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Human hepatocytes response to pathological shifts in liver fibrosis

***Dr Chrysanthus Chukwuma Sr*[1]**

[1] *The Chrysanthus Centre for Future-oriented Studies, Abakaliki, Ebonyi State, Nigeria*

Abstract

Protracted liver assault results in hepatic fibrosis, frequently advancing into cirrhosis, hepatic failure, portal hypertension and hepatocellular carcinoma or degeneration. Hepatic fibrosis emanates from the wound-healing response of the liver to persistent assault. Following acute liver insult, such as viral hepatitis, parenchymal cells regenerate and substitute the necrotic or apoptotic cells. A salient proportion of the affected population of NAFLD advances to nonalcoholic steatohepatitis, NASH, and is characterised by inflammation, hepatocellular swelling, with ensuing eruption of deteriorating fibrosis. An untreated or persistent NASH can progressively culminate in liver cirrhosis and hepatocellular carcinoma. Chronic liver derangement results in pathologic ECM protein or liver fibrosis aggregation. In essence, the encompassing characterisation of human ECM molecular composition provides for excursions into mechanisms of liver disease or hepatocellular degeneration. Hepatocytes are characterized by elevated mitochondrial concentrations. The difference between NASH and fibrosis is evident that the progression of NASH to cirrhosis commences as inflamed liver tissue evolves into scar tissue or fibrosis that is capable of obliterating the liver from optimum functionality. A third or more of persons presenting with NASH develop cirrhosis , and also elevates and accelerates the risk in the development of liver cancer. The hepatic stellate cells are responsible for liver fibrosis as they are substantially involved in the initiation, progression, and regression of liver fibrosis via the secretion of fibrogenic factors which promote portal fibrocytes, fibroblasts, and bone marrow-derived myofibroblasts in the formation of collagen, and consequential propagation of fibrosis.

Keywords: NAFLD, Pathophysiology, Pathogenesis, Diagnosis, Treatment, Extracellular matrix, Nonalcoholic steatohepatitis (NASH).

INTRODUCTION

Liver cirrhosis is the ultimate pathological outcome of diverse chronic liver disorders, while fibrosis precedee cirrhosis[1]. Liver fibrosis patterns differ depending on the aetiological factors and agents. In chronic infections due to hepatotropic viruses, portal expansion is accompanied by periportal fibrosis, septal or bridging fibrosis, and cirrhosis[2]. The pathophysiology of liver fibrosis is depicted by the accumulation of extracellular matrix, RCM protein accumulation , predominantly Type I and Type III collagens, accompanied by fibrous scar production, culminating in impaired normal liver functionality[3]. Succinctly, there are four stages of liver fibrosis. The stages of fibrosis are: stratifications on liver biopsy to stages 0 to 4 applying the METAVIR scoring system of F0—no fibrosis, F1—portal fibrosis, F2—periportal fibrosis, and F3—bridging fibrosis, and F4—cirrhosis[4]. In liver disease, impaired hepatocytes discharge reactive oxygen species, ROS and fibrogenic mediators, trigger HSC activation, and promote the fibrogenic actions of myofibroblast[5]. Hepatocyte apoptosis is a ubiquitous scenario in liver injury and a contributory factor in the inflammation, fibrogenesis, and development in the tissue of cirrhosis.

Thus, obliterating the hepatocytes from apoptosis and stimulating regeneration of hepatocytes may be therapeutically beneficial measures in liver fibrosis and cirrhosis[1]. The cells which mediate liver fibrosis pathogenesis depict that hepatic fibrosis constitutes the usual pathway for a vast majority of chronic liver disorders. Ostensibly, the indicted cell for hepatic fibrosis is the activated myofibroblast. The myofibroblast is derivable from latent hepatic stellate cells, epithelial to mesenhymal transition, or from precursors of bone marrow[6]. In essence, the objective of this review is to systematically discuss the extant mechanisms in the development and progression of non-alcoholic steatohepatitis, NASH, and to generate new hypotheses for future studies aiming at tackling liver lipotoxicity, the central pathogenic factor of NASH and liver-related mortality, the emerging concepts of NASH pathogenesis, and potential new therapeutic opportunities[7-9].

Clinicopathological characterisations of liver disease

In the adult population, non-alcoholic fatty liver disease, NAFLD approaches epidemic proportions,

***Corresponding author:**
Dr Chrysanthus Chukwuma Sr
The Chrysanthus Centre for Future-oriented Studies, Abakaliki, Ebonyi State, Nigeria
Email:
chukwumasr@gmail.com

positing a global 25% prevalence, pari passu with NASH and propensity to culminate in cirrhosis. For instance, in both the USA and Europe, it has emerged as the prime indicator in liver transplantation[10]. Liver fibrosis is the resultant impact of persistent, reiterative liver assault, and the major determinant of NASH outcomes. Liver exhibits formidable inherent plasticity, because liver fibrosis can regress following eradication of the assaulting agent. This provides the latitude for the transformation of protracted outcomes therapeutically. Despite hepatocyte assault, it remains a factor in NASH. Multiple extraneous cell lineages in the hepatic fibrotic domain contribute substantially in propagating inflammation, mesenchymal cell activation, extracellular matrix accumulation and resolution of fibrosis. The components of this cellular interactome, and the diverse modalities of of the subpopulations incorporated in the fibrotic ambient interact to drive fibrogenesis need to be elucidated. Pertinent cellular ingredients of the fibrotic domain encompass endothelial cells, macrophages, passaging immune cell populations and myofibroblasts[10].

Liver fibrosis is a reversible wound-healing mechanism directed in the sustainability of organ integrity, and depicts as the crucial pre-stage of liver cirrhosis, with consequential advancement to hepatocellular carcinoma or degeneration in the absence of liver transplantation[11]. Fibrosis usually manifests from chronic hepatic injury due to multifarious factors, such as viral intrusion, schistosomiasis, and alcoholism. The defined pathological processes remain elusive, though. Despite the availability of multiple drugs which have exhibited antifibrotic activity, none of the drugs have established clinical efficacy. Indubitably, hepatic stellate cells, HSCs contribute immensely in the commencement, advancement, and retardation of liver fibrosis by secreting fibrogenic factors which enhance portal fibrocytes, fibroblasts, and bone marrow-derived myofibroblasts in the formation of collagen and consequential fibrosis proliferation. The cells are susceptible to intricately complex cross-talk with adjacent cells, culminating in scarring and resultant liver derangement[11].

NAFLD is a chronic liver disease characterized by accumulated lipids in hepatocytes devoid of exhorbitant alcohol intake[12]. Globally, NAFLD prevalence is accelerating. It is a disease spectrum encompassing disparate levels and varied prognoses. NASH is a progressive anomaly characterized by liver inflammation and hepatocyte ballooning in the absence or presence of fibrosis. NAFLD natural history is influenced negatively following the onset of NASH and progression to advanced fibrosis[12]. Pathogenic processes and cellular interactions resulting in NASH and fibrosis incorporate hepatocytes, liver macrophages, subpopulations of myofibroblasts, and the resident progenitor cell transect. The cells may be inculcated in regenerative modalities consequent to liver injury; and derangement of these modalities may result in NASH and fibrosis. Extra-hepatic organs or tissues, for instance, gut and adipose tissue may influence the development of NASH by interaction with hepatic cells via molecular pathways[12].

NAFLD is a continuum of untoward clinical presentations wherein NASH is distinctly associated with poor prognosis. Hepatocyte lipotoxicity is a major pathogenic factor for liver fibrosis and NASH[13]. Research has unravelled certain spectrum of complexity in hepatocyte lipotoxicity, wherein transcriptional networks sensitive to saturated fatty acids enhance cell mortality. Rigorous comparative human datasets and experimental validation identified transcriptional networks and biological mechanisms associated with hepatocyte lipotoxicity development.

Pathogenesis

In industrialised climes[14,15], NAFLD is the most ubiquitous chronic liver disease affecting circa 25% of the populace, and constituting an indefatigable health impediment in the general population[16]. NAFLD encompasses the entire spectrum of fatty liver disease in persons lacking substantial alcohol intake, extending from nonalcoholic fatty liver, NAFLD to NASH and cirrhosis. NASH presence is indicative of the metabolic syndrome and hepatic disorder, steatosis, hepatocyte injury or ballooning, inflammation, and in certain patients, progressive fibrosis manifest with resultant cirrhosis. NASH pathogenesis presents a complex mechanism and indicts cell interactions of liver parenchymal and nonparenchymal cells as well as crosstalk involving diverse immune cell liver populations[16]. Ostensibly, lipotoxicity constitutes the central driver of hepatic cellular injury through oxidative stress and endoplasmic reticulum, ER stress. This review focuses on the contributions of hepatocytes and nonparenchymal cells to NASH, assessing their potential applications to the development of novel therapeutic agents. Currently, there are limited pharmacological treatments for NASH; therefore, an increased understanding of NASH pathogenesis is pertinent to improve disease interventions in the future[17]. NAFLD presents as the predominantly prevalent liver disease globally, particularly in the adult population, and a significant proportion of NAFLD patients depict disease progression to NASH[18]. There is propensity to elevate the risk to develop cirrhosis, liver failure and hepatocellular carcinoma or hepatocellular degeneration. NASH patients present liver fibrosis that constitutes the major mortality determinant[18, 19].

Pathophysiology

NAFLD encompasses an array of hepatic presentations, such as liver steatosis that potentiates to NASH, cirrhosis or hepatocellular carcinoma or degeneration[20]. NAFLD constitutes a dire health and economic burden, with incidence accelerating locally, regionally and globally. Despite its manifestation primarily as a disorder of perturbed metabolism, NAFLD incorporates multiple overlapping immune cell-mediated inflammatory responses and mechanisms, especially on approaching the NASH level, whereupon inflammation integrates to the disease advancement. The hepatic immune cell spectrum is varied and expansive at steady state, and increasingly evolves in NASH with invariable repercussions for adverse disease presentation[20]. NAFLD is a sphere of metabolic liver disease[21] associated with obesity[22], and ranges from relatively benign hepatic steatosis to NASH[21]. The latter is characterized by persistent liver injury, inflammation, and liver fibrosis, which holistically elevate the risk for end-stage liver disorders, such as cirrhosis and hepatocellular carcinoma. Research has probed NAFLD/NASH, preferentially the role of genetic, epigenetic, and dietary factors and metabolic dysfunctionalities in extraneous tissues, driving excess hepatic fat accumulation and liver injury. Concomitantly, single-cell RNA sequencing studies reveal remarkable extent of the molecular aspect of liver cell heterogeneity, intrahepatic cross talk, and disease-related reprogramming of the liver immune and stromal vascular microambient[21]. In NASH, NKT cells induce fibrosis by elevating steatosis and hepatocellular perturbation. Platelets foster NASH fibrosis by promoting lipid storage and infiltration of immune cells. Furthermore, liver sinusoidal endothelial cells usually inhibit HSC activation and dissipate this fibrosis suppressive condition. The hepatic fibrosis Kupffer cells which are resident macrophages depict damaged hepatocytes, platelets, and aggregation of leukocytes. Consequentially, elevated mitochondria concentrations, reactive oxygen species and inflammatory mediator, such as platelet-derived growth factor, altering growth factors, connective tissue growth factor are discharged.

Extracellular matrix

The extracellular matrix provides ardent morphology for cells via regulation of cell behaviour and adhesion signals, as well as functioning as a reservoir of growth factors and cytokines[23]. Hepatic fibrosis is characterized by an excess extracellular matrix accumulation. The conventional extracellular matrix remodelling trajectory diversifies during fibrogenesis with resultant excessive accumulation of its components, preferentially collagens. The extracellular matrix discharges signals which trigger hepatic stellate cell activation. These form the cardinal source of extracellular matrix and abundance of liver myofibroblasts[23]. ECM remodeling in human liver disorders have been impeded due to deficient purified ECM. A decellularization process for

the purification of ECM scaffolds from human liver tissue by means of histological and electron microscopy indicated that ECM scaffolds, without plasma and cellular components sustained the three-dimensional ECM structure and zonal dissemination of ECM ingredients[24]. This has been ventured on liver biopsies of HCV-infected patients at disparate stages of liver fibrosis using METAVIR classification. Label-free nLC-MS/MS proteomics and computation biology analysed ECM molecular composition in liver fibrosis progression, and unravelled protein expression signatures unique to the HCV-related liver fibrotic levels. The ECM molecular composition of liver fibrosis presented dynamic modifications in matrix stiffness, flexibility and density relative to the dysregulation of salient collagen, elastic fibers and minor ingredients with both structural and signaling dimensions[24].

Fibrosis presents its pathological characteristics of assorted chronic inflammatory disorders which can affect a vast majority of organs with adverse repercussions and resultant mortality. Therefore, the main characterisation of fibrosis is the excessive abundance of ECM because of disrupted equilibtium in ECM production and degradation[25,26]. ECM protein overabundance has been the research focus on fibrosis, but untoward ECM degradation is preeminent as an accrued issue. Matrix metalloproteinase, MMP and the tissue inhibitor of metalloproteinase, TIMP system constitute the pivotal molecular system aiding and abetting ECM degradation, while macrophages are the key ECM regulators[25,26]. The association between macrophages, the MMP/TIMP system and the ECM is not clearly elucidated in the fibrosis framework.

Pathophysiological pathways

The signaling pathways associated with normal liver regeneration have been adequately characterised, but not for livers impaired by chronic tissue injury. These dysfunctional livers display untoward regenerative response that results in liver repair and fibrosis. The tumour suppressor Hippo pathway is critically involved in liver regeneration and repair[27]. The activation of the Hippo coactivators YAP/TAZ in normal liver regeneration enhances the production of a nascent bile duct network via direct BEC proliferation with invariable hepatocyte dedifferentiation to HPCs that trans-differentiate to BECs. Furthermore, the interaction of YAP/TAZ signalling with other signaling pathways mediates the emergence and activation of Kupffer cells. The latter release mitogenic cytokines for parenchymal and/or non-parenchymal cells and cellular debris phagocytosis. Also, YAP-mediated stellate cell, HSC activation promotes liver regeneration by means of extracellular matrix synthesis. During chronic diseased livers in which predetermined threshold for proper liver regeneration has been exceeded, YAP/TAZ activation emerges in a reparative trajectory characterized by liver fibrosis. Within this state, YAP/TAZ activation in parenchymal and non-parenchymal cells culminates in (a) differentiation of latent HSCs into myofibroblastic HSCs; (b) conscription of macrophages discharging inflammatory cytokines; and (c) macrophage polarization towards the M2 phenotype. Accumulation of deranged hepatocytes in chronic liver injury depicts a prominent risk factor for hepatocarcinoma development[27].

Explicating liver pathophysiology requires comprehensive quantitative proteome compendium at cell type resolution in order to predict outcome and design therapy[28]. NASH presupposes the advanced stage of NAFLD. It is characterized by liver steatosis, inflammation and disparate magnitude of fibrosis[29]. The defined mechanisms of fatty liver progression to NASH have not been elucidated, but intrinsic and adaptive immune responses may be pertinent regulators in the elucidation, progression, and chronic dispensation of the disease[29-31]. These preempt formation of pro-inflammatory cytokines, chemokines and damage-associated molecular patterns, DAMPs which upregulate activation of Kupffer cells, KCs and monocyte-derived macrophages, MMs susceptible to the polarization of the tolerogenic liver ambient to an immunogenic phenotype towards transdifferentiation of hepatic stellate cells, HSCs into myofibroblasts and culminating in fibrosis. Thereafter, dendritic cells, DCs activate CD4+ T cells polarize into pro-inflammatory lymphocytes Th1 and Th17 deteriorating the liver injury and inflammation[29].

Predictors of mortality

The histologic sphere of NAFLD extends from simple steatosis to NASH, fibrosis, and resultant cirrhosis[32]. Subjects with NASH and severe fibrosis detected on liver biopsy have an elevated risk for liver-associated morbidity and mortality in comparison to those presenting simple steatosis. As a result of high NAFLD prevalence, research has augmented its pace to develop veritable noninvasive markers and tests which can accurately predict advanced stage disease in the absence of liver biopsy. These tests may be dualised into (a) that predict NASH occurrence, such as markers of hepatocyte apoptosis, oxidative stress, and inflammation, including predictive model-based clinical variables; and (b) that predict fibrosis presence, such as simple and complex predictive models. For NAFLD predictors, evaluation of serum biomarkers extant either in routine practice or experimental, or proprietary and exhorbitant, suggested magnetic resonance imaging-derived proton density fat fraction, MRI-PDFF to be most veritable for the diagnosis of fatty liver[32]. Predictors of fibrosis in NASH cases are elevated liver enzymes, and ratio of AST: ALT greater than one[33]; but liver enzymes are insensitive and may not be reliable for diagnosis or stage the magnitude of fibrosis. The prime mortality predictor in non-alcoholic steatohepatitis, NASH subjects is hepatic fibrosis[34]. In decreasing order of magnitude, the most ubiquitous cause-specific mortality in persons with NAFLD and NASH is cardiovascular disease[35]>mortality from extra-hepatic cancer>liver-related mortality including hepatocellular carcinoma, HCC or hepatocellular degeneration>diabetes[36].

Diagnosis and treatment

NAFLD is a highly prevalent variety of chronic liver disease that poses challenges in diagnosis and risk stratification[37]. Non-alcoholic steatohepatitis, NASH, the aggravated progressive aspect of NAFLD is essentially challenging in diagnosis without histologic input. Liver biopsy is rarely executed because of its invasive nature, potential latitude for sampling error, and deficient inter-rater reliability. Non-invasive tests which accurately identify at-risk NASH patients or biopsy-proven NASH patients with NAFLD activity score [NAS] ≥4 and fibrosis stage ≥2 are requisites for pharmacologic therapy in registrational trials NASH-related fibrosis treatments. With emerging pharmacotherapy[38], non-invasive tests are required to track treatment response. Non-invasive tests for risk assessment of clinical outcomes, progression to cirrhosis, hepatic decompensation, liver-related mortality, and overall mortality are pertinent[37]. NASH is a common variety of chronic liver disease characterised by lipid accumulation, infiltration of immune cells, hepatocellular ballooning, collagen deposition and liver fibrosis[39]. There is a dire necessity for the development of treatments for NASH. An investigation pertaining liver fibrosis and characteristics of advanced clinical disease can be modelled applying in vitro microphysiological system, MPS was conducted. The NASH MPS model comprised a co-culture of primary human liver cells cultured in diverse states, such as +/− excess sugar, fat, exogenous TGFβ or LPS[39]. The modelled transcriptomic, inflammatory and fibrotic phenotype was characterised and compared by applying a system biology strategy to determine conditions which correlate with more advanced clinical disorder. The transcriptomic profile of the model correlated with the profile of patient samples and the model depicted a quantifiable fibrotic phenotype. Evaluation of the impacts of Obeticholic acid and Elafibranor as well as dietary interventions were done in the model, with significant reduction in inflammatory and fibrosis markers[39].

There are deficient agents for the treatment or reversal of liver fibrosis, thus necessitating urgent novel antifibrotic therapeutic modalities for

chronic liver diseases. Connective tissue growth factor, CTGF substantially contributes to liver fibrogenesis, causing CTGF to be a necessary target for antifibrotic agent development. Investigations identified a novel Nb against human CTGF that demonstrated antifibrotic effects in vitro through the regulation of the biological functions of human stellate cells, LX-2[40].

Hepatic fibrosis features as the prime mortality predictor in NASH patients. During the extant mechanisms, the activated hepatic stellate cells, HSCs are the principal cells mandating deposition of fibrous extracellular matrix, thus inducing hepatic scarring. The activation, migration, and proliferation of HSC are regulated by an intricately complex of signaling network of growth factors, lipotoxicity, inflammation, and cellular stress, whereas activated HSC clearance is imperative for resolution of extracellular fibrosis[41]. On that score, pathways regulating HSC fate may constitute therapeutic targets for prevention and treatment of NASH-related hepatic fibrosis. The anti-fibrotic drug development for NASH patients has not proven to br clinically beneficial. This underscores the intricately complex biology, constraints, challenges and opportunities associated in targeting these discrete cellular signaling processes[41].

Globally, NAFLD relates as the preferentially prevalent chronic liver disease, with liver fibrosis, LF presenting as a pivotal fulcrum in the progression of NAFLD[42]. Natural products exhibit predominant antifibrotic attributes, offering nascent trajectories for NAFLD treatment. It is pertinent to usher a comprehensive perspective for natural products potential as antifibrotic agents, with flavonoids, polyphenol compounds, terpenoids, and the contribution of Baicalin in NAFLD-associated fibrosis. Mechanistically, these natural products demonstrate the propensity to target an expansive array of signaling pathways, as well as Hedgehog, Wnt/β-catenin, TGF-β1 and NF-κB. In addition, there are possibilities to enhance the functionalities of antioxidant enzymes, suppress pro-fibrotic factors, and depress fibrosis markers[42]. It is relevant to underscore the relevant potential of natural products in canvassing NAFLD-related liver fibrosis via multifaceted mechanisms. It underscores the pertinence for clinical investigation to determine effectiveness with veritable insights for future therapeutic advancements[42].

DISCUSSION

This paper provides an overview of various noninvasive methods for detecting NAFLD and suggests a diagnostic algorithm that can be used in clinical practice. In this Review we examine advances in non-invasive tests to diagnose and monitor NAFLD and NASH.This review regards the functionalities of hepatocytes and nonparenchymal cells in NASH, and assessment of potential contributions nascent therapeutic agent development. There is a paucity of pharmacological treatments for NASH; thus, more understanding of NASH pathogenesis is imperative to augment disease interventions in the future. NASH is characterized by hepatic steatosis with impact on an excess of detectable hepatocytes, hepatocellular derangement with defined hepatocyte ballooning, signs of inflammation and diverse magnitude of fibrosis[43]. Thus, it is imperative to review the interactions among liver cells culminating in NASH fibrosis development, with predilection on drivers and repercussions of hepatocytes[44].

This review tends to present a conspectus of the prevailing information and knowledge of ECM remodeling in hepatic fibrosis. In this context, NASH pathogenesis commences when lipotoxic metabolites trigger excessive oxidative stress[45]. Fibrosis results from excess ECM production that is not conveniently balanced by degradation[46]. HSC activation is an adaptive response that assists the liver react to persistent pathogen and toxin exposure. Activation resulting from sustained liver injury culminates in excessive ECM accumulation, depicting as liver scar or hepatic fibrosis, being the hallmark of chronic liver derangement, such as NASH[47]. ECM degradation is pivotal to fibrosis recovery. Cells having ECM degradation potential resulting from secretion of diverse matrix metalloproteinases, MMPs emerged as nascent aspects to fibrotic disease treatment[48]. Hepatic fibrosis, as excessive accumulation of extracellular matrix, ECM emanates from chronic liver injury, sustained activation of inflammatory response and fibrogenesis. This study provides certain pathophysiologic intrinsic attributes regarding NAFLD/NASH, a metabolic-related variety of chronic liver disease, CLD with increased effect on vulnerable and the general population as well as emerging leading aetiology of CLD globally[49]. With regard to extant perception of the pathology, research is principally targeting aetiological molecular factors developing liver fibrosis. Simultaneously, the target is on experimental small molecules to stem or reverse hepatic fibrosis. Natural compounds, immunological, and genetic trajectories exhibit pronounced promising impacts[50].

CONCLUSION

Recent evidence underlines the contribution of extra-hepatic organs/tissues, for instance, gut and adipose tissues in influencing NASH development by interacting with hepatic cells through various molecular pathways. Thus, elucidation of the molecular mechanisms of liver fibrosis and their relationships with HSCs are essential unravelling new therapeutic targets. This review features the role HSCs display in liver fibrosis, and relates novel strategies to suppress HSC functionality, thereby presenting new insights into potential treatments for liver fibrosis. This narrative review undergirds the mechanisms for activation and inactivation of HSCs with special emphasis on NASH-associated hepatic fibrosis. With the presentation of an updated overview, this article emphasises cellular pathways having the potential value for future treatment modalities. This study assists to explicate the molecular bases underlying ECM remodeling in liver fibrosis with recommendations of new molecular targets for fibrolytic strategies.

Conflict of Interest

The author declare no conflict of interest.

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ORCID ID

Dr Chrysanthus Chukwuma Sr: https://orcid.org/0000-0001-9162-6604

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