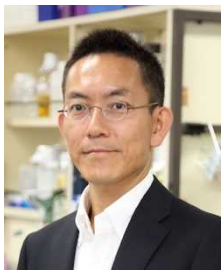
【Grant-in-Aid for Transformative Research Areas（A）】

Section Ⅲ



Title of Project： Multifaceted Proteins: Expanding and Transformative Protein World

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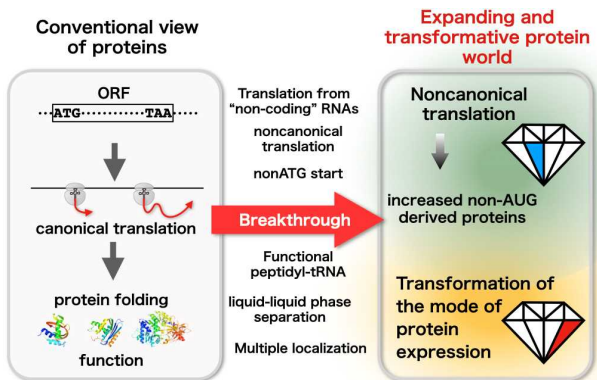
【Purpose of the Research Project】

Over the past few years, the traditional view of proteins has been updated. Current protein science has been based on the premise that the ribosome synthesizes the polypeptide from the start codon to a stop codon of the open reading frame (ORF) in the mRNA. The completed polypeptide chain folds into a three-dimensional structure, and then functions. However, recent breakthroughs in various discoveries and technological innovations have revealed novel aspects of protein science. For example, translation does not always initiate from the AUG start codon of the annotated ORFs. Translation often starts from a codon other than AUG, and sometimes stalls during the translation elongation, independent of stop codons. Accumulating evidence shows that a number of non-coding RNAs, which, by initial definition, do not code for proteins, is translated into physiologically relevant proteins. The repertoire of proteins that shape the proteome increases due to innovations in mass spectrometry-based proteomics. In addition, it has become clear that proteins do not always function by folding, and that they do not only function at specific locations. Furthermore, such noncanonical translation is closely related to diseases such as neurodegenerative disorders.

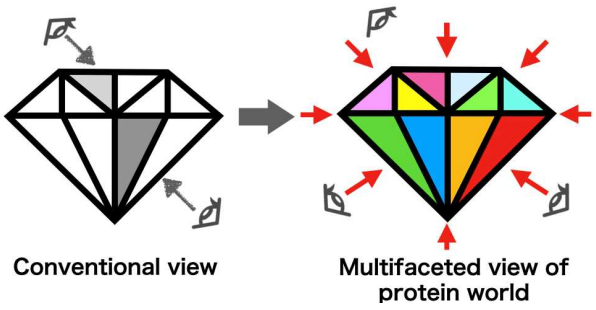
Thus, the "protein world" is expanding and transforming (Fig. 1). In other words, to truly understand the real protein world, it is necessary to update the conventional view on the translation, the repertoire, and modes of function.

Fig. 1　Expanding and Transformative Protein World



This project aims to construct a new paradigm by redefining the protein world from multifaceted perspectives, and to update the conventional view of proteins (Fig. 2).

Fig. 2　Concept of Multifaceted Proteins



【Content of the Research Project】

The following research will be conducted to achieve the aim.

1. Generality and function of proteins produced from noncanonical translation dynamics.
2. Exploration of previously unappreciated proteomes and their physiological functions.
3. Noncanonical translation involved in neurodegenerative diseases and its relation to pathology.
4. Novel aspect of protein function in the cell.
5. Development and application of new methodologies

【Expected Research Achievements and Scientific Significance】

The paradigm shift in protein science, achieved by this project, will have a great impact on basic science, but it will not be limited to the protein science. In addition, this field is expected to lead to seamless connections to the medical and industrial fields, such as the elucidation of the pathogenesis of neurodegenerative diseases, biomarkers for diseases, and *de novo* design protein research.

【Key Words】

Noncanonical translation: Translation that does not just initiate from the AUG start codon and end at stop codons in open reading frames. Also, noncanonical translation includes disease-related repeat-associated non-AUG-dependent translation (RAN translation).

【Term of Project】 FY2020-2024

【Budget Allocation】 1,211,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://proteins.jp