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学 位 論 文 内 容 の 要 旨

博士の専攻分野の名称： 博 士（食資源学）

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学 位 論 文 題 名

Application of untargeted lipidomics in biomarker studies related to gut health, obesity, and neurodegenerative disorders

（腸の健康、肥満、神経変性疾患に関連するバイオマーカー研究における
非標的リピドミクスの応用）

Abstract

Lipids are a structurally and functionally diverse group of essential biomolecules that play significant roles in maintaining cellular structure, regulating energy metabolism, and mediating signal transduction. Lipids are also involved in various physiological processes such as cell proliferation, apoptosis, immune responses, and inflammation, making them critical determinants of health and disease. Dysregulation of lipid metabolism is increasingly recognized as a hallmark of various diseases, including gut dysbiosis, obesity, and neurodegeneration. Altered lipid profiles also play crucial roles in the pathophysiology of these disorders, highlighting the need for detailed lipid-level investigations. The growing field of lipidomics, particularly untargeted approaches using high-resolution mass spectrometry, offers powerful tools for profiling lipid alterations and elucidating the complex roles of lipids in health and disease. Lipidomics enables the discovery of disease-specific lipid fingerprints and metabolic pathways, offering deep insights into disease mechanisms and aiding in the identification of novel lipid biomarkers for early diagnosis of the disease. Despite their significance, comprehensive lipidomic analyses across multiple disease conditions remain limited in biomarker research. This thesis addresses the gap by employing an untargeted liquid chromatography coupled mass spectrometry (LC/MS)-based lipidomics strategy across multiple biological contexts to uncover novel lipid biomarkers associated with metabolic and neurodegenerative disorders, including exploring the therapeutic potential of natural bioactive lipids as anti-obesity agents.

Chapter one provides an overview of lipids, their classification, and their essential roles in health and disease. The chapter also highlights the use of an untargeted LC/MS technique to profile lipid alterations in complex biological systems, emphasizing the significance of lipidomics in biomarker research. The chapter highlights the current limitations in applying comprehensive lipidomic analyses across multiple disease contexts for novel biomarker discovery. This chapter establishes a foundation for understanding how lipidomic analysis can be leveraged to investigate disease mechanisms and discover novel biomarkers for early diagnosis, therapeutic monitoring, and disease stratification.

In Chapter two, an untargeted LC/MS-based lipidomics technique was used to investigate the sex-specific effects of ethanol on the colonic lipidome in a murine model. A total of 186 lipid species were identified, revealing distinct lipidomic profiles between pair-fed and ethanol-fed groups in male mice

compared to female mice. This study offers new insights into the sex-dependent lipidomic responses to alcohol-induced gut-dysbiosis, highlighting potential lipid biomarkers such as PG (O-15:1/15:0) and PE (O-18:2/15:0) in both sexes upon ethanol exposures.

Chapter three transition to human samples, leading to the identification of novel gut microbial lipids. Through untargeted LC/MS analysis, 26 isomeric lipid species, including short- and medium-chain esters of hydroxy fatty acids (SFAHFAs and MFAHFAs), were detected. Notably, two new MFAHFAs were identified and characterized for the first time in human fecal samples. These findings provide the first evidence on unique microbial lipids, opening new avenues for exploring their physiological roles.

Chapter four describes the use of untargeted lipidomics in exploring lipid alterations in neurodegenerative disorders. Lipidomic analysis of saliva, plasma, and fecal samples from stage-specific groups of Alzheimer's disease (AD) revealed dynamic alterations in lipid profiles across disease stages in older adults. The study identified medium-chain fatty acids containing triacylglycerol as a potential early-stage non-invasive lipid biomarker for mild cognitive impairment patients. In parallel, brain lipidome alterations in AD, Parkinson's disease (PD), and Huntington's disease (HD) reveal distinct lipid profiles and highlight disease-specific lipid biomarker such as AHexCer (d(O-18:1)18:1/15:0;O), PC (O-22:5/19:3), and PS (O-17:0/22:6) that could aid in distinguishing these neurodegenerative disorders.

Chapter five focused on analyzing plasma samples of pre-adolescent children in the Hokkaido region using high-resolution LC/MS to explore lipidomic variations associated with sex, age, and overweight status. The untargeted lipidomics approach enabled the characterization of 219 lipid species, revealing distinct patterns across developmental stages and weight groups. The study revealed that overweight status influences plasma lipid composition in early childhood and identified TG (10:0/10:0/18:1) as a potential lipid biomarker associated with childhood obesity.

Chapter 6 investigates the therapeutic potential of seaweed-derived bioactive lipids by identifying a natural sphingomyelin synthase (SMS) inhibitor from *Undaria pinnatifida* (wakame). Through a combination of structural characterization techniques and *in-vitro* SMS assays, FA 20:5 was confirmed as the potent bioactive compound in wakame extract responsible for the inhibition of both SMS1 and SMS2. This study highlights the discovery of natural anti-obesity agents, offering new insights into lipid metabolism-related therapeutic strategies.

Overall, this thesis demonstrates the broad applicability of untargeted lipidomics in uncovering lipid biomarkers across gut dysbiosis, obesity, and neurodegenerative disorders. By integrating multi-disease approaches, this work advances our understanding of lipid dysregulation and its role in disease pathogenesis, offering new avenues for diagnosis and intervention.