



Lipidomic Analysis of Plasma Sphingolipids in an East Asian Population Identifies Novel Associations with Obesity- and Diabetes-Related Characteristics.

Deron R. Herr*, Wee Siong Chew, Federico Torta, Shanshan Ji, Hyungwon Choi, Husna Begum, Xueling Sim, Chin MengKhoo, Eric Yin HaoKhoo, Wei-Yi Ong, Rob M. Van Dam, Markus R. Wenk, E. Shyong Tai

Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore,

*Corresponding Author, Email: phcdrh@nus.edu.sg.

Abstract

Sphingolipids (SPs) are ubiquitous, structurally diverse molecules that consist of over 600 different confirmed species, but are likely to include tens of thousands of metabolites with potential biological significance. These include ceramides, hexosylceramides, sphingomyelins, and long chain bases that are produced by a well-characterized metabolic pathway. Individual SPs are known to be involved in the pathology of a number of disease states including obesity and diabetes. Therefore, it is likely that perturbations in plasma concentrations of these lipids will be associated with disease, as either a cause or a consequence. Identification of these associations may reveal prognostic or diagnostic biomarkers or may provide novel insight into disease processes. Historically, a complete understanding of the biological roles of these lipids has been limited by a lack of sensitive, discriminating, high-throughput analytical techniques. To address this knowledge gap, we utilized the latest mass spectrometry techniques to perform a lipidomics evaluation of over 100 molecularly distinct SLs in the plasma of 2,302 ethnically Chinese Singaporeans. These lipid profiles were compared to 445 matched clinical and demographic characteristics. We identified a number of significant associations with age, sex, body mass index, lipoproteins, insulin, and glycated hemoglobin. Notably, we found that these associations were not uniformly positive, which would be expected if global SP metabolism was elevated by age, obesity, and/or type 2 diabetes (T2DM). Instead, SP subclasses were elevated or depleted selectively, suggesting that the balance of SP metabolism, rather than overall SP accumulation, contributes to pathologies such as obesity. Furthermore, we identify specific SP molecules that are associated with T2DM incidence. Cumulatively, we report the first large-scale cross-sectional cohort of an Asian population, and identify putative biomarkers for obesity/diabetes risk.

Keywords: *Plasma Sphingolipids, Obesity, Diabetes, Biological roles of Lipids, Pathology, Perturbation*
