Research area in Strategic Objective *“Functional dynamics in the cell "*

Spatiotemporal dynamics of intracellular components

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Overview

This research area aims to gain an integrated understanding of the structure-function relationship of the cell by observing and measuring the dynamics in microspace of cellular higher-order structural components, from supramolecular complexes to organelles and membrane-less organelles, and analyzing their functional correlations.

In recent years, the development of observation and measurement techniques such as cryo-electron microscopy, super-resolution microscopy, and high-speed atomic force microscopy have greatly improved our understanding of intracellular microstructure and dynamics. This has led to a rapid increase in structural information on large membrane-protein complexes etc. and new phenomena, such as biological phase separation and inter-organelle contacts, which have led to a rethinking of the conventional concept of the cell. On the other hand, for an integrated understanding of the cell, it is necessary to promote bidirectional approaches by increasing the sizes of the targets for high-resolution structural analyses and in turn, by increasing the resolution of cellular imaging analyses, which allows us to obtain precise knowledge of the intracellular higher-order structural components and to integrate them.

In this research area, we aim to develop technologies for observation, measurement, and control of intracellular phenomena to overcome the above-mentioned issues, and to elucidate the functions of higher-order intracellular structural components by using these technologies, which will lead to advanced understanding of biological phenomena.

Research Supervisor’s Policy on Call for Applications, Selection, and Management of the Research Area

1. Background

In the life sciences field, various approaches based on advanced technologies have been used to elucidate biological phenomena. For example, in the field of molecular biology, the design, synthesis and control of nucleic acids and proteins have led to the clarification of their functions and mechanisms of action. In the field of structural biology, the precise structures of myriad of biological macromolecules have been determined and the understanding of their dynamics has advanced with the support of various instrumental developments, technological innovations, and computational science. Furthermore, in the field of cell biology, various microscopy techniques have led to the development of biology that allows a new understanding of intracellular phenomena based on the dynamics of intracellular structures.

In recent years, in addition to above, there has been an emerging research and development effort to understand the cell functions and homeostasis of cells in an integrated manner from the perspective of structures and compartments positioned in the intermediate layer between molecules and cells, and networks in which they work together. For example, research is in progress to directly observe the behavior of proteins, nucleic acids and their complexes in living cells and their interactions with higher-order structures. Apart from approaches to increase the resolution and amount of information needed to observe such molecules, research is also underway to elucidate the impact of intrinsic heterogeneity of intracellular environments and the mesoscale state generated by their constituents. For example, understanding of cellular droplets (membrane-less organelles) generated by biological phase separation (liquid-liquid phase separation) in cells is rapidly enhanced, and membrane-less organelles have been shown to exhibit a wide variety of biological functions that were previously difficult to interpret. The elucidation of the structures, dynamics and functions of cellular higher-order structural components at various levels in the cell is considered to be extremely important for an integrated understanding of biological systems from molecules to the cellular level.

2. Research themes

This research area invites proposals for (1) development of observation and measurement technologies, (2) development of manipulation technologies, (3) development and application of computational modeling and (4) elucidation of cellular system using these technologies, focusing on cellular higher-order structural components of various organisms from microorganisms to vertebrates and plants.

(1) Development of observation and measurement technologies to understand the structures and functions of cellular higher-order structural components in cells

In recent years, there has been remarkable progress in technologies to observe intracellular components and phenomena. For example, it is becoming possible to analyze intracellular phenomena with higher spatial resolution, which could not be achieved by conventional microscopy. On the other hand, there are still many limitations and challenges to overcome in the information obtained, that is, only snapshots can be taken for observation, the probes are not suitable for obtaining information on dynamics and intact morphology, and it is difficult to obtain sufficiently quantitative information. Therefore, in this project, we will promote development of innovative technologies to measure and quantitatively analyze the shapes, localization, dynamics, and interactions of biological molecules and their complexes as well as of organelles in cells, and to predict their functions.

Some examples of possible research are shown below. These are just examples, and we welcome ambitious research proposals to create new technologies.

- Development of various in-cell structural analysis techniques to assess the structures and dynamics of supramolecular complexes in cells.
- Development of technologies to obtain positional information and precise structural information of biological molecules in cells by cryo-electron tomography.
- Development of measurement technologies to capture structures such as membrane-less organelles with minimal artificial perturbation.
- Development of probes for super-resolution microscopy without interference in the acquisition of structural and dynamic information.
- Development of high-speed AFM to capture the dynamics of supramolecular complex to organelle-level structures with high spatial resolution and time resolution, and development of new observation techniques to replace them.
- Development of analysis technologies that can process imaging data acquired by advanced microscopy in a large amount and at high speed.

(2) Development of technology to manipulate and control the structures, functions and states of cellular high-order structural components in the cell.

In the field of molecular and cell biology, the identification of functional molecules and the analysis of their interactions have been extensively promoted with the aid of genetic engineering. In parallel, using click chemistry, synthetic compounds, and optical technology, etc. to perturb molecules and cells and analyze their responses is also a promising approach to understanding the cellular systems. Therefore, this research area promotes research and development on chemical, engineering and optical technologies to perturb higher-order structural components in cells, as well as manipulation and control of cells based on these technologies.

Some examples of possible research are shown below. These are just examples, and we welcome ambitious research proposals to create new technologies.

- Development of technologies to add perturbation to intracellular molecules, organelles, etc.
- Creation of novel compounds targeting intracellular protein complexes and development of technologies to control cellular functions.
- Development of technologies that can be applied to disease prevention, treatment and drug

delivery by manipulating membrane-less organelles.

(3) Elucidation of general principles for describing non-equilibrium and complex-system phenomena in cellular environments

Modeling the phenomena that occur in heterogeneous cellular environments by using mathematical and physical approaches will allow us to simulate the intracellular phenomena (ultimately the cell itself). Design followed by assembly and re-writing of the system based on models of living systems will also provide a powerful approach to understanding phenomena at the cellular structural component level. In promoting such research, collaboration with information science, mathematical science and physics is required to integrate and model the data obtained by various measurement technologies. This research area promotes interdisciplinary research aiming at constructing models of intracellular phenomena.

Some examples of possible research are shown below. These are just examples, and we welcome ambitious research proposals to create new technologies.

- Development of modeling techniques for higher-order cellular structures and heterogeneous mesoscale reaction fields by soft-matter physics.
- Development of machine learning technologies to integrate and analyze the data of structures and functions of cellular structural components.
- Development of simulation technologies for higher-order phenomena in cells using molecular dynamics simulations.

(4) Understanding the cell systems by elucidating structures and functions of higher-order cellular structural components

We will promote research and development to deepen our understanding of the dynamics and its relation to functions for cellular higher-order structural components such as intracellular supramolecular complexes, organelles, and membrane-less organelles.

Some examples of possible research are shown below. These are just examples, and we welcome ambitious research proposals to create new technologies.

- Elucidation of intracellular network entities and structure-function relationship of cellular structural components at the molecular level.
- Elucidation of biological molecule transport, actual signal transduction, their regulation and biological significance for cellular high-order structural components.
- Elucidation of the formation mechanism of cellular higher-order structural components and their involvement in intracellular phenomena.
- Elucidation of the mechanism of homeostasis of structural and functional networks constituted by cellular higher-order structural components and the mechanism of diseases

caused by their failure.

3. Including multiple themes

Since CREST is a team-type research program, we welcome research on elucidation of the functions of cellular higher-order structural components with incorporation of technological development and utilization of advanced technologies and research on development of technologies and model building with an awareness of elucidation of the functions of the above structural components. We also encourage formation of a research team involving a function elucidation group, technology development group and/or modeling group for synergetic collaboration. For these reasons, among the four research themes detailed above, we welcome proposals in principle on theme (4), but with active application of the results or technical advances in themes (1) to (3), or inspiring the development in themes (1) to (3). However, this does not apply to research proposals that are highly original and versatile and that, when realized, are expected to make a significant contribution to other research and development in the area, including (4), even if they are technology development alone as described in (1) to (3).

4. Other considerations

When applying in this research area, please clearly indicate the "goals to be achieved in three to five years after adoption" and the "impact of the results after completion of project". Although the research budget for each project is limited to 300 million yen (excluding indirect expenses), please note that research budget may increase or decrease depending on the progress of the research, as they are reviewed on a yearly basis. In this research area, we welcome the participation of researchers from different fields and of young researchers. We thus welcome small-scale projects with a total research budget of approx. 150 million yen or proposals that are implemented by a single group.

5. Cooperation and collaboration with other research areas

In the management of the research area, we will promote collaboration with other research areas including CREST "Creation of a quantitative analysis platform aiming at understanding spatiotemporal interactions between multiple cells", PRESTO "Intercellular interactions and their dynamics in multicellular systems" and PRESTO "Dynamic supra-assembly of biomolecular systems", and we will hold joint meetings and workshops as needed. We will also promote collaboration with AMED-CREST / PRIME "Understanding and medical application of proteostasis" and with related academic societies and research institutes etc., and organize symposia as needed to actively develop new research.