New role of BubR1: BubR1 localizes to centrosomes and suppresses centrosome amplification via regulating Plk1 activity in interphase cells

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Faithful chromosome segregation is maintained by a surveillance mechanism, a mitotic spindle checkpoint, which delays the onset of anaphase until all chromosomes have established bipolar attachment to the microtubules. Formation of a bipolar spindle is also essential for chromosome stability, since the numerical abnormality of the mitotic spindle poles leads to chromosome segregation errors. We previously reported that mutations of BUB1B gene (encoding BubR1, a critical component of the mitotic checkpoint) caused premature chromatid separation (PCS) syndrome, a condition characterized by constitutional aneuploidy and a high risk of childhood cancer. We here report that the cells from PCS syndrome patients have loss of regulation of the centrosome duplication machinery, resulting in centrosome amplification and multipolar mitosis. PCS syndrome cells showed increased activity of Polo-like kinase 1 (Plk1), overexpression of which enhances its activity and directly causes centrosome amplification. BubR1 localises to centrosomes and negatively regulates Plk1 activity in normal interphase cells. These results uncovered a crucial role of BubR1 in preventing centrosome amplification through negative regulation of Plk1, and demonstrate that PCS syndrome is a centrosome dysfunctional syndrome, in addition to the spindle checkpoint defect.