TITLE:

Clusterin: a player in alpha-Synuclein aggregation in Parkinson's disease human brain?

Giovanni Zanchi[1], Sara Pizzi[1,2], Alessandra M. Calogero[3], Samanta Mazzetti[3], Tiziana Triggiani[1], Chiara Rolando[1], Corrado Corti[2], Gianni Pezzoli[3], Isabella Russo[4], Graziella Cappelletti[1]

[1]*Department of Biosciences, University of Milan, Milan, Italy*
[2]*Eurac Research, Bolzano, Italy*
[3]*Fondazione Pezzoli per la Malattia di Parkinson, Milan, Italy*
[4] *Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy*

OBJECTIVES:

Clusterin (CLU) is a ubiquitous chaperone, involved in the clearance of misfolded proteins and implicated in neurodegeneration. Focusing on Parkinson's disease (PD), few studies reported a modulatory role of CLU on α-Synuclein (α-Syn) aggregation and clearance. This issue remains controversial and almost nothing is known about the interaction of CLU and α-Syn in human brain. Therefore, this study, performed in PD *post-mortem* human brain, aims to: *i)* analyze whether CLU is differently associated to α-Syn in *Substantia Nigra pars compacta* of patients compared to controls; *ii)* define whether CLU is involved in Lewy body (LB) formation.

METHODS:

Western Blots were performed on frozen *post-mortem* human brain to analyze Triton soluble and insoluble fractions, which contain monomeric and aggregated α-Syn, respectively. Immunofluorescence, Proximity Ligation Assay (PLA), and 3D reconstruction were used to analyze fixed brain slices.

RESULTS:

Biochemical analysis highlighted a positive correlation between CLU and α-Syn levels in all the fractions. Moving to fixed brain slices, no differences between controls and patients were observed in the co-localization of CLU with α-Syn. However, PLA analysis in different subcellular compartments revealed higher association between CLU and α-Syn in the somata showing α-Syn pathology. Interestingly, 100% of midbrain LBs were positive for CLU. Moreover, we evaluated how the distribution and association of CLU with α-Syn change during the LBs maturation process previously proposed in a model by our laboratory.

CONCLUSIONS:

Our findings strongly suggest CLU as a possible player in LB formation, paving the way to mechanistic studies aimed at unravelling the role of CLU in the modulation of α-Syn aggregation. This could place CLU as a promising target for a mechanism-based therapeutic strategy.

This work was supported by "The Michael J. Fox Foundation for Parkinson's disease", and by "Fondazione Pezzoli per la Malattia di Parkinson" (Italian "5 x 1000" funding).