A lipidome landscape of aging in mice

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Abstract

Understanding the molecular mechanisms of aging is crucial for enhancing healthy longevity. We conducted untargeted lipidomics across 13 biological samples from mice at various life stages (2, 12, 19 and 24 months) to explore the potential link between aging and lipid metabolism, considering sex (male or female) and microbiome (specific pathogen-free or germ-free) dependencies. By analyzing 2,704 molecules from 109 lipid subclasses, we characterized common and tissue-specific lipidome alterations associated with aging. For example, the levels of bis(monoacylglycero)phosphate containing polyunsaturated fatty acids increased in various organs during aging, whereas the levels of other phospholipids containing saturated and monounsaturated fatty acids decreased. In addition, we discovered age-dependent sulfonolipid accumulation, absent in germ-free mice, correlating with *Alistipes* abundance determined by 16S ribosomal RNA gene amplicon sequencing. In the male kidney, glycolipids such as galactosylceramides, galabiosylceramides (Gal2Cer), trihexosylceramides (Hex3Cer), and mono- and digalactosyldiacylglycerols were detected, with two lipid classes—Gal2Cer and Hex3Cer—being significantly enriched in aged mice. Integrated analysis of the kidney transcriptome revealed uridine diphosphate galactosyltransferase 8A (UGT8a), alkylglycerone phosphate synthase and fatty acyl-coenzyme A reductase 1 as potential enzymes responsible for the male-specific glycolipid biosynthesis in vivo, which would be relevant to sex dependency in kidney diseases. Inhibiting UGT8 reduced the levels of these glycolipids and the expression of inflammatory cytokines in the kidney. Our study provides a valuable resource for clarifying potential links between lipid metabolism and aging.