METABOLOMICS: HOW CAN WE USE IT FOR METABOLIC DISEASES - LESSONS FROM A MONOGENIC MITOCHONDRIAL DISORDER

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Abstract

The use of recently emerging metabolomic technologies - which aim at systematically measure all low-molecular weight compounds within a biological system - has provided some valuable insight into the global metabolic perturbations prevailing in several metabolic diseases. This presentation will illustrate the value of lipidomics, a subset of metabolomics focusing on lipids, in deciphering the biochemical consequences ensuing from mitochondrial dysfunction, a condition that underlies many rare and common age-associated chronic diseases. The focus will be on recent results obtained through the application of comprehensive untargeted and targeted lipidomics to samples from patients with Leigh Syndrome French-Canadian variant (LSFC), a mitochondrial disorder caused by mutations in the nuclear gene leucine-rich pentatricopeptide repeat containing protein (LRPPRC), and mice harboring liver-specific inactivation of *Lrpprc* (H-*Lrpprc*$^{-/-}$). LSFC is characterized by a tissue-specific defect in the assembly of oxidative phosphorylation complexes, principally complex IV in brain and liver, and to a lesser extent in muscle. This study extends our previous work on LSFC (*Thompson Legault et al. Cell Reports 13: 981, 2015; Cuillerier et al. Hum Mol Genet 15: 186, 2017)* and takes advantage of our recently validated high-resolution LC-QTOF lipidomic workflow (*Forest et al. J. Prot. Res. 17: 3657, 2018*). Results show plasma and hepatic changes in plasmalogens, bile acid conjugates, as well as of very long chain and odd chain acylcarnitines, which are reminiscent albeit more subtle than those reported in primary peroxisomal disorders. Of potential broader relevance, they also include major lipid changes evocative of hepatic steatosis, which is consistent with previous findings in H-*Lrpprc-/-* mice and LSFC patients. Collectively, these results underscore the value of untargeted lipidomics to unveil unexpected mechanisms underlying lipid dyshomeostasis ensuing from mitochondrial dysfunction, herein implying peroxisomes, which likely contribute to the pathophysiology of LSFC, but also other rare and common chronic diseases with mitochondrial dysfunction.

Keywords

Lipidomics, Mitochondria, Peroxisomes, Plasmalogens, Acylcarnitines, Monogenic mitochondrial disorder, Liver steatosis