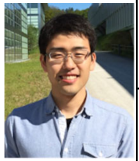
【Grant-in-Aid for Transformative Research Areas（B）】

Metabolons in Natural Product Biosynthesis



Principal Investigator	The University of Tokyo, Graduate School of Pharmaceutical Sciences, Associate Professor MORI Takahiro	Researcher Number : 60734564
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Purpose and Background of the Research

The biosynthesis of specialized metabolites has been extensively studied, with significant progress in elucidating biosynthetic pathways and enzyme functions across various organisms. However, the subcellular localization of these enzymes and the mechanisms regulating biosynthetic reactions via enzyme–enzyme interactions remain poorly understood.

In plants, enzyme–enzyme interactions have been reported in the biosynthesis of compounds such as flavonoids and lignans. Sequential enzymes often colocalize to form supramolecular complexes, enhancing metabolic efficiency via substrate channeling and preventing the degradation of unstable intermediates. These assemblies, known as "metabolons," control product selectivity through dynamic protein–protein interactions.

Despite these findings, the detailed mechanisms of enzyme interaction, substrate transfer, and enzymatic regulation remain largely unexplored. In microbes, although metabolon-like complexes are suspected, experimental evidence and structural insights are limited, and the universality and diversity of these systems across species remain unclear.

This research defines “specialized metabolons” as enzyme assemblies that enhance biosynthetic efficiency and regulate reaction outcomes. By uncovering and comparing their structural and functional properties in plants and microbes, we aim to clarify natural strategies for efficient metabolism, substrate channeling, chemical diversity, and evolutionary design. These insights will guide the development of next-generation biosynthetic systems for the efficient production of valuable compounds.

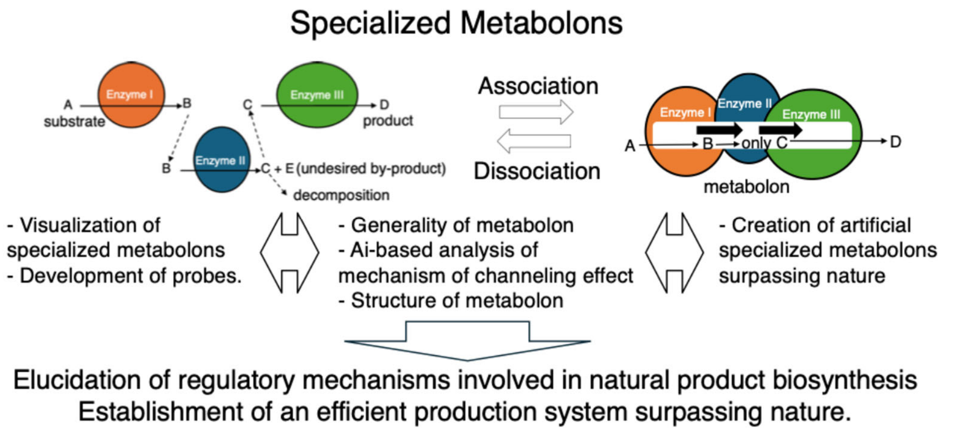

Figure 1. overview of research

Expected Research Achievements

● **Aim of Each groups**

Group A01 (Takahiro Mori) – Elucidation of Microbial Specialized Metabolons and Structural Analysis of Enzyme Complexes

This unit focuses on uncovering novel specialized metabolons and their modes of interaction in microbial natural product biosynthesis, where enzyme–enzyme interactions have been suggested but not fully characterized.

Group A02 (Toshiyuki Waki) – Specialized Metabolons Driving Structural Diversity in Plant Specialized Metabolites

This group aims to elucidate how conserved protein–protein interactions (PPIs) among plant enzymes correct the inherent ambiguity in product specificity observed in chalcone synthase (CHS) enzymes across land plants. The study seeks to uncover the mechanisms that enable the simultaneous preservation of evolutionary potential for chemical diversity and the enhancement of metabolic efficiency.

Group A03 (Eita Sasaki) – Development of Fluorescent Probes for Detecting Specialized Metabolons

This unit aims to develop innovative fluorescent tools to visualize enzyme–enzyme interactions and the formation of metabolons. Design of viscosity-sensitive molecules based on intramolecular twisting of rhodamine derivatives, enabling fluorescence on/off switching.

Group A04 (Naohiro Terasaka) – Construction of Artificial Specialized Metabolons for Enhanced Compound Production

By integrating experimental evolutionary techniques (e.g., mRNA display, microdroplet sorting) with computational protein engineering (e.g., virtual evolution algorithms), this group aims to engineer next-generation biosynthetic systems.

● **Ripple Effects**

A wide variety of specialized metabolites, such as polyketides, terpenoids, and alkaloids, are commonly found across diverse organisms, including not only plants and microorganisms but also insects and marine organisms. Expanding the scope of biosynthetic studies to address the specialized metabolons responsible for the production of such shared classes of compounds will open new avenues in the field of natural product biosynthesis, leading to the establishment of an emerging research area that focuses on large-scale, conceptual frameworks for specialized metabolite biosynthetic systems, which have thus far received limited attention.

Furthermore, this research direction is expected to bridge the gap between enzyme engineering, which aims to design artificial enzymes with desired functions, and synthetic biology, which seeks to construct efficient production systems for valuable compounds. By imparting self-assembly properties to engineered enzymes, it becomes possible to establish a biomanufacturing platform that integrates both subcellular localization and enzyme–enzyme interactions.

This approach will not only enable the effective utilization of bioactive compounds that have been overlooked due to their limited natural supply, but will also exert a significant impact on the fields of natural product chemistry, phytochemistry, and microbiology across both academia and industry. Additionally, it is anticipated to contribute to future drug discovery efforts.

Homepage Address, etc.	Homepage : https://sp-metabolon.elsi.jp/ Email : sp.metabolon@gmail.com