THE ROLE OF HISTONE MODIFICATIONS IN THE DEVELOPMENT OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE

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Introduction. Metabolic dysfunction-associated steatotic liver disease (MASLD) is a progressive spectrum of liver diseases that begins with liver steatosis, followed by metabolic dysfunction-associated steatohepatitis (MASH) and may progress to liver fibrosis. The underlying mechanisms of MASLD are multifaceted and involve both genetic and non-genetic (epigenetic) factors.

Aim. To discuss the role of histone modifications in the development of MASLD.

Materials and methods. The PubMed, Scopus, and Cochrane Library databases were searched to identify reports related to histone modifications in the development of MASLD.

Results. In recent years, the role of histone methylation in MASLD has attracted increasing attention. One study reported that increased trimethylation of the 27th lysine residue of histone H3 (H3K27) is associated with increased expression of genes involved in lipid synthesis. Enhancer of zeste homolog 2, a subunit of the polycomb repressive complex 2, identified as the specific methyltransferase responsible for H3K27 methylation, plays a significant role in modulating diverse MASLD phenotypes. Schuster S. reported that histone methylation influences the acute physiological alterations underlying the transition from liver steatosis to MASH.

Several studies have further suggested that histone acetylation may represent a potential therapeutic target for MASLD. The active phosphorylated form of FTY720 (fingolimod) was shown to reduce fatty acid synthase expression through alterations in histone acetylation. Interestingly, the expression of nuclear receptor subfamily 2 group F member 6 was increased in the livers of patients with MASLD and was reduced by metformin treatment in obese mice.

Ubiquitination and sumoylation have recently been identified as novel forms of histone modification. Studies have shown that post-translational modifications of transcription factors play an important role in regulating numerous biological processes. However, the role of these modifications in the development of MASLD remains poorly understood.

Conclusions. Genetic variation explains only a small fraction of environmental and hereditary disease risk, whereas epigenetic modifications, such as histone modifications, contribute to the majority of MASLD phenotypes. Research into the role of epigenetic mechanisms in MASLD is still in its early stages and requires further investigation.

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