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The pre-mRNA alternative splicing regulated by SRPK2: a new player in alcohol-associated liver disease?

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Alcohol-associated liver disease (ALD) represents a spectrum of liver pathologies that span from hepatic steatosis to steatohepatitis, which may eventually progress to cirrhosis and hepatocellular carcinoma (1). While alcohol-induced hepatic steatosis is reversible upon abstinence of alcohol, mounting evidence indicates that chronic hepatic steatosis promotes hepatocyte lipotoxicity, inflammation and progression of ALD (2). Hence, an in-depth understanding of the mechanisms by which alcohol regulates lipid metabolism in the pathogenesis of ALD is critical for the development of novel therapeutic strategies against ALD. Hepatic lipid homeostasis is regulated by at least four metabolic processes, lipid uptake and *de novo* lipogenesis for increasing whereas lipid secretion and fatty acid beta oxidation for decreasing levels of hepatic lipids, all these four steps can be affected by alcohol. Alcohol consumption increases adipose lipolysis and hepatic fatty acid uptake but decreases hepatic very-low-density lipoprotein secretion and mitochondrial fatty acid oxidation. Moreover, alcohol also increases *de novo* fatty acid and triglyceride synthesis via activation of hepatic sterol regulatory element-binding protein 1 (SREBP-1) and *Lipin 1*, respectively (2). There are three mammalian *Lipin 1* isoforms, *Lipin 1α*, *Lipin 1β*, and *Lipin 1γ*, which are generated from *Lipin 1* pre-mRNA alternative splicing by splicing factors. *Lipin 1γ* is mainly expressed in the brain whereas *Lipin 1α* and *Lipin 1β* are ubiquitously expressed in various tissues. LIPIN 1α localizes at nucleus and acts as a transcription co-regulator to control metabolic homeostasis. LIPIN 1β has phosphatidic acid phosphohydrolase (PAP) activity that converts phosphatidic acid to diacylglycerol for triglyceride synthesis. Alcohol increased the ratio of hepatic *Lipin 1*β/α (3), but the detail mechanisms of how alcohol regulates *Lipin 1* splicing and lipid metabolism in ALD remains largely unknown.

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Author's contribution

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Serine/arginine-rich protein-specific kinase 2 (SRPK2) is a member of the SRPK family of serine/arginine kinases. This enzyme is involved in the post-transcriptional regulation of gene expression through the phosphorylation of serine/arginine-rich splicing factors to regulate alternative splicing. Alternative splicing is a process that generates multiple mature RNA transcripts from a single gene by selectively including or skipping exons during pre-mRNA splicing. RNA-seq analysis of human plasma samples obtained from various stages of alcoholic cirrhosis revealed that the differentially expressed genes (DEGs) in advanced stages of alcoholic cirrhosis are enriched in the alternative splicing regulation pathway (4). Epithelial splicing regulatory protein 2 (ESRP2), a RNA-splicing factor that maintains the adult hepatocytes maturation, was suppressed in both human and experimental mouse severe alcoholic hepatitis. Loss of ESRP2 led to an increase of the relatively inactive splicing variants of Hippo kinases and active YAP/TAZ resulting in hepatocyte adult to fetal reprogramming and loss of liver functions (5). Altogether, these recent studies support a critical role of RNA splicing in the pathogenesis of ALD. In a study published in the current issue of Hepatology, Li et al now further shed new light on potential targeting hepatic SRPK2-mediated alternative mRNA splicing to ameliorate ALD (6).

Li et al. first observed an increase in SRPK2 levels in livers from patients with ALD and in mice subjected to chronic-plus-binge alcohol feeding. Importantly, inhibiting SRPK2 activity improved liver function and reduced fat accumulation by decreasing SREBP1-mediated expression of lipogenic genes. Mechanistically, SRPK2 could interact with Serine and arginine rich splicing factors 10 (SRSF10), resulting in increased alternative spliced isoform of *Lipin 1β* and ratio of *Lipin 1β/α*, which promoted hepatic lipid synthesis. Additionally, the expression of SRSF10 was also decreased by nearly 50% in alcohol-fed mice but was restored by SRPK2 knockdown, indicating SRPK2 inhibits SRSF10 expression. Moreover, other pre-mRNA targets of SRSF10, including pyruvate kinase isoforms, ATPase phospholipid transporting 8A1, and inner membrane mitochondrial protein, were also restored by SRPK2 knockdown. Taken together, these findings indicate that alcohol consumption increases SRPK2 leading to decreased SRSF10 to alter *Lipin 1* alternative splicing and promote hepatic lipogenesis.

How does alcohol increase hepatic SRPK2? Li et al found that alcohol induced mTORC1 activation and promoted SRPK2 protein accumulation in hepatocytes exposed to alcohol. Interestingly, fibroblast growth factor 21 (FGF21) acted as an endogenous inhibitor of SRPK2 to abolish alcohol-mediated induction of SRPK2 and its associated steatosis. The abundance of SRPK2 and phosphorylation of SR proteins, which representing the SRPK2 kinase activity, were markedly reduced in FGF21 transgenic mouse livers but increased in FGF21 knockout mouse livers. Silencing SRPK2 rescued persistent pathological phenotypes in alcohol fed FGF21 knockout mice. However, the mRNA levels of SRPK2 were not affected by FGF21, suggesting FGF21 may regulate SRPK2 at the posttranslational level. Intriguingly, rapamycin, a well-known mTORC1 inhibitor, repressed SRPK2 protein without affecting the SRPK2 mRNA in ethanol-treated hepatocytes. Chase studies revealed that inhibition of mTORC1 reduced SRPK2 protein stability, which may account for the inhibition of SRPK2 by FGF21. Overall, this study uncovered a novel mechanism by which FGF21 controls alternative splicing-mediated lipogenesis and slows the progression of ALD, which may have therapeutic implications for the treatment of ALD.

Despite advancing our understanding of a novel SRPK2-Lipin 1 splicing in ALD, this study has several limitations. While the authors have identified SRSF10 as a target of SRPK2, it remains ambiguous whether SRPK2 regulated other alternative splicing factors, which may also contribute to the pathogenesis of ALD. Another study has reported that SFRS10 (Splicing Factor, Arginine/Serine-Rich 10) can also alter the splicing of *Lipin 1* pre-mRNA (7). At the first glance, one would be easily confused with the nomenclature of SRSF10 and SFRS10. Notably, SFRS10's official gene name is TRA2B (Transformer 2 beta Homolog), while SRSF10 is referred to as SFRS13 (Splicing Factor, Arginine/Serine-Rich 13), and they are two distinct genes share little homology. Further research is necessary to determine whether SRPK2 or SRSF10 interacts with other splicing regulators and form a complex. In addition, while the evidence that SRPK2 regulates hepatic triglyceride synthesis through SRSF10-mediated *Lipin 1* splicing is compelling, how LIPIN 1β subsequently activate SREBP-1 remains unclear. Decreased hepatic TSC1 and DEPTOR contribute to mTORC1 activation in chronic-plus-binge alcohol-fed mouse livers (8, 9). However, whether FGF21 would inhibit alcohol-induced mTORC1 by affecting TSC1 or DEPTOR remains unknown. Nevertheless, FGF21 functions as a hepatokine in protecting against ALD appears promising. Exploring the impact of other hepatokines, such as Growth differentiation factor 15, on the progression of ALD presents an intriguing avenue for future research. The identification of small molecules targeting SRPK2 for potential human clinical applications could represent a promising future direction for therapeutic development against ALD.

In conclusion, this study provides important insights into the molecular mechanisms underlying hepatic SRPK2-mediated alternative splicing and lipogenesis in ALD. While further research is needed to fully understand the potential implications of targeting SRPK2 and alternative splicing for human patients with ALD, this study represents an important step forward in our understanding of this complex disease.

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Abbreviations:

ALD	Alcohol associated liver disease
DEGs	differentially expressed genes
ESRP2	Epithelial splicing regulatory protein 2
FGF21	Fibroblast growth factor 21
mTORC1	Mammalian target of rapamycin (mTOR) complex 1
SREBP1	Sterol regulatory element-binding protein 1
SRPK2	Serine/arginine-rich protein-specific kinase 2

SRSF10	Serine-arginine rich splicing factor 10
SFRS10	Splicing Factor, Arginine/Serine-Rich 10

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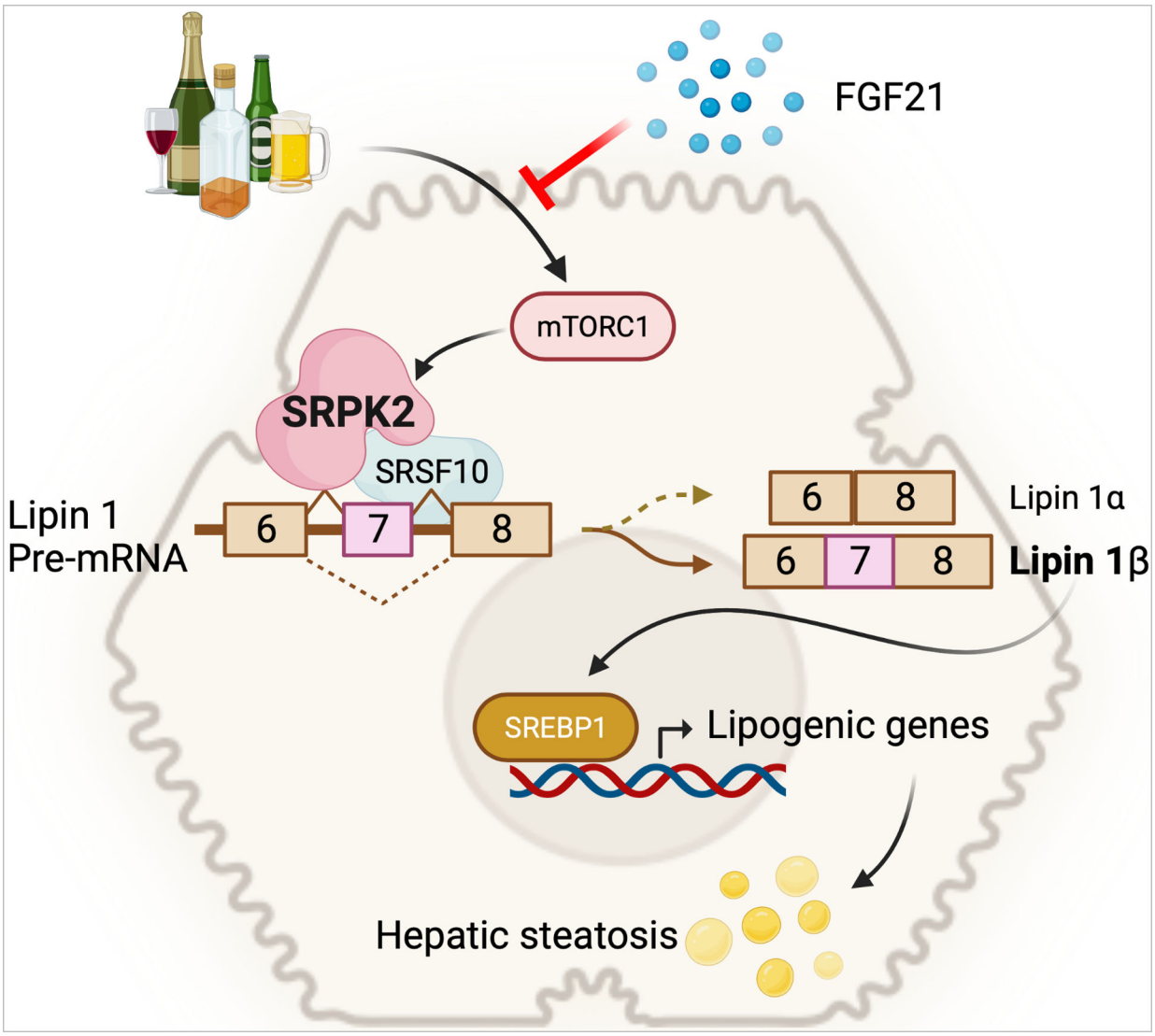

Fig. 1. Regulation of pre-mRNA alternative splicing by FGF21/SRPK2 in alcohol-associated liver disease.

Alcohol consumption induces stabilization and activation of the splicing kinase SRPK2 via the mTORC1 signaling pathway. Elevated SRPK2 interacts with SRSF10, leading to impaired alternative splicing of Lipin 1 pre-mRNA, which leads to increased exon 7 inclusion and generates the Lipin 1β isoform. Subsequently, Lipin 1β may activate the transcriptional factor SREBP-1 by not yet known mechanisms and enhance the expression of lipogenic genes resulting in alcoholic steatosis and hepatoxicity. Notably, overexpression of FGF21 attenuates the pathogenesis of ALD by inhibiting mTORC1-mediated SRPK2 protein stability and its downstream effects.