Metabolism Open 13 (2022) 100157

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.sciencedirect.com/journal/metabolism-open

DRAK2-SRSF6-regulated RNA alternative splicing is a promising therapeutic target in NAFLD/NASH

ARTICLE INFO

Keywords
DAPK
Death-associated protein kinase
DRAK2
Death-associated protein kinase-related apoptosis-inducing kinase-2
Nonalcoholic fatty liver disease
Nonalcoholic steatohepatitis
SRSF6
Serine/arginine-rich splicing factor 6
Splicing

Nowadays, nonalcoholic fatty liver disease (NAFLD) is spreading quickly worldwide, becoming one of the most common chronic liver disorder and affecting one quarter of the world population [1–3]. NAFLD comprises a disease spectrum ranging from steatosis, which is the accumulation of fat in the liver, to nonalcoholic steatohepatitis (NASH), and finally cirrhosis, which represents the most significant risk factor for hepatocellular carcinoma (HCC) [1,4]. However, due to the complexity and our limited understanding of the pathophysiology of NAFLD, NASH, which represents the advanced stage of NAFLD with serious consequences, currently lacks approved pharmacological therapies. Mitochondrial dysfunction and damage induced by overnutrition lead to inflammation, oxidative stress, liver cell death and collagen production, which advance hepatic steatosis to NASH, liver cirrhosis and, potentially, HCC [1]. Alterations in mRNA splicing constitute significant causal factors of disease, being involved in a plethora of human disorders [5]. Alternative splicing may generate many mRNAs and different proteins influencing more than 70% of human genes. Based on recent data, alternative splicing pathways may be associated with several metabolic-related components [6]. Indeed, accumulating evidence has highlighted the close association between the dysregulation of RNA splicing machinery and NAFLD development [7].

A very recent study by Li et al. published in Cell Metabolism [8] has revealed that the death-associated protein kinase-related apoptosis-inducing kinase-2 (DRAK2), a serine/threonine kinase, identified as a nuclear apoptosis promotor belonging to the to the death-associated protein kinase (DAPK) family, may be a potential therapeutic target in NAFLD. DRAK2 is markedly expressed in lymph nodes, thymus, B cells, and trachea, and slightly expressed in hepatic and pancreatic tissues, exhibiting pivotal properties in T cell survival and differentiation, islet survival, and apoptosis [9].

In this study, the authors firstly found that DRAK2 is markedly increased in the hepatic tissue of both NAFLD/NASH patients and NAFLD/NASH diet-fed mice. The upregulation of hepatic DRAK2 aggravated high-fat diet (HFD)-induced liver steatosis and inflammation. In contrast, adeno-associated virus (AAV)-mediated DRAK2 knockdown in the liver or hepatocyte-specific DRAK2 deficiency in mice protected against HFD-induced hepatic steatosis and high-fat/high-cholesterol plus high fructose (HFF) diet-induced hepatic steatohepatitis. Interestingly, they demonstrated that DRAK2 regulates mitochondrial function both *in vivo* and *in vitro*. Mechanistically, comprehensive phosphoproteome and transcriptome analyses have indicated a crucial role of DRAK2 in mRNA alternative splicing. The researchers have identified that DRAK2 binds directly with the serine/arginine (SR)-rich splicing factor 6 (SRSF6) and prevents its phosphorylation by suppressing its synergy with SRSF protein kinase 1 (SRPK1). Surprisingly, through transcriptomic exonic analysis, they found that the DRAK2-SRSF6 signaling pathway is implicated in the alternative splicing of a multitude of mitochondrial function-related genes, such as *Polg2, Rnasel, Guf1*, *Nudt13* and *Nme4*, which regulate the mitochondrial function during NAFLD progression. Importantly, they administrated a DRAK2 inhibitor, 22b, to the HFD and HFD with methionine and choline deficiency-induced NAFLD/NASH model mice, which diminished significantly hepatic lipid accumulation, the liver weight ratio, the levels of transaminases and hepatic fibrosis. These results further indicate the therapeutic potential of targeting the DRAK2-SRSF6 signaling pathway in the amelioration of the continuum of NAFLD/NASH pathologies. More studies are required to explore the DRAK2 enhancement in NAFLD progression, particularly in female mice and clinical cases as well as to

https://doi.org/10.1016/j.metop.2021.100157
Received 7 December 2021; Accepted 7 December 2021
Available online 8 December 2021

investigate whether DRAK2 presents also other substrates or modulates other splicing functions.

In conclusion, these findings provide a novel mechanism underlying NAFLD/NASH progression through the DRAK2-SRSF6 signaling-mediated dysregulation of mitochondrial function-related gene alternative splicing and suggest that targeting this mechanism may be a promising therapeutic approach in NAFLD/NASH. This study uncovered a cardinal role of DRAK2 in NAFLD/NASH development and proposed a potential therapeutic target for this common metabolic disorder.

Funding information

None.

Conflict of interest

None.

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