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Journal
Biophysical Journal, 106(2)

ISSN
0006-3495

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Publication Date
2014

DOI
10.1016/j.bpj.2013.11.392

308-Pos Board B63

NADH is an Endogenous Reporter for Alpha-Synuclein Aggregation in Live Cells

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Alpha-synuclein aggregation is amply investigated for its involvement in Parkinson's disease etiopathogenesis. It has been shown that alpha-synuclein monomers, under pathological conditions, self-assembly to form oligomeric species that further aggregate into amyloid fibrils. Alpha-synuclein fibrils are the main constituent of Lewy Bodies, which are one of the characteristic hallmarks of Parkinson's disease.

Alpha-synuclein aggregation is studied in vitro and in cellular models with the aim to correlate toxicity mechanisms to defined aggregation products. However, the characterization of the aggregation process in cells is a difficult task that typically needs cell lysis or fixation, or the use of exogenous dyes.

Moreover, several different toxic mechanisms were ascribed to alpha-synuclein aggregates, i.e. clearance mechanisms impairment, mitochondrial dysfunctions, oxidative stress, neuroinflammation. In particular, mitochondria seem to be a target for alpha-synuclein to exert its toxicity. Several independent results suggested that alpha-synuclein overexpression and/or aggregation may cause impairment of cellular metabolism due to mitochondrial fragmentation and complex I dysfunction.

On these premises, we report here the results obtained from the characterization of NADH fluorescence properties variation in vitro and in cell models during alpha-synuclein aggregation.

The application of the phasor approach for the study of NADH fluorescence lifetime and spectra allowed the determination of specific variation in the NADH fluorescence properties correlated to alpha-synuclein oligomerization and amyloid fibrils formation in vitro and in live cells.

The results presented here suggest that alpha-synuclein aggregation may be associated to impairment in cell metabolism due to damage to complex I in mitochondria and disruption of NADH and NAD^+ equilibrium. Moreover, NADH can be used as an endogenous fluorescence reporter for alpha-synuclein aggregation in vitro and in cellular models.

(Work supported in part by NIH grants P50 GM076516 and P41 GM103540, and by Aldo Gini Foundation.)