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Identification of a new ubiquitin-ligase independent role of parkin as a transcription factor in Parkinson's disease

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Parkinson's disease (PD) is a major of age-related neurodegenerescence in human beings. Even though its etiology is mainly sporadic, a subset of genetic cases characterized by early onset and exacerbated loss of dopaminergic neurons of the substantia nigra pars compacta has been identified. Parkin is responsible for most of the autosomal recessive cases of PD. The main function of this protein appeared to be related to its ubiquitin-ligase enzymatic activity and several lines of evidence supported that impairment of this function could contribute to the pathology.

Interestingly several evidences suggested a putative role of parkin as a transcription factor. Thus, parkin localizes in the nucleus, control of several genes in stress conditions and harbors a Ring-IBR-Ring structure that predicts possible transcription factor properties. Based on these arguments we have documented a novel function of parkin as a transcription factor capable of transrepressing p53. We have demonstrated that parkin reduces p53 promoter transactivation, mRNA and protein levels. The parkin-associated function was fully prevented by p53 depletion. We have described a physical interaction between parkin and the p53 promoter by both gel shift and chromatin immunoprecipitation assays and we established that parkin binds to p53 promoter via its Ring1 domain. Importantly, the influence of parkin on p53 was also observed in PD-affected brains. Interestingly, parkin-associated repression of p53 promoter transactivation was prevented by all familial mutations studied in our work, independently of their ability to abolish or preserve parkin ubiquitin-ligase activity. This data pinpoints the fact that some functions harbored by parkin may be independent of its canonic ubiquitin-ligase activity.

Biography

Cristine Alves da Costa has completed her Ph.D from Sao Paulo University (USP), Brazil, and postdoctoral studies from "Institut de Pharmacologie Moléculaire et Cellulaire", IPMC-CNRS, France. She is a senior director of research at INSERM, a governmental research organization. He has published more than 50 papers in reputed journals and serving as an editorial board member of several journals including Parkinson's disease, Current Neuropharmacology and Clinical Medicine: Geriatrics.

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