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Purpose and Background of the Research

● Outline of the Research

Metabolites are molecules that are broken down from nutrients to generate energy or to synthesize components of the body. Recently, it has been shown that metabolites have unexpected activities that differ from their original functions. However, the overall picture is unclear, and it remains terra incognita. Therefore, this study aims to discover novel functions of metabolites in intracellular responses and intercellular communication and to elucidate their mechanisms of action in metabolic control. Furthermore, by applying metabolic simulation, we aim to understand the nature of metabolic remodeling by environmental response from an informatics perspective, which will be used to develop new technologies for material production and drug discovery in the future. To this end, we will promote the following four themes (Fig. 1).

1. Chemical genetics using unique metabolite library
2. Novel functions of metabolites in cell response
3. Roles of metabolites in cell-cell communication
4. Development of methods for metabolic flux prediction by simulation

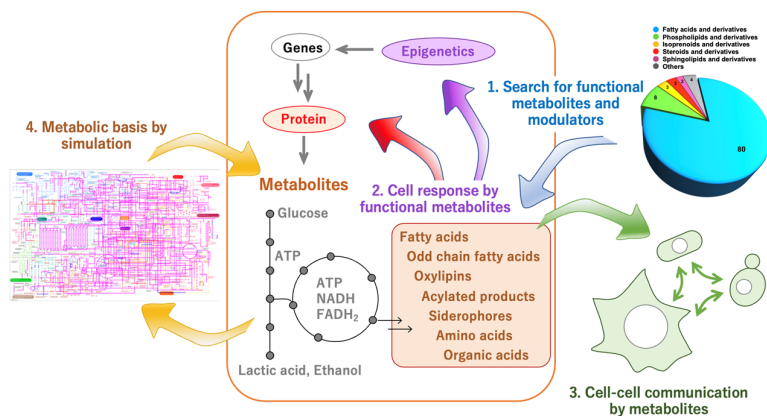


Fig. 1 Aiming at understanding of unknown functions of metabolites

● Academic Background

Acetyl-CoA, a metabolite for energy production and synthesis of biomolecules, regulates gene expression through acetylation of histones and other proteins. Thus, it has been known that a few metabolites have distinct roles other than metabolism. Recently, however, it has become clear that many metabolites have physiological roles far beyond those expected (Fig. 2). Thus, the most critical "question" is whether the majority of metabolites have hidden functions to regulate upstream gene expression, mRNA and protein functions. This study seeks to answer this "question" by elucidating the biological functions of metabolites discovered in our previous studies.

● Originality and Creativity

To explore the hidden functions of individual metabolites, comprehensive chemical biology that combines metabolite analysis, metabolite libraries, and inhibitor screening is necessary. We have developed a novel library consisting of more than 600 metabolites and found several fatty acid metabolites that have unexpected bioactivities. We have also found compounds that induce metabolic remodeling, such as activation of mitochondrial respiration. However, it is difficult to understand the entire metabolic flux, because metabolic pathways are complex. Therefore, we will develop an unprecedented method to understand the entire flux by metabolic network simulation and to perform artificial metabolic transformation.

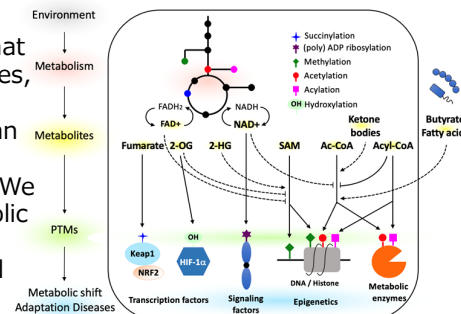


Fig. 2 Roles of metabolites in environmental responses

Expected Research Achievements

In this study, we will conduct (1) searches for new functional metabolites using endogenous metabolite libraries and natural product libraries; (2) cellular responses through lipid (fatty acid) metabolism; (3) cell-cell communication through metabolites; and (4) informatics using metabolic flux tools to discover new functions of metabolites (Fig. 1).

● Discovery of functional metabolites and their intra- and intercellular roles

To understand the unknown functions of metabolites, we will first conduct chemical genetics to discover new activities. Second, we will elucidate their intracellular response mechanisms involved in post-translational modification of proteins and epigenetics, and third, we will clarify intercellular communication via metabolites in the microbial ecosystem. For example, metabolites secreted by wild-type fission yeast that alter the amino acid uptake of various mutant strains will be focused (Fig. 3).

● Understanding of metabolic basis by simulation

We will construct a mathematical model of metabolic flux simulation to predict metabolic changes caused by nutritional conditions, genetic mutations, and compounds, as a basis for materials production or drug discovery (Fig. 4). We will build a system to understand how the entire metabolism is transformed in bacteria, yeast, and human cells, and predict their changes by flux balance analysis (FBA).

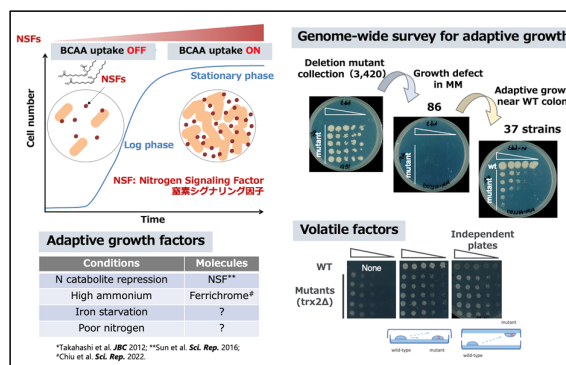


Fig. 3. Discovery of cell-cell communication molecules

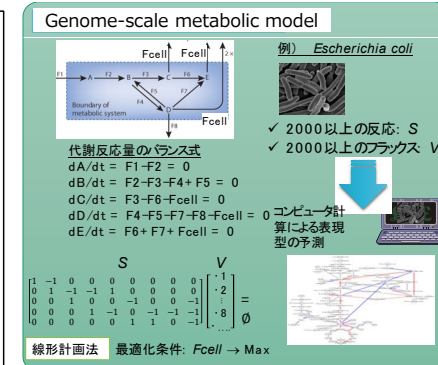


Fig. 4. A model for flux balance analysis