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REVIEW

Epigenetics and Liver Fibrosis

Eva Moran-Salvador and Jelena Mann

Institute of Cellular Medicine, Faculty of Medical Sciences, Newcastle University, Framlington Place, Newcastle upon Tyne, United Kingdom

SUMMARY

Liver fibrosis is a common end pathway of any type of chronic hepatic injury. It is now known that epigenetic mechanisms including DNA methylation, histone modifications and non-coding RNAs appear to orchestrate many aspects of liver fibrogenesis. This review considers recent gains in knowledge of epigenetic programming in the context of hepatic fibrosis, which is paving the way to discovery of epigenetic biomarkers as well as long awaited diagnostic and prognostic tools.

Liver fibrosis arises because prolonged injury combined with excessive scar deposition within hepatic parenchyma arising from overactive wound healing response mediated by activated myofibroblasts. Fibrosis is the common end point for any type of chronic liver injury including alcoholic liver disease, nonalcoholic fatty liver disease, viral hepatitis, and cholestatic liver diseases. Although genetic influences are important, it is epigenetic mechanisms that have been shown to orchestrate many aspects of fibrogenesis in the liver. New discoveries in the field are leading toward the development of epigenetic biomarkers and targeted therapies. This review considers epigenetic mechanisms as well as recent advances in epigenetic programming in the context of hepatic fibrosis. *(Cell Mol Gastroenterol Hepatol 2017;4:125–134; http://dx.doi.org/10.1016/j.jcmgh.2017.04.007)*

Keywords: Liver Fibrosis; Epigenetics; DNA Methylation; Histone Modifications; Chronic Liver Disease.

Chronic liver disease (CLD) comprises many different etiologies, with fibrosis being the common pathologic outcome of virtually all CLD, usually defined by the excessive accumulation of fibrous connective tissue in and around inflamed or damaged tissue.[1–3]

The liver is made up of many cell types whose composition as well as phenotype ultimately changes in CLD. It is now well-documented that cellular phenotype is at least in part under control of chromatin configuration at key regulatory genes; this in turn is governed by epigenetic mechanisms.[4] The term *epigenetics* describes reversible changes in gene expression that can be inherited through cell division that do not involve alterations to the underlying DNA sequence.[5] Epigenetic changes occur ubiquitously in all cells and are most readily observed in our bodies where a single genome gives rise to numerous different cell types.[4]

The epigenome is influenced by a number of factors including age, gender, the environment (diet, drug use, smoking), as well as the underlying genome through presence of single nucleotide polymorphisms.[6] The epigenome is governed by at least 3 systems, namely DNA methylation, histone modifications, and non-coding RNA (ncRNA) mediated gene silencing[7–10] (Figure 1). These separate but interacting and overlapping epigenetic mechanisms are currently considered to initiate and sustain DNA and chromatin modifications that underpin cellular phenotype by facilitating the control of gene transcription by sequence-specific transcription factors.[10–13] All 3 epigenetic mechanisms regulate the chromatin structure, modifications, and the initiation of transcription in a manner that alters the accessibility of genes to transcription factors and their cofactors that dictate the rate at which a gene is actively transcribed.[7–10] Therefore, it is not surprising that epigenetics has become a research area of much interest, linking changes in chromatin states to the cellular phenotype and, in turn, the functioning of an organ. Large numbers of studies have considered the impact of epigenetic changes on liver function in health as well as in disease states. Here we consider the epigenetic mechanisms involved in the pathogenesis of liver fibrosis as well as examine recent advancements in the field and discuss new epigenetic approaches and strategies for the treatment of liver fibrosis.[14]

The Epigenetic Code and Mechanisms

Genomic DNA contains all the information that a cell, and indeed the organism, requires for life. The DNA sequence, or the genome, is identical in all cells of a particular organism. However, the epigenome is entirely cell type specific, such that combination of the above-mentioned 3 epigenetic mechanisms is carefully defined and maintained to support the phenotype of that particular cell.[4,10,12,13] Therefore, although the genome of every cell in the body is the same, the epigenome will govern the phenotype, such that a

Abbreviations used in this paper: **CLD, chronic liver disease; CpG, cytosine-phospho-guanine; DNMT, DNA methyltransferase; HDAC, histone deacetylase; HSC, hepatic stellate cell; miRNA, microRNA; NAFLD, nonalcoholic fatty liver disease; ncRNA, non-coding RNA; PPAR, peroxisome proliferator activated receptor; TET, Ten Eleven Translocation.**

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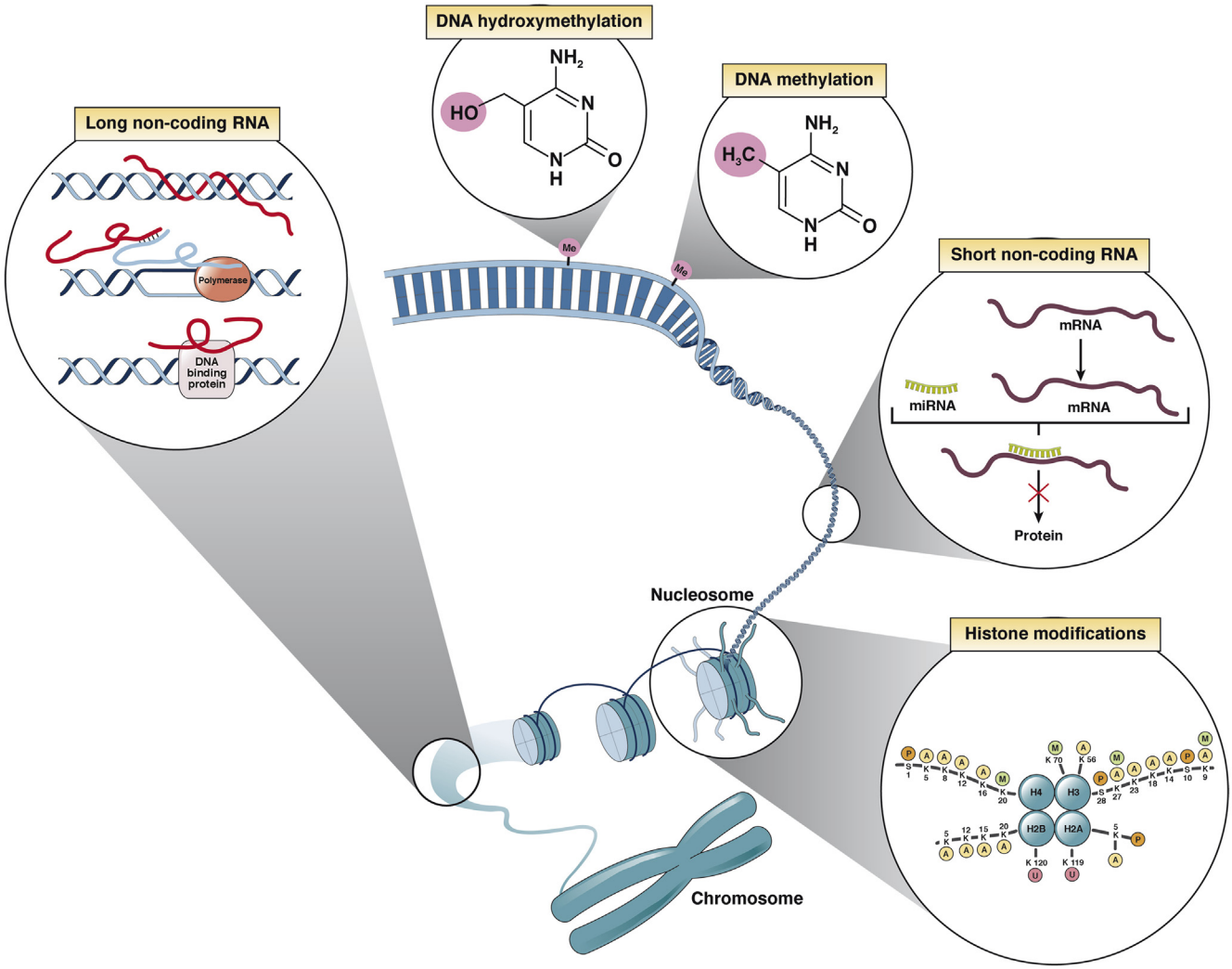

Figure 1. Epigenetic mechanisms of heritable gene expression regulation. There are several highly interdependent epigenetic mechanisms that are important in the control of gene expression, namely DNA methylation (and hydroxymethylation), histone post-translational modifications, and ncRNA-based pathways, including small and long ncRNA species.

hepatocyte will have its own defined epigenetic signature that will differ from that of an adipocyte or a nerve cell.[15,16]

DNA in a cell is not naked but rather packaged around histones into a structure known as chromatin. Chromatin is composed of ~146 base pairs of genomic DNA sequence wrapped around 8 core histones to form the basic unit of chromatin, the nucleosome. The main functions of chromatin are to efficiently package DNA into a reduced volume such that it can fit into the nucleus of a cell, protect the DNA structure and sequence, prevent chromosome breakage, and regulate gene expression as well as DNA replication. Each nucleosome contains a core of 8 histones (2 copies of H2A, H2B, H3, and H4), which are small, globular proteins with a long N-terminal tail that is subject to numerous post-translational modifications including acetylation, methylation, phosphorylation, SUMOylation, ubiquitination, or ADP-ribosylation. A large number of histone-modifying enzymes act to carry out more than 60 different possible modifications within each octamer of histones.

The presence of chemical groups on the histones creates binding sites for specific protein complexes that can promote either activation or silencing of gene transcription.[10] As an example, lysine residues within histones can be acetylated, which is mediated by histone acetyltransferases and associated with active gene transcription due to enhanced recruitment of other chromatin remodelling enzymes and prevention of chromatin compaction. Conversely, gene silencing or repression is frequently associated with the removal of acetyl groups by histone deacetylases (HDACs).[17] Histone methyltransferases have the ability to add 1, 2, or 3 methyl groups to lysines or arginines within histones H3 or H4. The impact of methylation on gene transcription depends on the specific site of the covalent modification; for instance, histone 3 lysine 4 trimethylation causes transcriptional activity, whereas histone 3 lysine 9 or lysine 27 leads to transcriptionally silent chromatin.[10,18,19] Combinations of histone marks therefore provide changes in chromatin conformation and confer unique biological