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Inflammasomes and their roles in the pathogenesis of viral hepatitis and their related complications: An updated systematic review

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ABSTRACT

Inflammasomes are a set of innate receptors which are the responsible molecules for activation of pro-interleukin (IL)-1β and IL-18 and induction of inflammation. Due to the key roles of the inflammasomes in the induction of inflammation, it has been hypothesized that the molecules may be the main parts of immune responses against viral infections and the tissue damage. Because some cases of viral hepatitis infections, including hepatitis B and C, are diagnosed as chronic and may be associated with various complications such as liver cirrhosis and hepatocellular carcinoma (HCC), several studies focused on the roles played by the inflammation on the pathogenesis of viral hepatitis. Based on the roles played by inflammasomes in induction of inflammation, it has been hypothesized that inflammasomes may be the main parts of the puzzle of the viral hepatitis complications. This article reviews the roles of the inflammasomes in the pathogenesis of hepatitis B and C viral infections and their complications, liver cirrhosis, and HCC.

1. Introduction

Hepatitis B (HBV) and C (HCV) viruses are responsible for the induction of hepatitis in human [1]. Although innate immune responses play crucial roles against viral hepatitis, they are the primary cause for induction of acute and chronic inflammation in the liver of the patients [2]. Liver cirrhosis and hepatocellular carcinoma (HCC) are the most prevalent and lethal complications in the patients suffering from chronic inflammation and in those who are infected with chronic forms of viral hepatitis [3]. It has been demonstrated that several innate immunity related molecules can be considered as the factors that increase the risks of the chronic form of the diseases [3–6]. Therefore, the innate immunity related molecules may also participate in the liver cirrhosis and HCC pathogenesis [6–9].

Innate immunity intracellular sensors are the primary molecules and their roles in the induction of chronic inflammation have been documented [10]. Inflammasomes are a set of well-known intracellular receptors that participate in the activation of Interleukin-1 beta (IL-1β) and IL-18 [11–13]. The cytokines have either pleiotropic or agonist functions when produced simultaneously [14], and hence their responses against viral hepatitis and induction of the related complications are plausible. This review article collated the most related investigations regarding the roles of inflammasomes in the immune responses against viral hepatitis and also their roles in the liver cirrhosis and HCC pathogenesis.

2. Introduction of inflammasomes

Inflammasomes are cytoplasmic sensor/activators which show proteolysis functions in caspase-1 dependent manner, and especially target pro-interleukin (IL)-1β and pro-IL-18 to activate the cytokines. Absent in Melanoma 2 (AIM2), Neuronal Apoptosis Inhibitory Protein (NAIP), Nucleotide binding and oligomerization domain-like receptor family Pyrin domain-containing 1 (NLRP1), NLRP3, NLRC4, NLRP6, NLRP7, and NLRP12 are the main members of the inflammasomes [15,16]. Intracellular cytoplasmic Pathogen Associated Molecular Patterns (PAMPs) and Damage Associated Molecular Patterns (DAMPs) are recognized by the inflammasomes which lead to activation of IL-1β and IL-18 [17]. Following the inflammasomes/PAMPs/DAMPs interactions, Apoptosis-associated Speck-like Protein (ASC) is activated, accordingly. The ASC structure hasimportant domains including caspase activation and recruitment domain (CARD) and also pyrin domain, therefore it can

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interact with inflammasomes via pyrin domain (other than NLRC4 which does not have pyrin domain) and caspase-1, the activator of IL-1β and IL-18, via CARD domain [18–21]. However, NAIP activates caspase-1 directly in NLRC4 dependent manner [22]. Although the functions of the inflammasomes are the same and lead to activation of IL-1β and IL-18, their activators (ligands) are different. Several inflammasomes activators have been reported including exogenous PAMPs such as microbial ligands, and endogenous DAMPs such as β-amyloid, crystalline substances, the ionophoresnigericin and maitotoxin, potassium efflux, lysosomal membrane disruption, saturated fatty acids and reactive oxygen species (ROS) [23–25]. Additionally, ATP binding to the purinergic receptor P2 × 7 and activation of cathepsins result in activation of the inflammasomes [26–29]. There is some evidence which demonstrated that inflammasomes need priming signals to be activated by the ligands [28,30]. The priming signals are derived from other innate immunity receptors such as toll-like receptors (TLRs) [28,30]. The priming signals not only induce activation of the inflammasomes, but also increase expression of the molecules at both mRNA and protein levels [31,32]. Additionally, the priming signals may induce another form of inflammation in dependent of inflammasomes, namely pyroptosis [33,34]. Inflammasome-dependent pyroptosis can be associated with released DAMPs to induce more inflammation [35]. In other words, although pyroptosis plays a crucial role in homeostasis and elimination of unnecessary cells, it can further induce the activation of the pro-inflammatory cytokines, like IL-1β, to promote the inflammatory response [36]. This process is important in the pathology of inflammasomes and their related molecules.

3. Inflammasomes in viral hepatitis and their complications

Like other innate immunity related molecules, the inflammasomes also participate either in the progression of appropriate immune responses against infectious agents, such as viral hepatitis, or development of innate immunity chronic inflammatory related diseases. Accordingly, the controversial properties of the molecules in the viral hepatitis are discussed in the next sections.

4. Inflammasomes play key roles in the eradication of viral hepatitis

As mentioned earlier, innate immunity plays crucial roles against viral infections, including hepatitis viruses [8]. The inflammasomes, as the parts of innate immunity also participate in the eradication of viral hepatitis from human tissues. Accordingly, Di Pietro et al., showed that murine coronavirus, mouse hepatitis virus (MHV), led to death in the caspase-1 knockout mice, which suffer from a lack of inflammasome signaling [37]. They also reported that although lacking IL-1β results in MHV replication, it did not lead to reduced survival of the mice [37]. However, their results revealed that IL-18 knockout mice showed a similar pattern of MHV replication and survival to caspase-1 knockout mice [37]. Thus, it seems that IL-18 is more important than IL-1β to protect the liver from MHV and it also shows that the activated inflammasome plays key roles against MHV. However, the main roles of inflammasomes and IL-18 against MHV need to be described as a future direction. Although it was the sole research article regarding the roles of inflammasomes against MHV, there are some studies regarding the protective roles of inflammasomes against HBV and HCV. As an example, a study showed that human hepatocytes increase production of IL-18 in response to HBV via up-regulation of AIM2 inflammasome [38]. Furthermore, the inflammasomes also play important roles in the induction of proper humoral immunity against HBV. A study by Weinberger et al., revealed that inflammasomes, especially NLRP1, NLRP3 and NLRP12, significantly participate in the induction of immune responses against hepatitis B surface antigen (HBsAg) vaccine [39]. The study also demonstrated that the differences among young and elderly people regarding the inflammasomes can be associated with various immune responses to the primary but not to the booster vaccination [39]. To confirm the significant roles of the inflammasomes in the induction of appropriate immune responses against HBV, some investigations reported that HBV uses some mechanisms to down-regulate their expression and alter their functions. For instance, Yu et al., reported that HBV, by HBeAg, uses some mechanisms to suppress IL-1β production via inhibition of NF-κB pathway and inhibits LPS/ROS-induced NLRP3 activation [40]. HBV also decreases expression of inflammasomes, especially AIM2, by reducing the mRNA stability of IFN regulatory factor 7 (IRF7), the main transcription factor for AIM2 gene [41]. Thus, it seems that a suitable responsiveness to HBV vaccination is dependent on the functions of inflammasomes. Moreover, due to the synergistic roles of IL-18 by other cellular immunity-related cytokines, such as IL-12 [42], it may be concluded that inflammasomes induce both humoral and cellular immunity against HBV. The investigations regarding the protective roles played by inflammasomes against HCV had similar results. Accordingly, Chattergoon et al., reported that recognition of HCV by endosomal TLRs, such as TLR3, 7 and 8, is associated with up-regulation of inflammasomes and response to the virus [43]. Moreover, macrophages recognize HCV-related PAMPs and, hence, produce IL-18, which is a major activator of natural killer cells (NK cells) [44]. NK cells are the main innate immunity cells against viral infections [45]. Investigations also demonstrated that HCV-RNA is an important PAMP, which is recognized by NLRP3 inflammasome and induces maturation of IL-1β and IL-18 to eradicate HCV infection [46,47]. Taken together, the inflammasomes might be considered as the crucial candidate to recognize HBV and HCV related PAMPs and activate caspase-1 to active IL-1β and IL-18, which are the primary responses to viruses and induce several immune system cells and molecules. In other words, HCV and HBV can be detected by the inflammasomes and so they try to escape from the responses or alter these pathways to escape and survive (Fig. 1). Nevertheless, the cell source of inflammasomes may be considered as a critical factor for determining the interaction between HCV and inflammasomes. As mentioned previously, inflammasomes in the immune cells including monocytes and macrophages induce mature IL-1β and IL-18 against HCV, while they may show various roles in the hepatocytes in response to HCV infection. Accordingly, McRae and colleagues revealed that HCV uses NLRP3 inflammasome for replication in the human hepatocytes. HCV up-regulates NLRP3 inflammasome and consequently caspase-1, which results in degradation of insulin-induced gene proteins and then transportation of the sterol regulatory element-binding proteins (SREBPs) cleavage-activating protein complex to the Golgi. This transportation leads to the production of lipid droplets, which are essential for HCV replication and morphogenesis [48]. Based on the fact that this is a unique study, which showed the roles of inflammasomes in the replication of HCV, it appears that more investigations are needed to confirm the results.

5. Inflammasomes; the crucial inducers of chronic inflammation viral hepatitis complications

It has been demonstrated that chronic inflammation is the leading cause of several human diseases including tissue fibrosis and cancers [49–51]. Accordingly, the molecules which participate in the induction of chronic inflammation can be considered as molecular investigations for their roles in the human pro-inflammatory based disorders. Due to the pro-inflammatory functions of the inflammasomes, it has been hypothesized that the molecules may be considered as risk factors for induction of fulminant hepatitis, liver chronic inflammation, liver cirrhosis, and HCC. An investigation showed that targeting the liver macrophages, the main source of inflammasomes, can be considered as an important strategy to treat hepatitis [52]. Inflammasomes are also the molecules responsible for induction of inflammation in the liver following injection of alum [53]. NLRP3 inflammasome and its signaling molecules also significantly participate in the induction of

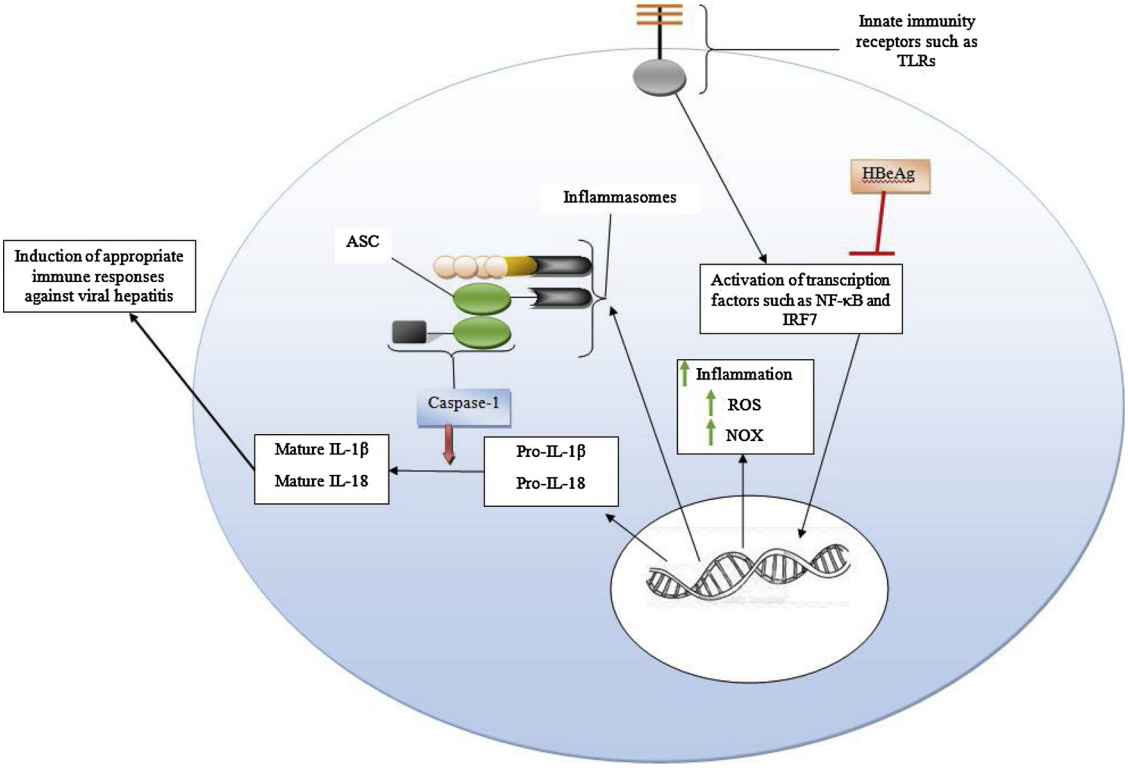

Fig. 1. The roles played by inflammasomes against viral hepatitis. The figure illustrates that following interaction of HBV/HCV antigens with innate immunity receptors, the inflammasomes are up-regulated and primed to interact with ASC/caspase-1 molecules to activate the immature forms of IL-1β and IL-18 to induce appropriate immune responses against the viruses. Accordingly, the viruses use some mechanisms to escape from these immune responses. For example, HBeAg inhibits up-regulation and priming of the inflammasomes.

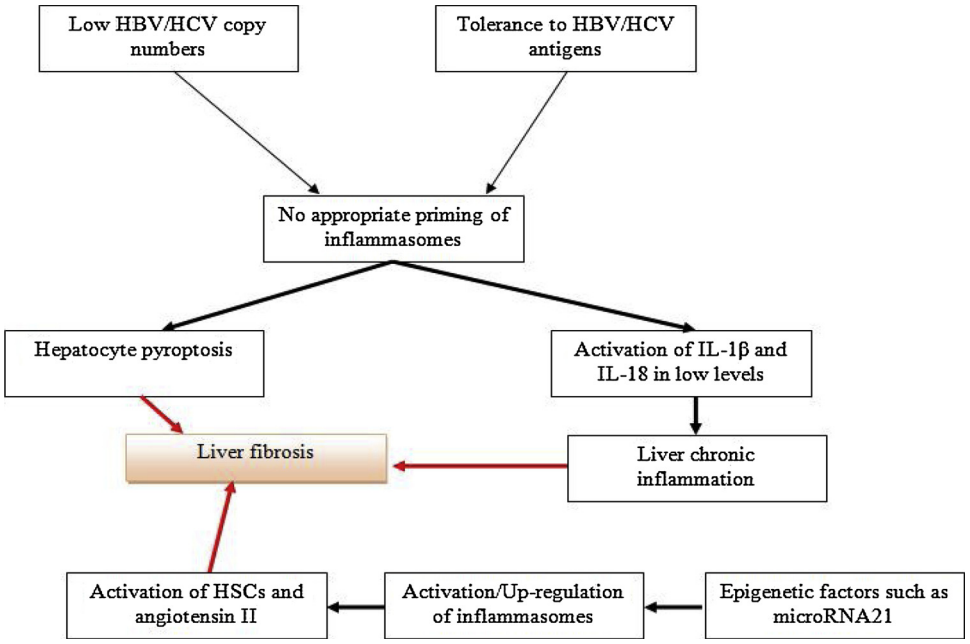

Fig. 2. The plausible mechanisms lead to liver fibrosis in the inflammasome dependent manner. Low HBV/HCV copy numbers and immune tolerance to the virus's antigens leads to no appropriate priming of the inflammasomes and it is a plausible mechanism to induce Hepatocyte pyroptosis and activation of IL-1β and IL-18 in low levels which are the risk factors for induction of liver fibrosis. Epigenetic factors, such as microRNA21, are the plausible risk factors for induction of liver fibrosis through activation of hepatic stellate cells (HSCs) and angiotensin II in the inflammasome dependent manner.

fulminant hepatitis by MHV [54]. However, studies regarding HCV and HBV revealed the induction of chronic hepatitis by inflammasomes and their related molecules, including ASC, caspase-1, IL-1β, and IL-18 [55–57]. Another investigation demonstrated that NLRP3, but not NLRP1 and NLRC4, significantly increased in the chronic HBV infected patients [15]. Molyvdas and colleagues reported that NLRP3, caspase-1, and IL-1β are the main factors for induction of liver chronic inflammation and raised liver enzymes in the HBV infected patients [58]. However, the investigators were unable to find the significant correlation between IL-1β levels and the degree of liver fibrosis among the HCV infected patients [58]. Additionally, they have concluded that there are other factors and related pathways responsible to induce fibrosis in the HCV infected patients in an independent manner of IL-1β levels [58]. Moreover, the investigation, in parallel with other studies [59,60], demonstrated that HCV may induce partial activation of NLRP3 and IL-1β secretion in the case of hepatoma cell lines infection

in monoculture condition. HCV infection of the hepatoma cell lines in the co-culture condition with LX2 stellate cells, did not lead to activation of the inflammasome and also secretion of IL-1β [58]. Therefore, it appears that the outcome of inflammasomes activation during HCV infection of hepatocytes may be related to cross-talk between immune and non-immune cells with the infected hepatocytes. The roles of AIM2 inflammasome in the induction of inflammation in the chronic HBV infected patients have been documented by Han and colleagues [61]. Interestingly, they have reported that AIM2 expression in the patients had positive correlations with caspase-1, IL-1β and IL-18 [61]. Yang et al., showed that the inflammasomes are the parameters which participate in the induction of sterile inflammation and then exacerbation of HBV-associated liver injury via recognition of DAMPs and subsequently activation of IL-1β and IL-18 [62]. In parallel with the investigations, a study on HCV also had similar results and demonstrated that HCV, in the chronic form, uses NLRP3 inflammasome and IL-1β to induce hepatitis [63]. Therefore, it seems that the inflammasomes not only participate in the virus eradication, they also play dominant roles in the induction of chronic inflammation, which are illustrated in Fig. 2. Inflammasome may induce inflammation either directly, via the mechanism that was introduced previously, or indirectly through production of other molecules involved in the induction of inflammation such as auto-antibody [64]. Due to the fact that chronic inflammation is a main risk factor for induction of HCC, and based on the roles of the inflammasomes in the induction of chronic inflammation, hence, it has been hypothesized that the inflammasomes may significantly involve in the induction of HCC. Additionally, there is some evidence, which suggests the roles of inflammasomes in the induction of liver fibrosis and HCC. Ning and colleagues reported that microRNA-21 activates NLRP3 inflammasome and then hepatic stellate cells (HSCs) in angiotensin II dependent manner [65]. Angiotensin II and HSCs are the main responsible parameters involved in the fibrosis of the liver [66,67]. Moreover, the roles played by microRNA-21 in the induction of liver fibrosis have been documented previously [68,69]. For instance, it has been reported that transforming growth factor beta (TGF-β) is an important molecule, which participates in the induction of inflammation and also fibrosis in the liver via interaction with receptor-regulated SMAD (mothers against decapentaplegic drosophila homolog) proteins (R-SMADs) [4,70]. Additionally, recent animal studies revealed that SMAD family member 7 (SMAD7) is an antagonist molecule for TGF-β and attenuates the TGF-β-mediated fibrosis [71,72]. In this context, microRNA-21 is a main epigenetic factor that suppresses the translation of SMAD7 mRNA, and hence, results in increasing the profibrogenic TGF-b signaling [73]. Therefore, it may be concluded that microRNA-21 not only induces liver fibrosis via altered functions of HSCs in angiotensin II dependent manner, it also mediates the fibrosis via down-regulation of SMAD7. A complex interaction between altered functions of HSCs and microRNA-21 may be considered for further investigations. Investigations also demonstrated that angiotensin [1–7] down-regulates NLRP3 inflammasome, via inhibition of angiotensin II and NADPH oxidase (NOX)-dependent oxidative stress, and consequently decreased rates of liver fibrosis [74,75]. Therefore, inflammasomes can be considered as the inducers of liver fibrosis. Interestingly, there are some evidences to confirm the roles of HCV to induce hepatitis complications in inflammasomes dependent manner. Accordingly, Di Pietro et al., revealed that hepatitis C has a synergistic effect on the inflammasomes induced-reactive oxygen species (ROS), which is a main cause of liver fibrosis [37]. Due to the significant roles of ROS in the hepatitis pathogenesis [76], it appears that ROS uses inflammasomes to induce the complication as a crucial mechanism. HCV also induces pyroptosis in either infected or bystander liver cells via activation of NLRP3 inflammasome and then caspase-1 [77]. Pyroptosis is an essential main mechanism to induce inflammation, fibrosis and also HCC in the liver. Therefore, it may be hypothesized that, in addition to induction of inflammation, ROS and pyroptosis by inflammasomes, activation of the cells involved in the fibrosis like HSCs is another mechanism used by inflammasome to alter liver functions. However, to the best of our knowledge there are no studies regarding the roles of inflammasomes in the HBV-related liver fibrosis and HCC. It is worthy to note that the roles of the inflammasomes in the pathogenesis of HCC are controversial. For example, Ma et al., demonstrated that the inflammasomes by targeting the rapamycin (mTOR)-S6K1 pathway reduce HCC cells proliferation [78]. Wei and colleagues also reported that estrogen suppresses HCC cells proliferation via up-regulation of the NLRP3 inflammasome [79]. Another investigation by the author revealed that expression of NLRP3 inflammasome and its components were completely lost or significantly down-regulated in both HCC and the bystander cells and this down-regulation was significantly associated with poor pathological differentiation [80]. The recent investigation by Ma et al., revealed that high mRNA levels of NLRC3 are associated with favorable clinical outcome (more favorable prognosis) in the patients suffering from HCC [81]. Furthermore, they reported that NLRC3 is down-regulated in the HCC when compared to normal tissues and also its reduction is significantly correlated with metastasis and Edmondson grades [81]. Ma et al., also produced a knock down NLRC3 HCC cell line, using shRNA specific for NLRC3 mRNA, to show the effects of NLRP3 on the cell line. They showed that cell proliferation and apoptosis were increased and decreased, respectively, following down-regulation of NLRP3 [81]. These investigations support the positive roles of inflammasomes against HCC. In contrast with the investigations, some studies reported the significant participation of the inflammasomes in the induction of HCC. For example, Ac-YVAD-CMK, an inhibitor of caspase-1, is able to suppress the anti-cancerous effects of interferon-inducible 16 (IFI16) in both HCC tissues and cell lines [82]. Chinese herbal therapy of HCC animal models led to NLRP3 inflammasome suppression, and subsequently inhibited proliferation and metastasis of HCC [83]. It has been documented that mitophagy is a biological process to remove the dysfunctional mitochondria, which is a main cause of cancers [84]. FUN14 domain containing 1 (FUNDC1), a well-characterized mitophagy receptor, mediates mitophagy and consequently suppresses HCC induction through inhibition of inflammasome activation, including caspase-1 and IL-1β [68]. Additionally, it has been demonstrated that increased background non-tumorous hepatocyte levels of NLRP3, NLRC4, and caspase-1 have significant correlations with poor HCC prognosis [85]. Based on the studies, it seems that the inflammasomes play dual roles in the pathogenesis of HCC and it may be concluded that some extra factors determine the directed functions of the molecules during HCC. In other words, it may be hypothesized that some known or unknown factors may determine the main roles played by the inflammasomes during HCC. For example, participation, or not, of other innate immunity pathways such as TLRs, may be considered as the important reason for the involvement of the inflammasomes in the HCC protection or progression because of their roles in the production of priming signals [28,30]. Previous investigations showed that microRNA223 has anti-cancerous properties [86,87]. Accordingly, Visalli et al., showed that there is a negative correlation between microRNA223 cytoplasmic levels with the expression of inflammasomes [88]. Interestingly, another study also confirmed the anti-cancerous roles of microRNA223 and revealed that the molecule inhibited and promoted HCC cell proliferation and apoptosis, respectively, via direct targeting of NLRP3 and indirect targeting of caspase-1, IL-1β and IL-18 [89]. Therefore, epigenetic factors, like microRNAs, are another factor for determining the roles of inflammasomes in the pathogenesis of HCC. However, the roles of viral hepatitis and their related PAMPs in the functions of the inflammasomes in the HCC are unclear. Sasaki et al., showed that HCV induces cysteine-cysteine chemokine ligand 5 (CCL5) secretion from macrophages, which leads to activation of inflammasomes in the HSCs and subsequently increases the risk of HCC [90]. However, another *in vitro* investigation presented contrasting results and reported that HCV infection of HCC cell lines is associated with increased apoptosis in the inflammasomes dependent manner [77]. Therefore, it seems that more *in vitro* and *in vivo*

Table 1
The roles of inflammasomes in the HBV/HCV infection.

Viral hepatitis	Inflammasomes roles	Description	Ref
MHV	Protective	Inflammasomes significantly protect the animals against MHV, especially via maturation of IL-18	[37]
HBV		Hepatocytes increase production of IL-18 in AIM2 inflammasome dependent manner	[38]
HBV		NLRP1, NLRP3 and NLRP12 inflammasomes induce proper humoral immunity against HBsAg	[39]
HBV		HBV suppresses IL-1β production and LPS/ROS-induced NLRP3 activation	[40]
HBV		HBV decreases AIM2 levels by targeting IRF7	[41]
HCV		Increased expression of inflammasomes in TLR3, 7 and 8 dependent manner	[43]
HCV		HCV/ inflammasomes interactions lead to production of mature IL-18 and consequently NK cells activation	[44]
HCV		HCV-RNA induces maturation of IL-1β and IL-18 by NLRP3 inflammasome	[46,47]
HCV	Negative	Hepatocytes NLRP3 inflammasome increases HCV replication in SREBPs dependent manner	[48]
MHV	Inflammation	MHV induces fulminant hepatitis in dependent NLRP3 inflammasome	[54]
HBV		NLRP3 increases the chronic inflammation	[15,58,62]
HBV		AIM2 increases the chronic inflammation	[61]
HCV		NLRP3 increases the chronic inflammation	[63]
HCV	Fibrosis	HCV has a synergistic effect on the inflammasomes induced-ROS	[37]
HCV		HCV induces pyroptosis activation of NLRP3 inflammasome	[77]
HCV	Hepatocellular carcinoma	HCV induces CCL5 to activate inflammasomes in the HSCs and increases the risk of HCC	[90]
		HCV can induce apoptosis in the hepatoma cell line in inflammasomes dependent manner	[77]

CCL5: cysteine-cysteine chemokine ligand 5, MHV: Mouse hepatitis virus, AIM2: Absent in Melanoma 2, NLRP1: Nucleotide binding and oligomerization domain-lLike rReceptor family Pyrin domain-containing, LPS: Lipopolysacharide, IRF7: IFN regulatory factor 7, TLR: Toll like receptor, NK cell: Natural Killer cell, SREBPs: Sterol regulatory element-binding proteins, ROS: Reactive oxygen species, HSCs: Hepatic stellate cells.

investigations need to be performed to determine the effects of HBV/HCV interaction with the inflammasomes on the HCC progression. Table 1 illustrates the results presented here.

This issue is complicated with considerable information regarding the association of the polymorphisms within the inflammasomes related molecules with chronic viral hepatitis and their complications. Vergara et al., showed that IL-18 gene polymorphisms are associated with altered serum levels of the cytokine in the HCV infected patients [91]. Association of IL-18 promoter genotype -137 G/G and allele -137 G with decreased serum levels of the cytokine and chronic HBV infectivity, respectively, has been reported by Jiang and colleagues [92]. IL-18 gene polymorphisms also have a significant correlation with liver cirrhosis and HCC in the patients infected with HCV and HBV [93]. More investigations also confirmed the association of IL-18 promoter 137 G/G genotype and G allele with increased risks of HBV chronic form incidences, its related HCC and decreased expression of IL-18 [94–96]. The protective roles played by the -137C allele against the chronic form of hepatitis B and HCC related complications have also been confirmed by investigators [97,98]. However, Zhu et al., revealed that the IL-18 -137 G/C polymorphism is not associated with the risks of HCC complication of hepatitis B [99]. Associations of other polymorphisms of IL-18 gene have also been reported by previous studies [100,101]. Additionally, there are several investigations which proved the roles of IL-18 polymorphisms in the risk of HCV chronic infection and its related complications [102–107]. Like IL-18, IL-1β and its receptor gene polymorphisms also have significant correlations with viral hepatitis chronic forms, the virus's replication and virus related liver cirrhosis and HCC [108–112]. Table 2 summarizes the evaluated polymorphisms within IL-18, IL-1β and IL-1β receptor genes and their related to HBV and HCV infections as well as their related complications. The controversial results demonstrated that the polymorphisms need to be explored by further investigations to raise a definite conclusion.

6. Conclusion

Results demonstrate the inflammasomes can be considered as the important parts of the chronic inflammation following viral hepatitis infections in the human. Thus, it seems that the inflammasomes either participate in the induction of appropriate immune responses to viral hepatitis or play key roles in the induction of chronic inflammation, which is the main risk factor for induction or stimulation of viral hepatitis related complications. The main mechanisms which lead to determining the output of the inflammasomes activation are yet to be clarified, however, it may be hypothesized that the following plausible mechanisms can be considered for more investigations: 1. Due to the various responses of inflammasomes against HCV and HBV, it may be concluded that the bystander effects of the immune and non-immune cells on the infected hepatocytes may be considered as an important factor for activation of inflammasomes against HCV or participation in the etiology of HCC, 2. The epigenetic factors such as microRNAs may play key roles in either physiological or pathological roles played by inflammasomes and other fibrosis related pathways such as SMAD proteins in the induction of both liver fibrosis and HCC, 3. Activation of some pathways including ROS and NOX production by the inflammasomes is not only a protocol for response against viral infections, it can lead to transformation of hepatocytes to HCC, 4. Caspase-1 is the main enzyme in the inflammasome pathways and consequently induction of chronic inflammation, the main cause of tumor induction, while it also participates in other pathways such as apoptosis and also induction of immortality [113]. Therefore, the controversial roles played by the inflammasomes in the HCC may be related to the various activities of caspase-1. 5. Due to the information presented in previous section, the cell source of the inflammasomes is also a critical factor for determining the inflammasomes roles during HBV/HCV infection. Accordingly, macrophages and monocytes, as the immune cells use inflammasomes to induce inflammation and it could result in two categories, including acute inflammation, which is associated with eradication of the viruses, and chronic inflammation, the main cause of induction of fibrosis and HCC. However, hepatocytes as another source of inflammasomes tell a different story and inflammasomes, especially in the chronic HCV infection, help the virus to replicate in the hepatocytes. But, HCV uses NLRP3 inflammasome for replication in the human hepatocytes through degradation of insulin-induced gene proteins and then transportation of the SREBPs cleavage-activating protein complex to the Golgi and consequently, production of lipid droplets, the essential factor for HCV replication.

Nevertheless, there are several gaps regarding the inflammasomes and viral hepatitis which need to be elucidated such as the genetic variations of the inflammasomes and their related molecules, the considerable interaction between the inflammasomes and other innate immunity pathways and adaptive immunity, the various ligands of the molecules and the plausible interactions among inflammasomes.

Ethics approval and consent to participate

Not applicable.

Table 2
The polymorphisms within inflammasome related genes and their association with HBV and HCV infection and their related complications.

Viral hepatitis	Inflammasomes roles	Description	Ref
HCV	Gene polymorphism	IL-18 gene polymorphisms are associated with increased IL-18 serum levels	[91]
HCV		IL-18 polymorphisms are associated with the risk of HCV chronic infection and its related complications	[102–107]
HCV		IL-1β gene polymorphism is associated with HCV infection and its related HCC	[109]
HCV		IL-1β gene polymorphism is associated with treatment responses in chronic patients infected with HCV genotype 4	[110]
HCV		IL-1β gene polymorphism influences the outcome of hepatitis C virus infection	[111]
HBV		IL-18 promoter polymorphism is associated with decreased serum levels of the cytokine	[92]
HBV		IL-18 137 G/G genotype and G allele have a significant positive correlation and 137C allele has protective relation with liver cirrhosis and HCC	[93–98]
HBV		IL-18 -137 G/C polymorphism is not associated with the risks of HCC	[99]
HBV		IL-18genotype AA and the allele A at position rs1946518 are closely associated with the resistance to chronic hepatitis B	[101]
HBV		IL-18 -148C, +8925 G, and +13925C alleles are associated with the presence of HCC and the 148 G > C SNP is functionally important in determining disease outcome	[100]
HBV		IL-1R1 gene polymorphism can be considered as a risk for HBV infection	[108]

The studies have investigated the polymorphisms within IL-18, IL-1β and IL-1β receptor. The controversial results demonstrated that the polymorphisms need to be explored by further investigations to raise a definite conclusion.

Availability of data and materials

Not applicable.

Competing interests

Authors have no conflict of interest to declare.

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