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Molecular chaperones and Parkinson's disease: exploring the role of clusterin in the dynamic process of alpha-synuclein aggregation

Ileana Ramazzina[1,2,3], L. Chiara[1,4], F. Rizzi[1,2,3]

[1]Department of Medicine and Surgery, University of Parma, Parma, Italy
[2]Centre for Molecular and Translational Oncology (COMT), University of Parma, Parma, Italy
[3]Biostructures and Biosystems National Institute (INBB), Rome, Italy
[4]B-Cell Neoplasia Unit, Division of Experimental Oncology, San Raffaele Scientific Institute, Milan, Italy

Introduction: The integrity of the proteostasis network (PN) is essential to assure cell viability, as its failure leads to abnormal protein aggregation that is associated with different human neurodegenerative disease, e.g. Parkinson's disease (PD). Under proteostasis impairment, α-Synuclein (αSyn) forms toxic aggregates in neurons that represent the hallmarks of PD [1]. Key effectors of PN are molecular chaperones and hence the modulation of their expression represents a compelling PD therapeutic strategy [2]. Clusterin (CLU) is chaperone predominantly expressed in brain and reproductive tissues. At present, the role of CLU has been characterized in relation to Alzheimer's disease [3]. However, its role in PD has not yet been extensively elucidated.

Objective: The focus of the research was to explore the involvement of CLU in the cellular response caused by both αSyn up-regulation and aggregation process.

Methods: We used the SH-SY5Y neuron-like cells overexpressing αSyn, either in absence or in presence of MG132, to induce mild or strong proteostasis impairment. In these experimental models, we performed CLU loss-of-function studies, by using CLU siRNA sequences.

Results: We demonstrated that the overexpression of αSyn causes up-regulation of CLU expression, without affecting Hsp27, Hsp70 and Hsp90 levels, which are the chaperones recognized to be able to counteract αSyn burden. Following MG132 treatment, we showed an increase of CLU levels in the fraction where oligomeric and high molecular weight forms of αSyn were detected. We also provided evidence that CLU down-regulation favors or exacerbates αSyn aggregation. Finally, we found that CLU and αSyn co-localize inside the cell and that the two proteins exhibit a direct molecular interaction.

References

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