Form 3

Report for Joint/Usage Research Program for Endocrine/Metabolism (Fiscal Year 2025)

Date：2026/05/31

To Director of Institute for Molecular and Cellular Regulation, Gunma University

Principal Applicant	
Institution	Showa University School of Medicine The University of Michigan Medical School
Position	Associate professor/lecturer
Name	Masahiro Hosonuma

We report on the results of joint research in fiscal year 2025 as below.

（Program No.　　）

1．Research Title	Epigenetic Regulation of Macrophages by the Enterobacterial Metabolite Isobutyric Acid
2．Purpose and Significance of the research project	The principal applicant and colleagues have demonstrated that isobutyric acid, a gut microbial metabolite derived from indigestible proteins, induces macrophage differentiation toward the M1 phenotype. As a possible mechanism, isobutyrylation, a type of epigenetic modification, was suggested. Therefore, this project aims to perform detailed epigenomic analyses and identify the mechanism by which isobutyric acid induces macrophage differentiation through isobutyrylation. This study is expected not only to provide the first evidence that isobutyrylation regulates disease pathogenesis, but also to demonstrate the potential therapeutic application of isobutyric acid as a novel postbiotic and indigestible proteins, its substrates, as novel prebiotics.
3．Period of The Program	April 1, 2025～ March 31, 2026

4．Project Members

Name	Age	Sex	Affiliation	Position	Role
(Principal Applicant) Masahiro Hosonuma	35	M	Showa Medical University, Department of Pharmacology The University of Michigan Medical School, Department of Internal Medicine	Associate professor/lecturer	Project director
(Research Collaborators) Naoko Hattori	47	F	Gunma University, Institute for Molecular and Cellular Regulation	Professor	Epigenomic analysis
Tatsunori Oguchi	38		Showa Medical University, Department of Pharmacology	Professor	Cell analysis
Eiji Funayama	27		Showa Medical University, Department of Pharmacology	Assistant professor	Animal experiments

5. Collaborating Researcher of IMCR		Name of Laboratory		Name	

6. Research Plans

The original aim of this project was to elucidate the epigenetic mechanisms by which the gut microbial metabolite isobutyric acid regulates macrophage function. In particular, we planned to investigate whether isobutyric acid induces histone isobutyrylation and thereby modulates inflammatory macrophage differentiation. After discussion with Prof. Naoko Hattori, we decided to first focus on the upstream metabolic process leading to isobutyric acid production. Because valine is a major substrate for isobutyric acid generation by gut microbiota, we prioritized the investigation of differential gut microbial metabolism of L-valine and D-valine and their effects on intestinal inflammation in a DSS-induced colitis model. We planned to compare the effects of L-valine and D-valine supplementation on DSS-induced colitis severity, gut microbiota composition, and predicted microbial metabolic pathways, with particular attention to branched-chain fatty acid-related metabolism.

7. Research results:

In this fiscal year, we investigated the effects of L-valine and D-valine supplementation on gut microbial metabolism and DSS-induced colitis. Based on discussions with Prof. Naoko Hattori, we focused on the metabolic difference between L-valine and D-valine as upstream substrates for isobutyric acid production. In the DSS-induced colitis model, L-valine supplementation, but not D-valine supplementation, exacerbated colitis severity. This finding suggests that the stereochemistry of valine critically influences its biological effects under inflammatory conditions. We further analyzed gut microbiota composition and predicted microbial metabolic pathways. L-valine supplementation induced characteristic alterations in the gut microbiota. In addition, pathway analysis suggested that C5-branched dibasic acid metabolism was specifically increased after L-valine supplementation, whereas this change was not evident after D-valine supplementation. These results suggest that L-valine and D-valine are differentially metabolized by gut microbiota and that L-valine-associated microbial metabolism may contribute to the exacerbation of intestinal inflammation. The collaboration with Prof. Hattori was essential for refining the research direction from downstream epigenetic regulation by isobutyric acid to the upstream microbial metabolic processes that generate branched-chain fatty acid-related metabolites. Based on these findings, we are currently continuing the original aim of this project by investigating whether isobutyric acid induces epigenetic modifications, including histone isobutyrylation, and thereby regulates macrophage function during intestinal inflammation.

８．Present status of academic conference presentations and research papers associated with the results of the joint research, and exchange of information on the joint research with the collaborating researcher at IMCR.

① Please list the publications that include the name of the collaborating researcher from IMCR and send a reprint of each publication to IMCR.
None at present.

② Please list the publications that include a description that the research was supported by the Joint Research Program with IMCR and send a reprint of each publication to IMCR.
None at present.

③ List up to 3 conferences (name of conference, date of conference, and title of the presentation).
None at present.

④ Exchange of information exchange with collaborating researcher from IMCR (please list main points of communication).
We exchanged information with Prof. Naoko Hattori regarding the research direction, interpretation of the results, and future experimental plans. Through these discussions, we decided to prioritize the analysis of L-valine and D-valine metabolism by gut microbiota as an upstream process leading to isobutyric acid production.