GUEST LECTURE SERIES

December 7, 2023

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Exploring the Biochemical Complexity of the Lipid Metabolic Network in Inherited Metabolic Diseases

The metabolism of lipids represents a complex network of biochemical reactions. Unravelling novel insights into the biochemical details of lipid metabolism often proves challenging due to constraints such as limited enzyme knowledge, purification difficulties, and the substantial impact of dietary factors. Findings derived from in vitro studies frequently do not seamlessly translate into insights about the manifestation of lipid metabolism in vivo. Furthermore, enzymes within the lipid metabolic network frequently engage with a diverse array of accepted substrates, complicating the determination of their true physiological roles.

However, inherent metabolic errors present a valuable resource for thoroughly investigating lipid metabolism. This is particularly potent when coupled with LC-MS/MS-based lipidomics approaches, offering a powerful tool to unravel the in vivo contributions of lipid biochemical pathways.

For instance, the rare inherited disease Barth Syndrome, characterized by severe mitochondriopathy, served as a model system for our exploration into the intricacies of cardiolipin side chain remodeling. Using this disease as a model system, we could elucidate the molecular mechanisms that are responsible for establishing tissue specificity of cardiolipins. Similarly, the study of HSD10-deficiency allowed us to investigate the postulated function of HSD10 in cardiolipin homeostasis, revealing fundamental discrepancies between in vitro and in vivo observations. A further example are our examinations of plasmalogen metabolism, with a specific focus on PEDS1, a pivotal enzyme that is crucial for forming up to 20% of the total phospholipid mass in mammalian tissues. Despite its importance, PEDS1 detailed function remained elusive. Through a PEDS1-deficiency model, we achieved a comprehensive understanding of this enzymes biochemical specificities and its role in mammalian phospholipid metabolism. Therewith we could also shed light on the diverse physiological functions of plasmalogens.

In conclusion, continued research efforts are still needed to comprehensively elucidate the convoluted biochemistry of the lipid metabolic network. For achieving this, the combination of informative disease model systems with state-of-the-art analytical techniques and dedicated bioinformatics tools synergizes particularly well, paving the way for the discovery of numerous novel scientific insights.