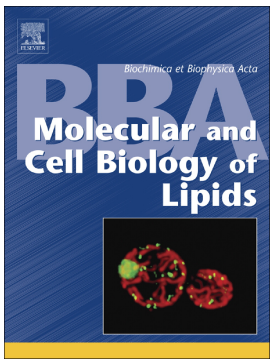

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Inactivation of Ceramide Synthase 2 catalytic activity in mice affects transcription of genes involved in lipid metabolism and cell division

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Abbreviations: BAC, bacterial artificial chromosome; CerS, ceramide synthase; CK, cytokeratin; DAG, diacylglycerols; DTA, diphtheria toxin A; ES-cells, embryonic stem cells; FC, fold change; FDR, false discovery rate; FFA, free fatty acids; frt, Flp recognition target; (e)GFP, (enhanced) green fluorescent protein; GS, glutamine synthetase; GO, gene ontology; gWAT, gonadal white adipose tissue; HEK, human embryonic kidney cells; HR, homologous region; iBAT, interscapular brown adipose tissue; igWAT, inguinal white adipose tissue; IRES, internal ribosomal entry site; loxP, locus of X-over P1; MEF, mouse embryonic fibroblasts; NBD, nitrobenzooxadiazole; pgk, phosphoglycerate kinase; PCNA, proliferating cell nuclear antigen; qRT-PCR, quantitative Real Time-PCR; SOE, splicing by overlap extension; TAG, triacylglycerols; TF, transcription factor; TLC, Tram-Lag1-CLN8; vs., versus

Abstract

The replacement of two consecutive histidine residues by alanine residues in the catalytic center of ceramide synthase 2 in a new transgenic mouse mutant (CerS2 H/A) leads to inactivation of catalytic activity and reduces protein level to 60% of the WT level. We show here by qRT-PCR and transcriptome analyses that several transcripts of genes involved in lipid metabolism and cell division are differentially regulated in livers of CerS2 H/A mice. Thus, very long chain ceramides produced by CerS2 are required for transcriptional regulation of target genes. The hepatocellular carcinomata previously described in old CerS2 KO mice were already present in 8-week-old CerS2 H/A animals and thus are caused by the loss of CerS2 catalytic activity already during early life.

Keywords

Cell division, ceramide synthase 2, hepatocellular carcinoma, lipid metabolism, sphingolipids, transcriptional control