the still unsolved conformational changes in a client protein motivated by the chaperone mode of action. Moreover, I will study several disease-related Tau mutants, the role of cochaperones in this cycle, as well as the effect of inhibitors to better understand the mechanism of Hsp-substrate interaction. In addition, the detailed structural information that will be obtained in this project will provide the basis to chemically optimize available inhibitors and test their cellular effect in the last phase of the project. The opportunity to carry out this ambitious project represents a significant step forward for my future independent career, being deeply involved in state-of-the-art methodological and biological tutoring in a scientific environment that is tightly connected to the industry sector.

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