Review

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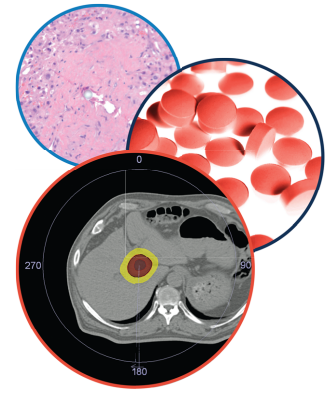

Hepatic Oncology

Hepatitis B-related hepatocellular carcinoma and stress: untangling the host immune response from clinical outcomes

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Chronic hepatitis B virus (HBV) infection is a major public health challenge on the global scale. Affecting hundreds of millions worldwide, HBV is a leading risk factor for hepatocellular carcinoma (HCC). Clinical outcomes from chronic HBV infection are varied and appear to be influenced by a complex and dysregulated host immune response. In turn, much attention has been given to the immunologic response to HBV in an effort to identify host factors that lead to the development of HCC. However, the role of non-immunologic host factors, such as chronic stress, in HBV-related HCC is poorly defined. Indeed, a growing appreciation for the effects of stress on chronic liver diseases raises the question of its role in chronic HBV infection. In this light, the present review will untangle the roles of key host factors in HBV-related HCC with an emphasis on chronic stress as a viable contributor. First discussed is the interplay of stress, inflammation and chronic liver disease. The host immune response's role as a driver of HBV-related HCC is then reviewed, allowing for a close exploration of the effects of stress on immune function in chronic hepatitis B and as a potential risk factor for HBV-related HCC.

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The hepatitis B virus (HBV) is a noncytopathic pathogen that takes residence in the liver. Perinatal infection with HBV is the predominate route of transmission in highly endemic regions of the world, including most of Asia and Africa [1]. Clinical outcomes from HBV exposure vary widely, ranging from a self-limited course to chronic infection with the heightened risk of cirrhosis and hepatocellular carcinoma (HCC) [2].

As an estimated 250–350 million individuals are chronically infected with the virus [3]. Clinical factors that determine outcomes with chronic HBV infection carry substantial public health importance. HBV is the most significant hepatocarcinogen [4], accounting for 25% of cases of liver cancer in developed countries and nearly 60% of cases in developing countries [5,6]. HCC can manifest in patients with chronic hepatitis B (CHB) with and without underlying cirrhosis [7,8], where the 5-year cumulative HCC risk in those with and without cirrhosis is respectively 9.7–15.5% and 0.6–2.4% [9]. While the incidence of HCC in those afflicted with CHB has decreased since the advent of antiviral therapy [10–13], the risk of HBV-related HCC is not eliminated [14–16].

The heterogeneity of clinical outcomes seen with CHB is the product of viral, host and environmental factors [17,18]. Prior research has identified multiple environmental and viral factors associated with worse outcomes with CHB, including specific viral genotypes and viral gene mutations [19,20], as well as concomitant exposures such as dietary aflatoxin [21]. The consequential contributions of host immune responses to HBV infection and subsequent development of HCC also remains an area of active investigation, as liver injury is considered an immune-driven process in CHB [22].

The effect of longstanding psychosocial stress on host immunity has gained increasing attention in the context of various chronic diseases, including cancer [23] and chronic liver diseases [24]. Indeed, commonly encountered in the

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Table 1. Types and tools to measure stress.

A. Types of acute and chronic stress		
	Acute	**Chronic**
Psysiologic stressors on the liver		
Alcohol	Yes	Yes
Metabolic	No	Yes
Viral	Yes	Yes
Psychosocial stressors		
Employment or personal finance challenges	Yes	Yes
Impaired quality of life from medical condition	Yes	Yes
Interpersonal conflicts	Yes	Yes
Psychological disorders (anxiety and depression)	Yes	Yes
B. Common tools to measure psychosocial stress		
Instruments	**Description**	
GHQ−12	Screening instrument to measure mental health disorders and stress burden	
LDQoL instrument	Validated questionnaire to gauge quality of life in those with chronic liver disease	
PHQ-9	Screens depressive symptoms via nine self-reported items	
PSS	Measures self-reported stress levels	

Table 1A illustrates the types of acute and chronic types of stress. Physiologic causes focus on stressors on the liver. Table 1B highlights common instruments used to measure psychosocial stress.
GHQ-12: General health questionnaire; LDQoL: Liver disease quality of life; PHQ-9: Patient health questionnaire; PSS: Perceived stress scale.

clinical setting are patients who complain of stress-related symptoms related to their liver diseases. The potential importance of host factors, such as psychosocial stress, was recently exemplified in an observational case series of three HBV infected families that included identical twins, where chronically infected offspring manifest a range of clinical outcomes despite having identical HBV genotypes and similar host genomes [25].

Here, we review the host factors that contribute to HBV-related HCC, emphasizing the burgeoning intersection of chronic stress and chronic HBV infection. First discussed is the interplay of stress, inflammation and chronic liver disease. In turn, the host immune response's role as a driver of HBV-related HCC is reviewed, allowing for a close exploration of the effects of stress on immune function in CHB and as a potential risk factor for HBV-related HCC.

Stress, inflammation & chronic liver diseases

Stress describes a state of behavioral, physiological and psychological responses to environmental demands that exceed a person's natural regulatory capabilities (Table 1A & B). Acute stress responses are generally considered physiologic, eliciting physiological changes that lead to tissue injuries. Conversely, chronic psychosocial stress, which includes adverse life experiences, history of childhood trauma and poor social support [26], can have pathological effects that culminate in chronic inflammation.

Physiological stress to the liver include alcohol, fat, toxic metabolites and replication of viral hepatitis that can acutely confer oxidative stress to hepatocytes [27]. Oxidative stress manifests by overproduction of free radicals, reactive oxygen species or reactive nitrogen species beyond the neutralizing capacity of hepatocytes [28]. Consequently, damaged mitochondria of hepatocytes trigger NF-κB-mediated inflammatory pathways, releasing inflammatory mediators (cytokines and chemokines) to recruit phagocytes (neutrophils and monocytes) and lymphocytes to remove offensive agents [28]. Although the inflammatory pathway is the body's first-line defense mechanism, the levels and/or duration of oxidative stress beyond the physiological condition can result in the overly ambitious release of reactive oxygen/nitrogen species and inflammatory mediators by recruited cells at the already injured site. In addition, cells that normally resolve aberrant inflammation, including Treg, alternatively activated (M2) macrophages and myeloid derived suppressor cells, become dysfunctional as inflammation persists (Figure 1) [29–32].

This amplification and perpetuation of inflammation is the common key driver of advanced liver diseases, including alcoholic liver disease, nonalcoholic fatty liver disease, liver fibrosis and liver cancer. Not surprisingly, anti-oxidant agents have become a focal point of therapeutic strategies to break the progressive oxidative stress

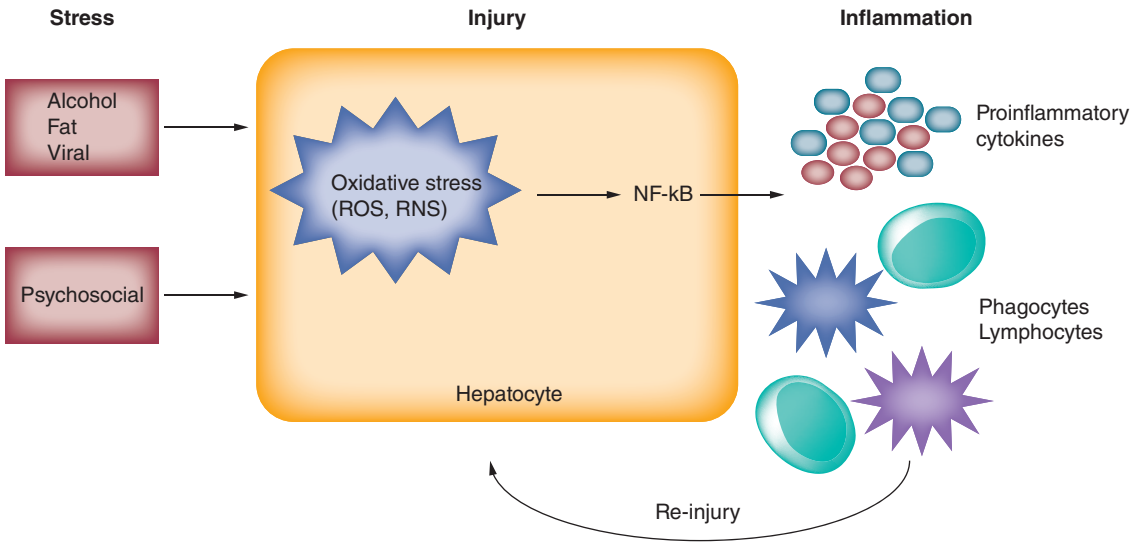

Figure 1. Hepatocyte injury-inflammation cycle from pathophysiological stressors. Alcohol, fat and viral infection are established hepatic stressors. Psychosocial stress may also lead to a similar pattern of hepatic injury. Pathophysiological stressors can trigger an oxidative stress reaction via overproduction of ROS and RNS. These oxidative species can precipitate NF-κB-mediated inflammatory pathways, leading to release of pro-inflammatory cytokines and recruitment of phagocytic cells (neutrophils and monocytes) and lymphocytes. This inflammatory milieu within the liver can lead to continued hepatocyte injury.
RNS: Reactive nitrogen species; ROS: Reactive oxygen species.

and inflammation cycle [33]. Recent meta-analysis have shown that statins (HMG-CoA reductase inhibitors) are associated with both significantly reduced risk of cirrhosis development in HBV or hepatitis C virus patients, as well as decreased risk of cirrhotic complications [34,35]. These findings indicate that anti-inflammatory approaches may have important clinical value in mitigating advancement of liver disease. Similarly, Chinese medicinal herbs have gained attention due to their anti-oxidant and anti-inflammatory activities along with mild adverse effect profiles, which are reviewed in detail elsewhere [36].

Notably, growing appreciation for the ramifications of chronic psychological stress on poor health outcomes has brought to light the impact of stress on chronic liver disease. A recent meta-analysis by Russ *et al.* [37] demonstrated a dose–response correlation between psychological stress and mortality from advanced liver diseases among 166,631 individuals pooled from multiple health examination studies in the UK over 14 years. Although this study does not prove a cause–effect relationship 3 [38], it provides population-based evidence that links psychological stress to poor prognosis of liver diseases. Such a correlation was upheld even after controlling for other health behaviors, including alcohol consumption, diabetes mellitus, BMI and socioeconomic status.

Increasing clarity of the mechanisms underlying psychological stress-mediated liver damage has grown. Acute psychological stress can induce transient hepatic hypoxia and reperfusion injury, consequently leading to the release of damage associated molecular patterns (DAMPs), overactivation of natural killer (NK) cells, and polarization of Kupffer cells to a pro-inflammatory phenotype [39]. Furthermore, chronic psychological stress can lead to dysregulated effects of glucocorticoids and norepinephrine, which are respectively released by the hypothalamic–pituitary–adrenal axis and sympathetic adrenomedullary system (Figure 2) [24,40–42]. Whereas glucocorticoids typically have anti-inflammatory properties under normal physiological circumstances, chronic stimulation of hypothalamic–pituitary–adrenal axis via psychological stress decreases its sensitivity to negative feedback loops leading to the amplification of pro-inflammatory cytokine milieu [43–47]. Norepinephrine can also promote secretion of inflammatory mediators through adrenergic receptor activation on innate immune cells [48]. Notably, animal models have shown that chronically elevated levels of corticosteroids and catecholamines promote production of hydroxyl radicals by hepatocytes [49], as well as production of Th2 pro-inflammatory cytokines (e.g., IL-6) by Kupffer cells and hepatocytes [39,48,50,51].

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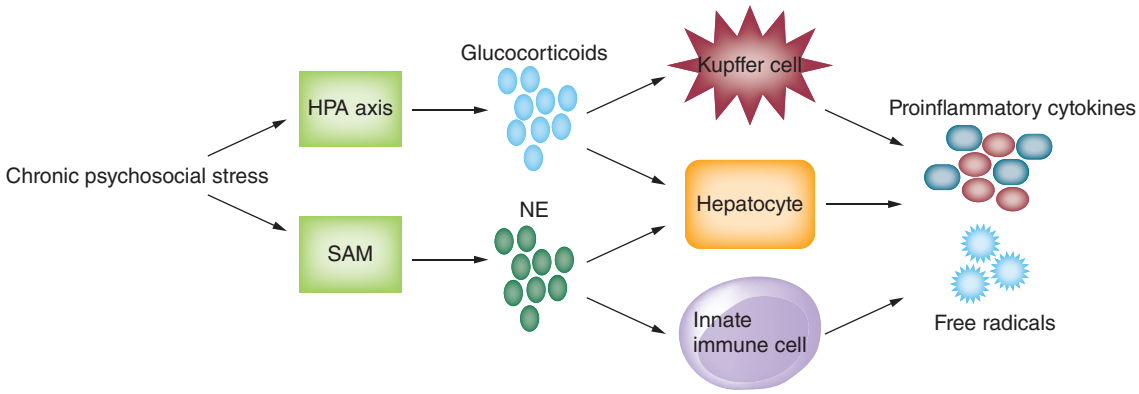

Figure 2. Proposed mechanisms of hepatic injury from chronic psychological stress. Chronic stress can promote release of NE via SAM system, activating innate immune cells possessing adrenergic receptors and leading to production of pro-inflammatory cytokines. Chronic stimulation of the HPA axis from psychosocial stress can decrease its sensitivity to negative feedback loops, leading amplification of pro-inflammatory cytokines by Kupffer cells. Both chronic glucocorticoid production and NE release can also stimulate hepatocytes to produce hydroxyl free radicals. HPA: Hypothalamic–pituitary–adrenal; NE: Norepinephrine; SAM: Sympathetic adrenomedullary system.

Moreover, strong inflammatory profiles due to psychological stress was reported by Pace *et al.* [52], who demonstrated that patients' severity of depression independently correlated with higher levels of pro-inflammatory markers (e.g., IL-6, NF-κB) after undergoing induction of acute stress via the Trier Social Stress Test.

Collectively, the pathological repercussions of stress on chronic liver disease, whether physiological or psychological in nature, all converge on chronic inflammation initially triggered by mitochondrial dysfunction and DNA damage [44,53,54].

Host immune response as a driver of HBV-related HCC

The prevailing pathology that underlies HBV-related HCC is chronic inflammation driven by persistent infection. HBV is a non-cytopathic virus [55] capable of deftly evading and impairing host immunological responses, leading to a dysregulated inflammatory state with resultant chronic liver injury.

Indeed, aberrancies within all branches of the immune system have been demonstrated throughout the lifecycle of HBV and are reviewed extensively elsewhere [56,57]. Of note, HBV replicates vigorously without triggering type I IFN pathway, effectively evading pathogen-sensing mechanisms of the innate immune system. This includes dysfunctional DNA and RNA sensing pathways, such as toll like receptor-9 [58,59] and RIG-I, that result in poor maturation of dendritic cells (DCs) [60,61]. Consequently, exhaustion of HBV-specific T and B cells [62], characterized by expression of multiple inhibitory proteins such as arginase, Bim, CTLA-4, PD-1 and FoxP3 [61,63–65], further contribute to the chronicity of HBV infection. Their exhausted phenotypes result in ineffective clearance of virus-infected cells and amplification of a dysregulated inflammatory state, which promotes compensatory regenerative processes within damaged hepatocytes [65,66].

In sum, persistent HBV infection coupled with ineffective immune responses establishes a chronic inflammatory state with compensatory hepatocyte proliferation. This vicious cycle leads to the indirect accumulation of host genomic alterations that can confer cell growth advantage, heightening the host's risk of liver cancer [67–69]. This has been illustrated by prior studies that have highlighted the importance of deregulated hepatocyte apoptosis [70,71], T-cell-mediated liver injury, and aberrant cytokine networks [66,72,73] in the pathological process that leads to HBV-related HCC.

Effects of stress on immune function in CHB

Mounting evidence has linked psychosocial stress with CHB. Patients with CHB have significantly higher rates of depression [74], which has been consistently seen across different ethnicities, including Asian, European, and Middle Eastern populations [75,76]. Prior studies further indicate that most patients with CHB consider their associated symptoms to moderately impact daily life and view their diagnosis as a source of significant life stress [77–79]. Indeed, as we recently observed, hair cortisol levels are significantly repressed in patients with CHB compared with controls, further illustrating the chronicity of psychosocial stress within these patients [80].

Supporting these observations, an early study by Kunkel *et al.* found that higher scores on depression and psychosocial metric tests were associated with elevated transaminases in CHB patients [81], suggesting that these patients have higher background levels of hepatic injury. In regards to specific biological mechanisms for stress-mediated immune suppression, definitive evidences remain lacking, although adrenergic receptors are shown to be present in all lymphocytes [82,83]. Stressors also induce the release of other pituitary hormones such as growth hormone, the brain peptides melatonin, beta-endorphin, and encephalin that can regulate the functions and distribution of leukocytes through activation of multiple different receptors [84]. A more recent study by He *et al.* showed a correlation between levels of psychosocial stress and a Th2-biased cytokine profile [85]. Using the 10-point Perceived Stress Scale and State Trait Anxiety Inventory, He *et al.* demonstrated that increased psychosocial stress was associated with elevated levels of immunosuppressive cytokines (e.g., IL-10) and suppressed levels of immunoactivating cytokines (e.g., IFN-γ). Therefore, perturbation of nonspecific and HBV-specific immune cells from chronic psychological stress of CHB patients may lead to their quantitative and qualitative changes, though it may be subtle, and contribute to already impaired immunity and ongoing inflammation.

Stress as a risk factor for HBV-related HCC

Whether chronic stress in the setting of CHB contributes to either the onset or progression of HCC remains to be determined. To date, no study has examined the effects of psychosocial stress on HBV-related HCC. However, evidence supporting a link between chronic stress and malignancy has been found. Meta-analytic research showed that heightened levels of psychosocial stress is associated with an increased risk and poorer survival across an array of cancer types [23,86,87]. Indeed, a recent 5-year cohort study of 140,420 individuals from the Japan Public Health Center-based Prospective (JPHC) study found that chronically high levels of stress was linked to an overall 6% increase in cancer incidence, where the incidence of liver cancer was particularly elevated among those with persistently high levels of stress [88].

As described in [26], discordant clinical outcomes of identical twins infected with HBV at birth were observed, as one developed HCC at the age of 51 years and the other remained a healthy carrier. Considering that the twins had identical viral genotypes and near-identical host genomes, the possible role of nongenetic risk factors, such as stress, in the development of HBV-related HCC is poignantly underlined.

Finally, decreased levels of depressive symptoms and feelings of social isolation are associated with improved mortality outcomes in cancer patients [89,90]. Similarly, a large prospective cohort study of the Swedish population found that individuals' stress resilience, defined as an adaptive response to adverse events, strongly correlated with the reduction of their future risk of liver cancer [91].

Conclusion

The public health burden of hepatitis B underlines the importance of discerning the mechanisms that contribute to the virus' heterogeneous clinical outcomes. Illumination of the constellation of risk factors that predispose chronically infected individuals to HCC remains an essential goal of HBV research. Indeed, significant progress has been made in defining the interplay between HBV and host immune responses. This body of research has shown that the oncogenic nature of HBV is largely a byproduct of the inflammatory environment it creates. The virus' capacity to evade, exhaust and provoke dysynchronous immune responses fosters a pernicious inflammatory state within the liver that is susceptible to malignant transformation. Nevertheless, there remains much to be uncovered regarding the mechanisms that impair HBV-specific immune responses, particularly intrahepatic immune responses in CHB [92]. Clarifying these mechanisms could guide potential immunomodulatory therapies in both CHB and HBV-related HCC [93].

Future perspective

The impact of nonimmunological host factors on clinical outcomes with CHB remains largely unexplored terrain. As discussed here, this is particularly true regarding the implications of psychosocial stress in patients with CHB. While previous studies have shown psychosocial stress to be widely prevalent among patients with CHB, few studies have studied the immunological or clinical impact of chronic stress in this patient population. As CHB and chronic stress can cause both immune dysfunction and inflammation within the liver, there are shared and feasibly synergistic pathological effects. Moreover, chronic stress has also been shown to heighten individual's risks of cancer, including liver cancer. Despite these similarities, there is a dearth of literature on the potential role of psychosocial stress in the development of HBV-related HCC. This paucity of data provides an opportunity

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for further exploration and the potential identification of key players of inflammation that could provide novel therapeutic approaches for CHB- and HBV-related HCC.

Executive summary

- Hepatitis B remains a leading risk factor for hepatocellular carcinoma (HCC) despite the advent of antiviral therapy.
- Clinical outcomes from chronic hepatitis B virus (HBV) infection vary and are influenced by a dysregulated host immune response. The underlying pathology of HBV-related HCC is similarly driven by persistent viral infection and an inappropriate inflammatory state.
- Chronic stress can amplify and perpetuate inflammation that has negative consequences in both chronic liver disease and gastrointestinal malignancies.
- Immune function in chronic hepatitis B is impaired by chronic stress. This raises a plausible relationship between chronic stress and HCC development in chronic HBV infection. However, few studies have examined the impact of chronic stress on the development of HBV-related HCC.
- The paucity of research investigating the interplay between HBV-related HCC development and chronic stress warrants investigation at the pathophysiological and clinical level.

Author contributions

HW Hann conceived the idea for the manuscript. All authors were involved in the writing, editing and drafting of the manuscript.

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