presenting cells but to inhibit antigen-specific activation of T cells regardless of their co-stimulation requirement [125].

The detection of CX3CR1+ T cells in the liver of patients with PBC and viral liver diseases suggests that unlike $CD28^-$ CD4+ T cells, other T lymphocyte subsets do not decrease their CX3CR1 expression after receptor engagement. The group of cytotoxic effector lymphocytes defined by expression of the fractalkine receptor CX3CR1 includes γδ T cells, 70% of which display this receptor on their cell surface [117]. γδ T lymphocytes have been implicated in various autoimmune diseases, and their frequency is increased in peripheral blood and liver of patients with PBC and PSC [126, 127]. It seems likely, however, that CD8+ T cells, which are strongly implicated in the bile duct damage seen in PBC and which also frequently express CX3CR1, represent the major CX3CR1 + population in PBC liver. The co-expression of fractalkine and CX3CR1 on BEC, as seen in PBC [121], CHC, and acute hepatitis due to HBV infection [122], suggests that interactions between fractalkine and its receptor may also be involved in tissue generation, particularly the recruitment of epithelial cells and their arrangement into ductular structures.

Macrophage inflammatory proteins and monocyte chemoattractant proteins Although originally named for their ability to attract monocytes or macrophages, certain members of the macrophage inflammatory protein (MIP) and monocyte chemoattractant protein (MCP) families can also induce chemotaxis and transendothelial migration of T cells, in particular activated or memory CD4+ and CD8+ T lymphocytes [86, 128]. In normal liver, portal vessels constitutively express MIP-1α, MIP-1β, and MCP-1, sinusoids and bile ducts show no or only weak immunoreactivity, and hepatocytes are always negative [57, 98, 129, 130]. There is little information on the role of these chemokines in PBC and PSC. MCP-1 is not upregulated on BEC in PBC. However, mononuclear leukocytes in the portal tracts express MCP-1, MCP-2, and MCP-3, and this may in turn recruit additional T cells into this area. Mainly, however, MCP-2 and MCP-3 appear to be involved in the recruitment of macrophages and the formation of granulomata.

Concluding remarks

The existing data on T lymphocyte recruitment to PSC and PBC liver suggest the following scenario: inflammatory signals in both PBC and PSC liver induce or enhance the expression of adhesion molecules such as ICAM-1, VCAM-1, and MAdCAM-1, whereas VAP-1 expression is not altered. At the same time, a variety of chemokines are also upregulated. In PSC, expression of CCL25, CCL21, and CCL28 all are implicated in activating α4β7 integrins and thereby enhancing lymphocyte binding to MAdCAM-1. In addition, CCL21and CCL28 could promote adhesion to VCAM-1 by activating α4β1 integrin. The same holds true in PBC, except that CCL25 does not participate. Several of these chemokines have also been shown to enhance transendothelial migration. Data on other chemokines are largely confined to PBC. They indicate that induced or upregulated expression of MIG and IP-10 in portal tracts may also contribute to enhanced lymphocyte recruitment into PBC liver. Once lymphocytes have entered the portal tract tissue, they are recruited to, and retained around, the bile ducts by the combinatorial or sequential action of CXCL12 (SDF-1), CXCL16, fractalkine (CX3CL1), CCL28, and possibly MIG and IP-10. At this point, the relative importance of each of these chemokines in the recruitment or the retention of lymphocytes around the bile ducts remains unclear. These limited data underscore the complexity of lymphocyte recruitment and homing to the liver. The data also suggest that there is no liver addressin, but instead, liver homing is likely to require complex combinations of adhesion molecule ligands and chemokine receptors that provide not only entry into the liver but also localization to specific liver compartments.

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REVIEW

Liver architecture, cell function, and disease

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Abstract The liver is an organ consisting of the largest reticulo-endothelial cell network in the body and playing an important role in host defense against invading micro-organisms. The organ is comprised of parenchymal cells and many different types of non-parenchymal cells, all of which play a significant role. Even biliary epithelial cells are not only the target in autoimmune liver diseases but also have central role in orchestrating several immune cells involved in both innate and acquired immunity. Tissue damage caused by various agents results in inflammation, necrosis, fibrosis, and, eventually, distortion of normal hepatic architecture, cirrhosis, and functional deterioration.

Keywords Innate immunity · Kupffer cells · Cytokine · Chemokine · Toll-like receptor

Abbreviations

AIH	autoimmune hepatitis
aLMF	activated liver myofibroblasts
APC	antigen-presenting cell
BEC	biliary epithelial cells
cDC	conventional DC
CLEVER-1	common lymphatic endothelial and vascular endothelial receptor-1
CNSDC	chronic non-suppurative destructive cholangitis
DAMPs	damage-associated molecular pattern
DC	dendritic cells
ENA-78	epithelial neutrophil chemoattractant-78
GRO	growth-related oncoprotein
HSCs	Hepatic stellate cells
ICAM-1	intercellular adhesion molecule-1
IFN	interferon
IL	interleukin
HCC	hepatocellular carcinoma
JNK	jun N-terminal kinase
LPS	lipopolysaccharide
LMNC	liver-infiltrated mononuclear cells
LSEC	liver sinusoidal endothelial cells
MBP	myelin basic protein
MCD	methionine/choline-deficient
MCP-1	monocyte chemotactic protein-1
NASH	non-alcoholic steatohepatitis
NOD	nucleotide-binding oligomerization domain
PAMPs	pathogen-associated molecular patterns
PBC	primary biliary cirrhosis
pDC	plasmatoid DC
PRRs	pattern-recognition receptors
PSC	primary sclerosing cholangitis
ROS	reactive oxygen species
TLR	toll-like receptor
TNF	tumor necrosis factor
VCAM-1	vascular cell adhesion molecule-1

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Introduction

The liver has a particularly intriguing immunological milieu consisting of the largest reticulo-endothelial cell network in the body and being a major source of many components of the innate immune response including acute-phase and

complement proteins as well as inflammatory cytokines and chemokines. The organ is also a significant site of immune-mediated damage initiated by infectious, autoimmune, and malignant stimuli. Recent studies have demonstrated that the liver is also an important site of the innate immune system. The innate or natural immune system is the rapid first-line defense against environmental threats such as microbial infection and physical or chemical injury. Sequential activation of innate and adaptive immune response is crucial for elimination of microorganisms and for immune response orchestrated by dendritic cells linking innate and adaptive arms of immune system. Unique repertoires of dendritic and lymphoid cells including NKT cells and regulatory T lymphocytes modify the immune response in the liver. Non-immune cells of the liver including endothelial cells, hepatocytes, and biliary epithelial cells also contribute to local immunological potential. All of these elements play roles, together and independently, determining the outcome of immunological stimulation within the liver. In addition, immune response upon exposure to exogenous or autogenic agents varies depending on the host genetic backgrounds. The genetic basis of immune response will offer new approaches to understanding the pathophysiology, diagnosis, and management of patients with liver diseases.

Liver architecture

The liver is the largest organ comprising about 1/50 of the adult body weight. Structurally and histologically, the liver can be divided into five tissue systems: (1) vascular system, (2) hepatocytes and hepatic lobule, (3) hepatic sinusoidal cells, (4) biliary system, and (5) stroma. The organ is composed of many different cell types which are divided into parenchymal cells (hepatocytes) and non-parenchymal cells (Table 1). It has been estimated that the hepatocyte population accounts for approximately 78% of the liver tissue volume, while non-parenchymal cells constitute about 6.3% in which about 2.8% are endothelial cells, 2.1% Kupffer cells, and 1.4% hepatic stellate cells. The extracellular space represents approximately 16% of the liver tissue volume [10].

Vascular system

The liver receives portal blood enriched with nutrients absorbed by the intestine from splanchnic circulation via portal vein. The portal blood also contains substances secreted by the pancreas, intestine, and spleen. Hepatocytes take up, metabolize, biotransform, and store a great variety of incoming substances. They also de novo synthesize and secrete substances to other organs in the body. The role of the liver is to provide appropriate amounts of solutes needed for adequate functioning of distant organs such as the brain, heart, and kidneys. The interaction between blood and liver cells occurs at the level of the liver cell plate. In addition to the blood supply by portal vein, the liver is also perfused by hepatic artery which carries blood with a high oxygen content. This completes a perfusion circuit encompassing the splanchnic–sinusoidal–systemic circulation. There is another circuit to which the liver actively contributes: the entero-hepatic circulation.

Table 1 Cells comprising the liver

Parenchymal cells
Hepatocytes
Non-parenchymal cells
Sinusoidal endothelial cells
Kupffer cells
Hepatic stellate cells (Ito or fat-storing cells)
Pit cells (NK cells)
Hepatic dendritic cells
NKT cells
Biliary epithelial cells

Hepatocytes and hepatic lobule

The hepatic lobule is the structural and functional unit of the liver (Fig. 1) [53]. It consists of a roughly hexagonal arrangement of plates of hepatocytes which extend forming liver cell plates of one-cell-thick by 15–25 hepatocytes in length. Between the two cell plates, blood flows from the portal tract to the terminal hepatic venule, forming so called "sinusoid". All the hepatocytes seem to be apparently homogeneous by light microscopy. Although there are some functional differences between periportal hepatocytes which are located closer to the portal venule and centri-

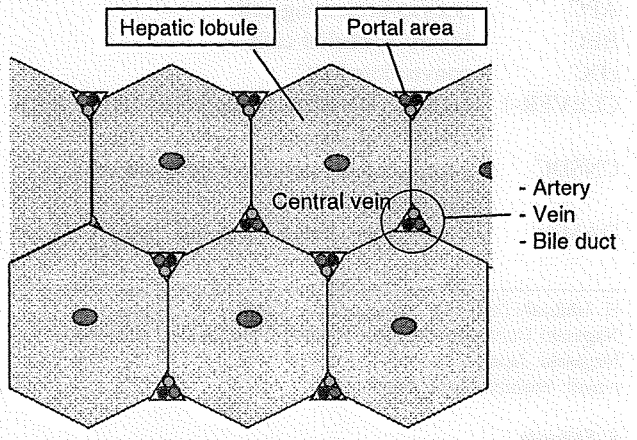

Fig. 1 Blood flows through the sinusoids and empties into the central vein of each lobule

lobular ones located closer to the central hepatic venule [9]. The portal tract contains a portal venule, a hepatic arteriole, and bile ducts. Blood flows from the portal vein into hepatic sinusoids, perfuses the liver cell plate, and flows out into the hepatic venule in the central acinus reaching systemic circulation.

Two structural characteristics are critical for liver functions to be accomplished: (a) hepatocytes located in different positions between the portal tract and the hepatic venule express different genes and attain distinct functional capabilities, and (b) given this functional compartmentation, the sequential perfusion of hepatocytes in the liver cell plate, from portal to hepatic venule, allows progressive qualitative modification of the sinusoidal blood composition as it traverses the liver.

Hepatic sinusoidal cells

Non-parenchymal cells encompass endothelial cells, Kupffer cells, hepatic stellate cells (or Ito or fat-storing cells), and Pit cells, all of which are located in sinusoids and called as "hepatic sinusoidal cells" [69]. Endothelial cells form the walls of the hepatic sinusoids (Fig. 2). The extended processes of the endothelial cells have pores or fenestrations through which solutes can apparently move freely into the perisinusoidal space of Disse. Alcoholics or cirrhotics who have developed liver fibrosis show disturbances in solutes exchange between blood and hepatocytes due to loss of the endothelial cell fenestrations concomitantly with the appearance of endothelial cell basal membranes. Kupffer cells are intravascular tissue macrophages which remove relatively large particles from the circulation, while endothelial cells take up rather small particles. Hepatic stellate cells (or Ito or fat-storing cells) are responsible for the storage of vitamin A and play a major role in the development of hepatic fibrosis in response to injury [17]. Pit cells which account for a small proportion of the non-hepatocyte liver cells are natural killer cells located beneath endothelial cells and fibroblasts.

Biliary system and biliary epithelial cells

Hepatocytes secrete bile into the bile canaliculi. Their flow is parallel to the sinusoids, but is opposite in direction to the blood flows (Fig. 3). Via biliary secretion, the liver excretes substances in feces and participates in intestinal functions such as intestinal absorption of fats by supplying bile acids. At the ends of the bile canaliculi, bile flows into bile ducts, which are true ducts lined with epithelial cells. Biliary cells form conduits (biliary system) carrying bile into the gall bladder and small intestine with bile flowing from hepatocytes near the hepatic venule to portal tract bile ducts. Bile duct cells also contribute to bile formation (ductular component of bile formation). Biliary epithelial cells represent about 3.5% of the liver nuclear population.

Distortion of normal hepatic architecture: cirrhosis

Cirrhosis is a consequence of chronic liver disease characterized by replacement of liver tissue by dense fibrous scar tissue as well as regenerative nodules formation which result in widespread distortion of normal hepatic architecture. It is most commonly caused by hepatitis B and C, alcohol-induced liver injury, autoimmune liver diseases and fatty liver disease but may have many other possible causes and be cryptogenic in some cases.

Loss of liver tissue due to injury results in fibrosis, regeneration and hyperplasia of liver cells and arterial growth (angiogenesis) induced by growth regulators which include cytokines and hepatic growth factors; e.g., hepatocyte growth factor, epithelial growth factor, transforming growth factor-α, tumor necrosis factor. Hormones, including insulin, glucagon, and change of intrahepatic blood flow patterns determine localization and peculiarities of nodules formation.

Portal hypertension is the most common complication of cirrhosis. Angiogenesis produces new vessels within the fibrous sheath that surrounds nodules. These new vessels

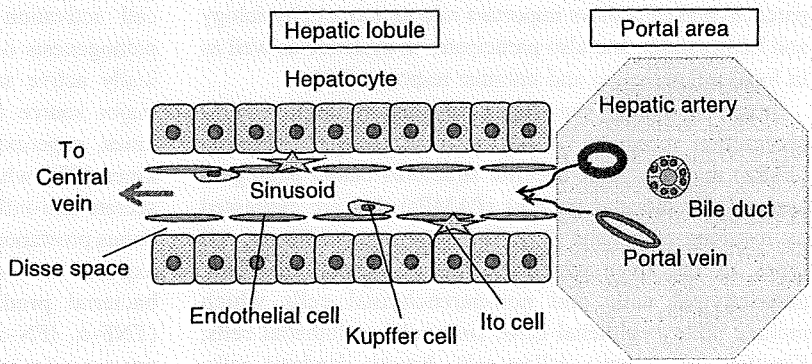

Fig. 2 Hepatocytes secrete bile into the canaliculi

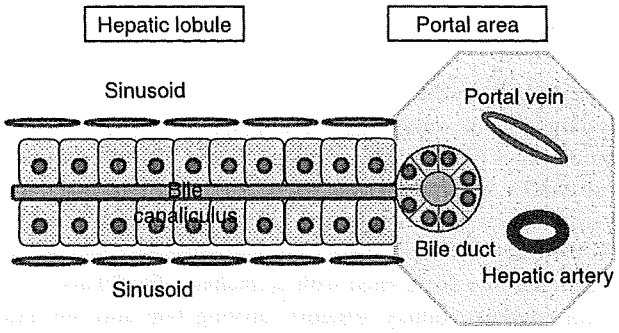

Fig. 3 The hepatic lobule is the structural unit of the liver

connect hepatic artery and portal vein to hepatic venules, thereby restoring intrahepatic circulatory pathways. Such interconnecting vessels provide relatively low-volume, high-pressure venous drainage and as a result, portal vein pressure increase. Such distortions in blood flow contribute to portal hypertension.

Progressive loss of hepatic architecture impairs hepatic function, leading to hepatic insufficiency which manifest as coagulopathy, renal failure, and hepatic encephalopathy. Hepatocellular carcinoma frequently complicates cirrhosis, particularly cirrhosis resulting from chronic hepatitis B and C.

Liver cells in innate immune response

The liver has a number of important functions in systemic and local host defense including both innate and adaptive immunity, and inflammatory reaction. The organ is perfused with antigen-rich blood from the gastrointestinal tract, cytokine-rich blood from the spleen, and oxygen- and metabolite-rich blood from the systemic artery through a network of sinusoids. The parenchymal cells (hepatocytes) secrete acute-phase proteins such as C-reactive protein, anti-α1-antitrypsin, ceruloplasmin, or haptoglobin in response to IL-6 secreted from Kupffer cells, thus controlling systemic and local inflammatory reactions. Each of the non-parenchymal cells plays important role in normal physiology and homeostasis, and also participates in systemic as well as in local inflammation and immune response [39].

Innate immunity can detect infection through pattern-recognition receptors (PRRs) such as Toll-like receptors (TLRs) that recognize specific structures called pathogen-associated molecular patterns (PAMPs) that are expressed by invading pathogens [21]. There are many different cell types in the liver which express a variety of TLRs: parenchymal cells and non-parenchymal cells which include biliary epithelial cells, sinusoidal endothelial cells, Kupffer cells, hepatic stellate cells, hepatic dendritic cells, NK cells, and NKT cells [56, 57]. TLRs are the key components of the innate immune system, which activate multiple inflammatory pathways and coordinate systemic defense against pathogens. In addition to TLRs, cytoplasmic pattern-recognition receptors, such as nucleotide-binding oligomerization domain (NOD)-like receptors and the RNA helicase family can detect microbial components that enter the cell's cytoplasm and induce innate immunity [34]. The best-defined PAMPs include LPS found on Gram-negative bacteria and peptidoglycan found on Gram-positive bacteria.

Kupffer cells

Kupffer cells reside within the lumen of the liver sinusoids; therefore, they are the first cells to be exposed to materials absorbed from the gastrointestinal tract [46]. These cells are resident macrophages of the liver and constitute 80~90% of the tissue macrophages presenting in the body. Kupffer cells are the principal liver cells for phagocytosis, antigen presentation, and production of pro-inflammatory cytokines. Activation of Kupffer cells by pathogenic agents results in the release of inflammatory mediators, growth factors, and reactive oxygen species (ROS) [8]. This activation appears to be required for the normal physiological functioning of the liver, such as removal of or tolerance to pathogens, as well as in acute hepatic injury [66]. Understanding the role of Kupffer cells in these diverse responses is a key to understanding mechanisms of liver physiology and pathology.

Kupffer cells express a variety TLRs, which participate in liver injury. The TLR4 protein has been detected on Kupffer cells and is likely involved in uptake and clearance of endotoxins, production of cytokines, and ROS. Expression of functional TLR2 has also been reported in Kupffer cells and activation of TLR2 leads to production of pro-inflammatory cytokines [42]. Kupffer-cell-derived cytokines play a key role in modulation of other cells. In response to LPS, Kupffer cells produce TNF-α and IL-10, which downregulate receptor-mediated antigen uptake and MHC class II expression on LSEC and DCs and decrease T cell activation [55]. Kupffer cells are involved in the pathogenesis of liver injury through the release of biologically active substances. Activated Kupffer cells are the major source of inflammatory mediators including cytokines, superoxide, nitric oxide, eicosanoids, and chemokines [52], while in the non-inflamed liver, Kupffer cells secrete anti-inflammatory mediators, such as IL-10, endogenous prostanoids and TGF-β [26]. Activated Kupffer cells exposed to pro-inflammatory mediators such as LPS or bacterial products, secrete pro-inflammatory cytokines (TNF-α, IFN-α), chemokines (MCP-I, IL-8) and reactive oxygen/nitrogen species which contribute to liver injury

[61]. Kupffer cells also stimulate profibrogenic response by production of TGF-β1, matrix metalloproteinases, platelet-derived growth factor, and ROS. Since Kupffer cells are the first cells to encounter gut-derived toxins including LPS, they are adapted to respond less to LPS, which is called "LPS tolerance" under the physiological environment.

Hepatic stellate cells and other liver sinusoidal cells

Hepatic stellate cells (HSCs) are located in the space of Disse and are the principal cellular sources for the production of extracellular matrix proteins, such as collagen type I, III, and IV in the liver. Upon TLR4 ligation, TLR4-signaling induces upregulation of pro-inflammatory molecules including chemokines (CCL2, CCL3, and CCL4) and adhesion molecules (VCAM-1, ICAM-1, and E-selection). TLR4 signaling also enhances profibrogenic signaling such as TGF-β signaling [58].

LSECs express TLR4, and TLR4 signaling induces production of TNF-α and ROS. Innate immune response in LSEC is also modulated by "LPS tolerance". Other cell types involved in innate immunity in the liver are hepatic dendritic cells (DC), plasmatoid DC (pDC) and conventional DC (cDC), liver NK cells, and NKT cells. Hepatic DC are professional antigen-presenting cells (APC) in the liver. pDCs are also the principal cells producing IFN-α in response to the ligands for TLR7 and TLR9, while cDC produces TNF-α and IL-6 in response to TLR4, TLR7, and TLR9 [56, 57].

Hepatocytes and biliary epithelial cells (BEC) express almost all TLRs at mRNA and protein levels. The ligation of TLR4 and 2 on both hepatocytes and BEC by LPS and lipopeptides, respectively, induces TLR signaling through NFκ B and p38/c-jun N-terminal kinase (JNK) resulting in pro-inflammatory cytokine production such as TNF-α, IL-6, IL-12 [14, 56, 57, 72].

TLRs and liver diseases

The interplay between TLRs and their exogenous and/or endogenous TLR ligands is involved in pathogenesis of various liver diseases [56, 57]. Since the liver is constantly exposed to microbial products from the enteric microflora that are carried through the portal circulation, innate immune response to TLR ligands is normally regulated partly through the modulation of TLR signals, namely "liver tolerance" [49, 56]. Therefore, a breakdown of this "liver tolerance" and/or excessive activation of TLR signaling may possibly be involved in the pathogenesis of various chronic inflammatory liver diseases such as alcohol-induced liver diseases, non-alcoholic steatohepatitis (NASH), hepatic fibrosis, ischemia/reperfusion liver injury, hepatocellular carcinoma (HCC) and hepatic autoimmune disorders including autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC).

Alcohol-induced liver injury

Excessive alcohol intake injuries intestinal epithelial barrier causing increased intestinal permeability followed by elevated LPS levels in the portal circulation [51]. The LPS then activates TLR4 on Kupffer cells to produce pro-inflammatory cytokines, such as TNF-α, leading to hepatocyte damage. Chronic alcohol consumption upregulates hepatic TLR1, TLR2, TLR4, TLR6, TLR7, TLR8, TLR9, and CD14 mRNA expression and sensitizes to the corresponding TLR ligands to enhance TNF-α production [12].

NASH

NASH is characterized by lipid accumulation in hepatocytes and inflammatory cell infiltration, which leads to hepatic fibrosis. In methionine/choline-deficient (MCD) diet-induced animal model of NASH, TLR4-signaling, and Kupffer cells play pivotal roles in the pathogenesis of NASH [54]. The loss of TLR4 attenuates hepatic lipid accumulation and hepatic fibrogenic markers, such as collagen α1 and TGF-β1 in MCD diet-induced steatohepatitis, indicating the importance of TLR4 in NASH [57].

Hepatic fibrosis

Hepatic fibrosis results from chronic liver injury, which is caused by a variety of liver diseases including viral hepatitis, autoimmune hepatitis, cholestasis (PBC, PSC), alcohol-induced liver injury, and NASH. In these diseases, TLR4 signaling is considered to initiate fibrogenesis by inducing pro-inflammatory and profibrogenic cytokines of Kupffer cells, which then activate HSCs. Endogenous CpG-DNA from damaged hepatocytes activates HSCs to produce collagen via TLR9, while endogenous DNA also provides a stop signal for migrating activated HSCs as soon as they sense apoptotic DNA [65]. CD14, LBP, TLR4, and Myd88 are critical for hepatic fibrogenesis induced by bile duct ligation and CCl_4 in mice [58]. The injection of TLR3 ligand poly-I:C inhibits HSCs activation mediated by IFN-γ from NK cells, which attenuating hepatic fibrosis. Chronic ethanol consumption abolishes this anti-fibrotic effect of TLR3, implying the mechanism by which alcohol induces liver fibrosis [57]. The genetic determinant for liver fibrosis is recently identified on TLR4 SNP [11].

AIH

In a mouse model of AIH induced by lymphocytic choriomeningitis virus infection, TLR3, but not TLR9 signaling, plays a critical role in development of hepatocyte damage and inflammation via IFN-α/β, TNF-α, and CXCL9 induction [33]. However, there has been no evidence for involvement of TLR signaling in the development of human AIH. Multiple conditions can cause sensitization to endotoxin-induced liver injury including drugs, toxins, metabolic factors, and pathogens. This sensitization via upregulation of TLRs is mediated by bone-marrow derived immune cells but not by liver parenchymal cells [19].

PBC

Monocytes from PBC patients appear to be more sensitive to the ligands for TLR2, TLR3, TLR4, TLR5, and TLR9, producing higher levels of pro-inflammatory cytokines, particularly IL-1β, IL-6, IL-8 and TNF-α [40]. In PBC patients, B cells are characterized by high expression of TLR9, namely CpG, stimulating B cells to significant production of immunoglobulin M and anti-mitochondrial antibodies, indicating that occurring hyper-responsiveness of B cells via TLR9 accelerate B-cell-mediated autoimmunity in PBC [25, 44]. The increased expression of TLR3 and type I IFN mRNA is found in both the portal tract and parenchyma of PBC-diseased livers derived from early-stage PBC patients, indicating the involvement of TLR3-type I IFN signaling pathway in the pathogenesis of PBC [62]. The marked increase of TLR3 proteins in small bile ducts of PBC-diseased liver indicate the involvement of TLR3 in pathogenesis of the bile duct damage in PBC, although the real endogenous or exogenous ligand for TLR3 is still unknown in PBC (Fig. 4) [47]. The expression of TLR4 is also increased in PBC-diseased livers [64]. These observations strongly indicate the involvement of TLR signaling in the pathogenesis of PBC.

PSC

PSC is characterized by progressive inflammation and fibrosis of the medium to large-sized hepatic bile ducts. High frequency of anti-BEC antibodies presence is found and the binding of anti-BEC antibodies to BECs induce production of pro-inflammatory cytokines and upregulation of TLRs. BECs expressing higher levels of TLR4 and TLR9 respond to their ligands interaction by production of higher levels of inflammatory cytokines, thus leading to destruction of BECs in PSC [7, 24].

In addition to the liver diseases mentioned above, TLR signaling is also considered to be involved in the pathogenesis of ischemia/reperfusion liver injury, liver regeneration, and development of HCC.

In conclusion, adequate strength of TLR signaling induces "beneficial" responses, such as microorganism clearance, regeneration, protection from cell death, and adjuvants for vaccination, whereas excessive TLR signaling triggers "harmful" responses, such as suppression of regenerative responses, chronic inflammation, necrosis, fibrosis, and induction of autoimmune liver diseases [50]. In order to identify the molecular target for the treatment of liver diseases, further studies are needed to clarify the role of innate immunity in the pathogenesis of these conditions.

Liver cells in hepatic inflammation

In the course of hepatic inflammation, where hepatocytes are the main target of immune-mediated destruction, non-

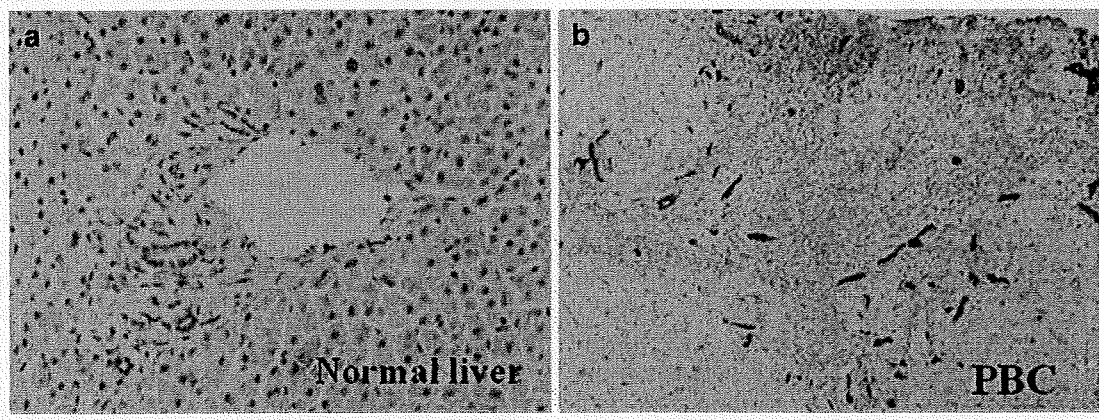

Fig. 4 Expression of TLR3 on intrahepatic biliary epithelial cells in normal and PBC livers. TLR3 is strongly expressed on intrahepatic biliary epithelial cells in vivo, especially at sites of ductular reactions, in livers from patients with PBC (b), whereas TLR3 is very weakly expressed in normal liver (a) (Ref. [47])

parenchymal liver cells contribute to pro-inflammatory and/or immunomodulatory functions. With distinct mode of actions, i.e., secretion of lymphocyte chemotactic factors, ability to support adhesion and to promote onward migration, antigen presentation, and T cell instruction, these cells exert substantial influence on inflammatory settings, as well as on basal normal state, where continual immuno-surveillance is in operation by professional immune cells.

Hepatocytes

As hepatocytes are indeed the major cell type in the liver, they might represent primary modulators of hepatic immunity, especially in the setting of chronic liver injury, where non-injured hepatocytes in close proximity are predisposed to inflammatory mediators as bystanders. A line of evidence may support this idea [67]. Wiegaed et al. [67] recently demonstrated that MHC-II expressing hepatocytes induced Th2-biased differentiation of uncommitted CD4+T cells, and that suppressed the ability of previously differentiated Th1 to secrete IFN-γ in vitro. Accordingly, in vivo, they found that MHC-II expression by hepatocytes was associated with impaired IFN-γ response and impaired lymphocytic choriomeningitis virus clearance [67]. MHC-II expressing hepatocytes in inflamed milieu may have strong influence on the chronicity of hepatitis, by instructing infiltrating CD4+T cells to differentiate into a less inflammatory phenotype [67]. Application of immunomodulatory properties of hepatocytes is still challenging. Recent report clearly described that ectopic expression of neural autoantigen myelin basic protein (MBP) in the liver, either in liver-specific MBP transgenic mice or in transient gene transfer in vivo, induced protection from autoimmune necro-inflammation in a mouse model of multiple sclerosis, via generation of MBP-specific CD4+ CD25+ Foxp3+ Tregs [38].

Sinusoidal endothelial cells

Lymphocyte recruitment to the liver, especially within the hepatic sinusoids, is characterized by special features: in addition to the classical endothelial adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), other adhesion receptors appear to play more specific roles for lymphocyte recruitments to hepatic sinusoids [59]. These non-classical adhesion molecules in the LSEC include certain scavenging receptors, such as mannose receptor and common lymphatic endothelial and vascular endothelial receptor-1 (CLEVER-1), VAP-1, a 170 kDa homodimeric glycoprotein that has monoamine oxidase activity, and CD44. CXCL9-11 and CXCL16, chemokines, secreted not only by LSEC but also by inflamed cholangiocytes and hepatocytes, and subsequently presented on sinusoidal endothelia, are also required for recruitment/adhesion of lymphocytes and transmigration across LSEC [59].

LSEC are specialized organ-resident APC, contributing to peripheral immune tolerance. With scavenger activity, they have been reported to have capacity to present exogenous antigens on both MHC-II and MHC-I molecules to CD4+ or CD8+T cells, respectively. Diehl et al. [6] recently demonstrated that cognate interaction with naïve CD8+T cells induced tolerogenic maturation of LSEC, characterized by the increased expression of co-inhibitory B7-H1: in contrast to dendritic cells (DC), tolerogenic maturation of LSEC was cell-autonomous, not controlled by exogenous mediators (such as TGF-β, IL-10). Tolerization of CD8+T cells by matured LSEC is a unique, non-deletional process, dependent on B7-H1/programmed death 1 (PD-1) interaction.

HSC and activated liver myofibroblasts

HSC perform potent APC function for stimulation of CD4+/CD8+T cells as well as NKT cells. Accordingly, mode of antigen presentation of HSC was demonstrated to be through either MHC-II/MHC-I, or CD1d, the latter of which presents lipid antigens. Additional work in mice clearly confirmed that antigen presentation by HSC promoted protection against *Listeria monocytogenes* infection in the liver. IFN-γ induced amplification of APC proteins, along with B7-H1 production, in turn adds immunomodulatory functions to HSC, giving rise to B7-H1 dependent T cell apoptosis in mice. HSC transdifferentiates into activated liver myofibroblasts (aLMF) through the interaction with inflammatory cells, resulting in transformation into prominent fibrogenic cells in the liver [68]. Holt et al. [18] recently observed that aLMF played a direct role in regulating the infiltration and positioning of lymphocytes through G-protein coupled receptor-dependent and -independent fashion in vitro, apparently relevant in chronic liver disease. In murine models of liver fibrosis, apoptosis of aLMF by macrophages is followed by spontaneous resolution of inflammation. Very recently, senescent aLMF in murine liver were demonstrated to exhibit gene expression profile consistent with reduced secretion of extracellular matrix components, enhanced secretion of extracellular matrix-degrading enzymes, and enhanced immune surveillance [29]. Consequently, senescent aLMF were poised for selective target of natural killer cells, resulting in fibrosis reversion with aLMF clearance. Finally, stellate-cell-mediated T cell instruction was proposed by Winau et al. [68]. HSC plays a pivotal role in vitamin A homeostasis, storing vitamin A and converting retinol into retinoic acid. Generation of induced regulatory

T cells from naïve CD4+T cells in the periphery is dependent on retinoic acid as well as on TGF-β. Contrarily, retinoic acid inhibits the TGF-β/IL-6-inducing differentiation of inflammatory TH-17 cells [68]. Taken into account that HSC are capable of producing retinoic acid, TGF-β, and IL-6, it is plausible to have a scenario that HSC play a vital role in the instruction of regulatory T lymphocytes in the liver.

Biliary epithelial cells

Biliary epithelial cells that line the intrahepatic biliary tract are the primary site of innate immunity against microbials in bile. We reported that unstimulated conditioned medium of human cholangiocytes in vitro were already rich in multiple humoral factors, including ELR+CXC chemokines, such as IL-8/CXCL8, growth-related oncoprotein (GRO), epithelial neutrophil chemoattractant-78 (ENA-78), known chemoattractants with wide range of non-leukocytic activities [27]. Moreover, human cholangiocytes were found to be permissive in TLR2, 4, and 3 dependent pathways in vitro, the former of which caused increase in the secretion of IL-6, monocyte chemotactic protein-1 (MCP-1), and IL-8, upon activation with LPS or LTA, respectively [72].

Biliary epithelial cells in immunological inflammation

Several hepatobiliary diseases, especially PBC and PSC, appear to be mediated by a breakdown of self-tolerance, in which the immune reaction occurs against autoantigens expressed on biliary epithelial cells. PBC is one of the organ-specific autoimmune diseases characterized by appearance of autoantibodies specific for epitopes of 2-oxo-acid dehydrogenase multi-enzyme complexes of mitochondria and histologically chronic non-suppurative destructive cholangitis (CNSDC). Liver-infiltrated mononuclear cells (LMNC) around small bile ducts are believed to destroy BECs. On the other hand, PSC may be mediated by an immune response against endothelial cells of the peribiliary capillary plexus, with secondary reactions to BEC antigens.

Cell populations within and around BECs in PBC

Cytokines produced by lymphocytes infiltrating around CNSDC are closely associated with the progression of bile duct injury in PBC because BECs bear several cytokine receptors against interleukin (IL)-4, IL-6, interferon (IFN)-γ, and tumor necrosis factor (TNF)-α [13]. In addition, BECs themselves also produce TNF-α and IL-6. It has been demonstrated that T cells are the predominant cell type of the inflammatory cells within the portal tracts in PBC [28, 70]. Moreover, in the development of cholangiopathy, the infiltration of immune cells within the biliary epithelial layer and the direct adhesion between BEC and immune cells are key events leading to cell-mediated cytotoxicity and apoptosis of BECs [15, 71]. A number of pro-inflammatory cytokines are known to be elevated in the local portal tract microenvironment in PBC, contributing to development of chronic inflammatory reaction around the bile ducts, and BECs, as well as immune cells, actively participate in this inflammatory process. Immunoreactivity and autoimmunity are regulated at least by three different types of CD4+ helper T cells; Th1, Th2, and Th17 subsets, principally subdivided by distinctive cytokine production and effector functions. Th1 cells which secrete IL-2, IFN-γ, involved in the cell-mediated response provide help to cytotoxic CD8+T lymphocytes, activate natural killer cells, and produce delayed hypersensitivity reactions. In contrast, Th2 clones secrete IL-4 and IL-10, while Th17 cells which produce IL-17 are now considered as commanders for autoimmunity [3]. The presence of predominant Th1 cytokine profile is demonstrated in PBC [2]. Cytokine profiles determined primarily from stimulated peripheral blood and liver-derived T lymphocytes may be misleading for defining a Th1/Th2 cytokine profile in PBC [37, 41]. In

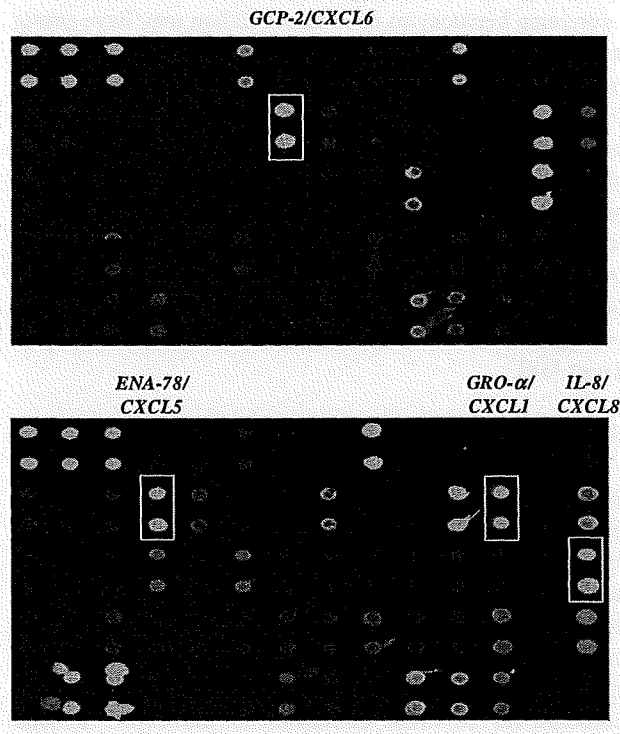

Fig. 5 Cytokines and chemokines produced by cultured BEC. BECs were studied under basal conditions for 48 h; thence cell-free culture supernatants were analyzed by a protein array kit to evaluate 174 different proteins simultaneously. Unstimulated cells produced detectable amounts of GRO-α/CXCL1, ENA-78/CXCL5, GCP-2/CXCL6, and IL-8/CXCL8 (Ref. [27, 60])

situ hybridization study reveals that IFN-γ mRNA-expressing mononuclear cells are more commonly detected primarily around damaged bile ducts in PBC livers than IL-4 mRNA-expressing cells and that the level of IFN-γ mRNA expression is highly correlated with the degree of portal inflammatory activity [16]. A recent study has reported that CD8+ and CD4+ (in particular, CD4+CD28−) T cells are markedly increased as intraepithelial lymphocytes within damaged bile ducts in PBC [20]. Since these unique CD4+CD28−T cells proliferate in target tissues of autoimmune diseases and are associated with Th1/Th2 balance in the regulation of spontaneous autoimmune diseases by possessing high expression of IFN-γ and auto-reactive and cytolytic function, CD4+CD28−T cells may be involved in the pathogenesis of autoimmune-mediated bile duct damage of PBC [22, 36].

Additionally, with these three CD4+T cells (Th1, Th2, and Th17), regulatory T cells must be mentioned. Regulatory T cells have two types; natural occurring CD4+CD25+Foxp3 +T cells and acquired IL-10-producing Th3 cells. Autoimmunity will occur when regulatory T cells decrease functionally or numerically. Recently, it is reported that natural occurring regulatory T cells are decreased around CNSDC in PBC [32].

Chemokine and bile ducts

Leukocyte migration depends on existence of a chemoattractant gradient created by a large family of molecules known as chemokines. Because of their role in inflammation, chemokines and their receptors are known to play a crucial part in directing the movement of mononuclear cells throughout the body, engendering the adaptive immune response and contributing to the pathogenesis of a variety of diseases [4]. The migration and accumulation of leukocytes in the target organs are a critical step in the pathogenesis of autoimmune diseases [43, 45].

Chemokines provide a sustained inflammatory bridge between innate and acquired immunity [31]. BECs are one of the sources of chemokines, and BECs spontaneously produce GRO-α/CXCL1, ENA-78/CXCL5, GCP-2/CXCL6, IL-8/CXCL8 (Fig. 5) [27, 60]. Fractalkine (CX3CL1), consisting of a membrane-bound form and a soluble chemotactic form, is produced by several epithelial cells and is associated with cell adhesion and the chemoattractant for its receptor (CX3CR1)-expressing cells such as CD8+ and CD4+T cells. In PBC, the expression of CX3CL1 is upregulated in injured bile ducts of PBC, and the CD4+ and CD8+ lymphocytes expressing CX3CR1 are found in portal tracts and within the biliary epithelial layer of injured bile ducts.

Defense against invading pathogens by cells of the innate immune system involves the rapid recognition of conserved PAMPs through members of TLR protein family [30, 35]. BECs locate in the pathway from the gut to the liver and constitutively express transcripts encoding several TLRs [5, 72]. Moreover, the expression levels of TLR-3 and -4 are high in the portal tract in PBC [62, 64] and stimulation with TLR3, BECs induce MIP-1α/CCL3, MIP-1α/CCL4, RANTES/CCL5, and IP-10/CXCL10.

It is reported that damaged BECs in PBC and, to a lesser degree and frequency, in other hepatobiliary diseases, expressed HLA DR antigens [48], and that the bile ducts in PBC liver tissues frequently expressed increased levels of CD40 associated with apoptotic BECs [1]. There were also some studies dealing with the differences of surface markers of BEC from PBC patients by immunohistochemical studies [63]. It was previously found that IFN-γ stimulates BECs to express HLA DR [23], and it is now shown that TLR3 ligands stimulate BECs to express HLA DR and CD40, indicating that the cultured circumstance of special condition makes BECs to change to the PBC phenotype. It is now suggested that PBC does not occur as a result by changed BECs, but BECs would change as a result of the developing PBC [60].

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＜特別寄稿＞

日本肝臓学会コンセンサス神戸2009：C型肝炎の診断と治療

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索引用語：　C型慢性肝炎　診断　治療　ガイドライン

はじめに

わが国のC型肝炎の特徴は，欧米に比し高齢であり肝組織所見の進展例が多く，経過観察中に高率に肝癌が生じてくることである．このため，患者背景の異なる欧米のガイドライン[1)]はわが国では当てはまらない事項もあり，日本の患者の実態に即した独自のガイドラインの策定が必要である．このような指針を求めて，第45回日本肝臓学会総会（工藤正俊会長）において，C型肝炎（病態・診断・予後・治療）をテーマとしたコンセンサス　パネルディスカッションが開催された．すでに，第5回，第7回，第10回の日本肝臓学会大会においても，同一テーマで討議されているため，今回が4回目となる．エビデンスレベルが高く，発表者と座長のコンセンサスが得られた事項で有益な情報をInformative statementとし，推奨すべき指針をRecommendationとして取り上げた．エビデンスレベルが低いため欧米のガイドラインでは採用されていないか，発表者と座長の予備検討において全員の賛同が得られなかった事項については，アンサーパッドで学会参加者に意見を求めた．その際，回答者の2/3以上の承認が得られればConsensus Statementとして採用した．アンサーパッドの参加者は200人であり，内訳は内科医が88%，肝炎診療の経験年数が10年以上の医師が83%，肝臓学会専門医も83%を占めた．本稿では，紙面の都合でInformative statementやRecommendationは明記せず，パネルディスカッションにおいて活発な討議が行われ，結論が得られたConsensus Statementのみ全文を記載した．

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1）病態・診断・予後

1．C型肝炎の発症機序

C型肝炎ウイルス（HCV）の肝細胞への感染はHCV E2タンパクがCD81と結合することが必要であると報告されたが，その後scavenger receptor class B type I（SR-B1）やclaudin-1（CLDN1）といった宿主タンパクも関与することが示された．さらに2009年になってoccluding（OCLN）がHCV感染に不可欠であることが明らかとなった．興味深いことにCLDN1とOCLNはともにtight junctionに存在する分子であり，HCVが肝細胞に接着した後の細胞内への取り込みに重要であると考えられている．さらにCD81とOCLNはHCV感染の種特異性に関与する分子であることも示されている[2)]

HCVの持続感染が成立するためには，宿主の自然免疫からの回避が必要である．最近，HCVによる自然免疫の抑制機構が明らかにされた．すなわち，複製中のHCV RNAの一部はPAMPとしてRIG-IやTLRに認識される．RIG-Iに認識されたシグナルはIPS-1を介して内因性のインターフェロン（IFN）シグナルを活性化する．産生されたIFNはIFNレセプターに結合してJak-STATシグナルを活性化してIFN応答遺伝子の発現を促す．しかし，HCV NS3/4A proteaseはIPS-1を断裂することでIFNシグナルを阻害しIFN産生を抑制する．また，HCVコアタンパクに誘導されるSOCS-3はJak-

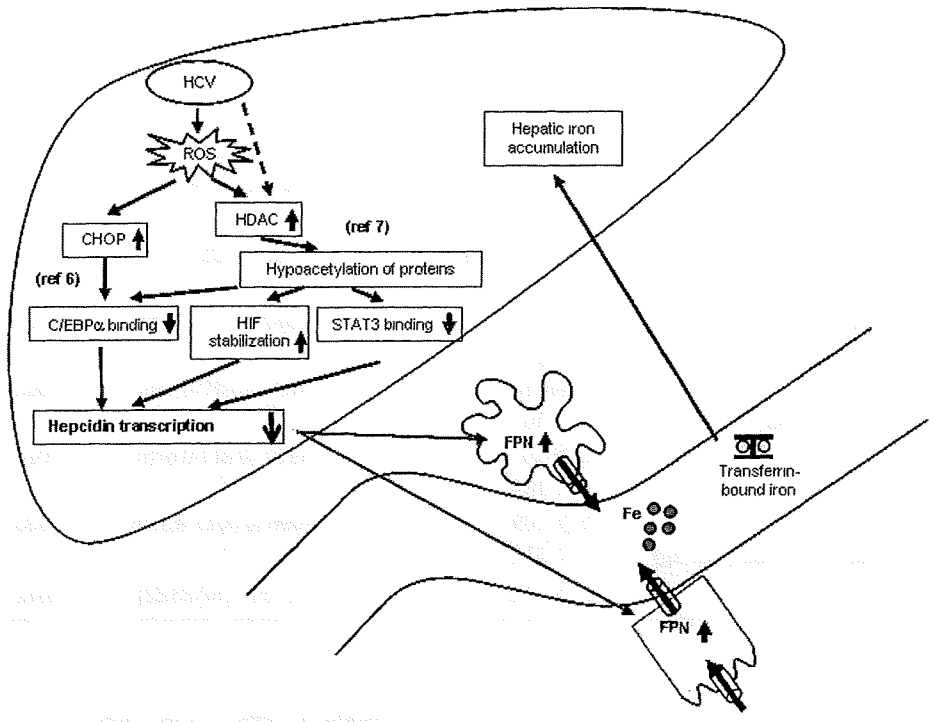

Fig. 1　Schematic diagram depicting the mechanisms underlying the hepatic iron accumulation induced by HCV
HCV-induced ROS reduces hepcidin transcription through the inhibited binding of CHOP and/or STAt3 to the hepcidin promoter, and/or stabilization of HIF that is negative hepcidin regulator.
HCV, hepatitis C virus; ROS, reactive oxygen species; HDAC, histone deacetylase; CHOP, C/EBP homology protein; C/EBP, CCAAT/enhancer-binding protein; HIF, hypoxia inducible factor; STAT, signal transducer and activation of transcription; FPN, ferroportin

STATシグナルを阻害してIFN応答遺伝子の発現を抑制し，NS5Aタンパクは IL-8の産生を亢進し，おそらくIFN応答遺伝子の発現を変化させることでIFNの抗ウイルス効果を減弱させる．更には，NS5AやE2タンパクはPKRに結合して，PKRの酵素活性を抑制することでIFNのウイルスタンパク翻訳抑制効果を阻害する[3]．HCVは以上に示したような様々な機構で宿主の自然免疫を回避すると考えられる．

HCVの持続感染成立後の肝細胞障害では，酸化ストレスが重要な役割を担っている．HCVコアタンパクはミトコンドリアを傷害し活性酸素を産生し肝臓に酸化ストレスを引き起こす[4][5]．さらにはTNFαやSOCS-3を介したinsulin receptor substrate（IRS）の抑制によるインスリン抵抗性の亢進，MTP抑制やSREBP1亢進による肝脂肪化，hepcidinの転写抑制を介した鉄蓄積などを引き起こし，C型肝炎に特徴的な病態を引き起こす（Fig. 1）[6][7]．これらの病態は肝発癌とも深く関連しており，さらにはペグインターフェロン（PEG-IFN）・リバビリン（RBV）併用療法の治療効果にも影響を与えることが報告されている．但し，肝内鉄過剰と抗ウイルス効果との関係については未だ一定の結論に至っていない

Consensus Statement 1:
インスリン抵抗性と肝脂肪化はPEG-IFN・RBV併用療法の治療効果と関連する．(Level 2a, Grade C)

このようにC型肝炎の発症機序は次第に明らかにされつつあるが，肝発癌予測と抗ウイルス療法の効果予測に不可欠なのが肝線維化の評価である．最近ではelastographyを用いた非侵襲的な肝線維化の評価もなされているが，中等度の線維化の評価は未だ困難である．「肝線維化の評価のために肝生検は必要か？」という質

Table 1 Factors associated with sustained virological response to 48-week peginterferonribavirin combination therapy in patients infected with HCV genotype 1b, identified by multivariate analysis (n=114) [11]

Factor	Category	Risk ratio (95% confidence interval)	P
Amino acid substitution in core region	1: double wild	1	
	2: non-double wild	0.102 (0.022-0.474)	0.004
LDL cholesterol (mg/dL)	1: < 86	1	
	2: ≥ 86	12.87 (2.177-76.09)	0.005
Gender	1: male	1	
	2: female	0.091 (0.017-0.486)	0.005
ICG R15 (%)	1: < 10	1	
	2: ≥ 10	0.107 (0.017-0.678)	0.018
γ-GTP	1: < 109	1	
	2: ≥ 109	0.096 (0.0011-0.819)	0.032
Ribavirin dose (mg/kg)	1: < 11.0	1	
	2: ≥ 11.0	5.173 (1.152-23.22)	0.032

問に対して，今回のアンサーパッドの集計では74%の賛同が得られた．

Consensus Statement 2:

肝発癌や抗ウイルス療法の治療効果と関連する宿主側因子として肝組織の線維化の程度（staging）が重要であるが，stagingの評価には肝生検が推奨される．（Level 1，Grade C）

2. ウイルス変異と病態

C型肝炎の診断にはHCV RNAの測定とともに，ウイルス量，型（genotype）の測定が重要である．さらにHCV RNA遺伝子の変異について新たな知見が得られている．これらの因子はC型肝炎に対するIFN療法（RBVの併用療法を含む）の治療効果の予測に非常に重要である．ウイルス量の測定法は，2000年以降アンプリコアHCVモニター法が用いられてきたが，2007年末から高感度かつ広範囲の測定レンジをもつreal-time PCR法を用いた測定が可能となっている．このようなウイルス量とウイルスの型（genotypeまたはserotype）の測定はIFN治療の効果予測や治療中の抗ウイルス効果をみるなど臨床的な有用性が高い[8]．

ウイルスの遺伝子変異は，主としてgenotype 1b型のウイルスで多く検討されている．IFN単独投与におけるNS5A aa2209-2248（interferon sensitivity determining region；ISDR）領域のアミノ酸変異数が治療効果に関係することが明らかになった．HCV-Jのアミノ酸配列と比較してISDRのアミノ酸変異数が多い場合，IFN単独療法でのSVR率が高いことが報告されている[9]．さらに現在治療の主体である，PEG-IFNとRBV併用療法（48週間）においてもISDRの変異数は効果予測に重要である[10]．

Table 2 Effect of the IFN treatment on the annual incidence of hepatocellular carcinoma in each fibrosis staging

	Control	IFN-treated		
		All	SVR	non-SVR
Patient's number	490	2400	789	1658
Staging				
F1	0.45%	0.08%	0.11%	0.07%
F2	1.99%	0.54%	0.10%	0.78%
F3	5.34%	1.95%	1.29%	2.20%
F4	7.88%	4.16%	0.49%	5.32%

Data were adopted from IHIT study[16]

Consensus Statement 3:

ISDRの変異は，IFN単独またはRBVとの併用療法におけるSVRに関係するので，治療前に測定すべきである．（Level 2a，Grade B）

さらに，HCV Core領域のアミノ酸置換の有無（70番目と91番目の変異）がPEG-IFNとRBV併用療法の

治療効果に関係することが報告された（Table 1）[11]．米国の報告でもCore領域の70番目のアミノ酸置換が抗ウイルス作用に関係することが示された[12]．

Consensus Statement 4:

Core領域の70番目，91番目のアミノ酸置換は，IFN・RBV併用療法におけるSVR，NVRに関係するため，治療前に測定すべきである．（Level 2a，Grade B）

またNS5A領域のaa2334-2379（IFN/ribavirin resistance determining region，IRRDR）のアミノ酸変異数がPEG-IFN・RBV併用療法の治療効果に関係するという報告もある[13]．さらに新規治療薬であるプロテアーゼ阻害剤では，NS3領域の遺伝子変異が耐性に関係すると報告されている．一方，発癌との関係では，Core領域のアミノ酸置換の有無やNS3蛋白の二次構造が関係するという報告もなされているが，これらの点に関しては，さらなる検討が必要である．

3. 自然経過とIFN治療適応（高齢者，PNALTを含む）

C型急性肝炎の60～80％が慢性化するとされているが，輸血後肝炎以外では感染時期が特定できないことが多く，また，無症状で緩徐な経過をたどることが多いためC型慢性肝炎の自然史には不明な点が多い．比較的若くHCVに感染した者を追跡した欧米の報告では，HCV感染が感染者全体の生命予後に与える影響は少なく，20年近く経過した症例でも多くは肝線維化の進展も軽度にとどまるとしている[14]．この成績は，輸血後肝炎患者においては平均20年～30年の経過で肝硬変へ進展し，平均30年～40年の経過で肝癌を併発するというわが国の報告とは進展速度が大きく乖離する[15]．一方，C型慢性肝炎の肝線維化の進展度と肝癌の発生との間の密接な関連性は多くの論文で示されており，わが国における肝硬変の年率発癌率は5～8％に至る（Table 2）[16]．このため，以下のコンセンサスが得られた．

Consensus Statement 5:

わが国の肝硬変患者の年率発癌率は欧米より高く，5～8％であることを考慮して治療適応を選択すべきである．（Level 2b/3，Grade B）

C型慢性肝炎患者の線維化の進展速度は症例によりまちまちであるが，Poynard Tら[17]は無治療のC型慢性肝炎平均の年率肝線維化進展率が0.133（stage）であると報告し，Shiratori Yら[18]も同様に0.10（stage）であるとしている．ALT持続正常のC型慢性肝炎患者では線維化の進展はさらに緩徐で，5年後の肝組織の線維化に著変なかったとする報告や，年率肝線維化進展率が平均0.05（stage）であったとする報告がある[19]．最近では，アルコール多飲以外にも，肝組織への鉄の過剰沈着，肝脂肪化，インスリン抵抗性がC型慢性肝炎の肝線維化を促進する因子であり，生活習慣の改善が重要であるとされている．

以前より血清ALT値の高い肝硬変では発癌率が高かったが，ALT値が40 IU/l以下のC型慢性肝炎でも血清ALT値と発癌率が関連することが示された．実際の臨床の場では，C型慢性肝炎患者の血清ALT値は30 IU/l以下に治療の目標値を設定すべきである．

Consensus Statement 6:

肝発癌予防のためにはALT値を30 IU以下に保つべきである．（Level 2a，Grade A）

また，わが国でC型慢性肝炎患者に対するIFN治療が始まって20年以上が経過し多くの患者が著効を得ているが，著効後にも肝癌が発症することが知られ，治療前の肝組織の線維化進展例，高齢者，男性に肝癌併発のリスクが高いことが報告されている．Burno Sら[20]は著効を示した肝硬変症例の年率発癌率は非著効例の3分の1ではあるが，依然，0.66％であることを示した．

Consensus Statement 7:

C型慢性肝炎や肝硬変患者では定期的な肝癌のスクリーニング検査を行うべきである．IFN治療で著効が得られても，特に肝線維化進展例，高齢，男性患者では肝発癌のリスクが高く，定期的な画像診断・腫瘍マーカーによる検査が引き続き必要である．（Level 2b，Grade A）

C型慢性肝炎に対する抗ウイルス療法ではPeg-IFN・RBV併用療法が第一選択の治療法であるが，両薬剤には多くの副作用がある．特に高齢者ではグレード3以上の副作用の発生率が高く，両薬剤の減量を余儀なくされることも少なくない．しかし，IFN治療の年齢制限については，上限なし35％，75歳まで64％という意見であり，わが国では高齢者にも積極的にIFN治療を導入していることが明らかとなった．AASLDのガイドラインでは，治療適応は病態の重症度，副作用のリスク，完治の可能性，生命予後への影響，患者の治療への意欲などを総合的に捉え，個別化して判断すべきであるとしている[1]．さらに，Zeuzem Sら[21]が遺伝子型1型のALT持続正常のC型慢性肝炎患者に対するPeg-IFN・RBV併用療法の著効率が40％であることを報告