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Review

Epigenetic modifications by histone deacetylases: Biological implications and therapeutic potential in liver fibrosis

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ABSTRACT

Liver fibrosis is an important pathological repair process in reaction to liver injury characterized by progressive accumulation of extracellular matrix (ECM) components. Mechanism that orchestrates this fibrotic disorder is the activation of hepatic stellate cell (HSC) that requires extensive alterations in gene expression. Reversible deacetylation of histone proteins is one of the most abundant epigenetic modifications and is crucial in modulating gene expression. Recent evidence has highlighted a pathological imbalance between the acetylation and deacetylation of histone proteins regulated by histone deacetylases (HDACs). In the past several years, the role of HDACs in liver fibrosis initiation and progression, as well as the therapeutic effects of HDAC inhibitors, has been well studied. Here, the innovative aspects of histone deacetylation will be presented, with respect to the roles of HDACs in liver fibrosis, the affected genes and signal pathways involved in HSCs activation, as well as significant data emerging from the field in support of HDAC inhibitors as potential therapeutic targets for the treatment of liver fibrosis.

1. Introduction

Liver fibrosis is an excessively plentiful and reversible wound healing process that results from most types of chronic liver diseases no matter of the etiologies. Persisting fibrogenesis is widely recognized as the major driving force eventually leading to liver cirrhosis and hepatic failure [1,2]. This fibrotic process is characterized by the excess production and deposition of extracellular matrix (ECM) components enriched in type I and III fibrillar collagens [3]. The ongoing accumulation of ECM during chronic liver injury is driven by a heterogenous population of myofibroblasts that migrate and accumulate at the site of injury. Numerous studies have led to the conclusion that hepatic myofibroblasts mainly originate from hepatic stellate cells (HSCs) and are principal source of ECM during liver fibrosis [4]. HSCs are resident vitamin A-storing cells located in the subendothelial space of Disse, between the basolateral surface of hepatocytes and the antiluminal side of sinusoidal endothelial cells [5]. In the normal liver, they display a quiescent phenotype, characterized by the expression of a large number of adipogenic genes and neural markers. Upon liver insults and the resulted pro-fibrotic mediators, such as transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF),

Abbreviations: ECM, extracellular matrix; HSC, hepatic stellate cell; TGF-β, transforming growth factor-β; PDGF, platelet-derived growth factor; α-SMA, α-smooth muscle actin; MMPs, matrix metalloproteinases; TIMP, tissue inhibitor of metalloproteinase; EMT, epithelial-to-mesenchymal transition; HDACs, histone deacetylases; HATs, histone acetyltransferases; SIRT, sirtuins; DNA, deoxyribonucleic acid; NAD^+, nicotinamide adenine dinucleotide; Sir2, yeast silent information regulator 2; HDACIs, HDAC inhibitors; SCFAs, short chain fatty acids; VPA, valproate; NaB, sodium butyrate; PBA, phenyl butyrate; PTBA, 4-(phenylthio) butanoic acid; TSA, trichostatin A; SAHA, suberoylanilide hydroxamic acid; HNHA, *N*-hydroxy-7-(2-naphthylthio) heptanomide; TPX, trapoxin; ac, acetyl; SIRT1LKO, hepatocyte-specific SIRT1 knockout mice; HGF, hepatocyte growth factor; CCl_4, carbon tetrachloride; DMN, dimethylnitrosamine; BDL, bile duct ligation; NF-κB, nuclear factor kappa B; DIP, DNA immune-precipitation; CYLD, cylindromatosis; BMP, bone morphogenetic protein; BAMBI, bone morphogenetic protein and activin membrane-bound inhibitor; TβR, TGF-β receptor; TSP-1, thrombospondin-1; LPS, lipopolysaccharide; Ang II, angiotensin II; TLR, toll-like receptor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MDA, malondialdehyde; IL, interleukin; Arp, actin related protein; ADDL, adducing-like protein; CLP, cecal ligation and puncture; PAI-1, plasminogen-activatorinhibitor-1.

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HSCs lose vitamin A-containing lipid droplets, proliferate and differentiate into myofibroblast-like cells with remarkable up-regulation of α-smooth muscle actin (α-SMA) and collagens, which is referred to as the activation of HSCs [3,6,7]. This activation process of HSCs is well accepted as a defining event in the development and maintenance of liver fibrosis, for this reason, characterizing the mechanisms governing acquisition of a myofibroblastic phenotype of HSCs and inhibition of HSC activation are crucial goals for intervention in the hepatic fibrogenesis cascade. Although some progress has been made to understand the mechanism of the development of fibrosis, current therapeutic options are limited to emerge as an effective anti-fibrotic agent in humans [6]. Therefore, it is necessary to acknowledge the evolving challenges that lie ahead and update our understanding of fibrosis for presenting novel therapeutic strategies against tissue fibrogenesis.

More recent advances in the cellular and molecular biology of the fibrotic wound healing response have moved into surprising new frontiers, especially epigenetic mechanisms. The view that epigenetic deregulation is a major driver of liver fibrosis onset and progression is rapidly gaining acceptance by researchers [8]. Epigenetic events have been identified as additional mechanisms driving HSCs activation and during trans-differentiation, the switch of transcriptionally active genes into silent ones is often mediated by epigenetic processes, such as histone deacetylation. Evidence is now emerging to uncover a fundamental role of histone deacetylation in liver fibrosis and the contribution of the complexity of gene regulation by the acetylation state of the histone molecules in HSCs [9–11]. Following recent advances in the epigenetic mechanisms of fibrosis, this review will present comprehensively updated information regarding the pharmacological role of histone deacetylation in the progression of liver fibrosis with special focus on the multiple roles of HDACs, the transcriptional regulation of specific target genes mediated by HDACs, the potential applications of histone deacetylases inhibitors in treatment of liver fibrosis and the emerging signal pathways regulated in HSCs by histone deacetylation.

2. Overview of histone deacetylation

Chromatin structure and gene transcription are tightly regulated by the acetylation state of the histone molecules in the nucleosome. Histone acetylation is a reversible process closely linked to gene transcriptional activation, while histone deacetylation consistently results in gene transcriptional repression [12,13]. The balance between the acetylated and deacetylated states of histones is controlled by the antagonistic actions of two types of enzymes: histone acetyltransferases (HATs) and histone deacetylases (HDACs) [14]. HATs can catalyze the transfer of acetyl groups from acetyl coenzyme A to the ε-amino group of the lysine residues. Introduction of the acetyl group to lysine neutralizes the positive charge of the histone lysine residue and increases the hydrophobicity. As a result, a relaxed chromatin structure is formed, enabling greater accessibility of the transcriptional machinery to the deoxyribonucleic acid (DNA) and initiating gene transcription [12]. In the opposing deacetylation reaction, HDACs promote the removal of the acetyl groups from the acetylated residues and restore the positive charge. As a consequence, a dense chromatin configuration is constituted, being impermissible for gene transcription [13]. HDACs not only alter transcription, but also promote either the establishment or erasure of alternative post-translational lysine modifications such as methylation, ubiquitination, and sumoylation [15]. It is well established that lysine acetylation also occurs in a considerable number of non-histone proteins, such as transcription factors, and affects gene transcription and other cellular processes [16].

3. HDAC classes and HDAC inhibitors

HDACs have emerged as crucial transcriptional co-repressors in highly diverse physiological and pathological systems. To date, eighteen mammalian HDACs have been identified and divided into two categories (the zinc-dependent HDACs and the nicotinamide adenine dinucleotide (NAD^+)-dependent HDACs) and four subfamilies (classes I, II, III, and IV), depending on sequence identity and domain organization. Classes I, II and IV fall under the first category; Class III falls under the second (Table 1) [17]. Class I HDACs include HDACs 1, 2, 3, and 8, and share high sequence homology in their catalytic sites with yeast transcriptional regulator RPD3 [18]. In general, Class I HDACs are ubiquitously expressed and predominantly localized in the nuclear compartment of the cell and exert a strong catalytic effect on histone lysine residues [18]. The protein structure of Class I HDACs is characterized by a highly conserved deacetylase domain flanked by short amino- and carboxy-terminal extensions [19]. Class II HDACs (HDAC4, 5, 6, 7, 9, and 10) are closely related to yeast HDA1 band. This class is further subcategorised into Class IIa (HDACs 4, 5, 7 and 9) with only one catalytic site and Class IIb (HDACs 6 and 10) with two catalytic sites [20]. Unlike Class I HDACs, Class II HDACs display a more tissue-specific expression in mammals and are primarily located in the cytoplasm but can shuttle in and out of the nucleus in response to cellular signals and thus are, at least in part, cytoplasmic and, in some cases, acting on non-histone protein substrates [21]. Class III HDACs are structurally and enzymatically distinct from members of the classical family consisting of seven NAD^+-dependent members named sirtuins (SIRT1, 2, 3, 4, 5, 6, and 7), which share sequence homology with the yeast silent information regulator 2 (Sir2) protein [15]. An interesting characteristic of Class III is their localizations, with SIRT1 and SIRT2 in the nucleus and cytoplasm, SIRT3 in the nucleus and mitochondria, SIRT4 and SIRT5 exclusively in the mitochondria, SIRT6 only in the nucleus, and SIRT7 in the nucleolus [15]. HDAC11 is currently the sole member of Class IV localizing in the nucleus and uniquely shares sequence homology with the catalytic domains of both Class I and II HDACs [22].

HDAC inhibitors (HDACIs) are compounds that have the ability to inhibit the functions of HDACs and prevent the deacetylation of lysine residues within the N-terminal tails, resulting in hyperacetylation of target proteins and altered gene expression patterns [23]. HDACIs are under investigation as promising drugs candidates in the treatment of a wide range of diseases, including cancer [24] and fibrotic disorders [14]. Most inhibitors share a zinc-binding domain, which can mimic the substrate and occupy the active site channel. The major mechanism of these HDACIs is to chelate a critical Zn^{2+} ion, which is necessary for the catalytic function of HDAC enzymes [25]. On the basis of their chemical structure, HDACIs are categorized into four classes (Fig. 1): short chain fatty acids (SCFAs), hydroxamic acids, benzamides and cyclic peptides [23]. Compared with other HDACIs, the short chain fatty acids are relatively small, simple-structured compounds, which display selective inhibition of Class I HDACs and class IIa with negligible effects on other HDACs. The most notable drugs within this class include valproate (VPA, valproic acid, usually used as its sodium salt), butyric acid, sodium butyrate (NaB), phenyl butyrate (PBA), and 4-(phenylthio) butanoic acid (PTBA) [26,27]. The hydroxamic acids are more broad-spectrum inhibitors capable of inhibiting Class I, II and IV HDACs with roughly equal potency and composed of trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA) and *N*-hydroxy-7-(2-naphthylthio) heptanomide (HNHA) [26,27]. As opposed to the other HDACIs described thus far, benzamides represent a new relatively selective class of HDACIs containing MS-275 and RGFP136, which inhibit Class I HDACs with increased selectivity toward HDAC1 and HDAC3 respectively