# 学 位 論 文 の 要 約

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## 学 位 論 文 題 名

Characterizing the cell division machinery in human somatic tetraploid cells
（四倍体ヒト体細胞における細胞分裂装置の性質）

Tetraploid cells arise through whole-genome duplication (WGD) in normal development, aging, or tumorigenesis. Elucidating how WGD changes cellular characteristics at the molecular level is important for understanding the principles of WGD-mediated bioprocesses. Recent studies highlight the increased dependence on mitotic regulators in tetraploid cells. However, the characteristic of cell division machinery in tetraploid cells is unclear. In this study, I investigated ploidy-dependent changes in the cell division regulation using side-by-side comparison of diploid and tetraploid cells.

Mechanism of ploidy-dependent centrosome scaling
I established isogenic tetraploid HCT116 cell lines by cytokinesis failure and observed mitotic cells. In tetraploid cells, centrosomal protein accumulation and microtubule generation ability are increased at mitosis compared to diploid counterparts. Observation of centrosome accumulation in acute tetraploid cells reveal that ploidy-dependent centrosome scaling is governed by ploidy/centrosome ratio. To address the molecular mechanism, I established the precise gene dosage control system using Auxin inducible degron technology and revealed that the dosage of centrosome scaffold protein CEP192 is a determinant of ploidy-dependent centrosome scaling.

Ploidy-dependent change in centrosome characteristics
I found that the depletion of centrosome homeostasis regulator TRIM37 in tetraploid cells promote multipolar spindle formation and genomic instability. Importantly, CEP192 half-depletion suppressed spindle multipolarization in TRIM37-depleted tetraploid to the level equivalent to diploid. These results indicate that ploidy-linked increase in CEP192 dosage contributes to the aggravation of spindle multipolarization upon TRIM37 depletion.

Ploidy-dependent change in cell shape stability during cytokinesis
I also found irregular protrusive deformations in tetraploid cell during cytokinesis. While RhoA and anillin correctly accumulated at the equatorial cortex, myosin II was over-accumulated near the cell poles in tetraploid. Suppression of myosin II activity by ROCK inhibitor Y27632 restored smooth cell morphology during cytokinesis. These results suggest that the dysregulation of myosin II is a primary cause of cell shape abnormality during cytokinesis in tetraploid cells.

Throughout these investigations, I revealed the mode change in mitotic centrosome and cytokinesis regulation upon WGD and identified the key molecular targets. These findings provide fundamental insights into whole-genome duplication-mediated biological processes.