Parkin transcription factor function in Parkinson's disease

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Résumé

Since its identification as a gene product involved in Parkinson's disease (PD) Parkin's has been characterized as an E3 Ubiquitin ligase ubiquitinating many substrates in the cytoplasm. When PK is mutated, or epigenetically modified, it no longer ubiquitinates its substrates that accumulates contributing to a stress leading to cell death, mainly by apoptosis. Interestingly, PK is also present in the nucleus, has a RING domain that suggests a DNA binding capacity and some works suggest that PK could regulate the expression of genes independently of its ligase function. While investigating PK involvement in apoptosis, we found that PK acts as a genuine transcription factor that directly binds to the promoter of the proapoptotic factor p53 and down regulates its transcription. We show that PK transcriptional activity directly regulates Presenilin 1 and 2 levels and thus impacts on γ-secretase activity. Consequently PK controls both β-Amyloid and AICD production and apoptotic processes. Moreover, via its transcriptional activity, Parkin regulates either directly or indirectly, gene products associated to Parkinson's and/or Alzheimer's disease, like DJ-1 and PINK1. In conclusion, PK is not only an E3-ligase but also a transcription factor, and we have to take into account these two functions of PK and its epigenetic regulation to better understand PK involvement is physiological processes and in neurodegenerative diseases.

Mots-Clés: Parkinson's disease, parkin transcription factor

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