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HISTONE ALTERATION AS EPIGENETIC DETERMINANTS OF METABOLIC DYSFUNCTION-ASSOCIATED STEATOTIC LIVER DISEASE PATHOGENESIS

Abstract. Metabolic dysfunction-associated steatotic liver disease (MASLD) occupies a prominent position in hepatology and is increasingly recognized as a global epidemic. Accumulating evidence indicates that MASLD represents the hepatic manifestation of a systemic metabolic disorder. The pathogenesis of metabolic diseases is complex and multifactorial, involving the interplay of genetic and epigenetic determinants. Although genetic susceptibility plays a well-established role in MASLD pathogenesis, the rapidly increasing prevalence of the disease cannot be adequately explained by genetic predisposition and environmental exposures alone. Epigenetic regulation, encompassing reversible and heritable modifications of gene expression without changes in the underlying nucleotide sequence, constitutes a

critical mechanistic link in this context. Growing evidence supports the pivotal role of epigenetic mechanisms in the initiation, progression, and clinical heterogeneity of MASLD.

Keywords: metabolic dysfunction-associated steatotic liver disease, metabolic dysfunction-associated steatohepatitis, epigenetic, histone methylation, histone acetylation, histone phosphorylation, histone ubiquitination

Deoxyribonucleic acid in eukaryotic cells is highly organized within the nucleus in the form of chromatin, a dynamic nucleoprotein complex whose fundamental structural unit is the nucleosome. The nucleosome consists of an octameric core formed by four pairs of histone proteins, namely H3, H4, H2A, and H2B. These histone proteins play a key role in chromatin organization and are subject to numerous post-translational modifications catalyzed by specialized histone-modifying enzymes. A wide spectrum of histone alteration has been identified, including methylation, acetylation, lactylation, phosphorylation, dopaminylation, and ubiquitination, among others, which collectively regulate chromatin structure and gene expression [1].

Aberrant regulation of histone methylation is associated with functional disturbances that contribute to the progression of numerous pathological conditions, including diabetes mellitus, arterial hypertension, atherosclerosis, fatty liver disease, malignancies, and autoimmune disorders [2]. In recent years, growing attention has been directed toward the involvement of histone methylation in the pathogenesis of MASLD. Experimental evidence indicates that elevated trimethylation at lysine 27 of histone H3 (H3K27me3) is associated with increased expression of genes involved in lipid biosynthesis. Enhancer of zeste homolog 2, a catalytic subunit of the polycomb repressive complex 2 and a key methyltransferase responsible for H3K27 methylation, has been shown to play a crucial role in regulating different phenotypic manifestations of MASLD by targeting distinct gene sets at various stages of disease progression [3].

Evidence from experimental studies using inbred laboratory mouse strains (C57BL/6J and DBA/2J) fed a methyl-deficient, adipose-derived diet demonstrated the development of phenotypic features characteristic of metabolic dysfunction-associated steatohepatitis (MASH). These alterations were accompanied by changes in histone methylation patterns, particularly at lysine 9 and lysine 27 of histone H3 as well as lysine 20 of histone H4, highlighting the critical contribution of histone methylation to both the initiation and progression of MASH [4].

According to Schuster S., histone methylation influences not only the acute molecular and physiological processes underlying the transition from simple hepatic steatosis to MASH but also modulates key mechanisms involved in hepatic inflammation. These include hepatocellular lipotoxicity, mitochondrial dysfunction, endoplasmic reticulum stress, and other pathogenic pathways implicated in MASLD development [5].

In addition to methylation, histone demethylation has also been implicated in the pathogenesis of MASLD. Experimental findings indicate that overexpression of lysine demethylase 7A can remove the repressive epigenetic marks H3K9me2 and H3K27me2 from the promoter region of the diacylglycerol O-acyltransferase 2 (DGAT2) gene. This epigenetic modification enhances DGAT2 transcription, leading to increased triglyceride synthesis and accumulation within hepatocytes, ultimately promoting hepatic steatosis. Given that stearoyl-CoA desaturase 1 and DGAT2 are considered promising therapeutic targets and are currently under investigation in clinical trials, regulators of histone methylation such as PHD finger protein 2 and KDM7A may represent potential epigenetic targets for future MASLD therapies [6].

Several studies have indicated that histone acetylation may represent a promising therapeutic target in MASLD. The biologically active phosphorylated metabolite of FTY720 (fingolimod), a prodrug widely used in the treatment of multiple sclerosis, has been shown to attenuate the expression of fatty acid synthase through modulation of histone acetylation. In experimental models of diet-induced MASLD in mice, this mechanism was associated with reduced ceramide synthesis and a decrease in hepatic lipid accumulation [7].

Notably, increased expression of nuclear receptor subfamily 2 group F member 6 has been observed in liver tissue from patients with MASLD, whereas metformin administration in obese mouse models resulted in suppression of NR2F6 expression. These findings suggest that pharmacological inhibition of NR2F6 could represent a potential therapeutic strategy for MASLD, possibly mediated through mechanisms involving histone acetylation [8].

Histone acetylation is also capable of regulating the transcriptional activity of multiple genes simultaneously. For instance, experimental models carrying a homozygous knock-in mutation involving substitution of serine with alanine at the phospho-Caspase-9 site of liver X receptor alpha demonstrated the development of hepatic steatosis while simultaneously preventing excessive cholesterol accumulation, inflammation, and fibrotic remodeling. Such molecular alterations were associated with a delayed progression from simple hepatic steatosis to MASH [9].

In addition to acetylation and methylation, other post-translational histone alteration have recently attracted increasing attention. Ubiquitination, defined as the covalent attachment of ubiquitin molecules to specific residues of target proteins, and sumoylation, which involves conjugation of small ubiquitin-like modifier proteins to substrates, represent additional regulatory mechanisms of chromatin function. Accumulating evidence indicates that post-translational modification of transcription factors during protein maturation plays a crucial role in the regulation of numerous cellular and metabolic processes [10].

An analysis of hepatic gene expression networks in obese individuals with MASLD demonstrated that signaling pathways associated with hepatic fibrosis were predominantly enriched within the group of upregulated genes, whereas pathways related to endoplasmic reticulum stress and protein ubiquitination were among the most significantly suppressed gene clusters.

Beyond ubiquitination, transcription factors may undergo a variety of additional post-translational alterations, including acetylation, phosphorylation, and glycosylation. However, the precise contribution of these regulatory mechanisms to

MASLD pathogenesis remains insufficiently understood. Likewise, only limited evidence is currently available regarding the role of histone ubiquitination and phosphorylation in the initiation and progression of MASLD.

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