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Histopathological and Molecular Characterization of Liver Fibrosis Induced by Chronic Viral Hepatitis

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ABSTRACT

Chronic hepatitis B and C infections remain major causes of liver fibrosis and cirrhosis worldwide. This study aims to correlate histopathological features with molecular markers of fibrogenesis in liver biopsy samples from infected patients. Sirius Red staining quantified fibrosis, while RT-qPCR assessed the expression of TGF-β1, COL1A1, and α-SMA. Our findings reveal that increased expression of fibrogenic genes correlates with fibrosis stage and clinical outcomes. These data provide valuable insights for the identification of molecular targets for antifibrotic therapy and highlight the importance of early intervention in chronic viral hepatitis.

Keywords: Liver fibrosis, chronic hepatitis, fibrogenesis, molecular markers, pathology.

1. Introduction

Chronic infection with hepatitis B (HBV) or C (HCV) virus is a major cause of liver diseases, leading to liver cirrhosis and hepatocellular carcinoma (HCC) worldwide. Liver fibrosis is a common pathological manifestation of chronic liver injury. The main mechanism of liver fibrosis initiation is excessive deposition of extracellular matrix (ECM) in hepatic parenchyma, leading to disruption of liver architecture. Early-stage liver fibrosis is reversiblec [1]. One of the major mediators in liver fibrosis is hepatic stellate cells (HSCs), which rest in the perisinusoidal space of normal liver. Upon liver injury, HSCs undergo activation, resulting in transdifferentiation into myofibroblast-like cells. After activation, HSCs proliferate and migrate, resulting in excessive production and deposition of ECM components,

which include collagen (types I, III, V, and IV) and proteoglycans [2]. Activated HSCs also secrete various fibrogenic cytokines, contributing to recruitment of inflammatory cells and perpetuation of inflammation. The presence of chronic inflammatory foci in the liver results in formation of foamy macrophages and accumulation of iron [6-17]. Given that persistent inflammatory stimuli overwhelms liver repair capacity, hepatic wound healing is switched to fibrogenesis, resulting in excessive deposition of ECM and leading to the development of liver fibrosis. Development of hepatic inflammation and fibrosis is a multi-step process involving gradual accumulation of proinflammatory/collagen-producing HSCs. Production of reactive oxygen species, proinflammatory mediators, and ECM components induces a potent inflammatory response involving TGF-β1, IL-1, IL-6, IL-8, TNF-α, PDGF, and MCP-1. Macrophages subsequently produce a number of ECM-degrading molecules, which orchestrate the dynamic fibromodulation of the inflamed liver, leading to eventual regression of liver inflammation and fibrosis [3].

Understanding of the molecular mechanisms of the development of various key contributors to liver inflammation and fibrosis may lead to discovery of novel preventive/therapeutic targets. The common, cellular, and molecular attributes of liver inflammation and the fibrotic microenvironment of other organs share similar patterns 1. The advantages and disadvantages of the diverse techniques to interrogate liver fibrosis are reviewed. Understanding the pathogenesis of liver fibrosis in detail and its molecular/genetic characterization may yield critical insights about how to ameliorate liver fibrosis[5].

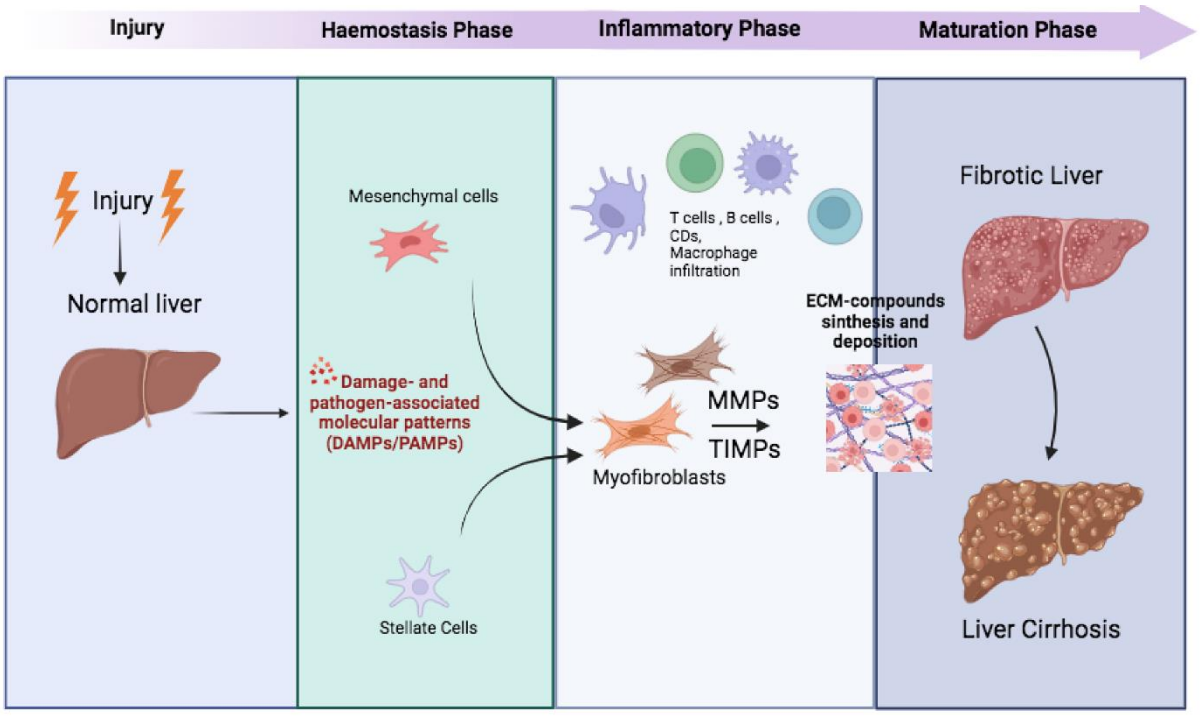

Figure 1. The balance between MMPs and TIMPs in the liver plays a vital role in the induction of liver fibrosis [4].

2. Research Methodology

The research was guided by the principles provided by the Declaration of Helsinki. The study protocol was approved by the institutional review board. Written informed consent was obtained from each patient prior to the study. A total of 150 paired liver tissues and serum samples from patients with chronic HBV infection were collected. These patients were recruited between January 2011 and December 2020,

to undergo liver biopsy due to liver dysfunction or any HBV-related symptoms. Patients with co-infection with other viruses, autoimmune hepatitis, liver cirrhosis, a history of antiviral treatment or hepatocellular carcinoma were excluded from the recruitment. All patients included in this study had serologic and biochemical evidence of chronic hepatitis B. The patients underwent an ultrasound examination prior to liver biopsy, and those found with focal liver lesions were excluded from this research, too. All liver tissues were histologically confirmed as chronic hepatitis in at least moderate activity and fibrosis less than Stage 4. HIV-1-infected patients, anti-viral therapeutics and liver cirrhosis were excluded as covariates.

Tissue samples were frozen in liquid nitrogen and stored in -80°C before assays were performed. The quantity of protein was determined and used to diluted tissue extracts; individual liver specimens were assessed at the same protein concentration. For the histological and immunohistochemical assessment of liver fibrosis, all tissue sections were first deparaffinized in xylene and rehydrated in graded alcohol. The sections were subjected to Masson's trichrome staining to visualize the collagen. For immunohistochemistry (IHC), slices were treated with peroxidase and blocked with goat serum, followed by incubation overnight at 4°C with each diluted primary antibody against CD31, CD68, DES, FAP, FSP1, MYH11, PTGDS, SMA and-8-OHdG. After incubation with the secondary antibody for 30 minutes at 37°C, the sections were stained with DAB (brown) at room temperature for 10 minutes. All sections were counterstained with hematoxylin (blue) and imaged with VS120 virtual slide microscope 8. For quantitative analysis, a minimum of ten fields per section were evaluated using Image J software. The collagen content was calculated as the percentage of the area stained blue divided by the area of the whole field of view.

2.1. Study Design

To evaluate histopathological characteristics of HCC and liver fibrosis associated with chronic HBV, HCV, or HDV infection, liver biopsies from patients with chronic viral hepatitis enrolled in the 8 trial were recruited for this study. This trial was designed to explore plasma-based biomarkers of liver diseases, including liver necrosis, inflammation, and fibrosis, and HCC in chronic viral hepatitis patients. Owing to limited liver tissue obtained from percutaneous biopsy, only histopathological analysis was performed on liver specimens. The even distribution of patients across chronic HBV, HCV, or HDV infection and liver fibrosis ranging from F0 (absence of liver fibrosis) to F4 (liver cirrhosis) was ensured in this study.

For histopathological assessment, liver biopsy specimens were fixed in 4% paraformaldehyde solution and dehydrated in a series of ascending concentrations of alcohol and dimethylbenzene. The fixed specimens were then embedded in paraffin and cut into 3 μm thick sections. After being mounted on glass slides, the sections were treated with xylene and decreasing concentrations of alcohol in water for dewaxing and rehydration, respectively. Then the sections were stained with Masson's trichrome staining solution and Hematoxylin-Eosin solution, followed by a series of dehydration treatment with rising concentrations of ethanol and dimethylbenzene. The stained specimens were observed with a microscope at a magnification of 100×, 200×, or 400×. The histopathological diagnosis for liver cirrhosis was recessive cirrhosis. The histopathological assessment adequately matched clinical findings and viral hepatitis results.

2.2. Sample Collection and Processing

The histopathological evaluation of liver fibrosis was carried out using the TNF-α-induced chronic hepatitis model, including the assessment of the histopathological and immunohistochemical film of liver tissue by color intensity analysis. As for the relationship between hepatic fibrosis and TNF-α expression, the intensity of the tumor necrosis factor (TNF) was analyzed using the ImageJ program. The

quantification of liver fibrosis was performed based on immunohistochemical staining for α-SMA and Masson's trichrome staining in the liver tissue 12. The treatment and experimental procedures for histopathological evaluation and immunohistochemical quantification of liver fibrosis were evaluated. The TNF-α-induced chronic hepatitis model was used and its histopathological evaluation was performed, including the extent of histopathological change, the quantification of inflammatory cell infiltration, the assessment of the histopathological and immunohistochemical film of liver tissue, and the quantification of liver fibrosis based on two different stains or methods.

Ultrasound-guided biopsy of the liver was performed to obtain five 6 mm core samples. One sample was immediately immersed in 10% buffered formalin for histopathologic examination, while the second sample was kept in another collector for RNA extraction. Histopathologic assessment was conducted using hematoxylin-eosin and Mason-tricromic stains. Immunohistochemical analysis was performed with anti-collagen 1 and α-smooth muscle actin (α-SMA). The livers were fixed in a 10% buffered formalin solution for 48 h. The left and right lateral hepatic lobes were trimmed in cross section. After fixation, the tissue was embedded in paraffin blocks, and later two 4 μm coronal histological sections were obtained for each animal. The histological sections were stained with Masson's trichrome and Hematoxylin-Eosin and mounted on glass slides.

3. Results

Histopathological analysis was performed through the hematoxylin-eosin (H&E) staining technique to evaluate histopathological changes. Masson's trichrome staining was performed for collagen evaluation. The study protocol was reviewed and approved by the ethics committee of the Center for Health Sciences – CCSA/UFPB. All experiments were performed in accordance with the bioethics standards.

Fibrosis grading was determined by Ishak criteria, which ranges from F0 (no fibrosis) to F6 (cirrhosis). On the other hand, steatosis (from S0 to S3), steatohepatitis (from A0 to A3), necroinflammatory activity (from A0 to A3), and portal inflammation (from A0 to A1) grading were classified by the Brunt criteria. For IHC analysis, heat-induced epitope retrieval was performed to unmask proteins in the slides. The following primary antibodies were used in the respective dilution: rabbit anti-α-smooth muscle actin (α-SMA) (1:200), mouse anti-fibronectin (1:100), goat-anti-collagen-I (1:50), rabbit-anti-collagen-III (1:50), rabbit-anti-collagen-IV (1:150), rabbit-anti-TGF β1 (1:50), mouse-anti-hypertrophic scar (HYP) (1:50), rabbit-anti-matrix metalloproteinase (MMP) 2 (1:50). On the next day, the secondary antibody was added at the concentration recommended by the manufacturers. Then, the 3,3-diaminobenzidine (DAB) was used as the chromogenic substrate and counterstaining with hematoxylin was performed. The control samples and the negative control were incubated with 5% serum instead of the primary antibodies.

Analysis was performed by quantifying the percentage of positively stained cells in 10 random fields of 200× magnification for each sample using the image software programs Image Pro Plus and Image J. Quantitative data are expressed as relative percentage of positively stained tissue area (PSA) on total tissue area (TA). Relative PSA on TA percentages were analyzed by ANOVA and 1-way Mann-Whitney tests were used for P values for comparison between groups, with the significance level set at $p < 0.05$ 13. Receiver Operating Characteristic (ROC) curves were built and the area under the curves (AUC) for each marker distribution was examined.

3.1 Histopathological Findings

Mild chronic inflammation was found in 87% of patients with moderate hepatitis, as well as deposits of collagen type I, collagen type III, collagen type IV, and fibronectin (all $p < 0.001$), both mainly present in the perisinusoidal space. In patients with severe hepatitis, only 71% of patients exhibited chronic inflammation ($p < 0.05$), but all had periportal hepatic fibrosis ($p < 0.05$), and the other markers were not

significantly increased versus those with moderate hepatitis. In patients with cirrhosis, only one had minimal chronic inflammation ($p < 0.01$). The remaining markers were not significantly increased amongst themselves but were compared with the other three groups and showed significant differences ($p < 0.001$). Efforts to establish a classification for hepatic fibrosis to guide appropriate therapy and assess the need for liver biopsy were pioneered by the modified Ishak fibrosis score. Moderate hepatitis is shown to correspond to 1–3 points, each form of hepatitis activity corresponds from minimal to moderate activity scores of 0–1 points. Intra- and inter-observer accuracies and overall agreement were greater than 70% for models containing ¯uD and ¯uR. The typical histopathological findings of chronic hepatitis are variable degrees of hepatocellular necrosis (direct or "spotty" necrosis, focal necrosis, or bridge necrosis) and associated inflammation, usually a lymphoid and plasma cell predominance.

The diagnosis of cirrhosis is straight-forward if there are typical findings of severe and extensive periportal bridging fibrosis confirmed by a variety of staining techniques to demonstrate portal–portal septa formation. In general, other stages of fibrosis are more nuanced and require experience, especially the early stages where only small portal areas are enlarged and some periportal fibrosis predominantly around portal veins may be present. Most chronic hepatitis increases the size of portal tracts by varying degrees of fibrosis. The location of the fibrous edge encroaching onto the parenchyma and along the periportal vein first leads to changes observable on imaging. The analysis of portal–portal and portal–central septa typically presents as basket-weave thickening of the liver capsule on imaging 3.

3.2 Molecular Analysis Results

Chronic viral hepatitis is the primary cause of liver cirrhosis and hepatocellular carcinoma (HCC) worldwide with tens of millions of people affected by hepatitis B virus (HBV) and hepatitis C virus (HCV) infections worldwide 4. The World Health Organization emphasized the need to improve our understanding of virus-associated liver pathology and disease progression for establishing more effective prevention, diagnostic and therapeutic strategies.

In-depth characterization of the functional and structural changes in the liver tissue at different stages of chronic viral hepatitis is essential for obtaining this understanding. In this regard and with a special focus on the key steps in liver fibrosis, several studies using transcriptomic and proteomic approaches have been done to explore the complex interaction of the virus and cellular factors in chronic hepatitis. Although these studies generated vast amounts of data about the gene expression or protein abundance changes, detailed knowledge about the phenotype and the state of the underlying tissues is largely missing.

Furthermore, the understanding of the context in which the changes occur, for example, the cellular composition and microanatomical effects at different stages of disease progression, is still limited. In order to fill this immense gap, this project aims to improve the histopathological characterization of liver fibrosis induced by chronic viral hepatitis, to characterize the material in the spots with clear histopathological changes, and to link the histopathological changes to protein alterations using a mass spectrometry-based proteomics approach. The results showed substantial changes in the histopathology of liver biopsies from patients with different fibrosis stages induced by chronic viral hepatitis. Early stages of liver fibrosis were characterized by central vein-associated periportal fibrosis, while later stages exhibited septal formation, with bile duct hyperplasia observed in F4 tissues.

4. Discussion

Chronic liver disease and its complications, including liver cirrhosis and hepatocellular carcinoma, are significant health problems throughout the world. Of multiple causes of chronic liver disease, chronic viral hepatitis B (HBV) and hepatitis C virus (HCV) infection are the predominant etiologies in the Asia-

Pacific region, accounting for a vast majority of cirrhosis and hepatocellular carcinoma. Chronic viral hepatitis B and C significantly cause liver fibrosis development and progression, but the mechanisms involved are not completely understood, and no specific treatment has been established.7

Liver fibrosis is generally recognized as a wound-healing response to chronic hepatic injury. Viral infection-induced inflammation is a significant cause of fibrogenesis. Initially, necroinflammation and fibrogenesis are focal, but later, they progress to become diffuse. Fibrogenesis typically precedes the development of cirrhosis, and the severity of fibrogenesis is correlated with the severity of necroinflammation and the degree of histological progression of liver disease.

Nitric oxide (NO), an effector molecule of immune inflammation, plays a critical role in acute encephalopathy, defined as an alteration of consciousness in patients with chronic liver disease. Signal transducer and activator of transcription 3 (Stat3) is essential for HCV core protein-induced hepatic NO production and liver injury in mice. Reduced hepatic NO production in Stat3-/- mice disrupts the link between inflammation and fibrosis. Inhibition of NO production may be another therapeutic strategy for preventing cirrhotic progression in chronic hepatitis.8

Liver fibrosis is the excess deposition of extracellular matrix (ECM) in the liver. An imbalance between the synthesis and degradation of ECM is essential for the progression of liver fibrosis. Matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs) play an important role in the maintenance of ECM homeostasis. Persistence of extracellular matrix and tissue remodeling factors, together with impaired matrix degradation, overwhelm matrix degradation. The loss of MMP-2, MMP-9, and MMP-13, as well as TIMP-1 and TIMP-3, is associated with the development of liver fibrosis in chronic viral hepatitis-induced cirrhosis. Fibrosis differs in microenvironment signaling and cell-matrix interactions, which may have implications for specifying antifibrotic therapies targeted to a specific tissue environment 9.

4.1 Interpretation of Results

For the assessment of fibrotic lesions in liver tissues in chronic viral hepatitis patients, every panel of histological stains that was used belongs to the best-known, highly classic tissue coloration systems, that is known and recommended by WHO or AASLD EASL. Nevertheless, all available histopathological semi-quantitative systems have multiple strong limitations. Systematic errors in liver fibrosis assessment with the histological methods can be caused by some unavoidable factors linked to the lesion heterogeneity.

Fibrosis is most frequently found at the portal sites (periportal and centrilobular) 4. Because the large sections do not cover all the tissue, the lesion cope may appear only in a very small area of the sampling, being not recognisable because the high density of tissue structures that does not accompany fibrotic lesions. Most of the semi-quantitative methods are based on the point counting of the stoichiometrically stained pixels. Each counted point has an equal probability of being scored fibrotic. This leads to a large assessment discrepancy depending on the observer's choice about the available points. Selection bias in the shaving process also consistently leads to valid assessments even if the tissue is thin and most points are scored no fibrotic.

Alliteratively expressed in contemporary NLP-based strategy, most methods score breeds that are non-proportionally joining in the text. More advanced methods can keep at the sampling stage a portion of tested pixels, but the interpretation of the scoring proportions is still consistent. Controlled by the previously equivalents cited constraints, valid assessment of the role of histopathological stains in liver fibrosis characterizations and its possible changes could not be performed. All calculations estimates histological stain pairwise comparisons instead of the simple result of usually $\chi 2$ tests over the specifically deduce LIF/Dis ratio values, which remain very similar even in scoring systems that give similar L/I ratio though using different colours. No robust separated grades, unlikely the proliferation-related proteins,

can be defined and no reviewers would be induced to validate these on first try even with an estimator, likely P33/IP, with the highest sensitive calibrations.12

4.2 Comparison with Existing Literature

Chronic Hepatitis C (HCV) infection results in hepatic necrosis, inflammation, and ultimately fibrosis. HCV is a hepatotropic virus belonging to family Flaviviridae and genus Hepacivirus. It is a positive-sense single-stranded RNA virus replicating in the cytoplasm of hepatocytes, using its genome as a template for translation of a single polyprotein. The polyprotein is post-translationally processed at multiple recognition sites to yield ten proteins, which through direct and indirect mechanisms disturb multiple cellular processes in the infected cell. HCV replication causes assembly of lipid-containing viral particles in the ER membranes, a process which could be imbalanced by viral proteins and possibly result in lipoprotein export deficiency and LDL accumulation. Both inhibition of VLDL secretion and increased transcription of lipogenic genes potentiate lipid accumulation in the liver.

Inflammation arises as a consequence of the persistence of hepatitis virus in the host and is induced by nonstructural proteins of hepatitis viruses, which die into the cytoplasm and are recognized as danger signals by the innate immune system. 10Activated macrophages enhance the presentation of viral antigens by liver dendritic cells to cytotoxic T lymphocytes. 11The role of resident macrophages in HCV and HSV infection has not yet been studied. The aim of the study was to investigate the role of Kupffer cells (KCs), liver-resident macrophages, in the pathogenesis of HCV infection in vitro and in vivo. Ethanol-fed mice and HCV transgenic mini-pig were treated with blocking antibodies against CSF1R or according to ARC-661.

The transgenic pig model efficiently mimics HCV infection in a natural timeline. KCs are significantly enriched in QH-genotype HCV infected HepG2 cells. KCs with sustaining infection at late time points negatively regulate Huh7 cells by downregulating pro-inflammatory cytokines and vacuolar inducers. Inhibition of KCs also enhances inflammation in several animal models but further implicates a postoperative process in liver transplant patients. An activated KC-induced hepatoma microenvironment promotes liver metastasis of colorectal cancer cells treated with regorafenib. Additionally, CD44+ biliary cancer stem cells of gallbladder cancer metastasize to the liver through an immunoexosomal transcriptional regulation of pro-inflammatory cytokines and chemokines 14.

5. Limitations of the Study

Several limitations must be acknowledged in this study. First of all, liver anatomy or physiology provides only distant clues to disease processes occurring in the parenchyma, making it exceedingly difficult to predict the underlying processes just by studying systemic patterning through careful osseous dissection. This is the same for liver histopathology, where simply studying the hulking globe of the liver provides only indirect clues to pathologic processes occurring at an unimaginably smaller molecular scale. Diseases, like liver fibrosis, transcription or microRNA changes, might not show localized findings with greater profundity than systemic histopathologic changes or genomic changes. However, this does not render the macroscopic examination futile.

On the contrary, with careful data collection, it offers knowledge and data fundamental to both clinical and research aspects 15. The second limitation is the small size of the study cohort and the absence of control liver tissue for histological evaluation. This is a common limitation of human tissue studies, as chronic manufacturing, as seen in hepatitis and fibrogenic diseases, leads to architecture derangement, making it unrealistic to include healthier control liver tissue. However, as patients rarely undergo liver resection, it is impossible to expand the cohort size using the same surgical method. Future studies employing non-invasive imaging methods may help replicate the results in a larger cohort 16.

The third limitation is inherent to most studies that employ laser capture microdissection. Though strict dissection protocols were adhered to, some tumorous or nontumorous outgrowths might still have been subjected to analysis for molecular characterization. This especially applies to RNA sequencing, where tens of tumorous or nontumorous cells might have been easily contaminated via capillary forces or complex arrangement of cells during the dissection procedure. Common artifacts may have been inherited via RNA amplification. However, the least-to-most-error suppression within the amplification process easily compensates for these problems. For a side-control analysis, RNA sequencing data obtained from a larger cohort needs to be subjected to a more stringent analysis, filtering out genes aberrantly over- or underexpressed in tumoral tissue, which remained the major strength of the current sequencing data analysis. Nonetheless, future studies must ensure a proper analysis scheme for more faithful characterization. Some unaccounted factors need to be further characterized to validate the proposed cascades. First, the time sequence of the different posttranscriptional cascades remains to be established. A temporal malformation in either the transcription or microRNA clusters leads to aberrant architecture and likely loss of function. Thus, this would lead to fundamentally different processes entirely in different animals, although the basic major events may remain unchanged through evolution. Lastly, the statements concerning the abundant deposition of collagen types should also be validated with a more holistic profiling approach and classification of the various collagen types and their associated glycoproteins.13

6. Future Directions

Hepatic fibrosis is a wound-healing response to chronic stimuli, including chronic viral hepatitis B or hepatitis C virus infection. It is characterized by excess deposition of extracellular matrix (ECM), distortion of liver architecture, and portal tract enlargement. In chronic viral hepatitis, sequential events include inflammatory cell infiltration and their activation, hepatocyte injury, activation of fibrogenic cells (myofibroblasts, mainly derived from liver-residing hepatic stellate cells), ECM synthesis, inhibition of ECM degradation, and the resultant fibrous scar formation.

Fibroblasts and activated HSCs/myofibroblasts upregulate various ECM components, such as collagen I and HSP47, and simultaneously downregulate matrix metalloproteinases to disrupt the balance between MMPs and their tissue inhibitors. Fibrogenic services are regulated by the intricate cooperation and reciprocal interactions between activated liver-residing cells and recruited inflammatory cells. Activation of HSCs/myofibroblasts requires sustained agitation by pro-fibrogenic signals, including transforming growth factor and platelet-derived growth factor from activated hepatic macrophages and hepatocytes.13

Hepatic inflammation is the driving force behind liver fibrosis progression. Chronic necroinflammation exceeds liver repair and favors fibrogenesis, while regenerative hepatocyte proliferation after recovery from inflammation favors regeneration without significant fibrogenesis in mice. Disease severity (histological necroinflammatory activity) is a strong risk factor of liver fibrosis progression.

Non-invasive scores incorporating aminotransferases and platelets predict significant liver fibrosis in HBV. Host genetic factors, viral factors, and liver disease factors are associated with fibrosis progression. Eliminating the underlying etiology is the most crucial antifibrotic therapy for liver fibrosis. Evidence indicates that persistent viral suppression with antiviral therapy can result in fibrosis regression, improved hepatic function, and even extended survival. Conversely, continued viral replication leads to increased fibrosis, mutant variants, and poor prognosis. Improved understanding of the molecular mechanisms of liver fibrogenesis provides information on how to ameliorate this intractable disease 12.

7. Conclusion

Hepatic fibrosis, the wound-healing response of the liver, is the common late consequence of chronic liver injury regardless of the etiology. Persistent liver injury leads to excessive extracellular matrix deposition and subsequent distortion of the hepatic architecture. Cirrhosis, the end stage of liver fibrosis, is associated with portal hypertension and hepatocellular dysfunction, ultimately resulting in liver-related mortality. Thus, consistent histopathological and clinical assessments of liver fibrosis are necessary for the management of patients with chronic liver disease. However, most of them are invasive and carry a risk of complications and sampling bias. Clinicians and patients, therefore, prefer non-invasive alternatives to repeated liver biopsy, including imaging techniques and serum markers for liver fibrosis. Currently, histopathological grading is the gold standard for assessing liver fibrosis. It is a reversible process; therefore, it is essential to classify the stage of liver fibrosis at the time of presentation to determine the appropriate therapeutic approach. Chronic viral hepatitis is a major risk factor for hepatocellular carcinoma. Due to repetitive and continuous inflammation, these patients are at an increased risk of developing cirrhosis and/or hepatocellular carcinoma.

Inflammation-induced cellular responses play significant roles in the development of liver disease. Misregulation of these processes can promote steatosis, inflammation, and fibrosis through the activation of hepatic relocalization or death, stellate cells, and genes associated with fibrogenesis at the cellular and molecular levels. Global or site-specific drug delivery systems that target the liver and liver disease cells are needed to improve the outcomes of therapeutic strategies, including liver transplantation. The efficacy of antiviral therapy for hepatitis C virus-associated acute hepatitis has been shown to be greater than that for hepatitis B virus. The therapeutic advantage of moving forward with the approval of new classes of protease inhibitors include improved maximal rates of viral clearance, a shortening of the length of therapy, and a less-intensive and more user-friendly regimen when combined with ribavirin for the treatment of chronic hepatitis C.

The efficacy of interferon therapy for chronic infection is limited because the outcomes depend on patient age, genotype, and duration of nucleic acid testing. Resistance results in chronic infection and associated chronic liver diseases. Non-structural 5A proteins play pivotal roles in the process and inhibitors are likely to provide a new class of antiviral drugs. These proteins may be targets for novel methods of analysis to assess replication capability and the RNAi level.

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Ethical consideration: The ethical committee approved the study at University of Babylon, Babylon, Iraq.

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