Doctoral Dissertation (Censored)
博士論文 (要約)

Cell mechanics in the collective migration with nematic order
（配向秩序を示す細胞集団運動の力学）

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Abstract

Multicellular movement is essential for the biological function of multicellular organisms, in that it underlies morphogenesis and homeostasis. Recently, observations on the tissue of cells with anisotropic shape have suggested that the relation between the pattern formation and the dynamics in such tissues are similar to that in a class of active matter, which is called active nematics. In the theory of active nematics, the characteristic phenomena are often explained from the coupling between the anisotropic force generation of the components and the nematic order, which is the alignment of cellular major axes. On the other hand, as for the experimental systems of multicellular tissues, although several results suggested the existence of the coupling, the anisotropic force from cells has not yet been directly observed. And thus, it is still to be elucidated whether the expected force generation is done by each cell or by cell-to-cell interactions.

In this study, we applied the traction force microscopy, which is the method to measure the cellular force, on the collective migration of two cell types with anisotropic shape, neural progenitor cells and SK-LMS-1 cells. The measured force field was compared with the nematic order of the tissue, and showed strong alignment with the special change of the pattern, as the active nematic theory predicts. Further, the strength of anisotropic force generation was estimated from the measured force field, according to the theory. We also measured the force from the isolated cells and found that the force distribution was anisotropic and was along on the angle of cellular axis, indicating that the force distribution was sufficient to couple with nematic order. From this measurement, the strength of individual cellular force was directly measured, and was compared with the counterpart in the collective system. This comparison revealed that the isolated force was too weak to explain the collective force, indicating that the collective force generation was likely due to the interaction between cells.

In chapter1, the basic knowledge on the cell movement was described from the viewpoint of biophysics, and subsequently, the reason why the multicellular sheet has been expected as the realization of active nematics was introduced. After that, the relation between the pattern formation and the force generation was derived. Finally, we explained the previous studies on cell migration which used traction force microscopy.

In chapter2, we showed the materials and methods. At first, the experimental methods were described; culturing, manufacturing the substrate for traction force microscopy, measuring the substrate stiffness, and imaging. Subsequently, the analytical methods were introduced; quantification of the nematic order parameter, estimation of the substrate stiffness, calculation of the substrate deformation and the traction force, and the tracking of cell nuclei.

In chapter3, the experimental results of the traction force microscopy on collective migration of neural progenitor cells were shown. First, comparison of the angles between the measured force field, the nematic order parameter and the net flow velocity of the cells indicated strong correlations of the traction force with the spatial gradient of the nematic order parameter, or of the flow velocity with the nematic order parameter. Further, we quantitatively compared the traction force with the distortion of nematic order to calculate the parameter which characterizes

the strength of force generation from the cells.

In chapter4, the experimental results for SK-LMS-1 cells were shown. First, as in the case of neural progenitors, the measured collective force was qualitatively and quantitatively compared with the nematic order parameter, indicating strong correlation between the force and the distortion of the nematic order. Along this comparison, we also estimated the force generation strength. On the other hand, we also measured the traction force field generated by the isolated cells, and the force generation strength was estimated again.

In chapter5, the results introduced in chapters 3 and 4 were compared. First, the estimated force generation strengths of isolated or collective SK-LMS-1 cells were quantitatively compared and it was found that the isolated force was too weak to construct the collective force, though the qualitative properties match well. As for the neural progenitor cells, we cited the force strength obtained in the previous study, and simulated the collective force generation based on that result, to compare with the collective force generation measured in this study. This comparison also indicated that the collective force was extremely stronger than the isolated force strength. Finally, we compared the scale of the force amplitude measured on the neural progenitors and SK-LMS-1 cells.

Contents

List of Acronyms

TFM Traction Force Microscopy
NPC Neural Progenitor Cell

Chapter 1

Introduction

本章については、５年以内に雑誌等で刊行予定のため、非公開。

Chapter 2

Materials and Methods

本章については、５年以内に雑誌等で刊行予定のため、非公開。

Chapter 3

Mechanics of Collective Neural Progenitor Cells (NPCs)

本章については、５年以内に雑誌等で刊行予定のため、非公開。

Chapter 4

Mechanics of Collective SK-LMS-1 Cells

本章については、５年以内に雑誌等で刊行予定のため、非公開。

Chapter 5

Discussion and Conclusions

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