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Biomarkers and related therapeutics of ALS/FTD

Andrea Malaspina
Queen Mary University of London, England

The search for molecular signals of disease initiation and progression in amyotrophic lateral sclerosis/frontotemporal dementia (ALS/FTD) has accelerated in the last few years as this is a point of vital importance in the choice of new therapeutic strategies. Optimal biomarkers have to be tested by point of care diagnostics to provide sensitive measurements of disease burden in accessible biofluids. The clinical stratification of ALS/FTD based on the biofluid expression of neurofilaments (NF), one of the main constituent of the axonal structure, has been a game changing event in this area of research. The characterization of the longitudinal NF expression has allowed the identification in pre-symptomatic mutation carriers of a phase of phenoconversion whereby ALS manifests in largely asymptomatic patients, opening the way for early therapeutic intervention. Additionally, the study of NF in ex vivo tissues from affected individuals has uncovered other important phenomena: the humoral response to the release of NF could be a biomarker in itself and immunocomplexes may have a toxic effect on axons and cells thus propagating the disease process. Similarly to the formation of brain insoluble protein aggregates, NF are found in membrane-less protein hetero-aggregates in circulation which appear to have a different sensitivity to the effect of proteases and may also represent vehicles of disease propagation. The study of the pathogenic role of NF and of their stoichiometry in the progression of a malignant neurodegenerative disorder like ALS may therefore provide a glance into novel treatment strategies for neurodegeneration, based on disaggregation and on the modulation of the adaptive immune responses.

a.malapina@qmul.ac.uk

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