BioISI - Biosystems & Integrative Sciences Institute

Extracellular regulation of Tau aggregation and amyloid cross-interactions in Alzheimer's Disease

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Protein aggregation is a central feature in several age-related neurodegenerative diseases. In Alzheimer's Disease (AD), misfolding of the disordered amyloid-β peptide (Aβ) and Tau protein leads to the formation of toxic aggregates that accumulate respectively in senile plaques and neurofibrillary tangles[1]. While the extracellular space is the primary site for Aβ aggregation, it is also known that intracellular Tau is promptly secreted and spreads pathology to nearby cells. Therefore, key molecular events underlying AD pathology, related to protein aggregation take place extracellularly. However, knowledge about extracellular chaperones is still limited.

Our laboratory has however recently discovered that S100 proteins, which are abundant in the brain and secreted by astrocytes nearby Tau and Aβ positive plaques, acts as a extracellular chaperones, inhibiting protein aggregation and decreasing amyloid-induced cellular toxicity[2]. Indeed, we put forward the possibility that S100 proteins play protective roles at early AD[3]. We showed that several S100 proteins are also able to delay amyloid aggregation and have a distribution in the brains of AD APP23 mice models similar to that of amyloid plaques[4].

In this proposal we will investigate the extracellular regulation of Tau aggregation, toxicity and cross-interactions with Aβ, combining molecular, biochemical and cellular approaches. For this we will: 1) obtain pure recombinant proteins resorting to bacterial expression systems, protein chromatography and biochemical methods for protein characterisation; 2) Determine effects of chaperones on amyloid aggregation using ThT-fluorescence monitored aggregation assays followed by mechanistic analysis; 3) Investigate seeding effects and proteotoxicity of aggregates formed in different conditions combining cell viability assays in cell models.

All resources (materials and instrumentation) required for this project are available at the host laboratory and at BioISI facilities.

Students selected for this project, after thesis registration, are eligible to apply to the BioISI Junior Programme (supporting 8 students with a 6-month Scholarship(BII), being the selection criterium the academic merit of the candidates.

More information at http://folding.fc.ul.pt/ or via email to cmgomes@fc.ul.pt

References

[1] C. L. Masters et al *Nature reviews. Disease primers* **2015**, *1*, 15056.
[2] J. S. Cristovao et al *Science advances* **2018**, *4*, eaaq1702.
[3] J. S. Cristovao, C. M. Gomes, *Front Neurosci* **2019**, *13*, 463.
[4] S. Hagmeyer et al *Frontiers in Neuroscience* **2019**, *13*.