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Hepatocyte-specific depletion of augmenter of liver regeneration (ALR) protein alters miRNA signature linked to lipid homeostasis leading to excessive steatosis

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Augmenter of liver regeneration (ALR) is a fundamental life protein expressed in all mammalian organs. ALR's presence in mitochondria is essential for their function and survival. Depletion of ALR from liver (hepatocyte)-specific $ALR^{flox/flox}$/Alb-Cre (ALR-L-KO) mice causes mitochondrial injury, robust lipid accumulation and apoptosis between 1 and 2 weeks post-birth. Steatosis is regressed upon reappearance of ALR by 4 weeks but continued death of Cre-expressing hepatocytes induces regeneration, inflammation and fibrosis. To delineate mechanisms of this pathological progression, we investigated whether ALR depletion alters expression of micro-RNAs (miRNAs), which play important roles in numerous biological processes including lipid homeostasis. We performed miRNA-seq analysis and profiled the hepatic miRNA expression in 1-, 2-, and 4-week old mice. Of the 765 micro-RNAs identified in WT and ALR-L-KO livers, 203 showed differential expression: 125, 106 and 141 miRNAs were up-regulated and 70, 97 and 61 miRNAs down-regulated at 1, 2 and 4 weeks respectively in ALR-L-KO compared to the WT mice. miR-708-3p, miR-540-3p and miR-541-5p, which have 3'UTR-binding sites for peroxisome proliferator-activated receptor (PPAR)α, carnitine palmitoyl transferase a (CPT1a) and mitochondrial transcription factor A (TFAM) (all down-regulated at 2 weeks in ALR-L-KO mice), were all found to be up-regulated at 2 weeks in ALR-L-KO compared to the WT mice. Increase in these miRNAs upon ALR depletion was also concurrent with increased expression of elongation of very long fatty acids 6 (ELOVl6) and steroyl CoA desaturase (SCD1) that are involved in de novo lipogenesis, and decreased expression of acyl CoA oxidase 1 (ACOX1) and CPT1 that promote β-oxidation of fatty acids. The effect of ALR depletion on these miRNAs was recapitulated *in vitro* in cultured hepatocytes. Likewise, hepatic expression of miRNAs implicated in inflammation and fibrosis (miR-199a-1-5p, miR-146b-5p, miR-194-1-5p, miR-1843a, miR-410-3p and miR-434-3p) was also altered in a way to promote these pathologies. These findings suggest that ALR's regulation of miRNAs is critical to hepatic lipid homeostasis with potential implications in nonalcoholic fatty liver disease/steatohepatitis.

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