Saturday, 16/Sept/2023 5:40pm - 6:00pm
ID: 885 / Symposium 9_1: 3
Symposium Speaker's Abstract Submission
Symposium Title: Misfolded Proteins and Mechanisms of Neurodegeneration (ID 568 - Carlo Ferrarese)

TDP-43 proteinopathies: the role of extracellular vesicles

Elena Casarotto[1], Letizia Messa[2], Marta Chierichetti[1], Laura Cornaggia[1], Marta Cozzi[1], Riccardo Cristofani[1], Veronica Ferrari[1], Mariarita Galbiati[1], Guglielmo Patelli[1], Margherita Piccolella[1], Paola Pramaggiore[1], Paola Rusmini[1], Barbara Tedesco[1], Stella Gagliardi[3], Stephana Carelli[2], Cristina Cereda[4], Angelo Poletti[1], Valeria Crippa[1]

[1]Dipartimento di Scienze Farmacologiche e Biomolecolari (DiSFeB), Department of Excellence 2023-2027, Università degli Studi di Milano, via Balzaretti 9, 20133 Milano (MI), Italy; [2]Centro di Ricerca Pediatrica "Romeo ed Enrica Invernizzi", Dipartimento di Scienze Biomediche e Cliniche "L. Sacco", Università degli Studi di Milano, via G.B. Grassi 74, 20157 Milano (MI), Italy; [3]Molecular Biology and Transcriptomics Unit, IRCCS Mondino Foundation, via Mondino 2, 27100 Pavia (PV), Italy; [4]UOC Screening Neonatale e Malattie Metaboliche, Dipartimento della Donna, della Mamma, del Neonato, ASST Fatebenefratelli Sacco - Ospedale dei Bambini "V. Buzzi", via Castelvetro 24, Milano (MI), Italy

TDP-43 proteinopathies are a group of diseases in which affected cells are characterized by an abnormal cytoplasmic deposits of the TAR DNA-binding protein of 43 kDa (TDP-43). These include amyotrophic lateral sclerosis (ALS), frontotemporal lobar degeneration (FTLD), Alzheimer's disease (AD), Parkinson's disease (PD), primary lateral sclerosis (PLS), progressive muscular atrophy (PMA) and inclusion body myopathy (IBM). In these diseases, TDP-43 undergoes a series of post-translational modifications (i.e. hyper phosphorylation, polyubiquitination and cleavage), resulting in abnormal TDP-43 fragmentation, localization and aggregation. TDP-43 aggregates exert toxicity by both loss and gain of function mechanisms, while their clearance is protective for cells. Soluble and aggregated TDP-43 are cleared primarily by the ubiquitin-proteasome system (UPS) and the autophagy–lysosome pathway (ALP) assisted by chaperones and co-chaperones proteins, respectively. Both UPS and ALP are impaired in TDP-43 proteinopathies, further worsening TDP-43 aggregation. Recently, it has been observed that cells can also release TDP-43 and its disease-associated species as free-proteins or incorporated into lipid bilayer-delimited particles, called extracellular vesicles (EVs). Since EVs can move through biological fluids, transport and release their content (i.e. proteins, RNAs and lipids) to other cells, we studied how and whether the impairment of cellular clearance systems may affect EVs compositions. In immortalized neuronal cells, we found that the secretion of disease-associated TDP-43 species into EVs is boosted when UPS, ALP or chaperones are impaired. Moreover, we observed that, under UPS or ALP blockage, EVs miRNAs cargo is different from that of physiologically secreted EVs. In particular, we identified commonly deregulated miRNA between UPS and ALP EVs, a number of which targets the prion disease pathway. These EVs were toxic to recipient cells.

Collectively our data suggest that EVs released in pathological condition can contribute to the spreading of TDP-43 disease via both proteins and miRNAs transport.

GRANTS: PRIN2020 nr.2020PBS5MJ