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The kinase HIPK2 regulates spastin protein: Implications in hereditary spastic paraplegia

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The alteration of axonal-transport is an early and causal event in many neurodegenerative diseases (ND). Among the mechanisms contributing to axonal-transport defects, the loss of microtubules dynamism is one of the key mechanisms. Spastin is a microtubule severing protein involved in cytokinesis and in axonal-transport. Mutations in *SPG4* gene encoding spastin are found in patients with hereditary spastic paraplegia (HSP), an autosomal dominant ND. Recently, it has been shown that to increase spastin levels rescues the pathological phenotypes in HSP-patient-derived cells suggesting that intervening to modulate spastin levels may be a valid therapeutic strategy in ND characterized by spastin misregulation. We found that spastin is regulated by the kinase HIPK2 in neural compartment. HIPK2 depletion leads to spastin down regulation in a proteasome-dependent manner and impairs axonal-transport. Wild-type-HIPK2 overexpression, but not kinase-defective-HIPK2, increases spastin levels and rescues axonal transport defects in spastin-deficient motor neurons. Mechanistically, we showed that HIPK2 phosphorylates spastin at S268. This phosphorylation stabilizes spastin and prevents its polyubiquitination and proteasome degradation. These results, in addition to expanding our understanding of the HIPK2/spastin axis in neural compartment, might provide the basis for the development of a new therapeutic approach to treat HSP.

Recent Publications

1. V Colicchia, M Petroni, G Guarguaglini, F Sardina, M Sahun Roncero, M Carbonari, B Ricci, C Heil, C Capalbo, F Belardinilli, A Coppa, G Peruzzi, I Screpanti, P Lavia, A Gulino and G Giannini (2017) PARP inhibitors enhance replication stress and cause mitotic catastrophe in MYCN-dependent neuroblastoma. Oncogene 36:4682-4691.
2. M Petroni, F Sardina, C Heil, M Sahún-Roncero, V Colicchia, V Veschi , S Albini, D Fruci, B Ricci, A Soriani, L Di Marcotullio, I Screpanti, A Gulino and G Giannini (2016) The MRN complex is transcriptionally regulated by MYCN during neural cell proliferation to control replication stress. Cell Death Differ. 23(2):197-206.

Biography

Francesca Sardina is interested in the study of DNA damage response during neuronal development and carcinogenesis. In this last years, she started to characterize the role of HIPK2, a kinase controlling DNA damage and cytokinesis, in the regulation of spastin protein closely involved in Hereditary spastic paraplegia, a neurodegenerative disease. Her studies could open the way to develop new and innovative therapeutic approaches in the field of neurodegenerative diseases.

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