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Metabolic reprogramming of sphingolipids in the pathogenesis of hepatic adenoma linked to GSD Ia

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Background: Glycogen storage disease Ia (GSD Ia) is a genetic metabolic disorder characterized by an impaired glycogen metabolism that leads to severe hypoglycemia and excessive glycogen accumulation. Although advanced dietary therapy has significantly improved metabolic control in GSD Ia patients over the last few decades, longterm complications such as hepatic adenomas (HCA) continue to be prevalent during the second or third decades of life. Recent studies have identified sphingolipid turnover as a hallmark of liver inflammation with endogenous sphingolipid profiles continually changing through metabolic reprogramming along the disease progression. Hence, we hypothesized that sphingolipids may be involved in the pathogenesis of liver-related complications in GSD Ia.

Method: Using liquid chromatography-tandem mass spectrometry, we developed and validated targeted sphingolipidomic analysis of 18 sphingolipid species from ceramide, sphingomyelin, hexosylceramide and lactosylceramide. The construction of sphingolipid profiles was successfully achieved using plasma and liver tissue samples obtained from GSD Ia mouse models (wild type n =5, GSD Ia n = 5).

Results: The analysis of sphingolipids in GSD Ia mouse models revealed a significant increase in 14 species in plasma and 10 species in liver samples. The diverse variation in the sphingolipid disruptions highlighted the proapoptotic role of long-chain ceramide in disease progression. The compositional analysis indicated that sphingolipid profiles in liver and plasma displayed unique characteristics, suggesting that sphingolipids may exert different functional effects in various physiological and pathological conditions Of note, the hepatic sphingolipid profiles of 2-week-old GSD Ia mice closely resembled the sphingolipid derangements typically observed in NAFLD, further underscoring the importance of sphingolipids in liver pathogenesis.

Conclusion: Significant disruptions in sphingolipid profiles were identified in GSD Ia mouse models, which may be associated with the liver inflammation. These findings suggest that sphingolipids have the potential to serve as biomarkers for monitoring intracellular liver conditions in GSD Ia.

Biography

Jae Yeon Park is a master's student in Dr. Mitchell's translational lab at the McGill University Health Centre (MUHC), where she has conducted research on targeted sphingolipidomics in GSD Ia (glycogen storage disorder Ia). Her primary focus has been to investigate the underlying metabolic imbalances of hepatic adenoma development in GSD Ia using a LC-MS/MS (liquid chromatography-tandem mass spectrometry) approach. Jae Yeon is an accomplished sphingolipid analyst with extensive experience in analyzing sphingolipids from a range of biological samples, including human blood, urine, mice plasma and liver tissue, as well as cultured cells.

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