Targeting MRG15 for the treatment of nonalcoholic steatohepatitis

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ABSTRACT

Non-alcoholic fatty liver disease represents the most common liver disease worldwide and the prevailing cause of liver-related morbidity and mortality. It encompasses a broad clinical spectrum ranging from nonalcoholic fatty liver to nonalcoholic steatohepatitis (NASH), advanced fibrosis, cirrhosis, and finally hepatocellular carcinoma. There have been many studies about the underlying mechanisms of NASH progression, fueling a solid therapeutic pipeline across a variety of potential targets to resolve steatohepatitis or fibrosis. Unfortunately, no therapeutic agent has been approved so far for NASH. In an interesting study, Wei et al. highlighted the role of MRG15 as a targetable epigenetic remodeler in the rhythmic regulation of hepatic lipid metabolism. Remarkably, a recent study from the same group uncovered a chromatin-binding independent working mechanism of MRG15 in regulating the progression from early liver steatosis to the advanced NASH stage with fibrosis and inflammation. Collectively, these studies have shown that MRG15 constitutes a key factor during different stages of NAFLD development. Nuclear MRG15 is recruited to promoter regions of liver lipogenesis genes by LRH-1, where it activates the rhythmic expression of lipid synthesis genes, leading to liver steatosis; while in mitochondria, MRG15 accelerates TUFM degradation, resulting in the aggravation of inflammation and fibrosis, and NASH progression. Blocking of MRG15 by CRISPR targeting or by the FDA-approved drug argatroban, which is an antagonist to MRG15, may attenuate liver steatosis. Further studies regarding the functional aspects of MRG15 in different cell types and its regulatory signals will shed light on the intriguing functions of MRG15 in lipid metabolism and tissue fibrogenesis.

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide with an estimated overall prevalence of 32.4% [1]. NAFLD has been associated with a plethora of metabolic risk factors such as overweight/obesity, type 2 diabetes mellitus, prediabetes, hypertension and dyslipidemia [2-15]. NAFLD is an umbrella term that covers a range of relevant liver disease conditions. The early stage of NAFLD is nonalcoholic fatty liver, characterized by simple hepatic steatosis. NAFLD can evolve to nonalcoholic steatohepatitis (NASH), which is characterized by severe liver steatosis, injury, inflammation and fibrosis [2]. The progression of NASH may lead to liver cirrhosis, liver failure and hepatocellular carcinoma [2].

There have been many studies about the underlying mechanisms of NASH progression. These studies have fueled a solid therapeutic pipeline across a variety of potential targets to resolve steatohepatitis or fibrosis. Unfortunately, no therapeutic agent has been approved so far for NASH treatment. For example, obeticholic acid, a semisynthetic analog of the bile acid chenodeoxycholic acid, is an agonist of farnesoid X receptor (FXR), and has shown promising protective effects against NASH. In phase 3 clinical trial, treatment with obeticholic acid at 25 mg daily has met the primary endpoint of fibrosis improvement by at least one stage with no worsening of NASH [16]. However, due to side effects including liver toxicity signals, severe itching and elevated low-density lipoprotein cholesterol (LDL-C) and total cholesterol levels, which may increase the risk of cardiovascular disease [3], obeticholic acid was rejected by the United States Food and Drug Administration (FDA) for NASH treatment in 2020. Other examples include resmetirom (MGL-3196), which is a thyroid hormone receptor β (THR-β) agonist, and liraglutide, which is a glucagon-like peptide-1 (GLP-1) analog. Both drugs have shown beneficial effects against NASH in phase 2 trials [17-19]. However, side effects were also observed. For example, resmetirom may cause diarrhea and nausea [18] while liraglutide could cause diarrhea, constipation, nausea, and reduction of appetite [19]. Therefore, although multiple drugs successfully entered clinical trials, there may still be a long way from getting the approval for NASH treatment. Identifying new targets or strategies with minimal side effects is an urgent need.

Progression of NAFLD generally starts with the accumulation of excessive liver lipids [20]. Fatty acids in liver are mainly originated from triglyceride lipolysis in the adipose tissue, de novo lipogenesis in the liver, and uptake of dietary-derived chylomicrons from plasma. In the liver, fatty acids are then consumed by mitochondrial beta-oxidation or triglyceride formation [2]. Hepatic triglycerides can also undergo lipolysis to release free fatty acids. Excessive hepatic fatty acids can result in the formation of lipotoxic substances which cause endoplasmic reticulum stress, oxidative stress, liver injury and inflammatory activation [2]. The hepatic stellate cells are subsequently activated by liver injury and inflammation signals, leading to liver fibrogenesis and NASH development [2].
The **MORF4**-related gene on chromosome 15 (MRG15), also called mortality factor 4-like protein 1 (**MORF4L1**), is a chromodomain protein that was previously found both in histone-acetylation and histone deacetylation complexes [21–23], playing an important function in chromatin remodelling, being implicated in both transcriptional activation and suppression. MRG15 was also known in modulating cell viability, development and DNA repair [24–29]; however its role in metabolism is less known. Interestingly, Wei et al. discovered that hepatic MRG15/Liver receptor homolog-1 (LRH-1) complex has a rhythmic genomic recruitment when animals are active and being fed, which actively turns on the genome-wide epigenomic switch of lipid synthetic genes and increases liver lipogenesis [30]. They further identified nuclear receptor LRH-1 that mediates the rhythmic MRG15 recruitment to lipid synthesis genes, presenting MRG15/LRH-1 as a counteractive complex with the Rev-erb/HDAC3/NCoR complex, which was reported to regulate rhythmic chromatin modifications in global transcriptional repression of lipid synthesis genes when animals are inactive and in starvation [31–33]. Moreover, blocking liver MRG15 via CRISPR technology or treatment with the FDA-approved drug argatroban, which is clinically applied as a thrombin inhibitor, but also acts as an antagonist to MRG15, significantly attenuates liver steatosis and improves hepatic lipid metabolism in animals subjected to high fat diet [30].

Remarkably, a recent study from the same group uncovered a chromatin-binding independent working mechanism of MRG15 in regulating the progression from early liver steatosis to the advanced NASH stage with fibrosis and inflammation [34]. In this study, Tian et al. discovered that MRG15 also associates with the outer membrane of mitochondria. They further identified TUFM (mitochondrial Tu translation elongation factor) that interacts with mitochondrial MRG15. Through this protein interaction, MRG15 deacetylates TUFM, leading to the accelerated TUFM degradation via the mitochondrial ClpXP protease system. TUFM plays a significant role in regulating mitophagy and innate immune responses [35–38]. Therefore, reduced liver TUFM may lead to impaired mitophagy, increased oxidative stress and activated NLRP3 inflammasome pathway in the liver, resulting in the progression of fatty liver to NASH. In addition, they found that liver inflammatory signals can further stabilize MRG15, increasing considerably the amounts of MRG15 and establishing thus a vicious circle of MRG15-TUFM that drives NASH progression [34]. Blocking MRG15 significantly protected liver from NASH development in animal models. More importantly, in line with the results in animal models, liver samples from NASH patients also showed a clear increase in MRG15 and correlated reductions in TUFM levels, suggesting the relevance of the MRG15-TUFM pathway in human NASH progression.

Collectively, the current studies have revealed that MRG15 constitutes a key factor during different stages of NAFLD development. Nuclear MRG15 is recruited to promoter regions of liver lipogenesis genes by LRH-1, where it activates the rhythmic expression of lipid synthesis genes, leading to liver steatosis; while in mitochondria, MRG15 accelerates TUFM degradation, resulting in the aggravation of inflammation and fibrosis, and NASH progression (Fig. 1).

Altogether, these studies highlight MRG15 as a potent target to treat NASH. Although FDA-approved argatroban exists as an inhibitory compound to MRG15, and animals treated with argatroban demonstrated reduced liver lipid accumulation [30], argatroban is a thrombin inhibitor, which can cause bleeding after long-term treatment. Novel compounds or strategies with specific MRG15 targeting need to be identified. In addition, some other questions about MRG15 emerge and need to be answered. For example, as MRG15 is also implicated in cell survival and DNA repair, will long-term targeting MRG15 may cause liver tumors? Are there other side effects by targeting MRG15? The long-term safety of liver MRG15 targeting requires thorough investigation. In addition, MRG15 was also previously identified as a target to treat pneumonia that occurs with lung injury [39]. Could targeting MRG15 in other tissues also present beneficial effects against tissue fibrosis?

Taken together, the above-mentioned studies have only started to reveal the intriguing functions of MRG15 in lipid metabolism and tissue fibrogenesis. Further studies regarding the functional aspects of MRG15 in different cell types and its regulatory signals will continue to shed light on the beneficial effects as well as the side effects of targeting MRG15.

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**Declaration of competing interest**

None.
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