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Proteasome lid bridges mitochondrial stress with Cdc53/Cullin1 NEDDylation status

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Abstract:

Cycles of Cdc53/Cullin1 rubylation (a.k.a. NEDDylation) protect ubiquitin-E3 SCF (Skp1-Cullin1-F-box protein) complexes from self-destruction and play an important role in mediating the ubiquitination of key protein substrates involved in cell cycle progression, development, and survival. Cul1 rubylation is balanced by the COP9 signalosome (CSN), a multi-subunit derubylase that shows 1:1 paralogy to the 26S proteasome lid. The turnover of SCF substrates and their relevance to various diseases is well studied, yet, the extent by which environmental perturbations influence Cul1 rubylation/derubylation cycles *per se* is still unclear. In this study, we show that the level of cellular oxidation serves as molecular switch, determining Cullin1 rubylation/derubylation ratio. We describe a mutant of the proteasome lid subunit, Rpn11 that exhibits accumulated levels of Cullin1-Rub1 conjugates, a characteristic phenotype of *csn* mutants. By dissecting between distinct phenotypes of *rpn11* mutants, proteasome and mitochondria dysfunction, we were able to recognize the high reactive oxygen species (ROS) production during the transition of cells into mitochondrial respiration, as a checkpoint of Cullin1 rubylation in a reversible manner. Thus, the study adds the rubylation to the list of cellular pathways regulated by redox homeostasis.

Keywords: 26S proteasome, mitochondria, NEDD8/Rub1, Rpn11, thiol switch, ubiquitin