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

Dynamic cell community science starting with bone imaging（Cell community）

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Purpose and Background of the Research

● Outline of the Research

Humans develop a relationship with society from the moment of birth. We spend our lives in connection with others, joining and departing various “communities” such as family, neighbors, school, workplace, and friends. Connections within such communities have a substantial impact on our social behavior and decision-making.

Our team has previously performed *in vivo* analyses of cellular dynamics in living mice using an intravital imaging technology; however, these types of detailed analyses of cell populations in a living tissue have raised more questions about the “logic” that controls group behavior. Here we introduces the new concept of “cell community.” This concept serves as an intermediate layer to the conventional hierarchy perception in biology, expanding our analytical views from single-cell dynamics to global cellular organization. Furthermore, this allows us to better capture cell society structure and ultimately elucidate the basic principles governing dynamic cell community (Figure 1).

In various subareas of the social sciences, it has been recognized that individual behaviors are strongly influenced by the circumstances of their neighbors rather than by the macro social/economic conditions. Translated into a cell population problem, this implies focusing on intercellular “connections.” This study investigates how individual cells react to the structure of cell communities through mathematical analysis methods recently used in social sciences. In sum, our goal is to establish a novel theory, “cell community science,” for understanding dynamic multicellular society, focusing on intercellular connections.

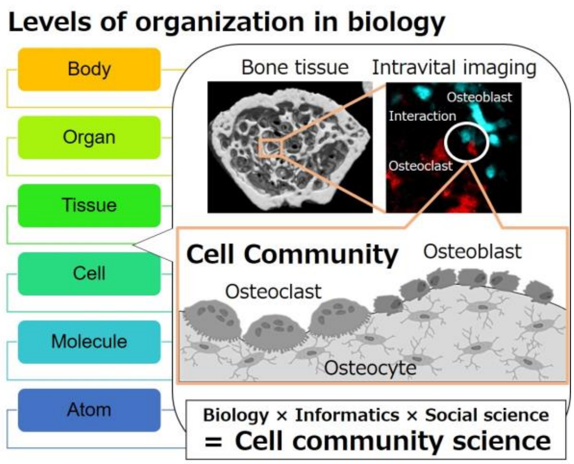

Figure 1. Establishment of “Cell community science”

● Background and purpose

Bone is a dynamic organ that is constantly remodeled. Osteoclasts, which dissolve old bones, and osteoblasts, which create new bones, work in cooperation to form the bone structure. We established an intravital imaging technology for visualizing inside living bone tissues. We were the first to successfully capture the moment of interaction between living osteoclasts (red) and osteoblasts (light blue), revealing that this physical intercellular contact regulates osteoclast function (Figure 2). Furthermore, we found that both osteoclasts and osteoblasts form communities of approximately 10 cells, alternately localized on the bone surface.

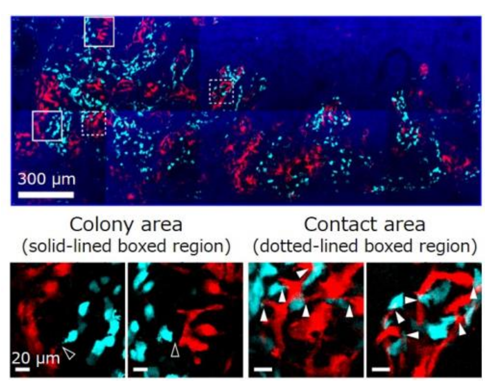

Figure 2. Intravital bone imaging

However, the "connections" between cell communities are still unclear, and questions such as "Why don't the communities of osteoclasts mix with those of osteoblasts?" and "First of all, why do they form communities?" remain unanswered.

Although most imaging studies focus on individual cell behavior, it is interesting to observe the "cell community" from a higher level. The movement of each cell is complex and seemingly random; however, within this global context, it appears to be well organized. Additionally, cell types and states can now be captured as a continuum. Technological resolution for cell observation is increasing to a level where we no longer classify phenotypes based on one single factor. The activity of cell societies is more than sufficiently complex to be understood with element-reductive approaches alone, and it is also considered important to use moderately abstract approaches.

In this study, we establishes a novel method for quantitative analysis linking intercellular interaction and gene expression, while retaining *in vivo* spatiotemporal information. Furthermore, we performs theoretical analyses of cell communities by incorporating the techniques of social choice theory and the analysis of evolutionary game theory.

Expected Research Achievements

●Achievement goals

Bone remodeling begins with old bone dissolution by osteoclasts. Subsequently, osteoblasts form new bones in the dissolved region, becoming buried in the bone matrix and differentiating into osteocytes. How do osteoclasts, osteoblasts, and osteocytes cooperate with each other to form bones? (Figure 3)

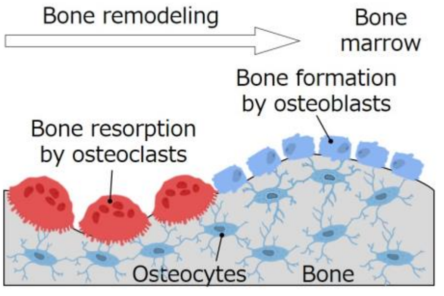

Figure 3. Schematic of bone remodeling

Bone is the hardest tissue in the body and, therefore, poses a difficulty for single-cell analysis. Furthermore, the "logic" behind the regulation of bone cell society is not well understood. This study introduces the concept of "cell community" beyond the conventional single-cell analysis and develop a novel imaging technology that quantifies "connections" between multiple cells while maintaining the *in vivo* environment. Using established technology, we also analyze the spatiotemporal interactions of each cell community in bone remodeling. Furthermore, through informatics analysis incorporating social sciences theories, we aim to understand the cell communities in bone society from a higher perspective and elucidate the basic principles determining bone remodeling.

●Ripple effects

New trends such as cell community science: The life science field has aimed to understand various life phenomena with element-reductive approaches using the "words of molecules". In contrast, this study creates the concept of "cell community," and produce a new academic trend that incorporates the knowledge of humanities and social sciences to analyze the behavior and decision-making patterns within groups. Biology has now become an "academic melting pot," in which various academic fields overlap and merge. Through the promotion of full-scale collaboration with humanities and social sciences, this study is expected to lead to new trends in life sciences.

Ripple effects on social science: Through the analysis of "cell communities" this study is expected to contribute to the understanding of communities in social sciences. Despite its importance, there are a lot of remaining problems on the mechanisms of communities, such as integration of immigrants and minorities. Hopefully, this study offers to a novel viewpoint for these problems by visualizing the universal principle of the "invisible hand" that drives society.

Homepage Address, etc.	https://cell-community.org/