



EDITORIAL

Signal transduction pathways in liver and the influence of hepatitis C virus infection on their activities

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Received: January 25, 2009 Revised: March 15, 2009

Accepted: March 22, 2009

Published online: May 14, 2009

Abstract

In liver, the most intensively studied transmembrane and intracellular signal transduction pathways are the Janus kinase signal transduction pathway, the mitogen-activated protein kinases signal transduction pathway, the transforming growth factor β signal transduction pathway, the tumor necrosis factor α signal transduction pathway and the recently discovered sphingolipid signal transduction pathway. All of them are activated by many different cytokines and growth factors. They regulate specific cell mechanisms such as hepatocytes proliferation, growth, differentiation, adhesion, apoptosis, and synthesis and degradation of the extracellular matrix. The replication cycle of hepatitis C virus (HCV) is intracellular and requires signal transduction to the nucleus to regulate transcription of its genes. Moreover, HCV itself, by its structural and non-structural proteins, could influence the activity of the second signal messengers. Thus, the inhibition of the transmembrane and intracellular signal transduction pathways could be a new therapeutic target in chronic hepatitis C treatment.

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Key words: Liver; Hepatitis C virus infection; Signal transduction pathway; Proliferation; Apoptosis

Peer reviewer: Thomas Bock, PhD, Professor, Department of Molecular Pathology, Institute of Pathology, University Hospital of Tuebingen, D-72076 Tuebingen, Germany

Dabrowska MM, Panasiuk A, Flisiak R. Signal transduction

pathways in liver and the influence of hepatitis C virus infection on their activities. *World J Gastroenterol* 2009; 15(18): 2184-2189 Available from: URL: <http://www.wjgnet.com/1007-9327/15/2184.asp> DOI: <http://dx.doi.org/10.3748/wjg.15.2184>

INTRODUCTION

Hepatitis C virus (HCV) was discovered by Choo *et al*^[1] in 1989. HCV is included in the Flaviviridae family within the distinct genus of *Hepacivirus*^[2]. According World Health Organization (WHO) data, there are currently about 170 million HCV-infected persons worldwide, which is approximately 3% of the human population. In Poland, the number of chronic HCV-infected persons is estimated to be 750 000, which is about 1.4 % of the general population^[3]. In the natural history of HCV infection, there is an 80% risk of chronic infection, as well as the high possibility of severe complications such as liver cirrhosis or hepatocellular cancer (HCC).

The main target cell for HCV infection is the hepatocyte, however the virus also infects B lymphocytes and affects other immune system components. The HCV replication cycle is intracellular and requires activation of many transmembrane and intracellular signal transduction pathways, which are mainly activated by cytokines such as tumor necrosis factor α (TNF- α), interleukins (IL-4, IL-6, IL-12 or IL-13), interferons, mitogens hepatocyte growth factor (HGF), epidermal growth factor (EGF) or transforming growth factor α (TGF- α) and growth inhibitors (TGF- β and activine).

TRANSMEMBRANE AND INTRACELLULAR SIGNAL TRANSDUCTION PATHWAYS

Janus kinase (JAK) signal transduction pathway

The JAK signal transduction pathway is activated by more than fifty different cytokines and growth factors. This intracellular pathway operates not only in hepatocytes but also in immune, hematopoietic and neural system cells. After extracellular ligand-receptor interaction, receptor multimerization and the activation

Table 1 STATs activation and function

STAT protein	Activating factor	Activation effect
STAT 1	IFN- α / β (type I INF) IFN- γ (type II INF)	Antiviral response, inflammation and hepatocyte damage development, apoptosis stimulation
STAT 2	INF- α / β i INF- λ	Antiviral response
STAT 3	IL-6 and its family, IL-10, IL-22, EGF, HCV proteins	Participates in antiviral IFN- α effect, direct cytoprotective and anti-inflammatory influence on hepatocytes
STAT 4	IL-12	Probably plays a critical role in hepatocytes damage during hepatic ischemia/reperfusion injury and in Th1 differentiation
STAT 5	Growth factors	Regulates the genes expression essential for hepatocytes metabolism, growth and differentiation
STAT 6	IL-4, IL-12 and IL-13	Participates in Th2 lymphocytes response during viral hepatitis and decreases hepatocytes damage during hepatic ischemia/reperfusion injury

of JAK1, JAK2, JAK3 and tyrosine kinase 2 (Tyk2) is observed. The receptor-kinase complex phosphorylates cytoplasmic SH-2-containing transcription factors: signal transducers and activators of transcription (STAT) 1, 2, 3, 4, 5, 6. Activated STATs present two main functions: signal and transcriptional by forming homo- and heterodimers, which translocate to the nucleus to influence transcription. STATs are specifically inhibited by protein inhibitors of activated STAT (PIAS)^[4] and by suppressor of cytokine signaling (SOCS) through negative feedback control (Figure 1A). SOCS proteins include SOCS 1, 2, 3 and cytokine-induced Src homology 2 protein (CIS), which bind to JAK kinase inhibiting its enzymatic activity^[5].

STATs perform different, often opposing functions in the liver. STAT1 is mainly activated by IFN type I (IFN- α / β) and IFN type II (IFN- γ). Its essential function in liver is the participation in antiviral immune defense, as well as in the development of inflammation and apoptosis. IFN- α / β and IFN- λ are ligands for STAT2, whose major function is antiviral defense. Membrane the IFN- α / β receptor (IFNAR) is a complex of two subunits: IFNAR1 and IFNAR2. IFNAR2 presents three diverse forms: full-length IFNAR2c is responsible for signal transduction and transcription process, whereas short form IFNAR2b and soluble form IFNAR2a inhibit these processes^[6]. The complex IFN- α / β - IFNAR activates JAK1 and Tyk2 kinases. IFN- γ takes effect by IFN- γ receptor (IFNGR): IFNGR1 and IFNGR2. STAT3 function is especially regulated by IL-6 and its family members such as cardiotrophin-1 (CT-1), oncostatin M (OSM), IL-11, leukemia inhibitory factor (LIF) or ciliary neurotrophic factor (CNTF), by IL-10, IL-22, EGF and HCV proteins. STAT3 participates in the acute phase response, stimulates hepatocytes regeneration and regulates lipid and carbohydrate metabolism in the liver^[7]. Moreover STAT3 is one of the main anti-HCV-defense elements that acts by increasing the IFN- α antiviral effect and by its direct cytoprotective and anti-inflammatory influence on hepatocytes^[8]. IL-6 and its related cytokines bind gp130 receptor protein, which plays a key role in liver regeneration.

Furthermore, Li *et al.*^[9] confirmed that gp130 activity is independent of the activities of other kinases, such as MAK. The ligand-gp130 complex activates JAK1, JAK2 and Tyk2. Recently, the influence of HCV infection on

STAT1-3 factors was demonstrated. HCV structural proteins C, E2 and non-structural protein NS5A were shown to reduce the number of membrane receptors (IFNAR1 and IFNAR2c) blocking STAT1-3 activation by IFN- α . STAT1-3 are also inactivated by ethanol and increased level of TNF- α , IL-1 β and IL-10^[7]. As a result, viral replication, as well as inflammation and fibrosis in the liver, is augmented and has a negative effect on IFN- α treatment response among patients with severe liver damage. However, HCV does not affect IFN- γ function, and in consequence, STAT1 activation^[10]. Moreover, Sun and Gao showed that IFN- γ produced by NK cells inhibits hepatocytes regeneration during HCV infection^[11]. STAT4 is the least known transcription factor. STAT4 has been shown to be activated by IL-12 and to play a critical role in hepatocytes damage during hepatic ischemia/reperfusion injury and in Th1 differentiation^[12]. STAT5 is mainly activated by growth factors and regulates the expression of genes encoding cytochrome P450, HGF and insulin growth factor 1 (IGF1), which are essential for hepatocytes metabolism, growth and differentiation. STAT6 is regulated by IL-4, IL-12 and IL-13. These factors participate in Th2 lymphocytes response during viral hepatitis and reduce hepatocytes damage during hepatic ischemia/reperfusion injury. A summary of STATs activation and function are shown in Table 1.

MAPK signal transduction pathway

EGF, HGF and TGF- α bind with membrane receptors having intrinsic tyrosine kinase enzymatic activity. Ligand-receptor complex multimerization and autophosphorylation are then observed. Ras proteins and GTP create a transient complex activating RAF kinases and MAPK kinases (MKK), which can activate MAPK by dual phosphorylation of threonine and tyrosine. Activated MAPK phosphorylates transcription factors such as cAMP response element-binding (CREB) and Ets-related transcription factor 1 (ELK-1). The MAPK signal transduction pathway is evolutionarily one of the oldest signal transduction pathways in eukaryotic cells. It contains three different signal tracts: the extracellular regulated protein kinase (ERK, p42/44 MAPK) tract, the stress activated protein kinase (SAPK, p38 MAPK, p38-RK or p38) tract, and the c-Jun-NH2-terminal kinase (JNK, p64/54 SAPK) tract (Figure 1B). All of

these pathways regulate processes such as cell growth, differentiation, maturation, proliferation and apoptosis. In mammalian cells every single pathway is activated by two MKK: JNK by MKK4 and MKK7, ERK by MKK1 and MKK2, and SAPK by MKK3 and MKK6. This dual role of MKK in the activation of the JNK, ERK and SAPK signal transduction pathways is still unclear^[13]. It has been shown that ERK play a key role in the regeneration of the majority of eukaryotic cells. However the role of SAPK, especially in hepatocytes regeneration, is as yet undefined. Physiologically, the activity of JNK in the liver is minimal but increases during liver regeneration, probably associated with high hepatic TNF- α levels^[14].

TGF- β signal transduction pathway

TGF- β is cytokine family member that plays a key role in the processes of cell growth, differentiation, adhesion, apoptosis, and synthesis and degradation of the extracellular matrix. In the liver, during HCV infection, TGF- β is responsible for hepatocytes regeneration and fibrosis, and for epithelial cells proliferation and differentiation. TGF- β 1 serum concentration in patients with chronic liver diseases, including chronic HCV infection, is higher the more severe the liver failure is, confirming the association between this cytokine and hepatic fibrosis^[15]. Concurrently, in patients with chronic hepatitis C, TGF- β 1 serum concentration decreases and normalizes after successful antiviral therapy^[16].

The TGF- β membrane receptor consists of two subunits having intrinsic serine/threonine kinase enzymatic activity: the type I receptor (T β R-I) and the type II receptor (T β R-II). After binding of the ligand to T β R-II, T β R-I is phosphorylated in the GS domain containing many glycine and serine amino acids. Activated T β R-I influences receptor-specific R-Smad proteins (Smads) and common-partner Smad (Co-Smad). SMADs are a class of proteins that modulate the activity of transforming growth factor beta ligands. Newly created complexes translocate to the nucleus and stimulate transcription and apoptosis^[17] (Figure 1C). During liver regeneration, elevated TGF- β concentration is observed, though it does not give rise to an increase of hepatocytes apoptosis, which is probably linked with parallel augmentation of the concentrations of Smads: Ski and SnoN, and other antiapoptotic proteins such as Bcl-2 and Bcl-X in hepatocytes^[18]. HCV, through the NS5A protein, inhibits TGF- β signal transduction pathway activity. NS5A reacts directly with T β R-I using the region between amino acids 148 and 237. As a result, Smads phosphorylation, complex creation and its migration to the nucleus are blocked. In contrast, NS5B protein has no inhibitory effect on T β R-I. TGF- β pathway inhibition can be the result not only of HCV infection, but also of other viruses such as hepatitis B virus (HBV), adenoviruses and HPV. This effect can be due to the direct interaction between the X protein and Smad4 (HBV), interaction between the E1 protein and R-Smad (adenoviruses) or through the inhibitory effect of the E7 protein on R-Smad and Co-Smad complex formation in the nucleus (HPV)^[19].

TNF- α signal transduction pathway

TNF- α is produced by macrophages, monocytes, mast cells and NK cells. TNF- α is one of the main mediators of the antiviral inflammatory response, which enhances lymphocytes proliferation and differentiation, acute phase proteins production and cell apoptosis. Two essential TNF- α membrane receptors are known: TNF-R1 (CD120a, TNF-55r or p55) and TNF-R2 (CD120b or p75). TNF-R1 plays a key role in the liver due to its presence not only in hepatocytes membrane but also in Kupffer cells and hepatic sinusoidal endothelial cells. TNF-R1 consists of three domains: extracellular, transmembrane and intracellular (known as the death domain (DD)). Activated TNF-R1 binds, *via* the DD, to an adaptor protein TNFR-associated protein with death domain (TRADD), which afterwards activates Fas associated death domain (FADD) proteins, TNF-associated factor-2 (TRAF-2) and receptor-interacting protein (RIP). All of these proteins influence different signal transduction pathways. FADD activates caspases 8 and 10 leading to Death-Inducing Signaling Complex (DISC) formation, which regulates apoptosis^[20], whereas TRAF-2 and RIP activate two tracts taking part in the anti-apoptotic effect of TNF- α : I κ B kinase (IKK) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B factor), as well as JNK and ERK from MAPK signal transduction pathway^[21] (Figure 1D). NF κ B is a transcription factor comprising two subunits: p50 having a molecular weight of 50 kDa and p65 (also known as RelA, v-rel reticuloendotheliosis viral oncogene homolog A or nuclear factor of kappa light polypeptide gene enhancer in B-cells 3) having a molecular weight of 65 kDa. The RelA subunit is mainly responsible for the anti-apoptotic function of NF κ B. In the cytoplasm, NF κ B, with inhibitor proteins I κ B α or I κ B β (IKK), creates the inactive form. TRAF-2/RIP activates IKK, which phosphorylates I κ B leading to its subsequent degradation in proteasomes. Activated NF κ B translocates to the nucleus where it binds with DNA through a zinc finger motif and stimulates transcription of genes encoding cytokines, acute phase proteins, immunoglobulins and adhesion factors^[22]. TNF- α linked with TNF-R1 leads, depending on activated cellular proteins, to cell proliferation or apoptosis. Kato *et al*^[23] showed that HCV core protein C and, to a lesser degree, NS4B protein, influence cell proliferation and production of proinflammatory cytokines such as IL-1, IL-2, IL-3, IL-6, IL-8, IL-12, TNF- α and INF- β stimulating three diverse pathways through NF κ B, activator protein-1 (AP-1) and serum response element (SRE). AP-1 is a complex of homo- or heterodimers encoded by c-jun and c-fos family genes. Moreover, AP-1 stimulates proliferation dependent on growth factors, oncogenes and inflammatory peptides. SRE regulates the promoters of immediate early (IE) genes such as c-fos and PIP92. MAPK cascade activation phosphorylates Elk-1 factor binding with SRE and serum response factor (SRF)^[24]. The thus created complexes affect transcription of genes taking part in cell proliferation.

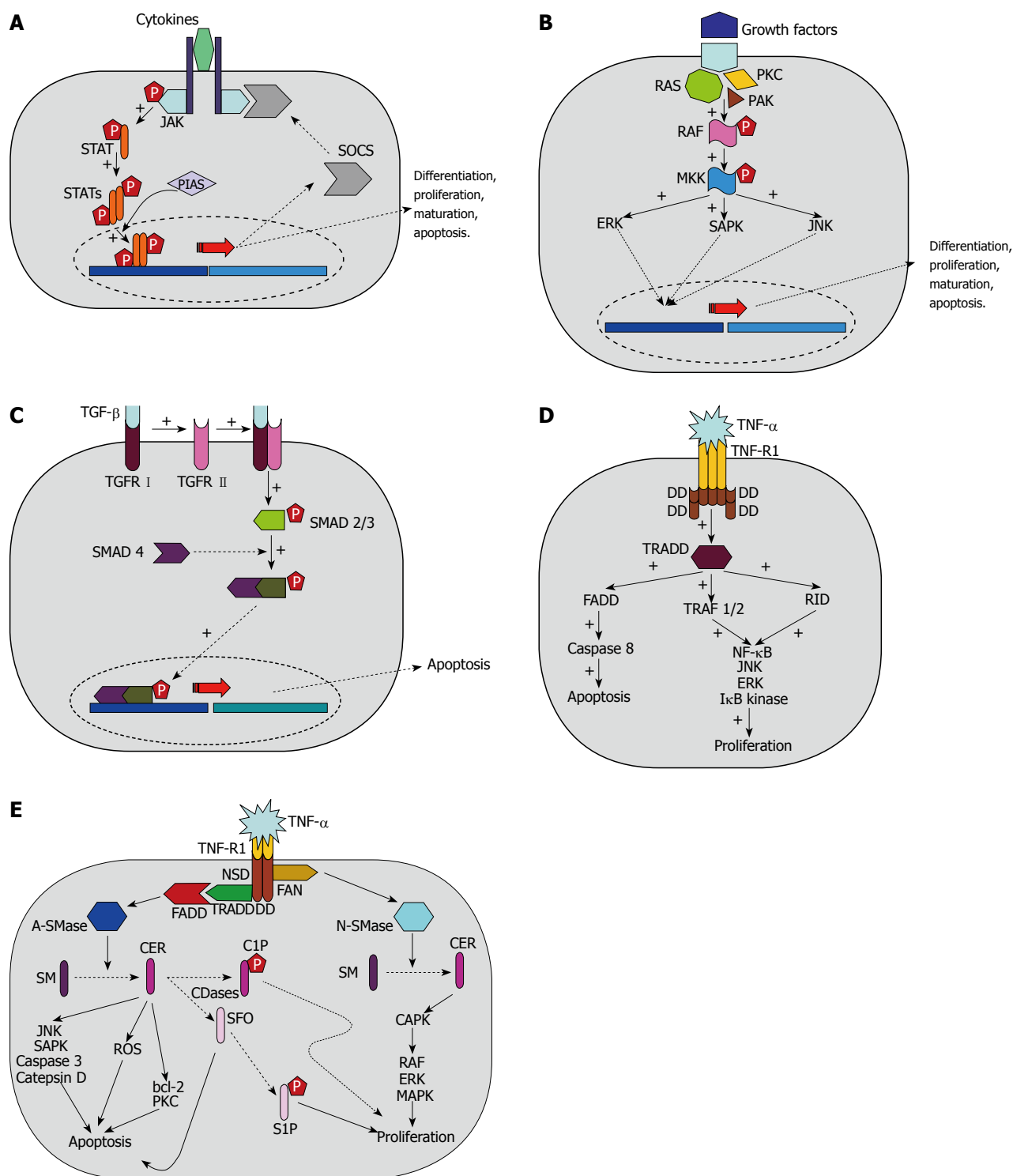


Figure 1 Signal transduction pathway. A: Janus kinase (JAK); B: Mitogen-activated protein kinase (MAPK); C: Transforming growth factor- β (TGF- β); D: Tumor necrosis factor α (TNF- α); E: Sphingolipid. +: Activation; P: Phosphorylation; STAT: Signal transducers and activators of transcription; STATs: Activated STAT; PIAS: Proteins inhibitor of activated STAT; SOCS: Suppressor of cytokine signaling; RAS: Small GTP-binding protein; PKC: Protein kinase C; PAK: P21-activated kinase; RAF: Serine/threonine kinase; MEK: Mitogen-activated protein kinase kinase; ERK: Extracellular signal-regulated protein kinase; SAPK: Stress activated protein kinase; JNK: C-Jun-NH2-terminal kinase; TGFRI and TGFRII: Membrane receptors of TGF- β ; SMAD: Class of proteins that modulate the activity of transforming growth factor β ligands; TNF-R1: Membrane receptor of TNF- α ; DD: Death domain; TRADD: TNFR associated protein with death domain; FADD: Fas associated death domain; TRAF 1/2: TNF-associated factor-2; RID: Receptor-interacting protein; NF- κ B: Transcription factor; NSD: TNF-R1 domain activating neutral sphingomyelinase; FAN: TNF-R1 adaptor protein; A-SMase: Acid sphingomyelinase; N-SMase: Neutral sphingomyelinase; SM: Sphingomyelin; CER: Ceramide; C1P: Ceramide-1-phosphate; CDases: Ceramidases; SFO: Sphingosine; S1P: Sphingosine-1-phosphate; ROS: Reactive oxygen species; CAPK: Ceramide-activated kinase.

Sphingolipid signal transduction pathway

Initially sphingolipids were demonstrated to be major components of eukaryotic plasma membranes and mediators of cell-to-cell interactions. Since 1989, many

studies have shown that sphingolipids are also the essential second messengers in transmembrane and intracellular signal transduction. This new pathway was called the sphingolipid signal transduction pathway^[25]. Generally,

it mediates specific cell reactions such as proliferation, growth arrest, differentiation, apoptosis and calcium homeostasis. It is activated by many proapoptotic and promitotic factors, such as cytokines TNF α and IL-1, Fas (Apo-1, CD95) receptor agonists, CD-40, CD-28, CD-5, DR-5, lymphocyte function-associated antigen-1 (LFA-1), CD-32 (Fc γ RII), CD-20, hormones (progesterone), vitamin D3, protein kinase C inhibitors, growth factors [platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and nerve growth factor (NGF)], infection (by *P. aeruginosa*, *S. aureus*, *N. gonorrhoeae*, *Sindbis virus* and *Rhinovirus*), γ radiation, UV and chemotherapeutics (such as doxorubicine and cisplatin)^[26]. The final effect of pathway activation (cell survival or death) depends on the inductive factor and the balance between the intracellular levels of its main components: ceramide (Cer) and sphingosine-1-phosphate (S1P). This balance is known as “the Cer/S1P rheostat”.

The most intensively studied second messenger of sphingolipid signal transduction pathway is ceramide, which is highly antiproliferative (Figure 1E). Firstly, Cer activates c-Jun kinase (JNK), stress activated protein kinases (SAPK), cathepsin D, methionine adenosyl transferase 1A (MAT1A) and caspase 3, which are responsible for destruction of the cytoskeleton, nuclear and plasma membranes^[27]. Secondly, Cer stimulates the mitochondria to release reactive oxygen species (ROS) and cytochrome c, activating the apoptotic proteases^[28]. Finally, Cer decreases, by dephosphorylation, the intracellular level of anti-apoptotic proteins of the Bcl-2 family and the activity of anti-apoptotic enzymes like kinases that depend on the intracellular Ca²⁺ levels [protein kinase C, (PKC), PKC α and PKC β /Akt]. Paradoxically, Cer synthesized from the hydrolysis of sphingomyelin (SM) by neutral sphingomyelinases (NSMases), enhances the activity of the ceramide activated protein kinase (CAPK) and afterwards the serine/threonine kinase Raf and Akt, extracellular signal-regulated protein kinases (ERK 1/2) and the mitogen-activated protein kinase (MAPK). All these kinases stimulate the proliferation process^[29]. Cer regulates the cell growth processes through its influence on PKC, kinase suppressor of Ras (KSR), Raf-1, MAPK and ceramide-activated protein phosphatase (CAPP), controlling the protein phosphatases PP1 and PP2. Cer also take a part in plasma membrane reorganization, facilitating transmembrane proapoptotic signal transduction and modulating the autophagocytosis^[30]. Autophagocytosis relies on degradation of damaged, dead or used cell structures to prolong cell life. Cer inhibits autophagocytosis by stimulating apoptosis^[31].

A further second messenger of sphingolipid signal transduction pathway is sphingosine (SFO). SFO is synthesized from the hydrolysis of Cer by ceramidases (CDases). SFO has a key role in apoptosis by stimulating ROS production in mitochondria and activation of caspase 3, 7 and 8^[32]. Additionally, sphingosine inhibits Akt, resulting in the augmentation of the cellular effects of cytochrome c and caspase 3^[33]. Moreover, SFO directly blocks DNA synthesis, methylation and replication. SFO also reduces the activity of protein kinases such as PKC, calmodulin-dependent protein

kinase and insulin receptor kinase. The PKC inhibition proceeds in two parallel ways: directly and indirectly by decreasing the level of intracellular diacylglycerol (DAG) and Ca²⁺ ions. The PKC inhibition leads to disturbances of nuclear proteins phosphorylation (RNA polymerase, topoisomerase II, histones and matrix proteins^[34]). Some studies underline the proliferative character of SFO. It seems that low cellular concentrations of SFO stimulate cell proliferation and DNA synthesis, whereas the high concentrations stimulate apoptosis.

Sphingosine-1-phosphate (S1P), synthesized from SFO, has a potent anti-apoptotic character. An increase in the intracellular level of S1P can activate cell proliferation and its passing from G₁ phase to S phase, augment the general number of cells resting in S phase, shorten the time needed for cell division, enhance survival rate of cells subjected to proapoptotic factors, mobilize calcium ions from intracellular compartments, influence cytoskeletal architecture and the processes of cell migration and adhesion. S1P modulates cell functions in two different ways: as an intracellular messenger and as a ligand of G protein-coupled receptors, known as endothelial differentiation genes (Edg) - Edg-1, -3, -5, -6 and -8^[35].

Cer may be phosphorylated by ceramide kinase to ceramide-1-phosphate (C1P), which can be dephosphorylated back to ceramide by C1P phosphatase. Similarly to S1P, C1P promotes cell proliferation^[36].

Recently, some studies have shown that the inhibition of sphingolipid metabolism can be a new therapeutic target for HCV infection^[37].

CONCLUSION

All phases of HCV replication cycle are intracellular and consequently require signal transduction to the host cell nucleus to regulate transcription of viral genes. Although the pathogenesis of transmembrane and intracellular signal transduction during HCV infection is still unclear, it has been shown that HCV could influence activity of the second signal messengers. This mechanism can regulate specific cell mechanisms such as hepatocytes proliferation, growth, differentiation, adhesion, apoptosis, and synthesis and degradation of the extracellular matrix, leading to severe complications of chronic HCV infection such as liver cirrhosis or hepatocellular cancer. For instance HCV, through the NS5A protein, inhibits the TGF- β , signal transduction pathway activity and through the core protein C and, to a lesser degree, the NS4B protein, influences production of proinflammatory cytokines such as TNF- α . Accordingly, it seems that the inhibition of the activity of the intracellular messengers and pathways could be a new therapeutic target for chronic hepatitis C treatment, leading not only to overall HCV elimination from hepatocytes and from other extrahepatic components, but also to decrease the possibility of developing chronic hepatitis C complications. Moreover, the discovery of the role of the JAK signal transduction pathway as the principal signaling pathway for IFN- α opens new research options for a better understanding of IFN- α resistance. HCV structural proteins C and E2 and non-structural protein NS5A have been shown to

reduce the number of membrane receptors IFNAR1 and IFNAR2c blocking STAT1-3 activation by IFN- α . As a result, viral replication, as well as inflammation and fibrosis in the liver, are augmented and has a negative effect on IFN- α treatment response among patients with severe liver damage. Therefore, a better understanding of these signaling defects might lead to new therapeutic strategies, making IFN- α therapy more effective in a larger percentage of patients with chronic hepatitis C infection.

REFERENCES

- 1 Choo QL, Kuo G, Weiner AJ, Overby LR, Bradley DW, Houghton M. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science* 1989; **244**: 359-362
- 2 Lindenbach BD, Rice CM. Flaviviridae: the viruses and their replication. In: Knipe DM, Howley PM, eds. *Fields Virology*. 4th edition, volume 1. Philadelphia: Lippincott-Raven Publishers, 2001: 991-1041
- 3 Czepiel J, Biesiada G, Mach T. Viral hepatitis C. *Pol Arch Med Wewn* 2008; **118**: 734-740
- 4 Shuai K. Regulation of cytokine signaling pathways by PIAS proteins. *Cell Res* 2006; **16**: 196-202
- 5 Krebs DL, Hilton DJ. SOCS: physiological suppressors of cytokine signaling. *J Cell Sci* 2000; **113**: 2813-2819
- 6 Heim MH. Intracellular signalling and antiviral effects of interferons. *Dig Liver Dis* 2000; **32**: 257-263
- 7 Gao B. Cytokines, STATs and liver disease. *Cell Mol Immunol* 2005; **2**: 92-100
- 8 Zhu H, Shang X, Terada N, Liu C. STAT3 induces anti-hepatitis C viral activity in liver cells. *Biochem Biophys Res Commun* 2004; **324**: 518-528
- 9 Li W, Liang X, Kellendonk C, Poli V, Taub R. STAT3 contributes to the mitogenic response of hepatocytes during liver regeneration. *J Biol Chem* 2002; **277**: 28411-28417
- 10 Larrea E, Aldabe R, Molano E, Fernandez-Rodriguez CM, Ametzazurra A, Civeira MP, Prieto J. Altered expression and activation of signal transducers and activators of transcription (STATs) in hepatitis C virus infection: in vivo and in vitro studies. *Gut* 2006; **55**: 1188-1196
- 11 Sun R, Gao B. Negative regulation of liver regeneration by innate immunity (natural killer cells/interferon-gamma). *Gastroenterology* 2004; **127**: 1525-1539
- 12 Wurster AL, Tanaka T, Grusby MJ. The biology of Stat4 and Stat6. *Oncogene* 2000; **19**: 2577-2584
- 13 Tournier C, Dong C, Turner TK, Jones SN, Flavell RA, Davis RJ. MKK7 is an essential component of the JNK signal transduction pathway activated by proinflammatory cytokines. *Genes Dev* 2001; **15**: 1419-1426
- 14 Diehl AM, Yin M, Fleckenstein J, Yang SQ, Lin HZ, Brenner DA, Westwick J, Bagby G, Nelson S. Tumor necrosis factor- α induces c-jun during the regenerative response to liver injury. *Am J Physiol* 1994; **267**: G552-G561
- 15 Flisiak R, Pytel-Krolczuk B, Prokopowicz D. Circulating transforming growth factor beta(1) as an indicator of hepatic function impairment in liver cirrhosis. *Cytokine* 2000; **12**: 677-681
- 16 Flisiak R, Jaroszewicz J, Lapinski TW, Flisiak I, Prokopowicz D. Effect of pegylated interferon alpha 2b plus ribavirin treatment on plasma transforming growth factor-beta1, metalloproteinase-1, and tissue metalloproteinase inhibitor-1 in patients with chronic hepatitis C. *World J Gastroenterol* 2005; **11**: 6833-6838
- 17 Schuster N, Kriegelstein K. Mechanisms of TGF-beta-mediated apoptosis. *Cell Tissue Res* 2002; **307**: 1-14
- 18 Herrera B, Alvarez AM, Beltrán J, Valdés F, Fabregat I, Fernández M. Resistance to TGF-beta-induced apoptosis in regenerating hepatocytes. *J Cell Physiol* 2004; **201**: 385-392
- 19 Choi SH, Hwang SB. Modulation of the transforming growth factor-beta signal transduction pathway by hepatitis C virus nonstructural 5A protein. *J Biol Chem* 2006; **281**: 7468-7478
- 20 Yoon JH, Gores GJ. Death receptor-mediated apoptosis and the liver. *J Hepatol* 2002; **37**: 400-410
- 21 Wajant H, Scheurich P. Tumor necrosis factor receptor-associated factor (TRAF) 2 and its role in TNF signaling. *Int J Biochem Cell Biol* 2001; **33**: 19-32
- 22 Beg AA, Finco TS, Nantermet PV, Baldwin AS Jr. Tumor necrosis factor and interleukin-1 lead to phosphorylation and loss of I kappa B alpha: a mechanism for NF-kappa B activation. *Mol Cell Biol* 1993; **13**: 3301-3310
- 23 Kato N, Yoshida H, Ono-Nita SK, Kato J, Goto T, Otsuka M, Lan K, Matsushima K, Shiratori Y, Omata M. Activation of intracellular signaling by hepatitis B and C viruses: C-viral core is the most potent signal inducer. *Hepatology* 2000; **32**: 405-412
- 24 Chung KC, Kim SM, Rhang S, Lau LF, Gomes I, Ahn YS. Expression of immediate early gene pip92 during anisomycin-induced cell death is mediated by the JNK- and p38-dependent activation of Elk1. *Eur J Biochem* 2000; **267**: 4676-4684
- 25 Okazaki T, Bell RM, Hannun YA. Sphingomyelin turnover induced by vitamin D3 in HL-60 cells. Role in cell differentiation. *J Biol Chem* 1989; **264**: 19076-19080
- 26 Gulbins E, Li PL. Physiological and pathophysiological aspects of ceramide. *Am J Physiol Regul Integr Comp Physiol* 2006; **290**: R11-R26
- 27 Llacuna L, Mari M, Garcia-Ruiz C, Fernandez-Checa JC, Morales A. Critical role of acidic sphingomyelinase in murine hepatic ischemia-reperfusion injury. *Hepatology* 2006; **44**: 561-572
- 28 Hearps AC, Burrows J, Connor CE, Woods GM, Lowenthal RM, Ragg SJ. Mitochondrial cytochrome c release precedes transmembrane depolarisation and caspase-3 activation during ceramide-induced apoptosis of Jurkat T cells. *Apoptosis* 2002; **7**: 387-394
- 29 Osawa Y, Uchinami H, Bielawski J, Schwabe RF, Hannun YA, Brenner DA. Roles for C16-ceramide and sphingosine 1-phosphate in regulating hepatocyte apoptosis in response to tumor necrosis factor-alpha. *J Biol Chem* 2005; **280**: 27879-27887
- 30 Bollinger CR, Teichgräber V, Gulbins E. Ceramide-enriched membrane domains. *Biochim Biophys Acta* 2005; **1746**: 284-294
- 31 Boya P, González-Polo RA, Casares N, Perfettini JL, Dessen P, Larochette N, Métivier D, Meley D, Souquere S, Yoshimori T, Pierron G, Codogno P, Kroemer G. Inhibition of macroautophagy triggers apoptosis. *Mol Cell Biol* 2005; **25**: 1025-1040
- 32 Chang HC, Hsu C, Hsu HK, Yang RC. Functional role of caspases in sphingosine-induced apoptosis in human hepatoma cells. *IUBMB Life* 2003; **55**: 403-407
- 33 Chang HC, Tsai LH, Chuang LY, Hung WC. Role of AKT kinase in sphingosine-induced apoptosis in human hepatoma cells. *J Cell Physiol* 2001; **188**: 188-193
- 34 Musashi M, Ota S, Shiroshta N. The role of protein kinase C isoforms in cell proliferation and apoptosis. *Int J Hematol* 2000; **72**: 12-19
- 35 Davaille J, Li L, Mallat A, Lotersztajn S. Sphingosine 1-phosphate triggers both apoptotic and survival signals for human hepatic myofibroblasts. *J Biol Chem* 2002; **277**: 37323-37330
- 36 Gómez-Muñoz A. Ceramide 1-phosphate/ceramide, a switch between life and death. *Biochim Biophys Acta* 2006; **1758**: 2049-2056
- 37 Sakamoto H, Okamoto K, Aoki M, Kato H, Katsume A, Ohta A, Tsukuda T, Shimma N, Aoki Y, Arisawa M, Kohara M, Sudoh M. Host sphingolipid biosynthesis as a target for hepatitis C virus therapy. *Nat Chem Biol* 2005; **1**: 333-337