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Deubiquitinase USP35 Regulates Mitosis Progression by Blocking CDH1-Mediated Degradation of Aurora B.

Authors : Jinyoung Park, Eun Joo Song

Abstract : Introduction: Deubiquitinating enzymes (DUBs) are proteases that cleave ubiquitin or ubiquitin-like modifications on substrates. Deubiquitination could regulate cellular physiology, such as signal transduction, DNA damage and repair, and cell cycle progression. Although more than 100 DUBs are encoded in the human and the importance of DUBs has been realized, the functions of most DUBs are unknown. This study aims to identify the molecular mechanism by which deubiquitinating enzyme USP35 regulates cell cycle progression for the first time. Methods: USP35 RNAi was mainly used to identify the function of USP35 in cell cycle progression. To find substrates of USP35, we analyzed protein-protein interaction using LC-MS. Several biological methods, such as ubiquitination assay, cell synchronization, immunofluorescence, and immunoprecipitation assay were used to investigate the exact mechanism by which USP35 affects successful completion of mitosis. Results: USP35 knockdown caused not only reduction of mitotic cell number but also induction of mitotic cells with abnormal spindle formation. Actually, cell proliferation was decreased by USP35 knockdown. Interestingly, we found that loss of USP35 decreased the stability and expression of Aurora B, a member of chromosomal passenger complex (CPC), and the phosphorylation of its substrate. Indeed, USP35 interacted with Aurora B and deubiquitinated it. In addition, USP35 knockdown induced abnormal localization of Aurora B in mitotic cells. Finally, CDH1-mediated ubiquitination of Aurora B level was rescued by USP35 overexpression, but not inactive form of USP35, USP35 C450A. Discussion: Our findings suggest that USP35 regulates Aurora B-mediated mitotic spindle assembly and G2-M transition by blocking CDH1-induced degradation of Aurora B.

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