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Cytokines and serum amyloid A in the pathogenesis of hepatitis C virus infection

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ABSTRACT

Expression of the acute phase protein serum amyloid A (SAA) is dependent on the release of the pro-inflammatory cytokines IL-1, IL-6 and TNF-α during infection and inflammation. Hepatitis C virus (HCV) upregulates SAA-inducing cytokines. In line with this, a segment of chronically infected individuals display increased circulating levels of SAA. SAA has even been proposed to be a potential biomarker to evaluate treatment efficiency and the course of disease. SAA possesses antiviral activity against HCV via direct interaction with the viral particle, but might also divert infectivity through its function as an apolipoprotein. On the other hand, SAA shares inflammatory and angiogenic activity with chemotactic cytokines by activating the G protein-coupled receptor, formyl peptide receptor 2. These latter properties might promote chronic inflammation and hepatic injury. Indeed, up to 80 % of infected individuals develop chronic disease because they cannot completely clear the infection, due to diversion of the immune response. In this review, we summarize the interconnection between SAA and cytokines in the context of HCV infection and highlight the dual role SAA could play in this disease. Nevertheless, more research is needed to establish whether the balance between those opposing activities can be tilted in favor of the host defense.

1. Introduction

Hepatitis C virus (HCV) infection represents a major health problem worldwide. HCV, initially referred to as non-A, non-B viral hepatitis, was first discovered in the late 1980s [1]. Today approximately 70 million individuals worldwide are infected with HCV, with the highest prevalence observed in Africa and the Middle East [2]. HCV is a hepatotropic single-stranded positive-sense RNA virus that belongs to the Hepacivirus genus of the *Flaviviridae* family. Once infected with HCV, the majority of individuals develop chronic infection. Indeed, HCV induces an acute infection that switches to chronicity in 8 out of 10 cases, while approximately 20 % of infected patients clear the virus. Chronically infected patients develop severe hepatic fibrosis, eventually leading to hepatic cirrhosis and hepatocellular carcinoma (HCC) [3]. In fact, chronic hepatitis C (CHC) infection is one of the leading indications for liver transplantation [4].

A 45 nm nucleocapsid, composed of the core protein, encapsulates the HCV genome (Fig. 1A). The nucleocapsid is surrounded by an envelope in which heterodimers of glycoproteins (E1 and E2) are embedded [5]. The 9.6 kB viral genome encodes a polyprotein, which is 3000 amino acids long. This polyprotein is processed by both host and viral proteases giving rise to three structural proteins (core protein/p22, glycoprotein E1/gp35 and glycoprotein E2/gp70) and seven nonstructural proteins (NS1/p7, NS2/p23, NS3/p70, NS4A/p8, NS4B/p27, NS5A/p56/p58 and NS5B/p68) (Fig. 1b). Following polyprotein processing, the NS viral proteins take on their respective roles in orchestrating viral replication, assembly and release [6].

Detection of HCV by pathogen recognition receptors (PRRs) of the host cell, for instance, toll-like receptor 3 (TLR3), TLR7 and retinoic acid-inducible gene-I (RIG-I), activates the innate immune system leading to the expression of type I and type III interferons (IFNs) [7,8]. Through their scavenger function, macrophages and dendritic cells (DCs) also play a role in the detection of HCV and subsequent antigen presentation. Plasmacytoid DCs release IFN-α in response to the virus. IFNs activate numerous interferon-stimulated genes, which display antiviral activity. Natural killer cells also serve to eliminate the virus via their cytolytic function and the expression of type II IFN [9]. However, IFNs are not the only cytokines involved in the HCV-mediated immune response (see section 2.1 for a more detailed discussion). Several constituents of the adaptive immune response are essential for

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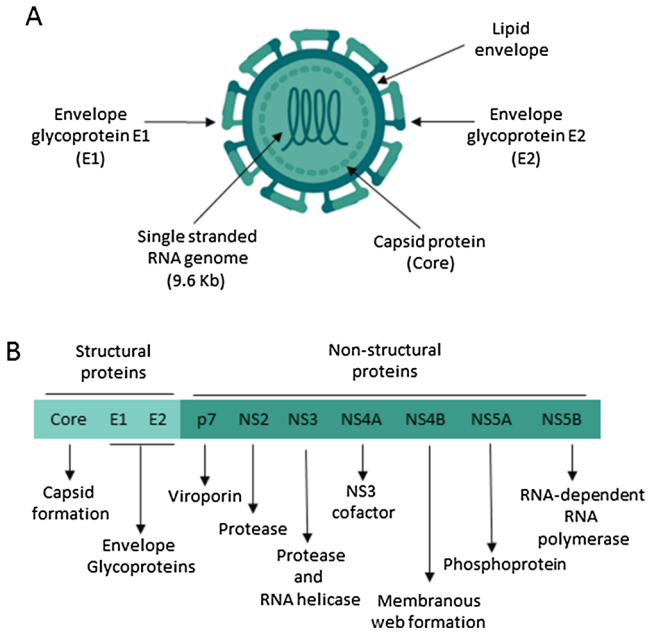


Fig. 1. HCV: structure and function of constitutive proteins.

the clearance of HCV. Indeed, a strong and sustained CD4 and CD8 T-cell response is crucial for the elimination of HCV [10]. Whether or not an efficient and multifunctional T cell response is mounted might depend on host genetics, since certain genetic variations in HLA, IL-12 and IL-28B/IFN-λ3 genes are linked to spontaneous viral clearance or even resistance [11]. Furthermore, rapid production of neutralizing antibodies directed against the virus is also associated with spontaneous resolution of the infection [12,13]. The production of neutralizing antibodies is directly linked to the presence of T follicular helper cells [13].

Although great strides have been made in understanding the molecular pathogenesis of the virus, much remains to be revealed. The acute-phase protein (APP) serum amyloid A (SAA) is relevant, as it has been described to have antiviral activity, but is rather understudied in the context of HCV infection [14,15]. SAA forms a family of proteins, conserved in a wide range of species ranging from sea cucumbers to humans [16]. Humans have four different genes coding for SAA, giving rise to SAA1, SAA2, SAA3 and SAA4. SAA1 and SAA2 have several polymorphic alleles: *SAA1.1*, *SAA1.2*, *SAA1.3*, *SAA1.4*, *SAA1.5* and *SAA2.1* and *SAA2.2*, respectively. SAA1 and SAA2 are expressed during the acute phase response (APR), whereas SAA4 is constitutively expressed. SAA3 was previously thought to be a pseudogene. However, a recent study has demonstrated otherwise [17]. SAA1 is perhaps the most widely investigated variant. SAA1, an 11.7 kDa apolipoprotein, is mainly produced by hepatocytes in response to the inflammatory cytokines interleukin (IL)-1β, IL-6 and tumor necrosis factor–α (TNF-α). Exogenous mediators such as lipopolysaccharide (LPS) have also been described to induce the production of SAA1. Moreover, the synthesis of SAA1/2 in organs other than the liver has been demonstrated [17]. In healthy individuals, the SAA1 plasma level is within 2–4 μg/ml. However, during inflammatory conditions, SAA1 plasma levels may exponentially rise, reaching 1000 μg/ml or more in some cases [17,18]. In this review, we explore the role of SAA in the pathogenesis of HCV infection.

2. SAA-cytokine interactions in the immune response against HCV

2.1. Activation of the immune system by HCV

Cytokines are key regulators of the immune response. The major cytokine expressing immune cells are monocytes/macrophages, DCs and T-cells. Several functions have been ascribed to cytokines such as induction of cell proliferation and differentiation, recruitment of leukocytes, promotion of wound healing and facilitation of the antimicrobial response [19]. Following infection with HCV, cells respond by expressing multiple cytokines to aid in viral elimination [20–23]. As previously mentioned, the activation of RIG-I and TLR3 by HCV genomic material induces the expression of IFNs [24,25]. In addition to the RIG-I like receptors (RLRs), TLRs are the most frequently described pattern recognition receptors (PRRs) that detect HCV-derived particles [26]. As evidenced in multiple studies, HCV core protein activates TLR2, with TLR1 and TLR6 functioning as co-receptors, leading to cytokine expression [27,28]. Although less frequently described, TLR4 activation by the core protein has also been reported in murine preadipocytes leading to the expression of IL-6 [29]. Similarly, NS3 has been demonstrated to activate TLR2, TLR6 and TLR4 [30,31]. NS5A binds TLR4 on monocytes leading to the expression of IL-10 [32]. Furthermore, activation of TLR3 by HCV dsRNA intermediates in cultured hepatoma cells triggers the expression of various chemokines such as CCL3, CCL4, CCL5 and CXCL10 [33]. HCV proteins also interact with several host receptors that do not specialize in pathogen recognition. Notably, while E2-CD81 interaction is required for virus entry into hepatocytes, it also induces the expression of cytokines in various cell types [34–36]. Table 1 provides an overview of the receptors functionally interacting with HCV proteins.

2.2. SAA-inducing cytokines are elevated during HCV infection

Various inflammatory cytokines, namely IL-1α, IL-1β, IL-6 and TNF-α upregulate SAA expression [17]. Although less frequently described, IL-17 and IL-18 have also been reported to induce SAA expression in keratinocytes, polyp epithelial cells or fibroblasts [37–39]. In situ hybridization revealed IL-1α and TNF-α expression in the liver tissue of HCV-positive patients. These cytokines were detected in the liver sinusoids, as well as in infiltrating inflammatory cells, including lymphoid cells and macrophages. Although at a lower frequency than in the aforementioned cells, IL-1α and TNF-α were also detected in HCV-infected hepatocytes. Immunocytochemistry confirmed these findings and showed expression of TNF-α mainly in hepatocytes, liver sinusoidal cells and leukocytes, including lymphocytes and macrophages in portal spaces. In contrast, cytokine expression was not significant in liver biopsies derived from HCV-negative individuals [40].

During the acute stage of HCV infection, IL-18 plasma levels are strongly increased in comparison to other SAA-inducing cytokines such as IL-1β, IL-6 and TNF-α. As a matter of fact, Chattergoon et al. suggested IL-18 as a more sensitive early marker of acute HCV infection than a well-established marker of liver injury such as alanine aminotransferase (ALT). IL-18 levels in plasma begin to decline during recovery from acute HCV infection but remain elevated during persistent infection [41]. Similarly, Sharma et al. compared IL-18 serum levels in CHC patients to those with resolved infection. CHC patients displayed a highly upregulated expression of IL-18 when compared to healthy controls, which correlated with the severity of hepatic cirrhosis. Southern hybridization of peripheral blood mononuclear cell (PBMC) lysates derived from CHC patients showed increased mRNA expression of IL-18, thus indicating that PBMCs are a principle source of IL-18 during HCV infection. Furthermore, IL-18 mRNA expression was also detected in the liver tissue of CHC patients [42]. The previous findings have also been confirmed by Bouzgarrou et al., who demonstrated elevated IL-18 plasma levels in CHC patients [43].

In a study carried out by Meng et al., a higher percentage of circulating PBMCs produced IL-17 in HCV-positive individuals in comparison to healthy controls, which declined following treatment [44]. El Husseiny et al. measured by ELISA enhanced IL-17 serum levels in HCV-positive patients, which positively correlated with the viral load [45]. In another study, serum IL-17 and IL-6 levels displayed an increase that

Table 1
Functional interaction between human receptors and HCV proteins.

HCV protein	Receptor	Cell type	Reference
Core protein	gC1qR	THP-1 derived macrophages	[176]
	TLR2 (TLR1/TLR6 co-receptors)	Monocytes	[28,177,178,179]
		Macrophages	[27,180,181]
		PBMCs	[48]
		B103 neuroblastoma cell line	[182]
		LX-2 hepatic stellate cell line	[183]
		HCE2 Corneal epithelial cell line	[184]
NS3	TLR2 (TLR1/TLR6 co-receptors)	Monocytes	[28]
		Macrophages	[27]
		HCE2 corneal epithelial cell line	[184]
		CHME3 microglial cell line	[30]
	TLR4	Macrophages	[31]
NS5A	TLR4	Monocytes	[32]
E2	CD81	$CD8^+$ T-lymphocytes	[36]
		(Plasmacytoid) Dendritic cells	[185,186]
		Natural killer cells	[187,188]
		Hepatic stellate cells	[189]
		Huh-7 hepatoma cell line	[190]
		Raji B-lymphoma cell line	[35]
		HuT 78 T-cell line	[191]
		Molt-4 T-lymphoma cell line	[192]
	LDL-R	Huh-7 hepatoma cell line	[190]
		Molt-4 T-lymphoma cell line	[192]
	SR-B1	HepG2 and Huh-7 hepatoma cell lines	[90,193]
		Receptor-transfected cell line	[90]
	DC-SIGN	Receptor-transfected cell line	[194,195]
	L-SIGN	Receptor-transfected cell line	[195,196]

corresponded to disease progression. In line with the results of El Husseiny et al., IL-6 and IL-17 levels demonstrated a positive correlation to viral titer [46].

2.3. HCV upregulates SAA-inducing cytokines via multiple pathways

2.3.1. HCV proteins induce the expression of SAA-inducing cytokines via Toll-like receptor (TLR) activation

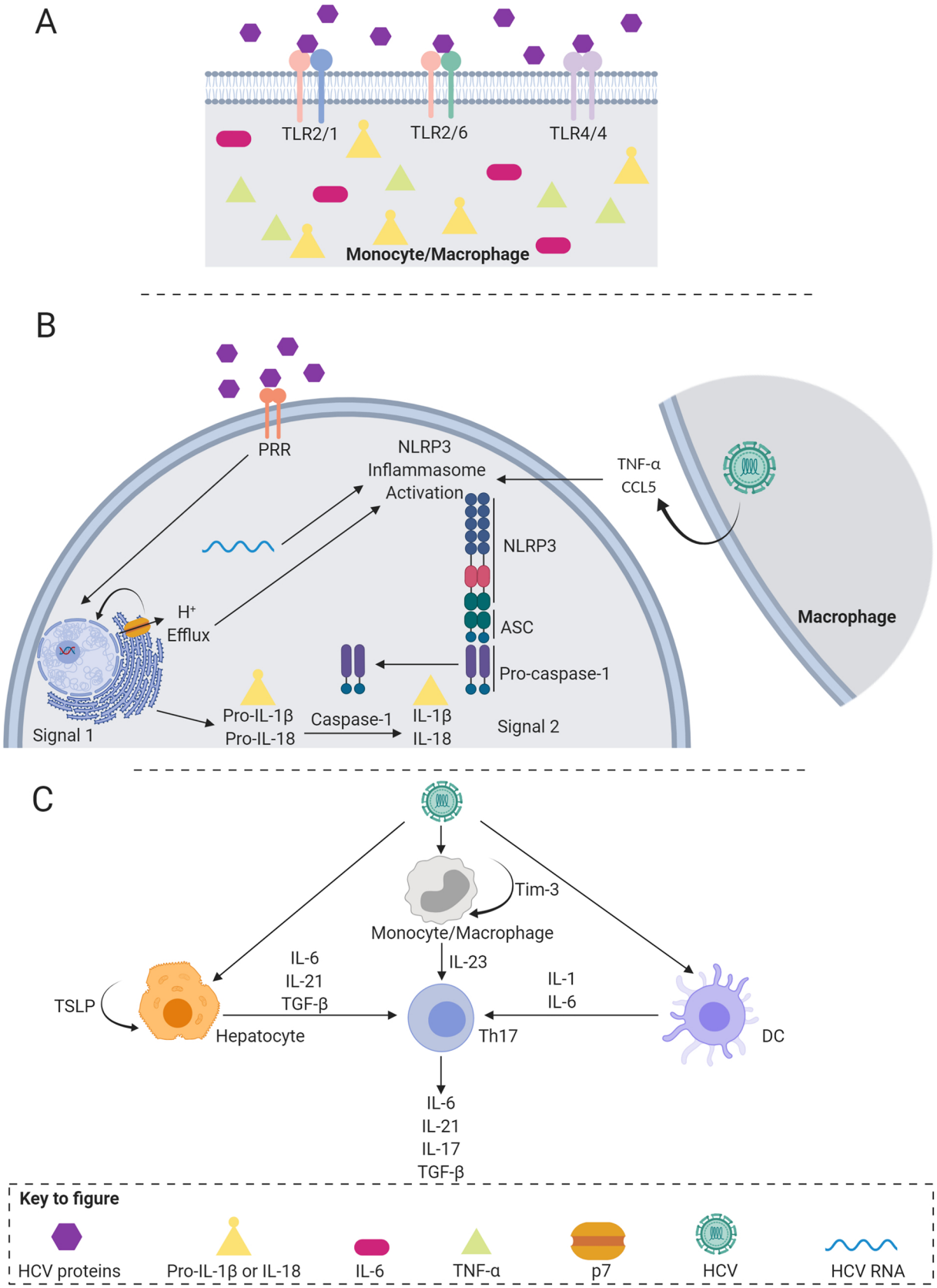
Various studies have investigated cytokine expression in response to HCV proteins. Both structural and non-structural HCV proteins directly induce the expression of various SAA-inducing cytokines. Woitas et al. showed a drastic increase in the number of IL-1β expressing monocytes when PBMCs from HCV-positive individuals were stimulated with the core protein, NS3, NS4, NS5A and NS5B. Furthermore, though to a lesser extent, TNF-α expression in monocytes was also upregulated in response to the core protein, NS3, NS5A and NS5B [47]. Multiple studies have revealed that HCV proteins utilize TLRs to induce cytokine expression (Fig. 2A). NS3 upregulated expression of IL-6 and TNF-α in the microglial cell line CHME3 via TLR2/TLR6 binding and downstream activation of the MyD88/NF-κB pathway [30]. NS3 or the core protein stimulated expression of TNF-α or IL-6 in PBMCs, monocytes, macrophages or HEK cells via TLR2, with TLR1 and TLR6 as co-receptors [27,28,48]. Additionally, NS3, NS4 and NS5 induced the expression of IL-1β or TNF-α in primary human Kupffer cells. In this experimental setting, TNF-α upregulation by NS3 was mediated via TLR4 activation [31]. The non-cytokine-mediated expression of SAA as a direct response to TLR activation has only been described in the context of TLR4 after the activation of primary human hepatocytes with its ligand LPS, thus prompting speculation on whether HCV proteins can directly induce SAA expression via TLR activation [49].

2.3.2. HCV activates the inflammasome complex leading to active IL-1 family cytokines

The structurally related IL-1β and IL-18 both belong to the IL-1 cytokine family [50]. The production of biologically active IL-1β and IL-18 requires two distinct signaling pathways. The first is through recognition of pathogen-associated molecular patterns or damage-associated molecular patterns, by PRRs, eventually leading to the production of the precursor cytokines via NF-κB activation. To activate these precursor cytokines, activation of the inflammasome multiprotein complex is required. The major component of the inflammasome complex is a cytoplasmic inflammasome sensor molecule, such as absent in melanoma 2 (AIM2), NLR family CARD domain-containing protein 4 (NLRC4), nucleotide-binding domain and leucine-rich repeat-containing receptor protein 1 (NLRP1), NLRP3 or pyrin. AIM2 and NLRP3 require an adaptor protein, apoptosis-associated speck-like protein containing a CARD (ASC), to function. The expression of some of the inflammasome sensors is also upregulated in response to NF-κB activation. The final constituent of the inflammasome is pro-caspase-1, which is, once recruited within the complex, auto-activated through the removal of its pro-domain. Caspase-1 can subsequently cleave pro-IL-1β/pro-IL-18 into their respective biologically active forms [51]. Inflammasome activation is triggered by a range of stimuli including micro-organisms (influenza virus, adenovirus, *Staphylococcus aureus* and *Candida albicans*) and markers of cellular stress and injury [extracellular ATP, reactive oxygen species (ROS) and hyaluronan released from injured cells] [52].

The HCV p7 protein has been suggested to function as an ion channel. Following p7 transfection of HEK293 cells and RAW 264.7 murine macrophages, loss of vesicular acidity was observed. Furthermore, following priming with LPS, IL-1β protein expression was further upregulated in p7-transfected HEK293 cells, whereas no regulatory effect of p7 was observed on TNF-α expression, thus indicating selective inflammasome activation by p7. Furthermore, in cells treated with the p7 inhibitor rimantadine, IL-1β production was significantly reduced. The authors concluded that the pH-shunting activity of p7 might provide the stimulus needed for activation of the inflammasome [53].

Shrivastava et al. demonstrated upregulated production of mature IL-1β and IL-18 following exposure of THP-1-derived macrophages and human Kupffer cells to HCV. They also detected upregulated expression of caspase-1, which was synonymous with decreased expression of pro-caspase-1 in HCV-exposed THP-1 cells. Furthermore, following the transfection of p7 in THP-1-derived macrophages, enhanced production of IL-1β in its mature form was observed, indicating that in THP-1 cells, HCV p7 was triggering both NF-κB and the inflammasome. To further



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ascertain the role of HCV p7 in the expression of IL-1β, macrophages were transfected with various HCV-derived proteins and only p7 induced production of mature IL-1β [21]. Chen et al. demonstrated IL-1β expression in primary human macrophages following transfection with HCV RNA, which was dependent on ASC, caspase-1, and NLRP3. Furthermore, inflammasome activation by HCV RNA was shown to be ROS-

Fig. 2. HCV activates multiple inflammatory pathways leading to the expression of SAA-inducing cytokines. (A) HCV proteins, including the core protein, NS3 and NS5A, have been described as TLR ligands. Activation of TLRs on monocytes and macrophages leads to the expression of the inflammatory cytokines IL-1β, IL-6 and TNF-α. (B) Several pathways have been identified by which HCV leads to inflammasome activation. Firstly, recognition of HCV proteins by pathogen recognition receptors (PRR) activates inflammasome signal 1, leading to production of IL-1/IL-18. Secondly, HCV RNA displays a direct effect on inflammasome activation in macrophages. Thirdly, exposure of macrophages to HCV induces the expression of CCL5 and TNF-α, which contribute towards inflammasome activation in hepatic stellate cells. Finally, the pH-shunting activity displayed by p7 also provides the signal necessary for inflammasome activation in macrophages. (C) HCV skews towards a Th17 phenotype via enhanced expression of Th17-polarizing cytokines through multiple pathways. HCV induces thymic stromal lymphopoietin (TSLP) expression in hepatocytes, which promotes the expression of IL-6, IL-21 and TGF-β. Moreover, HCV induces the expression of T-cell immunoglobulin and mucin domain-3 (Tim-3) in monocytes and macrophages, which plays a role in Th17 differentiation via the upregulation of IL-23. Finally, HCV stimulates dendritic cells (DCs) to express IL-1 and IL-6 thus contributing towards Th17 differentiation.

dependent [54].

Burdette et al. provided additional evidence regarding inflammasome activation by HCV. Indeed, HCV infection of Huh-7.5 cells induced the expression of several inflammasome complex components, including caspase-1, NALP3 and ASC [20]. Nevertheless, IL-1β expression was not observed following Huh-7.5 transfection with p7 expression plasmid, suggesting that other viral components contribute to inflammasome activation in this case [20].

Expression of inflammasome-related genes in hepatic stellate cells (HSCs) in the context of HCV infection was also investigated. Exposure of immortalized (LX2) and primary human HSCs to conditioned media (CM) derived from HCV-exposed THP-1 macrophages induced the expression of IL-1β and NLRP3 mRNA, probably in an NF-κB dependent manner. Utilizing CCL5 or TNF-α neutralization in combination with CM treatment, the authors demonstrated a significant but incomplete reduction in the expression of NLPR3 and IL-1β, indicating that CCL5 and TNF-α play a role in inflammasome activation in LX2 cells (Fig. 2B) [55].

2.3.3. HCV infection induces Th17 polarization leading to enhanced IL-17 expression

T helper cells polarized to produce IL-17 (Th17 cells) elicit protection against extracellular bacterial and fungal infections and maintain the microbiota and homeostasis at barrier sites. However, when IL-17 is excessively produced, it contributes to chronic inflammation [56]. Th17 cells display a unique cytokine expression profile that includes IL-17, IL-21, IL-22 and IL-23 (reviewed in reference [57]). Polarization towards Th17 cells occurs in response to the cytokines IL-6, IL-21, TGF-β and IL-23. Th17 cells have been linked to immunopathology during HCV infection. This T-helper cell population is associated with increased hepatic inflammation during CHC infection [58]. Indeed, an increase in circulating and intrahepatic $CD4^+$ $CD8^+$, IL-17-secreting T-cells was observed in CHC patients [58–60]. Furthermore, IL-17 levels were shown to be elevated in the serum of CHC patients in comparison to healthy controls [58,59].

HCV has been shown to promote Th17 polarization via thymic stromal lymphopoietin (TSLP) upregulation, an IL-17-like cytokine binding to IL-7 receptor alpha and proposedly playing a role in Th17 differentiation [61]. Lee et al. documented significant upregulation of TSLP in HCV-infected hepatocytes [22]. Further experiments on Huh-7.5.1 hepatoma cells demonstrated upregulated TSLP expression in response to HCV infection via NF-κB activation. To determine whether hepatocyte-derived TSLP may direct antigen-presenting cells to induce Th17 differentiation, conditioned medium derived from HCV-infected hepatocytes was added to THP-1 cells. Indeed, an increase in Th17 differentiation cytokines (TGF-β, IL-6 and IL-21) was observed, which was inhibited by anti-TSLP-neutralizing antibodies [22]. HCV antigens, NS3/5 in particular, were found to enhance IL-17 expression by $CD4^+$ T-cells, indicating that HCV proteins might have a direct effect on the polarization of $CD4^+$ T-cells into Th17 cells [58]. Interestingly, when combined with TSLP, NS3/5 displayed an additive effect on Th17 polarization [22]. Fang et al. demonstrated a direct effect of HCV on monocyte-derived DC expression of the Th17 polarizing cytokine IL-6. On the other hand, in a co-culture of HCV-exposed monocyte-derived DCs and allogeneic $CD4^+$ T cells, both IL-1 and IL-6 concentrations increased in contrast to concentrations of cytokines supporting the function of Th1, Th2, Th9 or Th22 cells, suggesting a selective effect of HCV on Th17 polarization. Indeed, IL-17 levels were 5-fold upregulated, signifying Th17 polarization in these co-cultures [23].

Another mechanism by which HCV regulates Th17 polarization is through T-cell immunoglobulin and mucin-domain-containing-3 (Tim-3), an immune regulatory checkpoint (Fig. 2C). Tim-3 is overexpressed on $CD14^+$ monocytes derived from chronically infected individuals. Interestingly, upregulated Tim-3 positively correlates with IL-23 (Th17 polarizing cytokine) and negatively correlates with IL-12 (Th1 polarizing cytokine). To this end, the authors co-cultured monocytes derived from healthy subjects, with Huh-7 cells transfected with HCV RNA. Upregulation of IL-23 and downregulation of IL-12 was observed in monocytes, which was reversed following Tim-3 neutralization. These data suggest that HCV skews the T-cell response towards Th17 via Tim-3 expression [62].

3. SAA expression during viral infections

The upregulation of SAA expression has been demonstrated in several animal models of viral infection [63–65]. Similarly, human SAA expression is upregulated during the acute phase of various viral infections, including cytomegalovirus, herpes simplex virus, measles virus, mumps virus, rubella virus and varicella-zoster virus, and returns to normal during the convalescent phase of infection [66,67]. In the study by Miwata et al., SAA titers were measured in children with CHC and chronic hepatitis B virus (HBV) and were found to be within the normal range [67].

As previously mentioned, hepatocytes are the primary producers of SAA in response to inflammatory cytokines [17]. As such, upregulated expression of SAA is anticipated during HCV infection. In a small scale study where SAA levels were measured in CHC patients, upregulated expression ($> 5\,\mu g/ml$) was detected in 16/94 patients [15]. Immunohistochemical staining of liver biopsies derived from HCV-infected individuals showed enhanced SAA expression during mild hepatitis. On the other hand, patients with more advanced fibrosis showed a decline in SAA expression [68]. These data suggest that SAA levels are likely elevated during the acute phase of HCV infection, but decline as the infection progresses towards a chronic state. Pertaining to acute infection, enhanced SAA expression might serve as a mechanism by which the innate immune system attempts to control the infection. However, long-term exposure to SAA-inducing cytokines might create a state of tolerance, thus leading to reduced SAA expression during CHC infection.

4. Anti-viral activity imparted by SAA

A limited number of studies have investigated the direct upregulation and function exerted by SAA during viral infections. To the best of our knowledge, only two studies have attempted to inquire into the role of SAA during HCV infection. SAA constitutes a ligand for the HCV receptor scavenger receptor class B type 1 (SR-B1) and was thus suspected to affect HCV entry into hepatocytes [69,70]. In agreement with this hypothesis, a dose-dependent inhibitory effect by recombinant SAA1 (rSAA1) on the entry of HCV in Huh-7 cells independent of HCV

genotype was demonstrated. The infectivity of HCV pseudotyped particles (HCVpp) was reduced to 10 % by 20 μg/ml of rSAA1. However, higher concentrations did not provide further inhibition [15]. In a similar study carried out by Cai et al., the antiviral effect imparted by rSAA1 was determined on Huh-7.5 cells, demonstrating a 50 % reduction in HCV infectivity at a rSAA1 concentration of 10 μg/ml. Furthermore, HCV infectivity was entirely suppressed by rSAA1 at concentrations of 50–100 μg/ml [14]. Immunoprecipitation studies revealed that rSAA1 interacts with HCV glycoproteins, thereby reducing infectivity [15].

Several APPs have been described to display direct antimicrobial activity towards pathogens. Pentraxin 3 (PTX3) provides an antiviral effect towards cytomegalovirus in a manner similar to that observed with SAA and HCV, i.e., via binding to the viral particle [71]. C-reactive protein (CRP) functions as a soluble pattern recognition receptor, activating antimicrobial host defenses. Furthermore, SAA and CRP function as opsonizing agents leading to the activation of the complement system and subsequent phagocytosis [72,73]. CRP and SAA were tested in parallel for inhibitory activity towards HCV, but no activity was displayed by CRP, indicating that this phenomenon is specific to SAA. Moreover, additional SR-B1 ligands such as the apolipoprotein A-I (apoA1) and apoE did not display antiviral activity against HCV [14]. Finally, the antiviral activity relayed by rSAA1 was not present with other positive-stranded RNA viruses, including yellow fever virus, bovine viral diarrhea virus, Sindbis virus, vesicular stomatitis virus and RD114 virus, suggesting that this effect is limited to HCV [15].

5. SAA and lipoproteins during HCV infection

5.1. SAA as an apolipoprotein

Acute phase SAA has been shown to associate with lipids and functions as an apolipoprotein. Although several studies conducted over the years suggested SAA1 to be vastly helical, the complete structure of SAA1 was up until recently unknown [74–76]. Lu et al. revealed SAA1 to be composed of four antiparallel α-helices with a C-terminal tail that wraps around one face of the structure providing stability via salt bridges and hydrogen bonds [77]. Structural analysis of SAA1 revealed helix one and helix three to be considerably hydrophobic, forming an apolar concave surface that contains the proposed lipid-binding site [78]. Under physiological conditions, apoA1 is the major circulating apolipoprotein. However, during the APR, SAA expression is highly upregulated, thereby becoming the major apolipoprotein. SAA has been suggested to account for 80 % of the total apolipoprotein portion of high-density lipoprotein (HDL) during the APR, with an estimated SAA: apoA1 ratio of 10:1 [18]. Early analysis of human serum revealed the majority of SAA to float at the same density as HDL_3 [79]. In line with this, murine SAA showed 75 % reactivity within high-density moieties following density gradient centrifugation [80]. As such, HDL particles are the prime carrier of SAA during the APR. SAA additionally binds low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL) [81,82]. The biological purpose behind the paramount increase in SAA expression is yet to be clearly defined. Nonetheless, one of the suggested roles of SAA is to aid cell repair via its cholesterol transport function [83]. Regarding its role in cholesterol transport, SAA has been linked to SR-B1. The SAA-HDL complex has been suggested as an SR-B1 ligand [84]. Moreover, rSAA1 has been shown to bind to SR-B1, indicating that this apolipoprotein functions as an SR-B1 ligand in its lipid-free form as well [70]. Indeed, a study by Cai et al. revealed an inhibitory effect on HDL binding to SR-B1 following the incubation of CHO cells with SAA [84]. Furthermore, Baranova et al. demonstrated HDL competition with lipid-free SAA for SR-B1 binding [69].

5.2. The interaction of HCV with lipoproteins

Analysis of plasma from HCV-infected individuals showed HCV to exist within a wide range of buoyant densities, i.e., between 1.03–1.20 g/ml. Moreover, electron microscopy revealed HCV particles to possess a diameter of 30–100 nm [85]. This structural heterogeneity is attributed to the association of viral particles with lipoproteins that modulate the virus infectivity. Thus, viral components associate with lipoproteins to form hybrid particles named lipo-viro-particles (LVPs). The recent lipidomic characterization of cell culture HCV (HCVcc) demonstrated that viral particles shared similar lipid composition to VLDL and LDL with cholesteryl esters accounting for almost half of total HCV lipids [86–88].

Of the numerous cell entry factors that are utilized by the virus during cell entry, the HDL receptor, SR-B1 and low-density lipoprotein receptor (LDL-R) are of particular relevance here (HCV cell entry factors are reviewed in reference [89]). The precise role of SR-B1 is yet to be fully elucidated. It seems to participate in multiple steps during viral entry. First, it interacts with virus-associated lipoproteins to facilitate virus attachment. Moreover, its lipid transfer activity mediates a post-binding event that is required for entry. Finally, the interaction of SR-B1 with E2 leads to enhanced cell entry [90–92]. LDL-R has been shown to play a role in HCV entry via mediating attachment of the viral particle to the cell surface. This is thought to occur through its interaction with the lipoprotein component of the LVP [93,94]. However, the precise role of LDL-R during infection remains controversial since some data suggest that it is involved in viral genome replication and that LDL-R-mediated internalization leads to non-productive viral entry [95]. Importantly, the lipoprotein receptors LDL-R, SR-B1 and VLDL-R have been recently shown to be redundant for HCV entry [96].

Lipoprotein interactions have been deemed to play a significant role during HCV infectivity [86]. A study performed on chimpanzees demonstrated HCV particles occurring at a density of ≤ 1.06 g/ml, the estimated density of LDL, to be infectious, whereas those occurring at a density higher than 1.16 g/ml were less infectious [87]. Characterization of virus produced in cell culture confirmed its association with lipoproteins [88]. The association of lipoproteins with HCV particles led to the hypothesis that HCV hijacks the VLDL biogenesis pathway for its assembly. This hypothesis was supported by data obtained using RNA interference and inhibitors targeting apoB, apoE or microsomal triglyceride transfer protein (MTTP) [97–99]. On the contrary, HCV pseudo particles (HCVpp) that correspond to retroviral particles harboring unmodified HCV envelope glycoproteins do not associate with lipoproteins which is due to the fact that HCVpp assemble as retroviruses and are produced in a kidney cell line, which does not synthesize lipoproteins [100–102].

Several SR-B1 receptor ligands have been shown to affect HCV infectivity. Whereas VLDL, LDL and oxidized LDL inhibit infection, HDL enhances HCV entry [86,91,103–106]. HDL promotes HCV infectivity through a dual mechanism: via providing protection against neutralizing antibodies [100,103,107] and through a rather indirect effect as an increased HDL uptake by SR-B1 mediates cellular changes that are thought to promote viral uptake [108].

Due to the interplay between lipoproteins and HCV particles, apolipoproteins such as apoE, apoB, apoA1 and apoC1 can also be found in association with HCV virions [88,109,110]. Apart from intact viral particles, HCV proteins also associate with lipoproteins. Monazahian et al. demonstrated the co-precipitation of recombinant E1 and E2 with VLDL, LDL and HDL [111]. The binding of recombinant E1 and E2 to liposomes was demonstrated later, confirming the interaction of HCV glycoproteins with lipoproteins [112]. Moreover, interactions between apolipoproteins and HCV proteins have been reported. Indeed apoE interacts with E2 and NS5A [113–116].

5.3. The interplay between SAA, lipoproteins and HCV

The sera of chronic HCV patients present variable levels of SAA with abnormally high levels in some cases [15]. Thus, the overall interactions between SAA, lipoproteins and HCV are certainly intriguing. In line with previous data, a 3-fold increase in the infectivity of HCVpp in Huh-7 cells was demonstrated in the presence of normal human serum, where HDL was identified as the enhancing component. Furthermore, the addition of SAA, in the presence of HDL, attenuated HCVpp infectivity by 30% (versus 90% in lipoprotein-deficient serum), suggesting a mild negative regulatory effect of SAA on the enhancing capacity of HDL. Interestingly, the pre-incubation of HCVpp with SAA prior to infection, in the presence of HDL, affected the inhibitory capacity of SAA to a lesser extent indicating that SAA has a dominant role when present before HDL. As such, SAA might bind HCV following release from hepatocytes, before its interaction with HDL, thus providing an inhibitory effect on HCV infectivity [15]. Alternatively, once in the serum, highly upregulated SAA may bind the majority of HDL, thus abolishing its enhancing effect on HCV infectivity.

The inhibitory effect of SAA on HCV infectivity probably depends upon its interaction with HCV glycoproteins and not upon SR-B1 binding [15]. Nevertheless, SAA might compete with the virus for SR-B1 binding in vivo, thus inhibiting cell entry. These data highlight a knowledge gap regarding the overall interaction of SAA, HCV and lipoproteins, indicating the need for further investigation.

6. SAA modulates hepatic fibrosis and hepatocellular carcinoma

6.1. Biological activity conveyed by SAA

Various biological functions have been ascribed to SAA. However, the complete biological activity of SAA will not be discussed in detail as it is outside the scope of this review (reviewed in reference [17]). The following section will discuss biological activities relayed by SAA that are thought to play a role in hepatic injury (Fig. 3).

The majority of commercially available SAA is recombinantly expressed in *Escherichia coli* (Table 2). A recently published study attributed the inflammatory potential of recombinantly produced SAA to contaminating bacterial lipoproteins. Upon treatment of rSAA1 with lipoprotein lipase, rSAA1 lost its capacity to induce cytokines in J774 cells. Taking into account the capacity of SAA to bind lipid-rich molecules, the authors attributed the cytokine-inducing effect of rSAA to bound bacterial lipoproteins [117]. Consequently, careful analysis is warranted before drawing conclusions from studies utilizing recombinant forms of SAA.

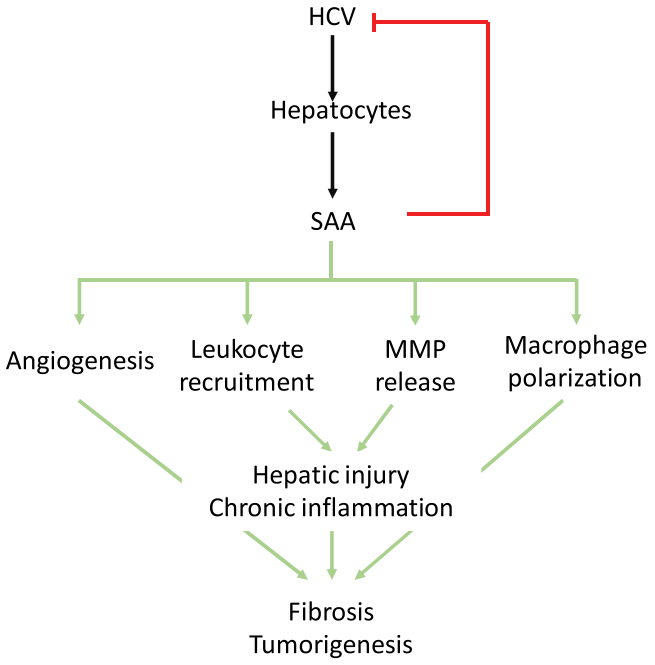

Fig. 3. An overview of the role of SAA during HCV infection.

6.1.1. Angiogenesis

Angiogenesis is central to the pathogenesis of fibrosis and hepatocellular carcinoma (HCC) [118]. SAA promotes angiogenesis of both microvascular and macrovascular endothelial cells. Mullan et al. studied the angiogenic capacity of rSAA on dermal-derived human microvascular endothelial cells (HMVECs). rSAA mediated dose-dependent migration of HMVECs. In addition, the authors demonstrated in vitro tube formation in response to rSAA. Through NF-κB activation, rSAA induced the expression of VCAM-1 in HMVECs, which is implicated in both angiogenesis and oncogenesis [119,120]. Lee et al. demonstrated the proliferation of macrovascular human umbilical vein endothelial cells (HUVECs) in response to rSAA stimulation. Utilizing the in vivo Matrigel plug assay, an increase in vessel formation was observed in response to rSAA. Furthermore, analysis of the formed vessels revealed an abundance of intact red blood cells suggesting the formation of functional vasculature [121]. Further studies have confirmed the angiogenic activity of SAA and revealed SAA to utilize a number of receptors, including SR-B1, during this process [122–125]. In a more indirect manner, rSAA induces vascular endothelial growth factor (VEGF), a crucial mediator of neovascularization [126]. The angiogenic activity of rSAA needs to be confirmed by non-bacterial-derived SAA.

6.1.2. Platelet activation and aggregation

Apart from their key role in liver homeostasis, platelets have been implicated in viral hepatic injury through delayed viral clearance, serotonin-induced microcirculation failure and cytotoxic T-lymphocyte-mediated liver damage. Platelets also stimulate fibrosis through the release of hepatic stellate cell (HSC)-activating inflammatory mediators [127]. In addition, platelets have been linked to the growth and metastasis of HCC [128]. At the same time, platelets may play a protective role through their contribution to the resolution of fibrosis and hepatic tissue regeneration [127]. Early studies by Zimlichman and colleagues demonstrated an inhibitory effect by serum-derived SAA on thrombin-induced platelet aggregation. Furthermore, SAA brought about a downregulation in thromboxane production and serotonin release from platelets [129]. More recently, the binding of platelets to SAA in a manner similar to that of other platelet-binding proteins such as fibrinogen and fibronectin was demonstrated by Urieli-Shoval et al. Thus, SAA may modulate platelet aggregation and adhesion at injury sites, thereby regulating platelet-induced viral hepatic injury [130].

6.1.3. Cell recruitment

Advances in understanding the underlying complex cellular network during hepatic fibrosis have corroborated the involvement of multiple cell types, including endothelial cells, monocytes, macrophages, neutrophils, fibroblasts and lymphocytes, to name a few [131,132]. Badolato et al. were the first to document the cell recruiting capacity of SAA. They described dose-dependent chemotaxis of polymorhonuclear leukocytes and monocytes in response to rSAA stimulation [134]. Moreover, rSAA1 synergizes with CXCL8 in the recruitment of neutrophils [133]. Confirming the in vitro data, subcutaneous injection of rSAA in mice resulted in dermal infiltration of monocytes and neutrophils. Furthermore, rSAA upregulated the expression of cell adhesion molecules (CD18/CD11b and CD18/CD11c) on neutrophils suggesting the contribution of rSAA to leukocyte migration in both a direct and an indirect manner [134]. Additional studies have confirmed both in vivo and in vitro recruitment of monocytes and neutrophils in response to SAA [133,135]. Moreover, the migration of immature

Table 2
Amino acid sequence of commercially available and naturally occurring SAA1.

Recombinant human SAA1 (rSAA1)	M[a]RS FFSFL GEAFD GARDM WRAYS DMREA NYIGS DKYFH ARGNY DAAKR GPGG V WAAEA ISDAR ENIQR FFGHG AEDSL ADQAA NEWGR SGKDP NHFRP AGLPE KY
[b]Recombinant SAA (rSAA; a hybrid form of SAA1.1 and SAA2.2,)	M[a]RS FFSFL GEAFD GARDM WRAYS DMREA NYIGS DKYFH ARGNY DAAKR GPGG V WAAEA ISNAR ENIQR FFGRG AEDSL ADQAA NEWGR SGKDP NHFRP AGLPE KY
Naturally occurring human SAA1.1	RS FFSFL GEAFD GARDM WRAYS DMREA NYIGS DKYFH ARGNY DAAKR GPGG V WAAEA ISDAR ENIQR FFGHG AEDSL ADQAA NEWGR SGKDP NHFRP AGLPE KY

[a] Residual methionine due to recombinant synthesis in *Escherichia coli*.
[b] Hybrid form of recombinant SAA that differs from human SAA1.1 by an additional N-terminal methionine. Position 61 is occupied by asparagine instead of aspartic acid and position 72 is occupied by arginine instead of histidine.

dendritic cells, T cells, mast cells, endothelial cells, smooth muscle cells and fibroblasts has been described in response to SAA stimulation [119,123,136–139]. The chemotactic activity of rSAA1 and rSAA2 has been linked to FPR2 activation [140,141].

6.1.4. Expression of matrix metalloproteinases (MMPs)

MMPs are key to both the fibrogenic and fibrinolytic aspects of HCV-induced hepatic injury. To prevent tissue damage by MMPs, endogenous inhibitors are present, namely tissue inhibitors of metalloproteinases (TIMPs). Therefore, a balance must be maintained between the action of MMPs and TIMPs [142]. Connolly et al. demonstrated the expression of MMP-1, MMP-2, MMP-3, MMP-9 and MMP-13 in primary fibroblast-like synoviocytes (FLS) in response to rSAA. On the other hand, TIMP-1 and TIMP-4 expression levels were not influenced by rSAA [143]. The acute phase protein also induces the expression of MMP-9 in human monocytic cells, via FPR2 activation, in a concentration-dependent manner [144]. Interestingly, MMP-9 cleaves SAA1, but the generated C-terminal fragment retains its synergistic interaction with CXCL8 in the recruitment of neutrophils [145]. Zhao et al. carried out microarray analysis assessing MMP-1 to MMP-28 and TIMP1 to TIMP4 expression in HUVECs following stimulation with rSAA. They observed the upregulation of MMP-10 and a slight augmentation of MMP-19 expression [146]. For more insight into the MMP-inducing capacity of SAA, the reader is referred to the recent review by De Buck et al. [147]. Taken together, these data suggest that SAA can modify disease progression via induction of MMP expression.

6.2. SAA modulates cell populations that are central to hepatic injury and healing

6.2.1. SAA regulates hepatic stellate cell (HSC) activity

Hepatic fibrosis is characterized by the accumulation of extracellular matrix in response to chronic liver injury. HSCs are the major cell type involved in liver fibrosis. In their quiescent stage, HSCs function as vitamin A storage units. However, once activated by inflammatory stimuli, HSCs undergo trans-differentiation acquiring a fibrogenic myofibroblast-like phenotype that constitutes a principal source of extracellular matrix [148]. Siegmund et al. studied the effect of rSAA on HSC activity. While rSAA did not induce any noticeable inflammatory activity on quiescent HSCs, it induced the expression of chemokines (CXCL8, CCL2 and CCL5) and MMP-9 through activation of the NF-κB and JNK pathways in activated HSCs. Furthermore, rSAA enhanced the proliferation of HSCs in an Akt-, Erk- and JNK-dependent manner. Interestingly, following NF-κB inhibition, rSAA induced apoptosis of HSCs suggesting that NF-κB functions as a switch between the proliferative and the apoptotic activity of rSAA. Thus, the authors concluded that rSAA does not play a role in the activation of HSCs but rather modulates the inflammatory activity relayed by these cells once they are activated [149].

6.2.2. SAA putatively alters macrophage subpopulations

Besides its effect on HSCs, SAA may regulate hepatic fibrosis through its influence on macrophage polarization. Macrophages are implicated in the development of fibrosis. Macrophages are activated in response to environmental stimuli, thus acquiring distinct functional phenotypes categorized as classic (inflammatory) or alternative (healing and tissue repair) macrophages, also referred to as M1 or M2, respectively. M2 macrophages are further classified into M2a, M2b and M2c, according to the polarizing stimulus and its downstream effect [150]. During fibrosis, macrophages have a direct effect on hepatic injury through the expression of inflammatory mediators such as cytokines, chemokines, growth factors and TIMPs. In addition, macrophages contribute to fibrosis in an indirect manner through the expression of HSC-activating factors. In contrast, macrophages also play a key role in the resolution of fibrosis through their phagocytic function and through the expression of proteases and molecules that induce apoptosis of HSCs [118]. Li et al. were the first to study macrophage polarization in response to SAA. U937 macrophages stimulated with SAA displayed a cytokine profile (IL-1β^{high}, IL-6^{high} IL-10^{high}, IL-12p35^{low}, TNF-α^{high} and CXCL8^{high}), which is characteristic of M2b macrophages [151]. In line with this, Sun et al. demonstrated M2 polarization of human CD14^{+} monocytes and murine bone marrow-derived macrophages (BMDMs) in response to rSAA, which was evident by augmented expression of IL-10, IL-1Rn, CCL17 and Mrc1, amongst others. Furthermore, stimulation of murine BMDMs with rSAA or IL-4 (M2 stimulus) resulted in a similar enhancement of arginase-1 expression and activity. In addition, murine BMDMs displayed enhanced efferocytosis following stimulation with rSAA that was dependent on interferon regulatory factor 4 (IRF4) [152]. The role of SAA in macrophage polarization has also been investigated in the context of chronic obstructive pulmonary disease (COPD). rSAA instigated a mixed M1/M2 phenotype following stimulation of blood monocytes derived from healthy controls and COPD patients. Macrophages displayed upregulated expression of IL-1β, IL-6 and the M2 surface marker CD163. In agreement with other reports, functional analysis of rSAA-induced macrophages revealed upregulated phagocytic and efferocytic activity. In vivo challenge of mice with SAA enhanced a macrophage subpopulation with CD11c^{high} and CD11b^{low} expression [153]. More recently, macrophage polarization by SAA in CCl_4-induced murine hepatic injury has been investigated. The authors made the observation of macrophages being the major SAA-binding cells during hepatic injury. Furthermore, upregulated expression of IL-1, IL-6, IL-10 and TNF-α with an increase of cell surface marker CD86, but not CD163, was observed in murine BMDMs stimulated with murine SAA. Interestingly, neutralizing SAA activity with an anti-SAA antibody resulted in an amplified fibrogenic effect, thus indicating that SAA conveys a protective effect against fibrosis in this model [154].

7. SAA as a biomarker during HCV infection

The potential of SAA as a marker of inflammation has long been proposed. SAA has been suggested as a biomarker for several inflammatory-mediated diseases, including rheumatoid arthritis, Crohn's disease and sarcoidosis [155–157]. Indeed, SAA possesses characteristics of an efficient biomarker, as SAA serum levels are exponentially enhanced in response to inflammatory stimuli. In a study carried out by McAdam et al., SAA serum levels showed an increase within 8 h following intramuscular administration of an inflammatory mediator,

etiocholanolone. Within 36–48 h, peak levels were achieved, displaying a 15-fold increase. SAA levels returned to normal within 4–5 days following stimulation [158]. Although SAA and CRP usually follow the same expression pattern, two distinct studies carried out by Maury et al. and Marhaug *et al.* showed SAA to be a more sensitive biomarker in comparison to CRP suggesting that SAA might function better than CRP in detecting minor changes in the inflammatory state [159,160]. In an animal model of hepatotoxicity, SAA expression was compared to other markers of liver injury, including, aspartate aminotransferase (AST) and ALT. ALT, AST and SAA levels peaked within 12 h of treatment with the hepatotoxic agent ritodrine. However, the fold increase was much higher for SAA than for both liver enzymes. In addition, SAA was more sensitive to lower doses of ritodrine treatment [161]. Immunohistochemical staining on liver biopsies obtained from HCV-infected individuals revealed SAA expression to be upregulated during mild hepatitis. This increase in SAA expression contrasted with normal ALT and AST levels, suggesting the potential of SAA as an early marker of hepatic inflammation. On the contrary, patients with advanced fibrosis showed declining levels of SAA [68]. Thus, SAA expression levels might be a useful parameter to differentiate between patients with mild and advanced hepatic fibrosis. A recent pilot study has shown that high levels of plasma SAA during the early stages of interferon/ribavirin therapy are linked to a more sustained virological response indicating the potential of utilizing SAA levels to predict response to treatment [162].

SAA may also serve as a biomarker in HCV-induced hepatocellular carcinoma (HCC). Elevated expression of SAA has been reported in numerous malignancies, including lung cancer, nasopharyngeal carcinoma and uterine carcinoma [163–165]. SAA expression was shown to be more upregulated in the later stages of cancer. Li et al. demonstrated high levels of SAA in the circulation of patients with advanced-stage cancer. They detected SAA1.1, SAA1.2, SAA1.3, SAA2.1 and SAA2.2 in the blood of patients [166]. Furthermore, several studies have evidenced a link between increased SAA expression in cancer patients and a poor prognosis [163,167,168]. A recently published meta-analysis demonstrated a correlation between elevated SAA levels and poor overall survival, disease-free survival and progression-free survival in patients with solid tumors [169].

Interestingly, SAA has been proposed to differentiate between cases of localized and metastasized cancer [167,170]. In the particular case of HCC, the identification of novel biomarkers is of relevance. To achieve curative treatment, early detection of HCC is of importance since symptoms only develop at an advanced stage. Currently, diagnosis is often based upon a liver biopsy, which requires an invasive procedure associated with risks. Several biomarkers have been investigated, such as the ratio of glycosylated alpha-fetoprotein to total alpha-fetoprotein, glypican-3, and des-gamma carboxyprothrombin. However, these biomarkers are more specific towards more advanced disease [171]. Several studies have suggested SAA as a biomarker in HCC. Ni et al. have shown that SAA expression is significantly higher in patients with HCC in comparison to those with benign lesions. In addition, higher SAA levels were linked to larger tumor size and elevated Barcelona Clinic Liver Cancer (BLCL) stage. Furthermore, an inverse relationship was detected between the expression of SAA and overall survival and disease-free survival, thus indicating that SAA may have the potential to predict the outcome of disease [168]. He et al. utilized a SELDI-ProteinChip approach to determine serum biomarkers for the prediction of HBV-related HCC. SAA was found to be a discriminatory protein in the detection of HBV-related HCC [172]. These data reveal the potential of SAA as a biomarker in multiple facets of HCV- or HBV-induced complications.

8. Treatment of HCV

HCV infection was previously treated with PEGylated-IFN (PEG-IFN) and ribavirin-based regimens, which displayed a modest cure rate (45–55%) and an unfavorable adverse effect profile [173]. Furthermore, IFN-based regimens were associated with numerous contraindications [174]. The discovery of direct-acting agents (DAAs) in 2011 marked a new era in the treatment of HCV infection. DAAs target the HCV protein complex NS3/4A (serine protease and RNA helicase), NS5A (IFN-resistance protein) or NS5B (RNA-dependent RNA polymerase), which play a vital role in viral survival and replication [6]. First-generation DAAs were used in triple therapy regimens in combination with ribavirin and PEG-IFN. These DAAs-based regimens displayed a 35 % increase in sustained virologic response (SVR) in comparison to IFN-based regimens. Nevertheless, first-generation DAAs have been recently discontinued owing to the discovery and development of second-generation DAAs, which are used in IFN-free regimens and display a superior SVR in 95–100% of the treated cases [175]. Due to the risk of resistance-associated substitutions, DAAs are used in combinations of two to three. Regimen selection during HCV infection depends on multiple factors including viral genotype, stage of liver disease, renal function, the presence of co-infections (primarily HBV and human immunodeficiency virus), reinfection and cost-effectiveness [173,174]. However, DAA-based therapies are associated with substantial costs, which precludes their accessibility to a large number of patients.

9. Concluding remarks

SAA possesses antiviral activity against HCV via direct interaction with the viral particle. Nevertheless, we have observed gaps in the current knowledge, which warrant further investigation. Taking into account, the role of SAA as an apolipoprotein raises several questions regarding the overall effect this acute phase protein would have on the HCV-modulating effects of lipoproteins. As such, SAA might relay an anti-viral effect on HCV via additional pathways. In addition, it is currently unknown whether SAA competes with receptors utilized by the virus during entry. Concerning HCV-induced complications, such as fibrosis and hepatocellular carcinoma, SAA may play a contributing role through its multiple biological effects. Further investigation of the impact of SAA on the pathogenesis of HCV-induced complications may reveal additional pathways by which hepatic damage occurs. Those new pathways could be exploited for future drug design.

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Declaration Competing Interest

No conflict of interest to be declared.

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