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

Dynamic supra-assembly of biomolecular systems

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Overview

○The multiple functions of cells are based on dynamic supra-assembly of biomolecular systems ranging from molecular complexes to organelles. This research area aims to investigate the properties of such dynamic supra-assembly of biomolecular systems based on molecular studies, and elucidate the universal mechanism of how cellular functions emerge from inter-hierarchical interactions among molecules, molecular complexes, and organelles.

Recently, the methodology for the observation and analysis of such cross-hierarchical phenomena been dramatically developed in the life science field. An example is biological droplet formation. Although it has been widely thought that the physical boundary between inside and outside of an organelle is comparted by lipid bilayer, recent studies has shown that some types of biomolecules self-assemble to form membraneless organelles, granules and bodies by liquid-liquid phase separation like phenomena. As for technology, the development of super-resolution microscopies and target specific molecular probes has made it possible to capture images with high spatiotemporal resolution and to analyze the detailed structures of dynamic supra-assembly of biomolecular structures. Such new science and technology are often developed from interdisciplinary collaborations of life scientists with physicists, chemists or researchers in different fields. Therefore, such interdisciplinary researches must always be encouraged.

This program pursues the promotion of cutting-edge researches for the elucidation of the fundamental mechanisms of who cellular functions emerge from cross-hierarchical interactions of supra-assemblies of biomolecules. We also promote researches that aim the creation of novel technologies that enable the measurement of dynamics of supra-assemblies with unprecedentedly high spatiotemporal resolution, as well as the researches with creative idea on mathematical and/or theoretical approaches.

Research Supervisor's Policy on Call for Application, Selection, and Management of the Research Area

1. Background

In life science, various approaches have been used to elucidate cellular functions. In addition, structural biology and biophysical studies have largely advanced our understandings of the structures, dynamics, and working mechanisms of biomolecules and biomolecular complexes. Furthermore, in cell biology, developments of microscopies and probe technologies have enabled to capture the vivid images of intracellular dynamics of biomolecules and their interactions with other molecules.

Recently, the reports are drastically increasing for researches on cross-hierarchical interactions among molecules and organelles, and on inter-organelle communications. Examples include the studies on spontaneous formation and regulation of intracellular droplets formed from intrinsically disordered proteins and RNA by the use of advanced microscopy systems.

2. Target of this research area

In this research area, we develop technologies for the structural analysis and imaging of supra-assemblies of biomolecules in cells and elucidate the mechanism on how cell functions emerge from dynamic cross-hierarchical interactions among supra-assemblies. In addition to the technology development for structural analysis and imaging, mathematical approaches for analysis of large-scale data that new technology will produce will be also strongly promoted. We also pursue the development of novel technologies to control dynamic supra-assembly biomolecular structures to verify the working hypothesis generated from imaging and analytical approaches. That would include optogenetics approaches and chemical biology approaches. In addition, we promote the simulation studies in virtual space or physical space (*) with the aim to verify working hypothesis by investigating the supra-assemblies of biomolecules in untestable conditions in real cells.

The below is the examples of research projects this program expects to promote. Note proposals of different idea or different approaches are also welcomed.

(*) Simulation in physical space indicates experimental verifications such as in vitro reconstitution in test tubes or microreactors.

①Development of platform technology for capturing and measuring dynamic supra-assembly biomolecular structures in cells

We develop platform technologies for measuring the quantification, localization, form, dynamics and interaction of cellular molecules, complexes, supramolecules and organelles.

1) Development of high resolution imaging and measuring technology for capturing spatial

coordinates, structures and reaction state of intracellular molecules

2) Development of measurement technology for membrane-less organelles

3) Development of quantification technology for number, form and function of molecules, molecular complexes, organelles and among others

4) Development of an imaging probe that does not interfere with structure and dynamics of molecules, molecular complexes, or organelles

5) Development of unstained quantitative imaging technology of dynamic supra-assembly biomolecular structures

6) Comprehensive and ultra-high-speed measurement technology for dynamic supra-assembly biomolecular structures

② Development of platform technology for control of dynamic supra-assembly biomolecular structures of cells

We develop platform technologies for perturbing molecules, supramolecular complexes, organelles and cells to elucidate their functions.

1) Development of real time measurement technology to control the number, form and/or function of dynamic supra-assembly biomolecular structures

2) Elucidation of the function and mechanism of organelles and membrane-less organelles using perturbation technology

3) Development of control technology for dynamic supra-assembly biomolecular structures using synthetic chemical molecules

③ Mathematical analysis and simulation of dynamic supra-assembly of biomolecules

We perform and develop modeling and simulation of cellular phenomena using mathematical science, physics, information science, and device engineering.

1) Understanding and synthesis of liquid-liquid phase separation like phenomena of biological droplets from the view point of soft matter physics and polymer chemistry

2) Development of machine learning technology for collecting, and analyzing the structure and function information of dynamic supra-assembly biomolecular structures for comprehensive understanding of dynamic supra-assembly.

3) Performing of computational simulation of dynamic supra-assembly biomolecular structures

4) Performing of molecular simulation in physical space, by reconstructing dynamic supra-assembly biomolecular structure in test tubes or microreactors

④ Elucidation and application of the mechanism of higher order cellular functions

We elucidate the mechanism of how higher order cellular functions emerge from dynamic interplay

of supra-assemblies of biomolecular structures, and apply the understandings for synthetic supra-assemblies.

1) Elucidation of the formation and disappearance mechanism of membraneless organelles

2) Elucidation of physiological significance of organelles contact

3) Elucidation of disease mechanism caused by dysfunction of dynamic supra-assembly biomolecular structure

4) Comprehensive understanding of functional mechanism of dynamic supra-assembly biomolecular structure

5) Design and functional expression of new dynamic supra-assembly biomolecular structures composed of synthetic molecules and biomolecules

In this fiscal year's selection, as in previous years, we expect ambitious application proposals based on individual ideas from a wide range of fields such as molecular biology, biochemistry, biophysics, structural biology, mathematical biology, chemical biology, soft matter physics, advanced optics, and device engineering. In particular, we also expect that the number of application proposals with strong perspectives on physics and mathematical, and technically sharp proposals about advanced measurement engineering, device engineering, chemical biotechnology, etc. will increase.

As this is the final year of open call of this research area, we are seeking for proposals on novel analytical technologies that will contribute to the development of next-generation analysis methods for studies on dynamic supra-assemblies in addition to proposals aimed at addressing biological issues. For this reason, we are looking forward to receiving excellent proposals with cutting-edge idea from a wide range of fields, including molecular simulation, structural analysis, spectroscopy, imaging technology, microfluidic/Lab on a chip, and data analysis/data mining technology. This research area principally emphasizes "addressing biological issues". However, technical proposals are not necessarily required to address a biological issue(s) within the research period. In this case, applicants should explain, in their research proposals, how the technology to be developed in PRESTO program will contribute to the study on supra-assemblies in the future. Such proposals will be evaluated as technological development ones. All of the research proposals should be based on the applicant's own original idea. Proposals will be evaluated on the strength and uniqueness of the proposed research.

3. Management policy

1) This research area not only promotes creative research proposals by individual researchers but also emphasizes the viewpoint of human resource development concerning whether they can break their own shells through interaction with researchers in other fields or make new "associate" who may work together for future research related to thermal science.

2) This research area will hold discussions on research actively and frequently. In the 2020 fiscal year, this PRESTO research is expected to utilize the opportunities of collaborations with researchers inside and outside the research area, including those in the CREST research area “Dynamics and functions of intracellular components”, which launched under the same strategic objective, to become an important step to assist the participants’ advancement in research. In this regard, we invite researchers to explain in their proposal how they would like to develop cell biology research in the future.

3) This research area expects that researchers with accepted proposals firmly understand the social background of the research and advance their own PRESTO research to support collaborations with industries in the future. For this purpose, researchers who participate in this research area are requested to actively study intellectual property rights during the research period.

4. Cooperation with other research areas

To maximize scientific achievements as a Strategic Basic Research Program in JST, we will collaborate with CREST "Creation of a quantitative analysis platform for understanding spatiotemporal interactions between multiple cells", PRESTO "Intercellular interactions in multicellular systems and their dynamics", and CREST " Dynamics and functions of intracellular components " research areas, and jointly hold meetings, workshops, and symposia as necessary. We will also hold joint symposiums and workshops together with AMED-CREST / PRIME "Understanding proteostasis and discovering innovative medical applications" and with related academic societies and research institutions.

The research period of PRESTO is 3.5 years, and the upper limit of research expenses is 40 million yen.