Poster Presentation

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Deciphering the activation of the E3 ubiquitin ligase parkin

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Parkin is an E3 ubiquitin ligase responsible for some autosomal recessive forms of Parkinson's disease. Even though parkin is a RING-type E3 ligase, it uses a hybrid RING/HECT mechanism for its activity. The crystal structures of full-length and the RING0-RING1-In-Between-RING-RING2 module of parkin reveal a conformation of parkin in which its E2 binding site is too far from its catalytic cysteine for the transfer of ubiquitin [1]. Many intramolecular interactions occur between the different RING domains, as well as with a repressor element, which, with RING0, are unique to parkin. Mutations of residues involved in those interactions lead to an increase of parkin activity. This suggests that parkin adopts an auto-inhibited state in basal conditions. Therefore, under stress-response conditions, parkin needs to undergo molecular rearrangements, modulated by post-translational modification and/or interactions with other proteins, to become active. The phosphorylation of serine 65 in the Ubl domain of parkin by Pink1, a kinase also found mutated in some Parkinson's patient, was shown to increase the activity of parkin. Recent publications have demonstrated that ubiquitin is also phosphorylated by Pink1 and, furthermore, that phosphorylated ubiquitin could activate parkin [2,3]. We have used different techniques of structural biology and protein-protein interactions to further characterize the interaction of phosphorylated ubiquitin with parkin. This work provides insight into the mechanism of activation of parkin and that causes Parkinson's disease.

[1] *J-F. Trempe, V. Sauvé, K. Grenier, et al, Science, 2013, 340, 1451-1455.,* ***[2]*** *L.A. Kane, M. Lazarou, A.I. Fogel, et al, J. Cell Biol., 2014, 205,143-153.,* ***[3]*** *F. Koyano, K. Okatsu, H. Kosako, et al, Nature, 2014, doi:10.1038/nature13392.*

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