The formation of carboxymethyl lysine and carboxyethyl lysine modify the protective capacity of alpha-synuclein on the reactive oxygen species and free radical formation

P01-24

H. Martinez-Orozco[I], M. Adrover[I], B. Vilanova[I]

[I]Universitat de les Illes Balears, Palma de Mallorca, Spain

α-Synuclein (α-syn) is a nuclear and synaptic intrinsically disordered protein.[1] In Parkinson's disease, it tends to aggregate by forming intracellular Lewy bodies,[2] which finally induce the neuronal death.[3] Several hypotheses have been proposed to explain the toxicity of α-syn aggregates. Among them, it can be highlighted their capacity to induce the formation of reactive oxygen species (ROS) and free radicals under the presence of free metal ions.[4] However, this does not result from a direct ROS-active form of the α-syn since *in vitro* studies have proven that α-syn is able to chelate Cu^{2+} and decrease the formation of ROS by radical scavenging and redox silencing.[5]

These results raise now the question whether chemical modifications (such as those associated to the non-ezymatic glycation) would affect the α-syn redox silencing capacity. Therefore, we have modified the fifteen Lys side chains in α-syn to finally have carboxymethyl lysine (CML) or carboxyethyl lysine (CEL). These modified α-syn have been used to study how the modifications influence the α-syn capacity to bind Cu^{2+}, to scavenger $OH\cdot$ and $O_2^{\cdot -}$ radicals, or to inhibit their formation. Overall, the obtained results reveal that CEL and CML reduce the redox silencing capacity of α-syn, and support the suggestions about the contribution of these post-translational modifications on the high oxidative stress observed inside of neurons in Parkinson's disease.

1. Maroteaux, L., Campanelli, J. T. & Scheller, R. H. *J. Neurosci.* 8, 2804–15 (1988)
2. Spillantini, M. G. *et al. Nature* 388, 839–40 (1997)
3. Stefanis, L. *Cold Spring Harb. Perspect. Med.* 2, a009399 (2012)
4. Deas, E. *et al. Antioxid Redox Signal. 24,* 376–391 (2016)
5. Pedersen, J. T. *et al. J. Am. Chem. Soc.* 138, 3966–9 (2016)