A feedback loop that drives cell death and proliferation and its defect in intestinal stem cells

Sulekh, Shivakshi

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学位論文の内容要旨

A feedback loop that drives cell death and proliferation and its defect in intestinal stem cells

細胞死と細胞増殖を同時に駆動するフィードバックループと、腸幹細胞におけるその異常

Graduate School of Medicine
Division of Developmental and Regenerative Medicine
Ichiro Hiratani

SULEKH SHIVAKSHI

Summary

Cell death and proliferation function as distinct signaling pathways, yet evidence indicates their involvement in crosstalk interactions. This study delves into such a crosstalk and uncovers a feedback loop that simultaneously influences both processes. The nuanced balance between proliferation and cell death emerges as a pivotal determinant of cellular fate.

Notably, this intricate model not only solves pre-existing ambiguities of TNF or JNK signaling but also aids in interpreting the context-dependent regulatory functions of the same in the domains of both cell death and proliferation.

While the enduring nature of intestinal stem cells (ISCs), against apoptosis has been acknowledged, the underlying mechanisms have remained elusive. We discover that the feedback loop was compromised at two subsequent levels: transcriptional and protein. Our ATAC-seq data reveal that ISCs employ chromatin modifications for transcriptional regulation. Furthermore, protein regulation relies on the impaired mitochondrial localization of the apoptosis inducer protein Reaper, providing a detailed molecular insight into the apoptosis resistance mechanisms of ISCs.

In conclusion, this thesis establishes a conceptual framework clarifying the dual roles of caspases in orchestrating both apoptotic and non-apoptotic functions in vivo. The utilization of *Drosophila melanogaster* midgut and wing imaginal disc as models enhances the depth of the study, expanding the scope of our findings and establishing variations of this feedback loop across different cell types.

神戸大学大学院医学研究科（博士課程）

論文審査の結果の要旨

受付番号	甲 第3390号	氏名	SULEKH SHIVAKSHI
論文題目 Title of Dissertation	細胞死と細胞増殖を同時に駆動するフィードバックループと、腸幹細胞におけるその異常 A feedback loop that drives cell death and proliferation and its defect in intestinal stem cells		
審査委員 Examiner	主査 Chief Examiner 南 康博 副査 Vice-examiner 児玉裕三 副査 Vice-examiner 内匠 透		

（要旨は１，０００字～２，０００字程度）

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Notably, this intricate model not only solves pre-existing ambiguities of TNF or JNK signaling but also aids in interpreting the context-dependent regulatory functions of the same in the domains of both cell death and proliferation.

While the enduring nature of intestinal stem cells (ISCs), against apoptosis has been acknowledged, the underlying mechanisms have remained elusive. The candidate and her colleagues discover that the feedback loop was compromised at two subsequent levels: transcriptional and protein. The ATAC-seq data obtained by the candidate *et al.* reveal that ISCs employ chromatin modifications for transcriptional regulation. Furthermore, protein regulation relies on the impaired mitochondrial localization of the apoptosis inducer protein Reaper, providing a detailed molecular insight into the apoptosis resistance mechanisms of ISCs.

The study establishes a conceptual framework clarifying the dual roles of caspases in orchestrating both apoptotic and non-apoptotic functions in vivo. The utilization of *Drosophila melanogaster* midgut and wing imaginal disc as models enhances the depth of the study, expanding the scope of our findings and establishing variations of this feedback loop across different cell types.

The candidate, having completed studies on the roles of caspases and JNK in regulating cell death and proliferation by using *Drosophila* as a model, with a specialty in genetics and molecular/cellular biology, and having advanced the field of knowledge in the area of cell fate determination and stem cell properties, is hereby recognized as having qualified for the degree of Ph.D. (Medicine).