

## ABSTRACT (ENGLISH)

Ubiquitin signaling is a key regulatory mechanism for many important cellular processes such as transcription, differentiation and cell division. Cell division requires duplication of all genetic material during S-phase followed by its precise partitioning between two daughter cells during mitosis. Misregulation of the complex mitotic machinery may lead to aneuploidy and genomic instability, known drivers of tumorigenesis. Indeed, systematic genetic analysis of many cancer tissues over the last decades, indicates the presence of severe chromosome abnormalities in thousands of cancer tissue samples. In this work, I investigated the function of two components of ubiquitin signaling, the deubiquitinating enzyme UCHL3 and the E3 ubiquitin ligase TRIM15. The hypothesized role of E3 ligase TRIM15 in the cell cycle regulation could not be confirmed by our experiments, but I observed an effect on cell adhesion and motility instead. UCHL3 was identified using high-content visual siRNA screen, as a critical factor controlling genome segregation and integrity. Interestingly, it has been previously reported that UCHL3 levels are altered in various cancer types, especially colon cancer. My data demonstrate that UCHL3 drives proper alignment of chromosomes at the metaphase plate by facilitating congression of polar chromosomes and by regulating recruitment of key kinetochore components necessary for formation of stable microtubule attachments. Depletion of UCHL3 leads to chromosome misalignment as well as defective kinetochore-microtubule attachments often leading to severe segregation errors such as lagging chromosomes. Using an unbiased proteomic approach, we identified a potential interactor and mediator of these phenotypes, the Aurora B kinase. I confirmed that UCHL3 interacts with Aurora B and I show that UCHL3 removes the non-proteolytic ubiquitin modifications of Aurora B. Since aneuploidy and the resulting genomic instability are hallmarks of many cancers, and cell adhesion plays an important role in tumor invasion and metastasis, our results suggest that both proteins could play a role in carcinogenesis.