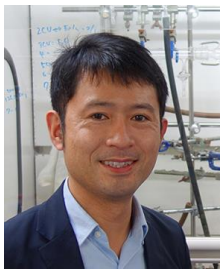
【Grant-in-Aid for Transformative Research Areas（B）】

Section II



Title of Project： Kinetics-Driven Supramolecular Chemistry

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Number of Research Area：21B205 Researcher Number：70509132

【Purpose of the Research Project】

Nature is full of asymmetric structures. From macroscopic scales such as living organisms to molecular scales such as proteins, many living organisms have highly complex and controlled asymmetric structures, and have acquired a diversity of structures and functions. Through the development of supramolecular chemistry, we have developed methodologies for constructing various molecular assemblies. However, most of them are limited to the construction of geometrically symmetric forms, and the bottom-up chemistry of asymmetric structures has not yet been established. We propose that “kinetic control”, which is universally observed in the construction process of biomolecules and biological tissues, is the key to constructing functional asymmetric structures. In this project, researchers specializing in organic chemistry, cell biology, structural biology, and computational physics elucidate and mimic the mechanism of building asymmetric structures in living organisms for the artificial construction of functional asymmetric structures. The aim is to construct a methodology of “Kinetics-Driven Supramolecular Chemistry” to synthetically construct functional asymmetric structures.

【Content of the Research Project】

In the process of constructing asymmetric structures at each level of the organism, we find that it involves one important and universal control method: kinetic control. All multicellular organisms have diverse and complex macro-scale shapes, all of which are created from a single fertilized egg. During the development of tissues from the fertilized egg, cell migration in certain directions and cell division are delayed, resulting in the construction of controlled asymmetric structures. Delayed processes are also observed at the molecular scale. The shape of a protein is created by folding of one or multiple polypeptide chains. In the process of folding from a random-coiled polypeptide chain, it is known that there are chaperone enzymes (holdases) that actively delay the folding process in order to prevent the progression of misfolding. Cell canceration, protein aggregation, and amyloidosis can be seen as the result of the failure of the delayed control mechanism, and it is clear that the delayed control in each biological tissue hierarchy maintains the vital functions. We propose that this seemingly paradoxical “promotion of functional 3D structure formation by delay” is the key to the methodology of creating various asymmetric structures unique to living organisms. In the cell, delayed control is achieved at the molecular and even molecular assembly scales, and it has been suggested that the two are interconnected. In order to construct a methodology of “kinetics-driven supramolecular chemistry”, we elucidate both scales in a collaborative system, leading to a chemical reconstruction. Three principal investigators specializing in protein structural biology, cell biology, and chemistry, and one subordinate investigator specializing in computational physics will work together to effectively promote this field.

Project A01: Elucidation of kinetic mechanisms in the protein folding process based on structural biology.

Project B01: Elucidation of kinetic mechanisms in the structural formation and functional expression of organelles based on cell biology.

Project C01: Development of synthetic molecules that exhibit kinetic control functions to control the folding of polypeptide chains by collaboration of computational science and organic chemistry.

【Expected Research Achievements and Scientific Significance】

As shown by living organisms, controlled and ordered structural diversity generates functional diversity. Therefore, mimicking and artificially establishing the asymmetric structure construction method found in living organisms will enable the formation of a variety of structures that are not bound by geometric structures, which will in turn lead to the development of various functional molecules and materials similar to biomolecules.

The promotion of "Kinetics-Driven Supramolecular Chemistry" will lead to the development of methodologies that enable the construction of asymmetric structures with controlled kinetics of molecules and molecular assemblies in chemistry, and the creation of new materials. Furthermore, it is expected to lead to a kinetics-based understanding of biological construction processes and mechanisms of biological function expression in biology. The knowledge obtained in this research area is expected to have a ripple effect on a wide range of fields from chemistry to biology.

【Key Words】
Kinetic control, supramolecular chemistry, protein folding, chaperons.

【Term of Project】 FY2021-2023

【Budget Allocation】 105,000 Thousand Yen

【Homepage Address and Other Contact Information】

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