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Application of Liquid Chromatography/Mass Spectrometry: Food Lipid Profiling and
Monitoring Lipid Dysregulation
(液体クロマトグラフィー質量分析法の応用：食品の脂質プロファイリングおよび脂質代謝異常の
モニタリング)

Lipids are essential macronutrients that are biosynthesized in cells and play key roles in energy metabolism. lipid analysis has become an important and rapidly developing research area. Recent advances in untargeted lipidomics using liquid chromatography–mass spectrometry have enabled comprehensive characterization of lipid compositions in both food and biological samples. This technology can be applied not only to the discovery of disease biomarkers, but also to investigations of food bioactivity, lipid nutritional value, and authenticity. However, research on global lipid profiling in foods and on lipid dysregulation remains limited. To address these gaps, this thesis comprises four studies: (1) Lipid profiling of Japanese edible sea cucumbers using non-targeted lipidomics, (2) Sex- and body part-specific lipid profiling of shishamo and capelin (Karafuto shishamo) using non-targeted lipidomics, (3) Identification of natural inhibitors of sphingomyelin synthase from shishamo smelt, and (4) Evaluation of the effects of combined hypothermic machine perfusion and hydrogen gas therapy on the lipidome of livers from rats subjected to cardiac arrest. Chapter 1 provides an overview of lipid classification, their biological importance, and current research issues. The limitations and scope of the present research are also discussed. Chapter

2 describes a comprehensive analysis of lipids in the skin, meat, and intestinal contents of three edible sea cucumber species, comparing their compositions and lipid nutritional values. Nutritional evaluation based on fatty acid composition suggests that consumption of red sea cucumber intestinal contents may offer significant health benefits. Chapter 3 presents the application of untargeted lipidomics to Hokkaido-origin shishamo and imported capelin (Karafuto shishamo) to investigate sex- and body part-specific lipid profiles and to validate authenticity. The results showed that the heads of female shishamo exhibited high triacylglycerol levels, with a composition similar to that of the roe. Chapter 4 describes the discovery of a naturally derived inhibitor of sphingomyelin synthase (SMS), a protein associated with fatty liver disease through sphingomyelin accumulation, from shishamo smelt. A cell-based assay using SMS-overexpressing HeLa cells was developed, and fraction-based screening revealed that the shishamo-derived SMS inhibitor is fatty acid (FA 18:1). Further investigations on its mode of action and structural elucidation are underway. Chapter 5 investigated the relationship between impaired liver function and lipid metabolism by administering combined treatment of hypothermic machine perfusion and hydrogen gas to rat livers after cardiac arrest. Analysis results suggest dysregulation of lysophosphatidylinositol metabolism in the liver during transplantation. Overall, this thesis compiles findings on lipid profiles in unexplored foods such as sea cucumber and shishamo, followed by biochemical insights into hepatic lipid dysregulation during transplantation. Furthermore, the SMS inhibitor derived from shishamo identified holds promise for application in cell and animal experiments toward the development of nutritional supplements and pharmaceuticals.