学 位 論 文 の 要 約

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学 位 論 文 題 名

Route-dependent principles of proliferative regulation following whole-genome duplication
(全ゲノム倍加の形成経路依存的な増殖性制御原理の解明)

Whole genome duplication (WGD) of diploid cells results in various cell fates, such as cell death, cell cycle arrest, and proliferation with chromosomal instability. Proliferative cells after WGD contribute to broad biological phenomena, including differentiation, tumorigenesis, or evolution. However, determinants of the post-WGD cell fates remain largely unknown. In this study, I revealed that mitotic slippage (MS) and cytokinesis failure (CF), two major routes of WGD induction, showed different consequences for viability and proliferation in human cells. Quantitative live imaging demonstrated poorer survivability of cells upon multipolar chromosome segregation at the first mitosis after MS than CF. Chromosome-specific labeling showed that more skewed homologous chromosome distribution, caused by the inefficient sister chromatid separation upon MS, than CF. The skewed homologue distribution frequently led to physical isolation of the centrosomes from all homologous centromeres, limiting these centrosomes from capturing any of these homologues. The difference in the frequency of nullisomic chromosome segregation between MS and CF at least partially explained their difference in the viability of the post-WGD daughter cells. Moreover, artificial separation of sister chromatids during MS induction improved the evenness of homologous distribution, restrained nullisomic chromosome segregation at the first mitosis, and significantly recovered the viability of their daughter cells. Furthermore, while the characteristic arrangement of centrosomes had no impact on the frequency of nullisomic chromosome segregation, artificial elongation of microtubules significantly reduced this value. These results demonstrate that sister chromatid separation during WGD induction defines the geometric arrangement of homologous chromosomes, regulating a distance-dependent probability of chromosome capturing, as a key factor determining the proliferative characteristics of subsequent progenies. The findings in this study would provide insight into route-dependent outcomes of WGD in proliferative properties in different biological processes.