MCW GRADUATE SCHOOL

Doctoral Dissertation Defense Announcement

"Modulation of gut microbial metabolism and energy expenditure by xenobiotics and bacterial metabolites"

Matthew A. Hadiono

Candidate for Doctor of Philosophy in Microbiology & Immunology

School of Graduate Studies

Medical College of Wisconsin

Committee in Charge:

John Kirby, PhD (Mentor)

Justin Grobe, PhD

Nita Salzman, MD, PhD

Christopher Kristich, PhD

Martin Hessner, PhD

Date: Thursday, May 9, 2024

Time: 11:00 AM (CST)

Defense Location: Kerrigan Auditorium

Zoom: https://mcw-edu.zoom.us/j/8534438321?pwd=MUQzY1V1bjNmN1IzWjZBZ1k4YjdLQT09

Meeting ID: 853 443 8321 Passcode: #8sT9QU0

Graduate Studies:

Advanced Bacterial Physiology

Bacterial Toxin-Mucosal Cell Interactions

Classical Papers in Microbiology and Immunology

Doctoral Dissertation

Ethics and Integrity in Science

Immunology Journal Club

Integrated Microbiology and Immunology

Microbiology and Immunology Seminar Course

Reading and Research

Research Ethics Discussion Series

Dissertation

"Modulation of gut bacterial metabolism and anaerobic energy expenditure by xenobiotics and bacterial metabolites"

Obesity is associated with serious comorbidities including heart disease, stroke, and cancer, and is one of the most challenging healthcare problems of our times. Thus, there is a critical need to identify and understand the mechanisms of obesity. Recently, the gut microbiome has been identified as a factor which can play a causative role in weight gain.

Studies in our lab demonstrated that the gut microbiota comprise a thermogenic biomass that contributes to resting metabolic rate. Acute reduction of bacterial biomass using cecectomy resulted in a ~10% decrease in total metabolic rate via suppression of anaerobic energy expenditure, which subsequently led to weight gain. Treatment with the antipsychotic, risperidone, suppresses anaerobic energy expenditure in a microbiome-dependent manner. In contrast, a specialized metabolite produced by *Limosilactobacillus reuteri*, reutericyclin (RTC), was capable of ameliorating risperidone-induced weight gain (RIWG) and restored energy balance in the presence of risperidone.

We performed comprehensive evaluations of energy balance in mice treated with risperidone, RTC, or in combination to identify a mechanism by which RTC affects energy balance to mitigate RIWG. We employed the Promethion metabolic phenotyping system as well as whole-animal calorimetry coupled with respirometry on C57BL/6J female mice to assess components of energy balance including resting metabolic rate. We observed that risperidone suppresses resting anaerobic metabolism and that RTC restores energy expenditure in the presence of risperidone. Treatment with either RTC or risperidone does not alter other components of aerobic energy expenditure. Because anaerobic energy expenditure has previously been demonstrated to be dependent on the biomass and composition of the gut microbiome, we performed sequencing on stool samples collected during the energy balance assessments described above. Risperidone and RTC treatments reciprocally modified the relative abundance of taxa known to participate in fermentation. For example, RTC administration resulted in increased relative abundance of *Akkermansia muciniphila*, which is consistently correlated with leanness in both humans and mice.

We also performed studies investigating the potential for RTC to promote lower body weight outside the context of risperidone treatment. Obese mice being fed a 60% high-fat diet exhibited reduced weight gain when treated with RTC. Additionally, mice treated with a relatively low dose of semaglutide exhibited enhanced weight loss when also treated with RTC. Treatment with RTC did not affect food consumption or digestive efficiency, indicating that RTC promotes lower body weight in these models through effects on energy expenditure. Interestingly, both semaglutide and RTC treatment led to increased relative mass of the cecum, which may drive enhanced anaerobic resting metabolism.

Together, our data demonstrate that treatment with RTC positively modulates anaerobic EE, possibly by enhancing fermentation of the gut microbial community, and may represent a novel therapeutic in the treatment of obesity. Further, combination therapy with low dose semaglutide and RTC may be an effective treatment for diabetes and obesity. These studies have expanded the foundation by which the fascinating direct connections between gut bacterial metabolism and resting anaerobic energy expenditure can be explored.

Matthew Andrew Hadiono

Curriculum Vitae
mhadiono@mcw.edu

Education

2019 – Present	Ph.D. Candidate Medical College of Wisconsin, Department of Microbiology & Immunology Advisor: John R. Kirby, Ph.D.
2017 – 2019	Medical Student (M1-M2) Medical College of Wisconsin, Medical Scientist Training Program
2012 – 2016	Bachelor of Science in Biology Case Western Reserve University

Research Experience

2019 – Present	Doctoral Student Medical College of Wisconsin, Department of Microbiology & Immunology Advisor: John R. Kirby, Ph.D.
2015-2017	Research Technologist Case Western Reserve University, Case Comprehensive Cancer Center Advisors: Sanford Markowitz, M.D., Ph.D. and Won Jin Ho, M.D.
2012-2015	Research Technologist Case Western Reserve University, School of Medicine - Department of Dermatology Advisor: Daniel L. Popkin, M.D., Ph.D.

National Presentations

2022	Modulation of Gut Microbial Metabolism and Energy Expenditure by Xenobiotics and Bacterial Metabolites. Poster, MD-PhD National Student Conference.
2022	Modulation of Gut Microbial Metabolism and Energy Expenditure by Xenobiotics and Bacterial Metabolites. Poster, Molecular Genetics of Bacteria and Phages Meeting
2019	Specialized Bacterial Metabolite, Reutericyclin, Deflects Antipsychotic-Induced Weight Gain: Investigating Modes of Action. Poster, Keystone

	Symposia (“Microbiome: Chemical Mechanisms and Biological Consequences”)
2019	Specialized Bacterial Metabolite, Reutericyclin, Deflects Antipsychotic-Induced Weight Gain: Investigating Modes of Action. Poster, Cold Stone Harbor Laboratory Microbiome Conference

Publications

Hadiono M, Burnett CL, Reho J, Kindel T, Grobe JL, Kirby JR. Reutericyclin mitigates risperidone-induced suppression of anaerobic energy expenditure. 2024. Submitted for publication at *Gut Microbes*.

Lozada-Fernández VV, deLeon O, Kellogg SL, Saravia FL, **Hadiono MA**, Atkinson SN, Grobe JL, Kirby JR. Nicotinamide Riboside-Conditioned Microbiota Deflects High-Fat Diet-Induced Weight Gain in Mice. mSystems, 2022. PMID: 35076278.

Ho WJ, Smith JNP, Park YS, **Hadiono M**, Christo K, Jogasuria A, Zhang Y, Broncano AV, Kasturi L, Dawson DM, Gerson SL, Markowitz SD, Desai AB. 15-PGDH regulates hematopoietic and gastrointestinal fitness during aging. PLoS One, 2022. PMID: 35587945

Griffith AD, Zaidi AK, Pietro A, **Hadiono M**, Yang JS, Davis R, Popkin DL. A requirement for slc15a4 in imiquimod-induced systemic inflammation and psoriasiform inflammation in mice. Sci Rep, 2018. PMID: 30262916.