

論文 / 著書情報
Article / Book Information

題目(和文)	四肢の多様な形態形成に寄与するプログラム細胞死とそのメカニズムの解析
Title(English)	Developmental Mechanisms for Programmed Cell Death Underlying Diverse Limb Morphology
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種別(和文)	論文要旨
Type(English)	Summary

論文要旨

THESIS SUMMARY

系・コース： Department of, Graduate major in	生命理工学 生命理工学	系 コース	申請学位 (専攻分野)： Academic Degree Requested	博士 Doctor of	(理学)
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要旨 (英文 800 語程度)
Thesis Summary (approx.800 English Words)

Programmed cell death during embryo development plays a crucial role in the proper formation of various organs, such as interdigital cell death, neural tube closure, mesonephros regression, and tail regression of tadpoles. These indicate that variations in programmed cell death have contributed to the evolution of diverse animal morphologies. This study focused on the mechanisms that induce programmed cell death during limb development in three different animals. 1. Air-breathing behavior underlies the cell death in limbs of <i>Rana pirica</i> tadpoles Amphibians shape their limbs by differential outgrowth of digits and interdigital regions. In contrast, amniotes employ cell death, an additional developmental system, to determine the final shape of limbs. Previous work has shown that high oxygen availability is correlated with the induction of cell death in developing limbs. Given the diversity of life history patterns of amphibians, it is conceivable that some amphibians are exposed to a high-oxygen environment during the tadpole phase and exhibit cell death in their limbs. This study explored whether oxygen modes of life history patterns influence the induction of cell death in limbs of aquatic tadpoles of the frog species <i>Rana pirica</i>. The experimental approaches revealed that <i>R. pirica</i> tadpoles exhibit cell death in the interdigital regions of their limbs, likely to be induced by oxidative stress. Furthermore, preventing air-breathing behavior led to a decrease in the number of cell death in interdigital regions of their limbs. This study proposes that increased oxygen availability caused by frequent air-breathing behavior leads to ROS production and cell death in developing limbs of <i>R. pirica</i> tadpole. An ecological shift may have led to unexpected morphological innovation that was integrated into developmental processes during evolution. 2. BMP-dependent modulation of ROS generation and scavenging controls interdigital cell death Interdigital cell death plays a vital role in shaping limb morphology in amniotes. BMP signaling has been shown to be essential for inducing interdigital cell death, but its relationship with reactive oxygen species (ROS), another driver of this process, remains unclear. This study investigated whether BMP signaling modulates ROS production to promote interdigital cell death and how BMP signaling regulates the balance between ROS generation and scavenging in the interdigital regions of chicken hindlimbs. Through transcriptome analyses, the candidate genes encoding molecular machinery involved in ROS production in response to the reduction of BMP signaling were identified. Furthermore, experimental approaches showed that ROS-generating enzymes (<i>Nox2</i> and <i>Nox4</i>) and ROS-scavenging enzymes (<i>Sod1</i>) were downstream of BMP signaling in interdigital regions of chicken embryos. This study proposes the model that BMP signaling regulates the expression of genes encoding both ROS-generating and ROS-scavenging enzymes, thereby modulating ROS levels and controlling cell death in interdigital regions of chicken embryos. Understanding the cooperation between BMP signaling and ROS production in programmed cell death provides insight into the evolutionary establishment of the interdigital cell death system. 3. Immobilization secondary to cell death of muscle precursors with a dual transcriptional signature contributes to the emu wing skeletal pattern. Limb reduction has occurred multiple times in tetrapod history. Among ratites, wing reductions range from mild vestigialization to complete loss, with emus (<i>Dromaius novaehollandiae</i>) serving as a model for studying the genetic mechanisms behind limb reduction. Previous work has shown that the emu forelimb exhibits intraindividual asymmetry in both the loss of joint cavities and the reduction in the length of forelimb skeletal elements, suggesting a by-product of decreased mechanical load. However, the underlying mechanisms of decreasing mechanical input in emu forelimbs are unclear. This

study investigated whether cell death is responsible for muscle reduction, which causes loss of mechanical input that forms the emu wing's asymmetrical skeletal pattern. Through single-cell RNA sequencing (scRNA-seq) of emu forelimbs, a subpopulation of muscle progenitors expressing both somite-derived myogenic markers and the lateral plate mesodermal cell markers was identified. These findings suggest that the absence of distal muscles in emus can be traced back to the cell death of these dual-identity muscle progenitors. The cell death, confirmed by TUNEL staining, indicates a developmental mechanism that potentially shapes the emu forelimb's morphology by reducing certain muscle progenitors. This research not only sheds light on the specific developmental pathways that give rise to the unique skeletal and muscle morphology of the emu forelimb but also provides valuable insights into the broader principles of evolutionary developmental biology.

備考：論文要旨は、和文 2000 字と英文 300 語を 1 部ずつ提出するか、もしくは英文 800 語を 1 部提出してください。

Note: Thesis Summary should be submitted in either a copy of 2000 Japanese Characters and 300 Words (English) or 1 copy of 800 Words (English).

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