学 位 論 文 の 要 約

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学 位 論 文 題 名

The Molecular Basis of Functional Exchangeability in Cytokinesis and
the Heterogeneity Caused by Cytokinesis Failure-driven Whole Genome Duplication
(細胞質分裂における機能的互換性の分子基盤と
細胞質分裂失敗による全ゲノム倍加が引き起す不均一性)

Cytokinesis, the last phase of mitosis, is crucial for the accurate transmission of genetic material. Failure in cytokinesis can result in whole-genome duplication, alter cell properties, and promote various diseases, including cancer. This research examines two main aspects: the molecular mechanisms that regulate normal cytokinesis and the consequences of cytokinesis failure on cellular characteristics, with the aim of elucidating the biological importance of cytokinesis.

Chapter I

During cytokinesis, the actin-based contractile ring drives membrane deformation, symmetrically separating daughter cells. This process relies on domains structurally similar membrane-actin associated proteins, whose redundancy ensures successful furrow ingression. Although ERM proteins are dispensable for cytokinesis, co-depleting anillin and supervillin causes ezrin to over-accumulate at the furrow, suggesting partial functional exchangeability among these membrane-actin associated proteins. However, it remains unknown whether their molecular domains support or limit their exchangeability in cytokinesis control. I investigated the molecular basis of ezrin's exchangeability with other membrane-actin associated proteins during cytokinesis. Using chimeric mutants, I found that ezrin's actin-binding domain-but not its membrane-binding domain-can functionally replace the corresponding domain in anillin to support cytokinesis and proliferation. Conversely, neither the membrane-binding nor actin-binding domain of anillin could substitute for the corresponding ezrin domains in controlling cortical blebbing at the cell poles. These results highlight specific designs of actin- or membrane-associated moieties of different actin-membrane associated proteins with

limited exchangeability, which enables them to support diverse cortical activities on the shared actin-membrane interface during cytokinesis.

Chapter II

Cytokinesis failure-induced whole genome duplication (WGD), which is a hallmark of tumorigenesis, has been observed in over 30% of solid tumors. Previous WGD-related studies compared 1 to 3 representative WGD subclones with the diploid. However, recent studies have shown that different WGD subclones exhibit varying degrees of drug resistance, suggesting heterogeneity among WGD cells. To date, the heterogeneity among subclones has not been fully evaluated. This study, using 7 to 15 WGD subclones, revealed diverse heterogeneity across the genome, transcriptome, and cellular properties of cells after whole genome duplication (WGD). Long-term microscopy and single-cell whole-genome sequencing revealed widespread multipolar chromosome segregation following WGD, leading to significant karyotypic abnormalities both within and across subclones. Over half of the WGD subclones exhibited distinct transcriptomic profiles. Further analysis revealed subclonal-specific regulatory mechanisms in key signaling pathways. The p53/p21 signaling pathway exhibited varying levels of activation among WGD subclones. While cyclin D1 compensated for the antiproliferative effects in most subclones, a particular subclone exhibited cyclin D1-independent proliferation regulation. Dysregulation of the HSP90-MYC regulatory axis, possibly caused by chromosomal copy number loss, may suppress subclonal proliferation. Furthermore, over half of the WGD subclones exhibited proliferation sensitivity to p62 depletion, suggesting a critical role for p62 in their survival. These findings suggest that WGD influences multiple regulatory pathways, leading to differential survival dependencies among subclones and emphasize the importance of fully considering cellular heterogeneity in future WGD studies.