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Opinion

Non-Alcoholic Steatohepatitis (NASH): A Critical Stage of Chronic Liver Disease

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Abbreviations

ER: Endoplasmic Reticulum; TNF-α: Tumour Necrosis Factor Alpha; IL-6: Interleukin 6; IL-1β: Interleukin 1 Beta; NAFLD: Non-Alcoholic Fatty Liver Disease; NASH: Non-Alcoholic Steatohepatitis; NLRP3: NOD-, LRR- and Pyrin Domain-Containing Protein 3; MCD: Methionine Choline Deficient; TG: Triglyceride

Non-alcoholic steatohepatitis (NASH) is a severe and progressive stage of NAFLD, in which hepatocyte damage, inflammation and fibrosis are present. Unlike simple hepatic steatosis, NASH may become a more prominent public health issue in the near future with the potential of becoming the leading indication for liver transplantation. In line with its seriousness of NASH, the prevalence has been estimated to exceed 20% (12% of the U.S. population in 2018) of the world population by 2030, which is alarming and should not be ignored. Therefore, increase NASH globally is putting people at an increasing risk of liver cirrhosis as well as hepatocellular cancer [1].

The pathogenesis of the transition from hepatic steatosis to NASH is complicated and, although it has been extensively studied in humans and animals, it remains unclear. It has been proposed that inflammation, endoplasmic reticulum (ER) stress, oxidative stress and mitochondrial dysfunction may be the dominant mechanisms of this disease. These factors are associated with the severity of NASH and progression to NASH with fibrosis, while other factors yet to be identified contribute to the progression to severe fibrosis. Despite the difficulty in determining NASH due to the lack of definite pathogenesis, animal studies have been used to identify the factors critically involved in the progression of NASH. According to the AASLD, NASH characterisations are presence of ≥ 5% hepatic steatosis (hepatic TG accumulation), inflammation, hepatocyte injury (e.g. hepatocytes ballooning) and with or without any fibrosis [2].

The developments have been revolutionized understanding of the Nod-like receptor protein 3 (NLRP3) in multiple manifestations of the metabolic syndrome, including NAFLD. NLRP3 has been identified and used to predict the pathogenesis and severity of NASH in both human [3] and animals [4,5]. The hepatic expression of the NLRP3 inflammasome significantly increased in NASH patients and methionine-choline-deficient (MCD) mice, where MCD mice are the ideal animal model to represent NASH. This increase induced the activation of IL-1β and others pro-inflammatory cytokines, including TNF-α, and IL-6, hence mediate liver inflammation and damage [6].

Development novel target of inflammasome seems to be promising therapeutic approaches against NASH. Despite the effectiveness of the NLRP3 inhibitors as a potential therapeutic target in the treatment of NASH, the insufficient information hampered the discovery and development of novel therapeutics against this target. Lacking full understanding of NLRP3 cellular molecular mechanisms into NASH progression is a major failure. In Addition, compacting inflammation is one component in the prevention of NASH, therefore, NLRP3 modulators may work best alongside other drugs against liver steatosis, damage and fibrosis. Thus, considering its effectiveness, NLRP3 modulator is a strong target for the treatment of NASH but additional studies are needed to explore more deeply its therapeutic effects in humans.

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