New insights into Parkinson's disease pathogenesis from the study of the synaptic alpha-synuclein proteome

A. Bellucci [1], M. Zaltieri [1], J. Grigoletto [1], L. Navarria [1], S. Castrezzati [2], R. Rezzani [2], A. Colivicchi [3],L. DellaCorte [3], M.G. Spillantini [4], C. Missale [1] and P. Spano [1,5]

[1] *Dept. Molecular and Translational Medicine, University of Brescia, Brescia, Italy;*

[2] *Dept. of Clinical and Experimental Sciences, University of Brescia, Italy;*

[3] *Dept.NEUROFARBA, University of Florence, Florence, Italy;*

[4] *Dept. Neuroscience and Cambridge Centre for Brain Repair, University of Cambridge, Cambridge, United Kingdom;*

[5] *IRCCS San Camillo, Venice, Italy.*

The neuropathological hallmarks of Parkinson's disease (PD) are the loss of nigro-striatal dopamine (DA) neurons and the presence of intraneuronal inclusions named Lewy bodies (LB). Alpha-synuclein (AS), the main component of LB, is crucially implicated in the regulation of synaptic physiology in dopaminergic neurons (Lundblad et al., 2012; Bellucci et al., 2012). AS interacts with- and modulates the expression, subcellular distribution and activity of numerous synaptic proteins as well as cytosheletal components, acting as a pre-synaptic modulator of striatal DA release. For instance, its accumulation and aggregation coincides with the onset of a marked redistribution of the synaptic proteins which are important for the control of DA synaptic release such as the DA transporter (DAT) and soluble N-ethylmaleimide-sensitive factor attachment receptor (SNARE) proteins (Bellucci et al., 2011; Garcia-Reibock et al., 2010). AS null mice show a decrease of DAT expression as well as a concomitant decrease of DA reuptake in the striatum (Chadchankar et al., 2011). In addition, studies in AS transgenic mice have shown that its overabundance in the nigrostriatal system leads to decreased vesicle density and reduced DA release correlating with the onset of motor deficits (Gaugler et al., 2012). Of note, AS shares numerous biochemical and functional similarities with synapsins, neuron-specific phosphoproteins controlling multiple steps of the synaptic vesicle life cycle and nerve terminal development. Synapsins modulate neurotransmitter release by participating to synaptic vesicle docking, fusion and recycling (Cesca et al., 2010). Likewise synapsins, AS can interact with synaptic vesicles and with actin filaments (Cesca et al., 2010,; Bellucci et al. 2012). In addition, AS and synapsin I are both members of the DAT proteome (Maiya et al., 2007) and both AS and synapsin III negatively regulate striatal DA release (Kile et al., 2010). We thus hypothesized that a reciprocal modulatory interaction between the AS, the DAT and synapsins, in particular synapsin I and III, may occur in DA terminals. We found that the expression and distribution of DAT and synapsin III in neuronal cells lacking AS was similar to that observed in primary dopaminergic mesencephalic neurons exposed to AS pro-aggregating insults. Overexpression of truncated 1-120 pathological AS altered the distribution of DAT, synapsin I and synapsin III. The expression and distribution of DAT and synapsin III in developing and mature striatal dopaminergic terminals were significantly changed in AS-null mice with respect of control mice. These changes were accompanied by significant alterations in synaptic vesicle pool arrangements as observed by electron microscopy. Consistently, AS null mice showed significant differences in basal and K^+-stimulated DA release as observed by microdialysis. These functional differences were paralleled by age-related divergences in the locomotor responses to the administration of cocaine and GBR-12935. Collectively, these findings indicate that AS controls dopaminergic synapse function by modulating DAT and synapsin III expression and distribution both during embryonic and postnatal development and adulthood. Furthermore, AS overexpression and aggregation can alter synapsin III and DAT expression and distribution thus suggesting that specific alterations of these proteins may occur in the early stages of PD when AS aggregation likely coincides with a loss of function of the protein.

References

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