TOPIC: Alzheimer’s disease co-pathologies

AFFILIATION: Department of Pharmacological and Biomolecular Sciences "Rodolfo Paoletti," Università degli Studi di Milano, Via Giuseppe Balzaretti 9, 20133 Milan, Italy.

AUTHORS: Federica Gorla, Ramona Stringhi, Andrea Pilotto, Caterina Martinuzzo, Chiara Tolassi, Alessandro Padovani, Monica Di Luca, Silvia Pelucchi, Elena Marcello

TITLE (25wordsMax): **Modeling Alzheimer’s disease co-pathology using patient-derived induced neurons**

ABSTRACT (300wordsMax):

Dementia diagnosis and treatment are challenged by marked clinical heterogeneity and the frequent co-existence of multiple pathologies. Alzheimer’s disease (AD), defined by amyloid-β and tau aggregation, often overlaps with α-synucleinopathies, such as Dementia with Lewy Bodies (DLB). Notably, up to 30% of AD patients exhibit concomitant α-synuclein pathology, complicating diagnosis and potentially reducing treatment efficacy (Pilotto A, et al., Alzheimer's Dement. 2023). Despite its clinical relevance, the biological mechanisms driving the onset and progression of these co-pathologies remain poorly understood, largely due to the lack of experimental models that faithfully recapitulate their complexity. Here, we took advantage of patient-specific induced neuron (iN) model to investigate α-synuclein co-pathology in sporadic AD (Mertens J, et al., Cell Stem Cell. 2015). Fibroblasts obtained from individuals with AD, AD with α-synuclein pathology, DLB (as a model of primary α-synucleinopathies), and age-matched healthy controls obtained in collaboration with University of Brescia, are directly converted into glutamatergic iNs. The iNs system preserves key aspects of donor-specific cellular identity, including aging. Neuronal populations are purified by PSA-NCAM-based fluorescence-activated cell sorting (FACS), enabling the analysis of homogeneous and well-characterized neuronal cultures. Here, we present the initial characterization of purified iNs derived from the different groups. This includes imaging-based approaches to assess neuronal purity following sorting, immunostaining for glutamatergic markers, and RNA-based profiling to validate neuronal identity. This platform enables the investigation of molecular and cellular pathways underlying selective neuronal vulnerability associated with aging and neurodegeneration, with a particular focus on mechanisms influenced by α-synuclein co-aggregation. By comparing disease groups, we aim to identify both distinct and shared biological signatures associated with AD, α-synucleinopathies, and their co-occurrence.