【Grant-in-Aid for Transformative Research Areas（B）】

Philostasis: A universal principle of "pausing" in multicellular tissues. (Mechanisms of multicellular pause)

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Purpose and Background of the Research

●Outline of the Research

The apparent inactivity of multicellular tissues, including developmental arrest in mammalian embryos, quiescence of tissue stem cells, and dormancy in cancers, is a widely observed phenomenon across species and timescales. Despite its ubiquity, the biological significance of this phenomenon remains diverse and underexplored. Traditional studies have often attributed these inactivity states to passive responses, such as the “consequences” of deteriorating nutritional conditions. However, our preliminary experiments suggest an alternative perspective: organisms may actively enter a dormant state through elaborate cell-cell interactions as a strategy to overcome environmental stresses.

To address this, we propose the term “Philo-stasis” (from the Greek philo- meaning “to prefer” and -stasis meaning “to pause”) to describe the phenomenon of programmed quiescence in multicellular tissues. This term aims to provide a unified framework for understanding the quiescence of multicellular tissues and the essential role of intercellular communication in their regulation.

Historically, significant advancements in understanding biological phenomena, such as apoptosis (programmed cell death) and autophagy (intracellular degradation), have arisen from identifying and systematizing their fundamental principles. Similarly, the study of quiescent states has progressed through independent investigations into phenomena such as diapause in embryogenesis, quiescence in tissue stem cells, and cancer dormancy. While these phenomena have been examined as isolated cases, they share common characteristics, including the suppression of cell proliferation and differentiation.

Through the lens of Philostasis, we aim to unify these seemingly disparate phenomena under a single conceptual framework. This approach seeks to uncover common principles governing programmed multicellular quiescence, transcending hierarchical boundaries and fostering a comprehensive understanding of intercellular dynamics in stress adaptation and tissue regulation.

Due to the diversity of species, timescales, and biological significance, inactivation phenomena have traditionally been treated as isolated events, with little emphasis on their interconnections. However, this research area seeks to bridge these gaps by utilizing cutting-edge technologies, including multilevel omics, genome editing, live imaging, advanced computational analysis, and photo-isolation chemistry (PIC). These tools will enable a comprehensive and fundamental understanding of quiescence phenomena across various multicellular tissues.

Building on preliminary findings unique to this field, this research aims to establish a new biological concept, “Philostasis”—a programmed quiescence in multicellular tissues. By integrating novel ideas that transcend existing academic frameworks with state-of-the-art analytical technologies, this approach aspires to revolutionize our understanding of tissue dynamics under stress. The outcomes of this work have the potential to drive transformative advances in biomedicine, offering profound insights into multicellular quiescence and its applications.

Expected Research Achievements

Philo-stasis: Unlocking the potential of the pause research through integration and innovation

The application of the concept of Philostasis offers a transformative opportunity to realize the full potential of quiescence research. Quiescence in multicellular tissues is a phenomenon observed across a wide range of life forms, including mammals, insects, plants, and cancer cells. Despite the high level of research activity in Japan across these individual areas, the true potential of this work remains untapped due to its compartmentalization within distinct fields. By adopting an integrated approach to Philostasis, this research area will synthesize diverse studies, leveraging their synergistic effects to achieve a fundamental understanding of quiescence phenomena. The originality of this field is unparalleled, with no comparable studies in Japan or globally.

This initiative employs cutting-edge technologies such as multilevel omics, genome editing, live imaging, and advanced computational analyses to uncover the universal principles underlying quiescence in multicellular tissues. To accomplish this, a team of young researchers, recognized as global pioneers in fields such as developmental embryology, stem cell niches, and cancer biology, will collaborate to integrate their expertise and advance this analysis.

Key contributors include Dr. Takaoka, renowned for groundbreaking work in early mouse embryogenesis and developmental pausing, as demonstrated by high-impact publications (Dev. Cell 2006; Nat. Cell Biol. 2011; Development 2012; Nat. Commun. 2017), and for expertise in genome editing technologies. Similarly, Dr. Nakanishi has made significant contributions to understanding homeostasis mechanisms through stem cell diversity, self-organization, and cell-cell interactions (Cell 2019; Nat. Cell Biol. 2017; eLife 2014).

The overarching vision of this initiative is to fully harness the imagination, creativity, and collaborative abilities of young researchers to redefine disciplinary boundaries and create a truly interdisciplinary field. This research area will foster close collaboration across specialties, enabling researchers to collectively explore the science of multicellular quiescence and establish philo-stasis as a unifying principle in life sciences.

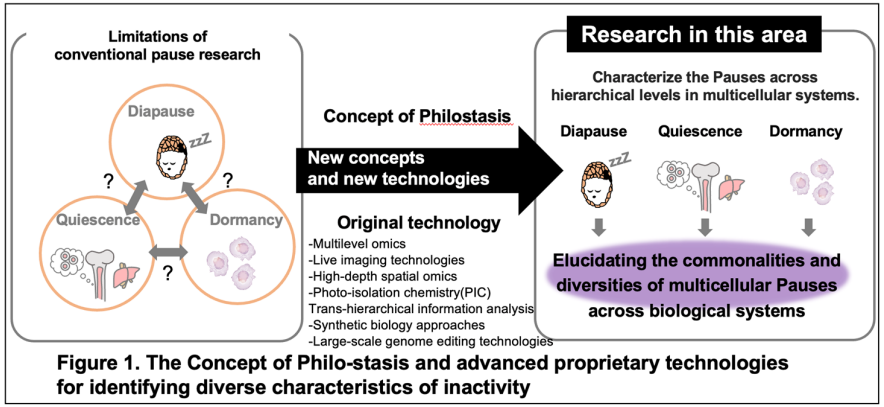

Figure 1. The Concept of Philo-stasis and advanced proprietary technologies for identifying diverse characteristics of inactivity

Homepage Address, etc.	https://philostasis.weebly.com/