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

Section III

# Title of Project： Biology of non-domain biopolymer

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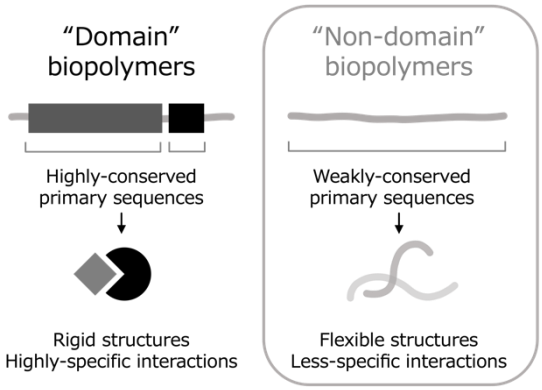
Number of Research Area：21A304 Researcher Number：50324679

## 【Purpose of the Research Project】

The primary sequences of biopolymers including RNA and proteins are widely conserved between different species, which are folded into specific three-dimensional structures, resulting in specific molecular interactions that regulate various biological reactions. This has long been a dogma of molecular biology. However, recent studies have identified a number of novel biopolymers that exert their molecular functions without known conserved functional domains. We designate these molecules as "non-domain biopolymers, which assumingly function without being folded into distinct structures. In this Research Area, we will reveal physiological functions of these non-domain biopolymers and understand novel molecular and cellular mechanisms, which are conserved between these molecules.




## 【Content of the Research Project】

The functions of non-domain biopolymers are not strictly dependent on the primary sequences of nucleotides or amino acids. It is therefore difficult to predict functions of non-domain biopolymer based on sequence homology to known conserved functional domains. On the other hands, a large number of noncoding and protein-coding genes still remains functionally unknown due to the lack of known functional domains, raising a possibility that they are indeed functional non-domain biopolymers. In this Research Area, we aim to identify novel non-domain biopolymers via reverse-genetic approaches by performing phenotypic analyses of mutant animals of these unannotated genes.

Representative examples of known non-domain biopolymers of important molecular functions include the long noncoding RNA NEAT1 that functions as an architectural component of non-membranous organelle paraspeckles, super-disordered Hero proteins that strongly inhibit the formation of disease-related molecular aggregates, and Dsup that controls outstanding ability of Tardigrade to survive extreme environments. The molecular mechanism how these non-domain biopolymers exert their functions, however, still remains elusive. Notably, a group of Hero proteins exhibit remarkable ability to maintain their molecular function even after randomly shuffling the primary amino acid sequences while keeping the composition of the amino acid constant. These observations suggest that classic dogma of molecular biology might not be applicable to non-domain biopolymers, and we have to develop a new concept to understand their molecular mechanisms. In this Research Area, we will reveal molecular dynamics and mechanisms characteristic to the non-domain biopolymers through multi-disciplinary approaches, including deep mutagenesis analyses, molecular dynamics simulations, structural analyses using cryogenic electron and super-resolution microscopy, together with conventional structural and omics analyses.

## 【Expected Research Achievements and Scientific Significance】

Understanding of common molecular mechanisms shared between non-domain biopolymers will reveal flexible strategies for the creation of novel functional biomolecules during the evolution of living organisms. In addition to the achievement in basic biology, we can expect technical application using non-domain biopolymers. For example, we will be able to develop a new clinical approach to treat neurodegenerative diseases such as ALS accompanied by the formation of toxic molecular aggregates, which formation is strongly inhibited by Hero proteins. We can also expect to develop novel highly efficient biochemical reaction systems or stress-resistant engineered cells by using tardigrade proteins that protects and stabilize cells/proteins from harsh environments.

## 【Key Words】

- RNA
- super-disordered proteins
- intrinsically disordered regions
- nonmembranous organelle
- phase separation
- neurodegenerative diseases

【Term of Project】FY2021-2025

【Budget Allocation】1,112,400 Thousand Yen

## 【Homepage Address and Other Contact Information】

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