Journal of Advanced Research 23 (2020) 37–45

Contents lists available at ScienceDirect

Journal of Advanced Research

journal homepage: www.elsevier.com/locate/jare

Overexpression of alpha-synuclein promotes both cell proliferation and cell toxicity in human SH-SY5Y neuroblastoma cells

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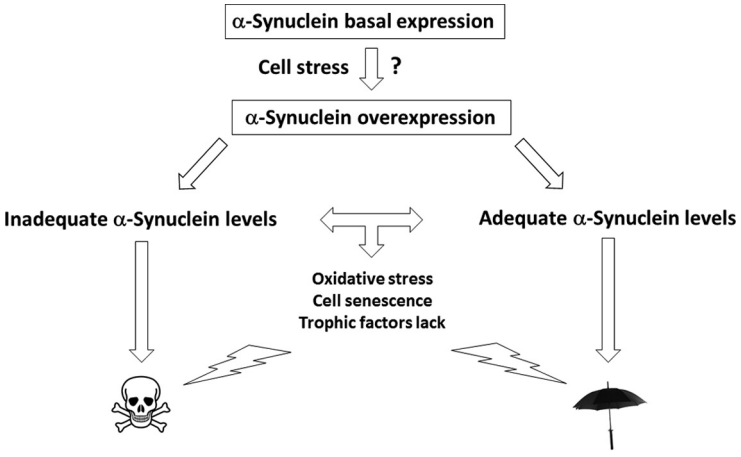
HIGHLIGHTS

- α-Synuclein (αS) is a synaptic protein up-regulated in Parkinson's disease.
- SH-SY5Y neuroblastoma cells were engineered to overexpress αS at low and high levels.
- High-αS overexpression stimulates cell proliferation and delay senescence.
- Low-αS overexpression causes toxicity, oxidative stress, and accelerates senescence.
- A fine-tuned up-regulation of αS is critical for neuronal maintenance and survival.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 4 August 2019
Revised 14 January 2020
Accepted 20 January 2020
Available online 22 January 2020

Keywords:
Alpha-synuclein
SH-SY5Y cells
Rotenone
Graphene oxide
Parkinson's disease
Cell senescence

ABSTRACT

Alpha-Synuclein (aSyn) is a chameleon-like protein. Its overexpression and intracellular deposition defines neurodegenerative α-synucleinopathies including Parkinson's disease. Whether aSyn up-regulation is the cause or the protective reaction to α-synucleinopathies remains unresolved. Remarkably, the accumulation of aSyn is involved in cancer. Here, the neuroblastoma SH-SY5Y cell line was genetically engineered to overexpress aSyn at low and at high levels. aSyn cytotoxicity was assessed by the MTT and vital-dye exclusion methods, observed at the beginning of the sub-culture of low-aSyn overexpressing neurons when cells can barely proliferate exponentially. Conversely, high-aSyn overexpressing cultures grew at high rates while showing enhanced colony formation compared to low-aSyn neurons. Cytotoxicity of aSyn overexpression was indirectly revealed by the addition of pro-oxidant rotenone. Pretreatment with partially reduced graphene oxide, an apoptotic agent, increased toxicity of rotenone in low-aSyn neurons, but, it did not in high-aSyn neurons. Consistent with their enhanced

Peer review under responsibility of Cairo University.

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[1] These authors contributed equally.

[2] **In memoriam:** This article is dedicated to the memory of José A. Aguirre PhD, coauthor of this work, and above all friend, who passed away.

https://doi.org/10.1016/j.jare.2020.01.009
2090-1232/