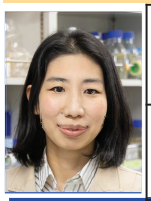
【Grant-in-Aid for Transformative Research Areas（B）】

Crossing the border between unicellular and multicellular organisms



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Project Information	Project Number : 26B304　Project Period (FY) : 2026-2028 Keywords : unicellular organisms, multicellular organisms, cell differentiation, spatial structure

Purpose and Background of the Research

●Outline of the Research

Our bodies consist of an enormous number of cells, with each one serving a distinct role. Before multicellular organisms evolved, however, life existed in the form of unicellular organisms, with each cell living independently. How, then, did unicellular organisms give rise to multicellular life? This transition from unicellular to multicellular life is regarded as one of the major turning points in the history of evolution, paving the way to the emergence of "complexity of life".

It is widely thought that the evolution of multicellularity is a process in which unicellular organisms first formed clusters with a specific spatial structure, and only afterward began dividing labor among themselves. In contrast, our research proposes a new hypothesis: a pathway where constituent cells differentiated prior to developing multicellularity (**differentiation-first pathway**). Our recent work shows that subpopulations of cells can undergo a metabolic shift, even at the unicellular stage, to emerge as distinct groups among the population; this shift in metabolism may have established a primitive form of differentiation. Such functional competency endows unicellular organisms with the potential for multicellularity prior to physical contact and structuralization. Therefore, in our research program, we challenge the conventional paradigm, reimagining the origin of the transition from uni- to multi-cellular as differentiation, not aggregation.

To test this hypothesis, we will bring together research on eukaryotes, prokaryotes, artificial cells, and theoretical biology. We aim to establish a new research area that bridges the boundary between unicellular and multicellular life. When common mechanisms can be identified across different kinds of living systems, we expect to gain a deeper understanding of the major evolutionary pathway from unicellular to multicellular life.

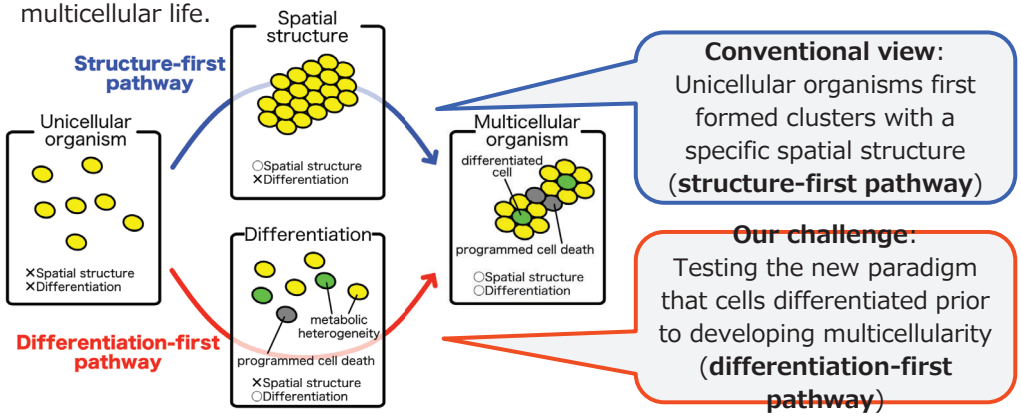

Figure 1. How did the transition from uni-cellularity to multi-cellularity occur?

●Cell-to-cell variation revealed by unicellular organisms

In recent years, discoveries have revealed that even within homogeneous populations of unicellular organisms, individuals with different properties may already exist. This raises a new question: could the prerequisite for multicellularity emerge even before the cells organize spatially? This idea is supported by two findings from our team. One is the discovery of latecomer killing in yeast by Oda, Hatakeyama, and colleagues, in which the fate of monoclonal cells depends on their response to environmental change. The other is Utada and colleagues' finding that, various metabolic states exist within bacterial populations from the same lineage. Both findings suggest that the seeds of division of labor may already exist in unicellular populations.

This project examines that possibility from four directions: yeast, bacteria, artificial cells, and theoretical biology. We will investigate how cellular heterogenetiy arises and how these cells interact; we will test whether such mechanisms can be reconstructed in artificial cells; and, we will use theory to explore the conditions under which division of labor and multicellularity emerge. With this multifaceted approach, we aim to clarify the mechanisms that bridge unicellular and multicellular life.

Expected Research Achievements

Cell differentiation requires both a division of labor among cells and a form of memory that maintains those distinct states. However, the mechanisms that generate cell-to-cell variation in unicellular organisms, and those that preserve such differentiated states, remain largely unknown.

To address these points, we will first clarify why cells with different properties arise within a single population. We will then examine how such differences may lead to cooperation and group formation among cells, with the aim of revealing the evolutionary path that links unicellular and multicellular life.

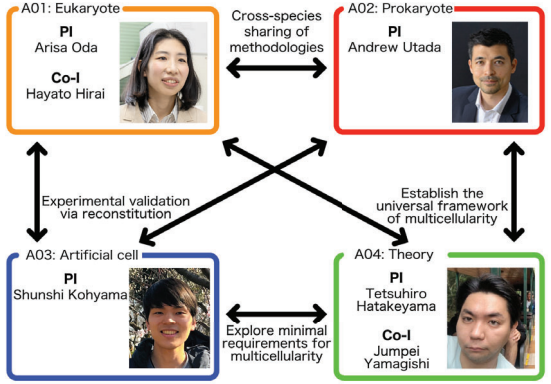

Figure 2. Planned Research Group members

●Research Content of Each Planned Research Group

A01 Eukaryote Group: This group studies yeast and fungi to clarify how cells with different properties arise within a unicellular population. It focuses on responses to environmental change and cellular memory, and examines how these processes relate to multicellularity.

A02 Prokaryote Group: This group studies bacteria to analyze how metabolically distinct cells arise within a unicellular population. By comparing these cells with collective structures such as biofilms, it examines how unicellular differentiation may lead to multicellularity.

A03 Artificial Biology Group: This group uses artificial cells to reconstruct the mechanisms of cell differentiation seen in unicellular organisms. It also seeks to reproduce, in a controlled way, the process leading to multicellularity.

A04 Theoretical Biology Group: This group theoretically investigates the conditions under which cell differentiation arises in unicellular populations and leads to multicellularity. Using mathematical models, it aims to identify general principles underlying this transition.

Website(s)	Research area web page: https://crosscell.elsi.jp