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

Integration of extracellular information by multimodal ECM activity（Multimodal ECM）

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Research Area Information	Number of Research Area : 23A302　Project Period (FY) : 2023-2027 Keywords : Extracellular matrix, Multicellular system, Multimodal ECM activity, Polymer gel

Purpose and Background of the Research

●Research Outline

Structures and functions in multicellular organisms are complex yet tightly organized. Although they emerge from the interplay between cells and the extracellular matrix (ECM – a gel-like supramolecular complex), biological research has largely focused on cells, often neglecting the ECM as merely a 'static scaffold'. However, recent advancements in ECM measurement and manipulation techniques have begun to unveil that the ECM is far more dynamic than previously thought, providing cells with a diverse array of biochemical (e.g. composition, adhesive and soluble signals) and physical (e.g. adhesion, viscoelasticity and geometry) cues. Together, this information represents the 'multimodal spatiotemporal information' found within the ECM. We anticipate that the ECM is crucial in establishing and integrating various biological layers (scales) and, thus, in governing dynamic and ordered multicellular phenomena, such as self-organization and morphogenesis.

This research area draws on the expertise of experimental biologists, polymer materials engineers and mathematical/data scientists through comprehensive interdisciplinary methods. The aim is to achieve a greater understanding and control of the dynamics and multimodal information encoded within the ECM. By unravelling the dynamic operating principles of the ECM, we endeavour to transform the prevailing cell-centric framework in biology.

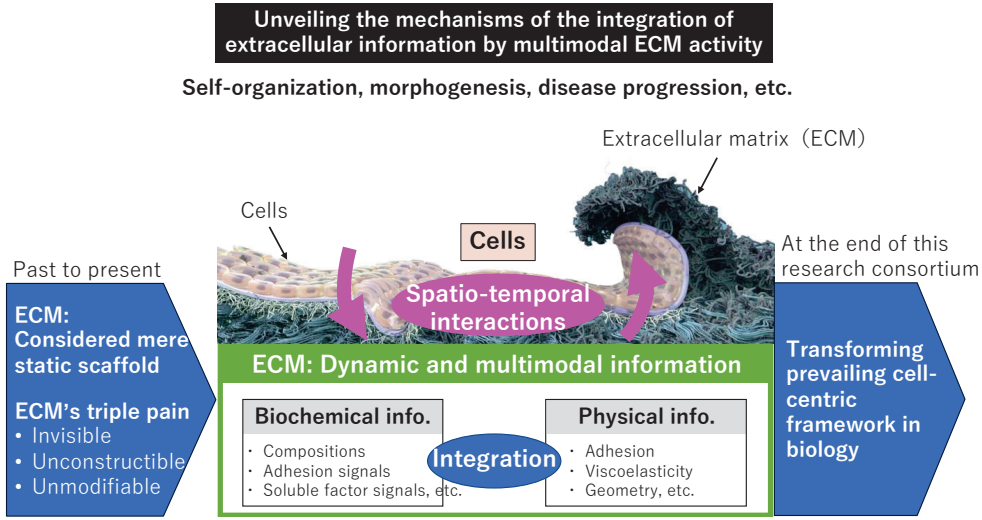

Figure 1. Diagram depicting the research outline

●Research strategy

The limited investigation into the ECM's dynamics and multimodal information stems from challenges in visualization and the ability to decouple the ECM's diverse biochemical and physical parameters. To address this, we set the following three key research groups: 'Operating principles of the ECM-multicellular dynamic unit (A01)', 'Manipulation of extracellular information by designer matrices (A02)', and 'Mathematical and data science for ECM-multicellular systems (A03)'.

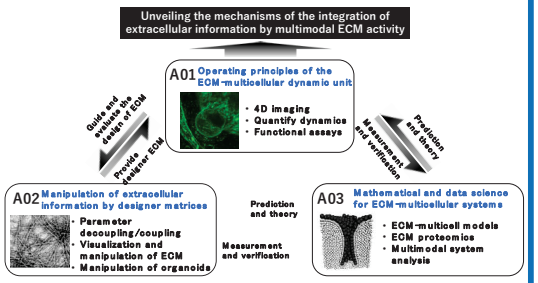

Figure 2. Research strategy and interactions between research groups

Expected Research Achievements

1) Elucidating the operating principles of the ECM–multicellular dynamic unit

We will elucidate the operational principles of the dynamic unit comprised of ECMs and cells, particularly focusing on how it orchestrates self-organization, tissue remodelling and the onset of diseases such as cancer. A key strategy will involve employing live imaging to visualize dynamic interplay between the ECM and cells, aiming to uncover the spatio-temporal changes and causal relationships between the two.

2) Manipulation of extracellular information by designer matrices

This research area will establish novel methodologies for the spatio-temporal control of multicellular systems, such as organoids, by creating designer matrices. These matrices, which include reconstructed ECMs, artificial ECMs and synthetic polymer hydrogels, will allow the visualization and manipulation of various biochemical and physical parameters of the ECM. Additionally, we will uncover the structural characteristics of the ECM that give rise to nonlinear viscoelastic changes in tissues.

3) Establishment of mathematical and data science for ECM–multicellular systems

We will develop 3D mathematical models capable of integrating the mechanical and biochemical interactions between ECM and multicellular systems. Application of these models to various biological phenomena will uncover the mechanism through which the ECM's multimodal information influences cell populations.

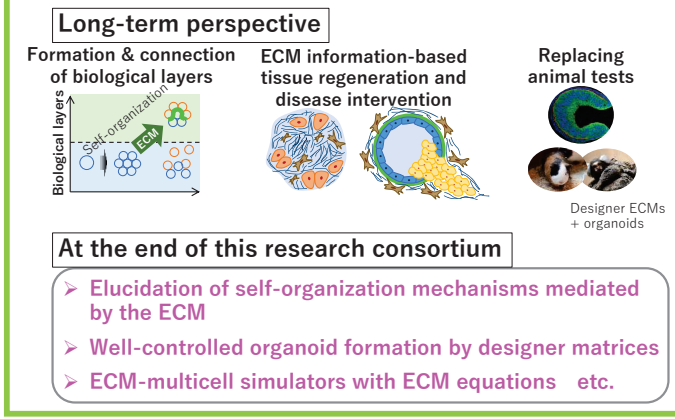

Figure 3. Expected research outcomes

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