DNA DAMAGE, P53 ACTIVATION AND APOPTOSIS IN A CELLULAR MODEL OF AMYOTROPHIC LATERAL SCLEROSIS

Barbosa, L.F.[1]; Cerqueira, F.M.[1]; Macedo, A.[1]; Sogayar, M.C.[1]; Augusto, O.[1]; Carrì, M.T.[2]; Di Mascio, P.[1]; Medeiros, M.H.G.[1].
[1]Departamento de Bioquímica, Instituto de Química, Universidade de São Paulo, São Paulo, Brazil. [2]Dept. of Biology, University of Rome "Tor Vergata", Italy.

Mutations of citosolic Cu,Zn-Superoxide Dismutase (SOD) have been linked to familial amyotrophic lateral sclerosis (FALS) leading to an as yet poorly understood gain of a “toxic function”. It has been suggested that FALS-mutant SOD induces motor neuron apoptosis. Oxidative damage in DNA and p53 upregulation have been detected in ALS neuronal tissues. We examined DNA damage (8-oxodGuo, 1,N^2-?dGuo and strand breaks), p53 activity and apoptosis in SH-SY5Y human neuroblastoma cells transfected with wild-type SOD (SOD-WT) and a mutant SOD (SOD-G93A) typical of FALS. Significantly increased levels of DNA damage (3-fold), increased p53 activity (3-fold) and a higher level of apoptosis (6-fold) were observed in SH-SY5Y cells transfected with SOD-G93A, while SOD-WT promoted protection, when compared to parental cells. Western blot analysis showed that SOD-G93A accumulates in the nucleus and is associated to the DNA to a greater extend than SOD-WT. These results indicate that this mutant SOD has a pro-oxidative and pro-apoptotic activity. Mutant SOD accumulation in the nucleus and its association to DNA may induce damage and trigger apoptosis by p53 activation.

Acknowledgements: FAPESP, CNPq, FINEP, Instituto do Milênio Redoxoma, USP.

Keywords: DNA damage, Cu,Zn-SOD and ALS.