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Parkin isoforms expression in gliomas

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Parkin (PARK2) is one of the largest genes in the human genome encoding for an E3 ubiquitin ligase. Its mutation is the cause of early-onset Parkinson's disease, but recently it is linked to other pathologies including cancer. Parkin acts as a tumor suppressor. It displays a wide neuroprotective activity by promoting the removal of damaged mitochondria via mitophagy and increasing proteasomal degradation of toxic substrates. PARK2 primary transcript undergoes to an extensive alternative splicing, which enhances transcriptomic diversification and protein diversity in tissues and cells. To date, GenBank lists 26 human PARK2 transcripts corresponding to 21 different alternative splice variants. These transcripts show different expression patterns and encode for proteins with different functions, molecular weight and isoelectric point. Previous studies identified inactivating somatic mutations and frequent intragenic deletions of PARK2 in human cancers including gliomas (Veeriah et al., 2010). Recently, it has been demonstrated that Parkin pathway activation is predictive for the survival outcome of patients with glioma (Yeo et al., 2012).

However, these papers focused on the expression of full length Parkin. In the present work we analyzed the expression pattern of Parkin isoforms in astrocytomas of different grade and we investigated their functions in a human glioblastoma multiforme cell line. Immunoblotting analysis by using two specific antibodies revealed that Parkin expression is generally higher in malignant glioblastoma than in less invasive astrocytomas, indicating a correlation between expression pattern of Parkin isoforms and tumor malignancy. Serum deprivation or treatment with a proteosome inhibitor MG132 or with carbonyl cyanide 3-chlorophenylhydrazone (CCCP), an uncoupling agent that dissipates the cells mitochondrial membrane potential, increased expression of 100-55-50 kDa parkin isoforms in glioma cells as compared to controls. These results, consistent with other studies, demonstrated a functional connection between Parkin expression, mitochondrial integrity and endoplasmic reticulum stress (Bouman et al., 2011). Parkin isoforms expression was also confirmed by confocal microscopy analysis. These results suggest that the characterization of some PARK2 isoforms may be usefull clinically to develop a prognostic tool in patients with brain tumor.

References

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Keywords

Parkin isoforms, glioma, tumor suppressor, mitophagy, proteasomal degradation.