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

In-cell chemical network driven by neo-PTMs（neo-PTMs）

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Research Area Information	Number of Research Area : 22B201　Project Period (FY) : 2022-2024 Keywords : Post-translational modifications, In-cell chemistry, Non-natural modifications, Protein, Catalyst

Purpose and Background of the Research

●Outline of the Research

The purpose of this research area is to understand the changes in intracellular chemical networks caused by the introduction of artificial post-translational modifications (*neo*-PTMs) to intracellular proteins, and to construct theories that can be used to make use of them. To that end, we set three tasks to (1) introduce, (2) connect, and (3) understand *neo*-PTMs, and formed a team of three researchers who have technical uniqueness in each of them. In this research area, we will clarify the molecular-level mechanisms by which living organisms respond to the environment, and establish new methods for controlling biological functions that cannot be achieved by existing methods that mainly regulate enzyme functions.

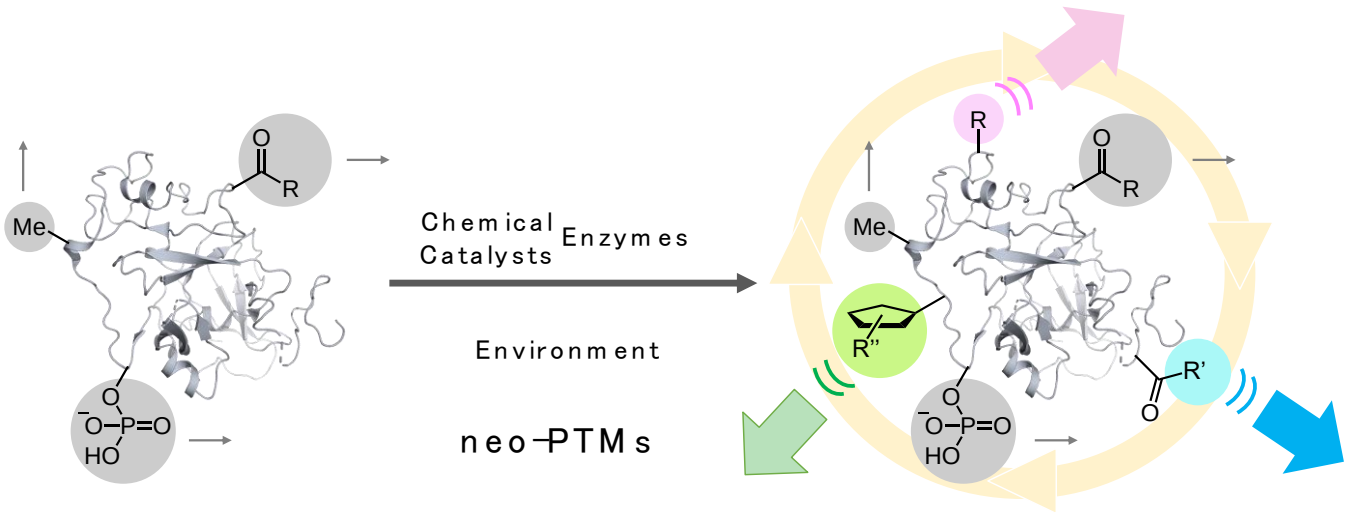


Figure 1. Research Aims

Proteins are molecules that play a central role in cell and biological functions. The human genome encodes only 20,000 to 25,000 proteins, but various post-translational modifications (PTMs) produce proteins with various functions. In other words, organisms acquire various functions through chemical modification of biomolecules and the chemical networks that they create. However, the structures and functions of molecules that can be constructed by chemistry are limitless, and there is no reason why the chemical modifications that biomolecules undergo should be limited to those originally found in *vivo*. In fact, in recent years, it has been found that dietary and environmental factors such as excessive alcohol consumption and the intake of food additives cause changes in *in vivo* metabolites and change the post-translational modification state of proteins, especially histones. Chemical modification changes of biomolecules in response to these exogenous stimuli have only just begun to be discovered. There is no attempt to artificially change the *in vivo* chemical network by introducing it into the living body.

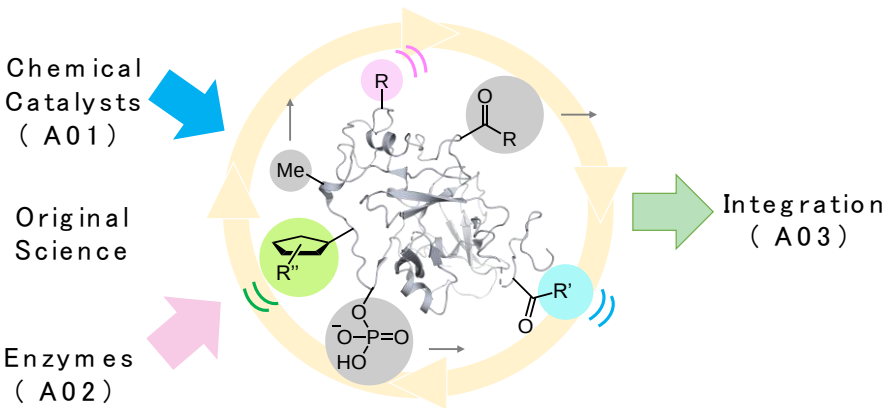
In this research area, we introduce infinite diversity of chemistry into cells in the form of artificial post-translational modifications (*neo*-PTMs), and construct the theory to understand and utilize the intracellular chemical networks newly created by them. This research area is different from the fusion of chemistry and cell biology that probes cell functions, which has been done so far. Instead, synthetic chemistry that creates a new chemical order in the cell, proteomics, and cell biology are fused. It is an emerging field. The achievement of this research is expected to contribute to biology and medicine by discovering a method of controlling biological functions that cannot be achieved by conventional methods based on the regulation of enzyme functions.

Expected Research Achievements

● Research Aims and Expected Outcomes

In this research area, *neo*-PTMs are defined as post-translational modifications of proteins that were not originally found *in vivo* or post-translational modifications whose existence is unknown. The goal of this research area is to introduce it artificially, understand how it affects various biomolecules and their chemical modifications, and utilize it. In this way, we aim to find a method of controlling biological functions that was impossible with conventional methods based on the regulation of enzyme functions, and to make a major contribution to biology and medicine.

Proteins acquire various intracellular functions through various post-translational modifications to the primary sequences defined in the genetic information. The modified proteins further interact with each other and a chemical network is formed by linking them together. However, the types of chemical modifications do not need to be limited to those that originally occur in living organisms, and the limitless variety of chemical modifications that can be introduced on the basis of synthetic chemistry can be used with a wider range of applications. It has hidden potential. In order to demonstrate this, in this research area, we introduce *neo*-PTMs into intracellular proteins through multifaceted approaches of synthetic chemistry (Group A01), chemical biology (Group A02), and biology (Group A03). By investigating changes in intracellular chemical networks and changes in cell functions, we will clarify the potential of approaches to regulate biological functions using *neo*-PTMs.



Before This Research

- Limited to endogenous PTMs
- Enzyme Inhibitors

neo-PTMs

Transform Existing Research

This Research

- ✓ Introduction of *neo*-PTMs
- ✓ Creation of In-Cell Network
- ✓ Find A New Function

Figure 2. Novelty, originality and potential of this research area

Homepage Address, etc.	https://neo-ptms.com