Implications for alpha-synuclein antisense transcript SNCA-AS1 in Parkinson's Disease: role in synaptogenesis and aging-related pathways

Federica Rey[1,2], Cecilia Pandini[3,4], Letizia Messa[5], Rossella Launi[1,2], Roberta Zangaglia[6], Gian Vincenzo Zuccotti[1,2,7], Stella Gagliardi[3], Cristina Cereda[3§] & Stephana Carelli[1,2,§]

[1]Department of Biomedical and Clinical Sciences "L. Sacco", University of Milan, 20157 Milan, Italy.

[2]Pediatric Research Center "Romeo ed Enrica Invernizzi", University of Milano, 20157 Milano, Italy.

[3]Genomic and post-Genomic Center, IRCCS Mondino Foundation, 27100 Pavia, Italy.

[4]Department of Biology and Biotechnology "L. Spallanzani", University of Pavia, 27100 Pavia, Italy.

[5]Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Milano, Italy.

[6]Parkinson's Disease and Movement Disorders Unit, IRCCS Mondino Foundation, Via Mondino 2, 27100, Pavia, Italy.

[7]Department of Pediatrics, Children's Hospital "V. Buzzi", Via Lodovico Castelvetro 32, 20154 Milano, Italy

§ These authors equally contributed to this work

Abstract

SNCA protein product, alpha-synuclein, is widely renowned for its role in synaptogenesis and implication in both aging and Parkinson's Disease, but research efforts are still needed to elucidate its physiological functions and regulation. In this work, we aim to characterize the long non-coding RNA SNCA-AS1, antisense transcript to the SNCA gene, and its implications in cellular processes. SH-SY5Y cells were stably transfected with either SNCA-AS1 or SNCA and through RNA-sequencing we assessed their transcriptional signature. Real Time-PCR and western blot were also used to verify SNCA-AS1's effect on SNCA's expression, and neurite extension was assessed via immunofluorescence analysis. The overexpression of SNCA-AS1 upregulates SNCA mRNA and protein, and both genes appear to strongly impact neurite extension and synapses' biology, through specific molecular signatures. We found a reduced expression of markers associated with synaptic plasticity, and we specifically focus on GABAergic and dopaminergic synapses, for their relevance in aging processes and PD, respectively. As part of this signature is co-regulated by the two genes, we discriminate between functions elicited by genes specifically altered by SNCA-AS1 or SNCA's overexpression, and we observed a highly relevant role for solely SNCA-AS1. We also highlight how numerous deregulated pathways are implicated in aging-related processes, suggesting that SNCA-AS1 could be a key player in cellular senescence, with implications for aging-related diseases. Specifically, the upregulation of SNCA-AS1 leads to alterations in numerous PD specific genes, with an impact highly comparable to that of SNCA. SNCA/SNCA-AS1 ratio is also significantly altered in PBMCs from PD patients versus healthy controls. Our results show that SNCA-AS1 elicits its cellular functions not only through the regulation of SNCA, but also through a selective and specific modulation of synaptogenesis and senescence, with strong implications for PD.