THE ROLE OF DNA METHYLATION IN THE DEVELOPMENT AND PROGRESSION 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 benign fat accumulation in hepatocytes (steatosis), followed by inflammation and damage to hepatocytes – nonalcoholic steatohepatitis (NASH) and progresses to liver fibrosis (LF) (Fig.1).

Elucidation of epigenetic factors, such as DNA methylation, that predispose an individual to MASLD may lead to development of noninvasive biomarkers for early diagnosis of MASLD and may allow early preventive and therapeutic strategies for the people at the high risk.

OBJECTIVE:

The aim of this review is to investigate the role of DNA methylation in the development and progression of MASLD.

MATERIALS AND METHODS:

The study included a review of integrative epigenomic analysis developed by the US National Institutes of Health Roadmap Epigenomics Mapping Consortium (Nature, 2015) and The Encyclopedia of DNA Elements project (Nature, 2012).

RESULTS AND DISCUSSION:

The epigenetic mechanisms modulate diverse physiological and pathological processes via the regulation of gene expression through alterations in epigenetic code accessibility within the chromatin. Growing evidence suggests that lean MASLD progression is substantially influenced by DNA methylation (Fig.2). DNA methylation is a universal chemical modification by which methyl groups are added to the DNA molecule.

In a study of liver mitochondrial DNA methylation by Pirola et al. (2013), significantly higher methylation of mitochondrial gene nicotinamide adenine dinucleotide dehydrogenase-6 and lower messenger RNA (mRNA) levels was reported in NASH patients in comparison to simple steatosis patients. This points towards an association of hepatic methylation and transcriptional downregulation of dinucleotide dehydrogenase-6 with the severity of MASLD [1].

Ahrens et al. (2013), using genome wide DNA methylation analysis from liver samples of 45 morbidly obese patients in different stages of MASLD, extracted 9 MASLD associated genes exhibiting variation in methylation [2].

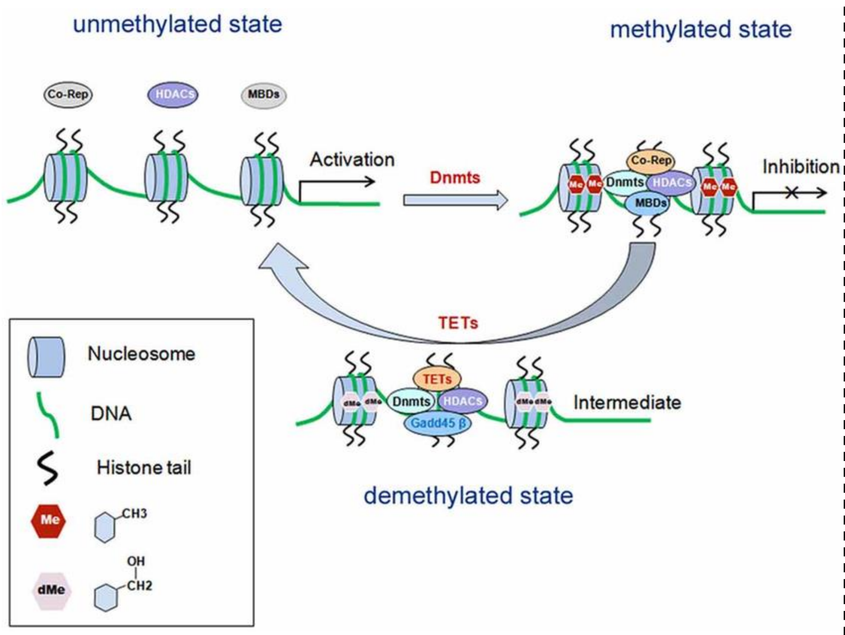

Fig. 2. Schematic diagram of DNA methylation in the regulation of gene transcription.

In the study by Baumeier C., et al. (2017) it was demonstrated that relationship of increased hepatic dipeptidyl peptidase-4 expression levels and corresponding reduction in DNA methylation was observed in human liver biopsies to different hepatosteatosis and NASH stages which suggested a very complex intertwined regulation of fuel metabolism through epigenetic modulation [4].

Nano J., et al. (2017), using epigenome-wide association studies identified eight genes associated with markers of liver function, among which altered DNA methylation at Solute carrier family 7 member 11 was linked with reduced incidence of hepatic steatosis, through favorable association with a panel of genes involved in lipid metabolism [5].

In an epigenomic analysis by Johnson N. D., et al. (2021), which used data from the Infinium Methylation EPIC array from 325 individuals with MASLD, it was demonstrated that DNA methylation is a mechanism underlying changes in the cellular composition of hepatocytes in the pathogenesis of MASLD, including the development of LF [6]. Recent studies suggest that altered gene expression due to abnormal DNA methylation may also be involved in the progression of MASLD to hepatocellular carcinoma (HCC).

Another study by Borowa-Mazgaj B., et al. (2019), using relevant mice models (diet induced MASLD mice, stelic animal model of NASH derived HCC as well as choline and folate deficient diet mice models exhibiting MASLD to HCC progression that resemble carcinogenesis in humans) characterized progressive increase in glycine N-methyltransferase promoter methylation and corresponding reduction of glycine N-methyltransferase expression [7].

CONCLUSION:

Thus, numerous studies in human and animal models suggest altered DNA methylation patterns at global and locus specific levels leading to hepatic lipid accumulation, steatosis, inflammation, and injury responsible for establishment and progression of MASLD. The study of DNA methylation is a promising field of modern science for understanding the influence of epigenetic factors on the development and progression of MASLD.

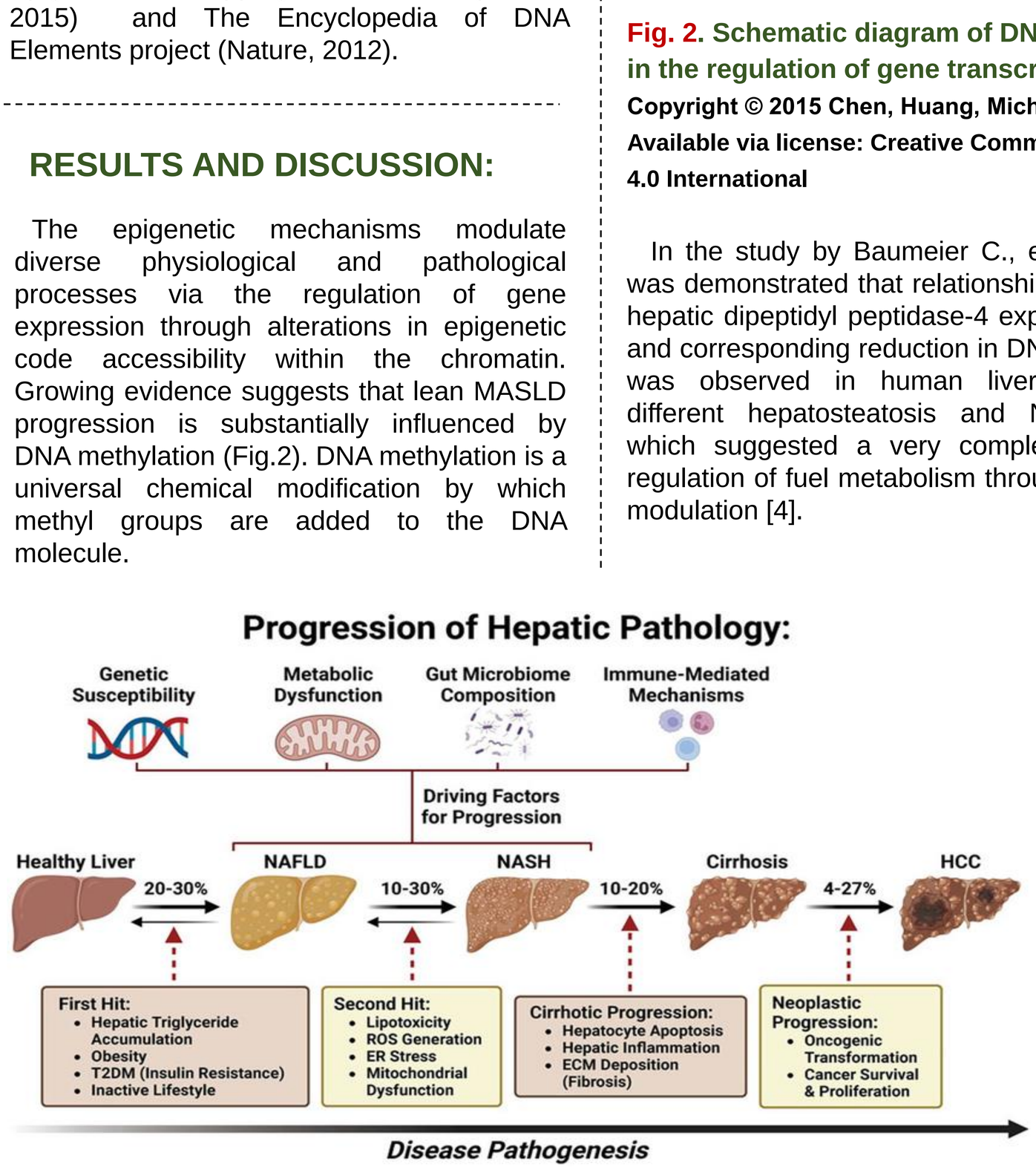

Fig.1. Pathophysiology of Metabolic dysfunction-associated steatotic liver disease (MASLD)

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