Tinjauan pustaka

ADIPONECTIN ACTIVITY IN ACUTE VIRAL HEPATTOBI

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SUMMARY

The mechanisms of hepatocellular necrosis in acute viral hepatitis, primarily through cytopathic immune mechanisms, however the processes of hepatic parenchyma necrosis also might be secondarily involved the roles of cytopathic non-immune mechanisms. Once of the defend mechanisms to the hepatic viral infection is through the releases of adiponectin. Adiponectin is a hormone secreted by adipocytes. The protective effect of adiponectin against liver injury likely involve multiple mechanisms, especially to the ability effects of adiponectin as a anti-inflammatory cytokines. Thus, decreased of the adiponectin concentration <10 mg/dl in the acute viral hepatitis, especially Hepatitis B and C perhaps as the early biomarkers of possibility progression to the chronic hepatitis.

Keywords: adiponectin, acute viral hepatitis.

INTRODUCTION

Adiponectin is a hormone secreted by adipocytes, can reduced blood glucose, decreased fatty acid and increased insulin sensitivity. Adiponectin, an adipokine with potent anti-inflammatory properties, is thought to play an important role in the regulation of inflammation.[1] Protective effect of adiponectin in against liver injury ukely involve multiple mechanisms including changes m fatty acid homeostasis. An anti-inflammatory effect of adiponectin through decreased TNF alpha expression, elsewhere anti fibrogenic effect mediated by inhibition | wp«ic stellate ceils activation and fibrogenic cytokine secretion.[2]

Acute viral hepatitis signed by acute inflammation and hepatocellular necrosis, is given to the mobilization of the innate immune system in response to signals of "danger". It is initiated by release chemicals messengers from activated cells include chemokines and cytokines.[3] In acute viral hepatitis, stellata cells (fat-storing cells, lipocyte) undergo an activation which represents a cascade of cellular events. The initiation of activation result from paracrine mediators from Sinusoidal endothelial cell/SEC Kupffer cells/KC and perpetuation of activation leads to several activation-dependent functional change. Hepatic stetosis can induce progression to chronic hepatitis, in hepatitis C infection and hepatitis B infection. The risk of chronicity after hepatitis virus infection will likely be conferred in part by environmental element and combined inheritance of multiple risk factors.[4]

Inflammatory and fibrogenic mechanism is linkage to disequilibrium of pro-inflammatory cytokine (tumor necrosis factor/TNF- alpha) and anti-inflammatory cytokine (interleukin/ IL-10). Thus antiinflammatory and anti-fibrotic effect not only caused by IL-10, IL-4 but also caused by adiponectin.[5] The role and mechanism of adiponectin in acute hepatitis is not well known. Adiponectin might be effect on cellular activation cascade, or perhaps as a specific biomarker inflammation in acute viral hepatitis through non-immune mechanism.

PATHOGENESIS MECHANISM OF HEPATITIS B VIRUS INFECTION

The annual mortality from hepatitis B infection and it is sequelae is 1-2 million people worldwide. But the precise pathogenetic mechanisms responsible for various forms of associated liver diseases are poorly defined. Most study indicate that the host immune response to the virus has a critical role in the pathogenesis.[6]

Cytophatic immune mechanism

The precise role of the unspecific innate immune response is not well understood. But well accepted that natural killer cells (NK cells) are importance in defense and clear virus. NK cells are the first cellular responded following viral infection. Whether and how NK cells play an important role during HB V infection remain elu-sive. The alteration of intrahepatic NK cells during chronic infection is not well understood. NK cells display at least two effector functions that contribute to infection control: they can directly kill infected cells by cell-cell contact; and they produce inflammatory cytokines with antiviral activity.[6]

Hepadna viruses are generally agreed to be noncytopathic. If the viral replication cycle is not itself injurious to hepatocyte, how does clinical and pathological changes. Early immune responses to infected hepatocytes, is a response normally designed for clearance infection. But not all of that can resolved and explained.[7] Cellular immune response to antigenic viral peptides are the initiating event in pathogenesis of viral related liver injury, and involve activation of CTL resuiting in the apoptotic death of hepatocyte. Excessive immune response may depend on the sensitivity of hepatocyte to the cytopathic effect of cytokine (TNF-alpha) resulting massive hepatic necrosis through the cellular cooperation ofT lymphocytes, macrophages and or neutrophil. Hepatic macrophages and Kupffer cells have been previously shown to responsible for IL-18 production in response to antigen and metabolic stimulation. In acute viral hepatitis, macrophages are activated by infected virus or CTL as well as by other factors such as adiponectin, endotoxin generated during liver inflammation. IL-10 plays amore important role in the inhibition of liver injury. Activated Th 1 cells induce Th2 cells that produce anti-inflammatory cytokines (IL-10), mac-rophages-derived chemokine (MDC).[8]

Cytopathic non-immune mechanism

The roles of CTL in liver injury may once of mechanism. In fact, large fields of viable hepatocytes surrounding isolated CTL infiltrates could be shown to have lost HBc Ag and viral DNA. This suggested that paracrine, noncytopathic mechanisms might be operating to much effect of viral clearance. It is now thought that cytokines as TNF-alpha, INF-gamma which released from CTL after contact with their targets, are major effectors of antiviral response. The molecular basis of this response is now under active study. Intrahepatic cytokine release is in fact an important determinant ofHBV clear-ance, and that is known others stimuli should produced similar result. Replication of virus in hepatic macrophage dramatically suppressed HBV replication in hepatocyte.

Does this form of noncytocidal antiviral mechanism operate during normal virus clearance? Significant decrement virus production was achieved in the period before histologic evidence of massive cellular infiltra-1 tion or hepatocyte destruction. Local production of TNF-alpha is demonstrable during this interval, although the | source of these cytokine is not yet clear-There are evidence indicates that innate immune system, possibly derived from natural killer T-cell in the liver, may be important sources of cytokine early in the infectious process, before the development of adaptive CTL response. However the basis of absence HBV-specific CTL

from chronic carriers is not understood.[7] Many study suggested that acute hepatic tissue injury result in activation of hepatic stellate cells and leads to increased ECM degradation thus enabling the recruitment of inflammatory blood cells or migration of resident liver cells. Anti inflammatory cytokine (IL-10, TGF-betha) responsible for down regulation ofthe MMP, and IL-10 inhibits the synthesis of proinflammatory cytokines by activated monocyte.

During acute liver injury followed by complete resolution, TNF-alpha and TGF-betha are expressed in distinct and different time points. TN F-alpha expression is induced early, whereas TGF-betha expression is up regulated later. TGF-betha acts as a negative feedback mechanism either directly by suppressing an initial TNF-alpha mediated MMP induction or indirectly through induction of TIMP production. The net effect would be the termination of ECM degradation and inflammatory process.[9] Transcription and replication of hepatitis B infection (HBV) were dependent on nuclear hormone receeotor PPAR-alpha (peroxisome proliferator-activated receptor-alpha).[10]

CLINICAL MANIFESTATION OF HEPATITIS B INFECTION

The clinical observation that HBV carrier can be asymptomatic and have minimal liver injury, despite extensive and ongoing intrahepatic replication of the virus clearly indicates that the HBV replication cycle not directly cytotoxic to the hepatocyte.The immune response against virus-infected cells is deemed responsible for there destruction, even though this immune response has not been completely clarified.

In acutely infected patients who successfully control the virus, the immune attack is mainly executed by CTL.The observation that the number of hepatocytes killed by direct engagement between CTL and their targets is very small and unable to account for extensive liver

damage. The recruitment of antigen-non specific inflammatory cells appears to play a pivotal role in the liver injury through the release of cytokines, free radicals and proteses.[11]

After acute hepatitis B virus (HBV>infection about 10 % of all adult patients become chronically infected. The mechanism of viral persistence in this minority of patients remains unclear. In patients with an acute self-limiting HBV infection a vigorous T-lymphocyte response to the core antigen and weaker response to surface antigen. It is suggested that the pro-duction of pro-inflammatory cytokine is mainly instrumental in inducing viral clearance.[12] Recent study reported that a high prevalence of hepatic steatosis (40.1 %) was seen in patients with chronic hepatitis B infection as well.[13]

LIVER INJURY AND PROTECTIVE EFFECT OF ADIPONECTIN

Adiponectin or Acrp30 is adipose tissue specific protein, has attracted considerable attention as a hormone secreted by adipocytes that can regulate glucose level In vitro study showed that visceral adipocytes secreted adiponectin more actively than subcutaneous adipocytes. On the other hand, the metabolism of adiponectin is still unknown.[1]

Lliver injury is a complex process involving both parenchyma and non-parenchymal cells resident in the liver, as well as the recruitment of other cells types to the liver in response to damage and inflammation. The progression of liver injury is marked by the appearance of a fatty liver and inflammation.
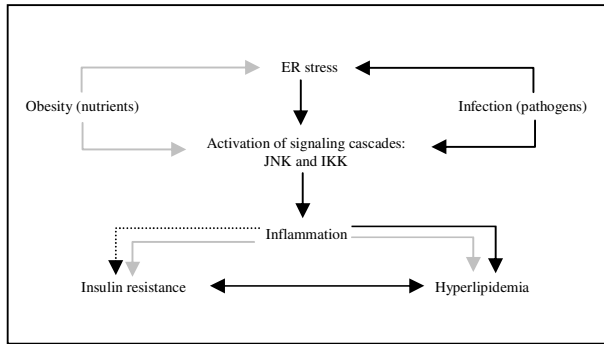
Fig.l. Nutrient and pathogen sensing or response systems have important overlapping features, and their modulation by obesity or infection can lead to overlapping physiological outcomes. Infection typically leads to a more transient and robust inflammatory response and short-term hyperlipidemia that aids in the resolution of the infection

The inflammatory response in the liver is mediated by activation of Kupffer cells and recruitment of neutrophils to the liver. Activation of the Kupffer cells increases production of inflammatory mediators, mediated by lipopolyssacharide (LPS). In particular, TNF-alpha production has been shown to be critical in the development of liver injury and hepatic fibrogenesis. Decreased circulating adiponectin concentration related to a number of disease condition including inflammation, diabetes mellitus, atherosclerosis and non-alcoholic liver injury. Adiponectin protects mice from liver injury induced by LPS. The protective effect of adiponectin against liver injury likely involve multiple mechanisms including fatty acid homeostasis, anti inflammatory effect through decreased TNF-alpha expression, as well as antitlbrogenic effect cemediated by inhibition of hepatic stellate cells activation and fibrogenic cytokine secretion.

Adiponectin has been shown to regulate the function of various cells and tissues including liver, muscle, and macrophages. The molecular mechanisms of adiponectin-mediated biological response to protective role of adiponectin hi liver injury are not clearly understood. It is clear that

future research into both impact of adiponectin on lipid homeostasis in liver, as well as anti-inflammatory effect on Kupffer cells.[2]

Adiponectin exerts anti-inflammatory effects at several level, which might be of importance in health and disease to counteract proinflammatory cytokines such as TNF-alpha. Liver might be as additional source of adiponectin. Concanavalin A-induced liver failure resulted in increased production of adiponectin by the liver and cells specific analysis revealed that most likely primary hepatic sinusoidal endothelial cells contributed to it is synthesis. And protective effects of adiponectin is mediated mainly via induction of IL-10. Adiponectin play arole of suppressing inflammation and macrophage activity and reduced its synthesis, might lead im-balance in favor of proinflammatory mediators.

Adiponectin inhibits proliferation and migration as well as expression of TGF-bethal, the main activator of extracellular matrix protein synthesis. Adiponectin also protects endotoxin-induced liver injury, these effects were accompanied by decreased level of TNF-alpha both systemically and locally in the liver. Adiponectin synthesis is correlative negatively with proinflammatory cytokine production such as TNF-alpaha. Adiponectin expression also regulated by other inflammatory mediators. Dexamethasone and 1L-6 can suppress adiponectin mRNA expression.[14]
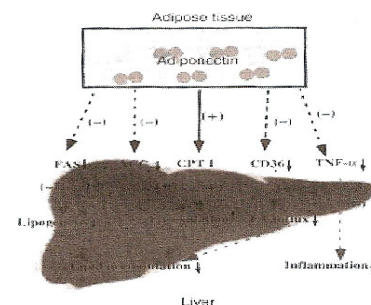

Fig.2. Schematic representation of the potential mechanisms that underlie the hepatoprotective actions of adiponectin

Among the various adipocytokines, adiponectin which is synthesized in adipose tissue, it has anti-inflammatory properties that include suppression of macrophage phagocytosis and TNF-alpha secretion and blockage of monocyte adhesion to endothelial cells in vitro.[15] Lipopolysacharide (LPS) activates Kupffer cells to secrete TNF-alpha, which important role ia liver injury. Otherwise IL-10, secreted by Kupffer cells in the liver after LPS stimulation, has a strong anti-inflammatory effects in the liver, and prevent liver fibrosis. Adiponectin inhibits the human phagocytosis of macrophage and TNF-alpha release, and induces IL-10 gene expression in human macrophage.[5]

The mechanisms by which adiponectin inhibits the fibrotic response remains to be fully elucitade. Adiponectin inhibited the proliferation and migration ofhepatic stellate cells. It is also decreased TGF-bethal gene expression. TGF-betha 1 is a major pro-fibrotic cytokine that has been implicated in the progression of fibrogenesis.[16]Adiponectin is an adipokine that exert a potent insulin-sensitizing effect by binding to its receptors such as AdipoR-1 and Adipo-R2 and leading to activation of PPAR-alpha.[17] Adipoinectin as a biomarker for PPAR-gamma activation.18

Once study assessing the role of chemokine re-ceptors2 (CCR2) in macrophage recruitment to adipose tissue, they show that CCR2 deficiency attenuated adipose tissue macrophage (ATM) accumulation and adipose tissue inflammation. Although role of ATM finding in number of studies, but its still not clear weather ATM related to insulin insistence. It reminds possible as a marker rather than a cause. Secretion of soluble factors by macrophage that act locally (paracrine effect) and systemically (endocrine effect) caused adipose tissue release same agent. Interaction of macrophage with adipose tissue is still not clear. Do the signals come from macrophage or adipose tissue or endothelial cells?

Other study have indicated that local tissue microhypoxia might play a role in chemotaxis and retention of macrophages in expanding adipose tissue depots. Adipogenesis and angiogenesis are tightly linked (hiring fat mass development.[19]

Adiponectin in hepatitis C infection

A new role has emerged for the adipose tissue as an endocrine organ. Plasma level of adiponectin inversely associated with steatosis and fibrosis in HCV infection, that suggest hypoadeponectinemia might contribute progression of fibrosis. Observation finding that elevated circulating TNFR in HCV infection significantly correlated with liver injury, another surprising result of study is the lack of a correlation of adiponectin and BM1 or insulin concentration in patients with HCV infection.[20]

The mechanisms of underlying steatosis during HCV infection are complex and multi factorial. Pathogenesis of steatosis in patients with hepatitis virus C (HCV) infection is not well understood. HCV genotype 3a has been linked to steatosis more strongly then other genotypes. Moreover, HCV related steatosis is not always viral related, and other factors may coexist. Two receptors of adiponectin has been cloned. Adiponectin receptor 1 is more abundantly expressed in skeletal muscle, whereas adiponectin receptor 2 is predominantly expressed in the liver. Surprising studies shown the lack a correlation between adiponectin with BMI or insulin concentration in patients HCV infection. The capacity of HCV to induce steatosis directly through interference with lipid metabolism may teleologically represent a mechanism favoring the entry of HCV into hepatocytes with a subsequent increase in viral replication. A growing body of evidence supports the view that steatosis plays a role in the progression of HCV to fibrosis providing the substrate or "first hit" for HCV-related oxidative stress and cytokine release the – "second hits" - to induce necroinflammatton, apoptosis, and fibrosis.[21]

Adiponectin and hepatitis A virus infection

Although the primary site of replication for HAV is the hepatocyte, the factors that determines this tissue tropism has not been elucidated. Any studies was performed, according host-cell receptor, glycoprotein, coproantibodies, immune complex, which is simply not understood Intrahepatic site of HAV replication has been difficult to demonstrate, but in experimental infection, HAV viral antigen have been observed in many glands, as likes tonsil, saliva, spleen, kidney and other glands. Detection of HAV in the glands shortly before appearance of virus in the blood, suggest that an early replicative event could occur in the glands.

There is little evidence that HAV is direct cytotoxic to hepatocyte, these findings suggest that virus induced cytopathology may not be responsible for the pathologic changes seen in HAV infection and liver disease may result primary from immune mechanisms. In vitro studies have shown evidence of cytolisis or hepatocellular necrosis and viral clearance by natural killer ceils (NKC), human leukocyte antigen (HLA), and cytotoxic T cells.[22]

Viral replication occur mainly within the hepato-cytes. though some evidence suggest that HAV may also replicate in the intestine. Acute event is followed by sustained immunity to the virus, capable of preventing reinfection.[11] In clinical studies, has been founded that high level of adiponectin in acute HAV infection, and suggested that adiponectin as once of defend mechanism through antiinflammatory effects, might be prevent to the fibrogenesis processes and chronic hepatitis.

Adiponectin in non-alcoholic steatohepatitis

Adiponectin appear blocks TNF-alpha release, and also have hepatic protective properties as well as shown delicate balance between proinflammatory cytokines (TNF-alpha and anti-inflammatory cytokine (adiponectin).Very low levels of adiponectein (<10 meg/ ml) were strongly association with fibrosis in NASH.[23]

LINKED OF ADIPONECTIN METABOLISM AND IMMUNITY

Metabolism and immunity are closely linked. The immune response, integration between macrophages and adipocytes makes sense, given that both cells type participate in the innate immune response : macrophage in their role as immune cells by killing pathogens and secreting inflammatory cytokines and chemokines while adipocytes by releasing lipids mediators, like hormone that may modulate the inflammatory state or participate to neutralization of pathogens. While is not yet known whether macrophages are drawn to adipose tissue in other inflammatory conditions, may macrophage accumulation in adipose tissue. Integration of metabolic and immune response in adipocytes and macrophages through shere mechanisms. In normal condition adipocyte regulate metabolic homeostasis, and macrophages function in inflammatory response. In other condition such as viral infection, adipocytes and macrophages share common features such as expression of cytokines, nuclear hormone receptors (PPAR-gamma, Liver X receptor)ₜfetty acid-binding proteins(FABP) and many others factors. In fection typically leads to a more transient and robust inflammatory response and short term hyper! ipidemia that aids in resolution of infection.

Overlapping metabolic and inflammatory signaling and sensing pathways in adipocyte and macrophages. Inflammatory pathways can be initiate by extracellular mediators such as cytokines and lipids mediators or by intracellular stresses such as ER stress (endoplasmic reticular stress) or excess of ROS (reactive oxygen species) production by mithochondria. Signals from all of these mediators converge on inflammatory signaling pathways, including the kinases JNK and IKK. These pathways lead the production of

additional inflammatory mediators through transcriptional regulation as well as to the direct inhibition of insulin signaling. Opposing inflammatory pathway are transcription factors from PPAR-alpha and LXR families, which promote nutrient transport and metabolism and antagonize inflammatory activity. More proximal regulation by FABP, which likely sequester ligands of these transcription factors, thus promoting a more inflammatory environment. The absence of FAB is anti-inflammatory, These cell must strike of balance between metabolism and inflammation.
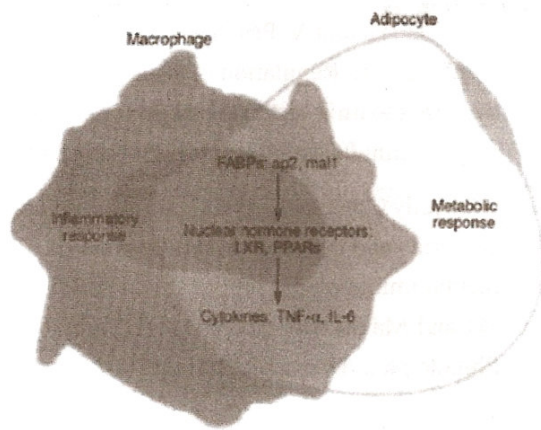

Fig3. Integration of metabolic and immune responses in adipocytes and macrophages through shared mechanisms. Under normal conditions, adipocytes store lipids and regulate metabolic homeostasis, and macrophages function in the inflammatory response, although each cell type has the capacity to perform both functions. PPAR© and LXR pathways oppose inflammation and promote cholesterol efflux from macrophages and lipid storage in adipocytes.

About one-third of patients with chronic hepatitis C develop type 2 diabetes mellitus. Stresses of infection can activated intracellular stress pathway such as JNK. and IKK-NFkB pathway. During viral infection, stress pathways activated by an excess of viral protein «the ER.

Some pathogen activate host intracellular signaling cascades, including P13K-Akt pathways, which is also critical for insulin signaling and inflammation. On the other hand, perhaps the inflammatory response is not simply an undesirable by product, but rather homeostatic mechanisms to prevent the organism reaching a point at which excess fat accumulation. Inflammation stimulates catabolism, including lipolysis from adipocytes.[24]
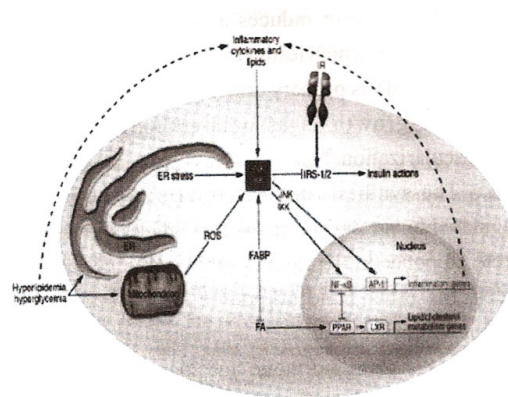

Fig.4. Model of overlapping metabolic and inflammatory signaling and sensing pathways in adipocytes or macrophages. Inflammatory pathways can be initiated by extracellular mediators such as cytokines and lipids or by intracellular stresses such as ER stress or excess ROS production by mitochondria. Signals from all of these mediators converge on inflammatory signaling pathways, including the kinases JNK and IKK. Opposing the inflammatory pathways are transcription factors from the PPAR and LXR families

Adiponectin is highly expressed in adipose tissue, and is the one non-cytokines fat derived peptides (FDP) that is protective from inflammation. Although many ofthese FDP have a role in metabolic homeostatis, many seen to lack distinct role in inflammatory pathogenesis. Some level of cytokine are increased because of hyperplastic characteristic of adipose tissue and their levels is better serve as a marker ofadipose

tissue hypertrophy.[25]

The adipose tissue produces several growth factors/hormone including leptin, TNF-alpha and adiponectin. Unique function of adiponectin as negative regulators for angiogenesis by inhibits endothelial cells proliferation and migfation,and prevent new blood vessel. Adiponectin induces a cascade activation of caspase-8,-9,-3, which leads cells death, adiponectin significantly inhibits primary tumor growth and decreased of tumor growth is associated with decreased neovascularization.[26]

The synthesis and secretion of adiponectin is regulated by several mechanisms Small adipocyte secrete adiponectin. leptin and other hormone like peptides, the other hand adipocyte hypertrophs (large adipocyte) cause decreased in production secretion of insulin sensitizing hormone and increases 11 resistant hormone. TNF-alpha produce by white adipose tissue suppresses adiponectin production. Inverse adiponectin inhibits endothelial cells production of adhesion molecules and negatively regulates TNF-alpha production in macrophage monocyte.[27]

CONCLUSION

The mechanisms of hepatocellular necrosis in acute viral hepatitis, primarily through cytopathic immune mechanisms, however the processes of hepatic parenchyma necrosis also might be secondarily involved the roles of cytopathic non-immune mechanisms. Once of the defend mechanisms to the hepatic viral infection is through the releases of adiponectin, which exert the one of adipocytokines produced by adipocyte, especially to the ability effects of adiponectin as a antiinflammatory cytokines. Thus, decreased of the adiponectin concentration < 10 mg/dl in the acute viral hepatitis, especially Hepatitis B and C perhaps as the early biomarkers of possibility progression to the chronic hepatitis.

REFERENCES

1. Sohara N, Takagi H, Kakizaki S, Sato K and Mori M. Elevated plasma adiponectin concentrations in patients with liver cirrhosis correlate w κ plasma insulin levels. Liver International 2005;25;28-32.

2. Park PH, Thakur V, Pritchard M, Mcmullen Ml and Nagy LE. Regulation of kupffer cell activM during chronic ethanol exposure: Role adiponectin. J Gastro Hepatol 2006;21 :S30-S37

3. O'farrelly C and Doherty DG. Basic immunological terms and concepts: a short primer of fundamental immunology. In: Gershwin ME, Vieiiing JM and Manns MP, editors. Liver immunology, Philadelphia: Hanley & Belfiis; 2002.p.1-14.

4. Meyer KH. General aspects of molecular biology and immunology for the treatment of intractable liver diseases. In: Tsuji, Higashi T, Zeniya M and Meyer KH, editors. Molecular biology and immunology in hepatology. Tokyo: Elsevier Science; 2002.p.3-21.

5. Matsumoto H, Tamura S, Kamada Y, Kiso S, Fukushima J, Wada A, Maeda N, Kihara S, Funahashi T. Matsuzawa Y, Shimomura I, Hayashi N. Adiponectin deficiency exacerbates lipopolysaccharide/D-galactosamine-induced liver injury in mice. World J Gastroenterol 2006;12:3352-8.

6. Chen Y, Wei H, Gao B,HuZ, Zheng S, and Tian Z. Activation and function of hepatic NK cells in hepatitis B infection: an underinvestigated innate immune response. J Viral Hepat 2005; 12:38-45.

7. Ganem DE and Schneider RJ. Hepadnaviridae: the viruses and their replication. In: Hollinger FB, Purcell RH, Gerin JL, Ganem DE and Feinstone SM,

editors. Viral hepatitis. Philadelphia: Lippincott Williams & Wilkins; 2002. p.55-102.

8. Yumoto E, Higashi T, Nouso K, Nakatsukasa II Fujiwara K, Hanaftisa T, Yumoto Y, Tanimoto t Kurimoto M, Tanaka N and Tsuji T. Serum gamma-interferon-inducing factor (IL-18) and IL-10 levels in patients with acute hepatitis and fulminant hepatic failure. J Gastro Hepatol 2002;17:285-94.

9. Koulentaki M, Valatas V, Xidakis K, Kouroumalis A, Petinaki E, Castanas E and Kouroumalis E. Matrix metalloproteinases and their inhibitors in acute viral hepatitis. J Viral Hepat 2002^:189-93.

10. Guidotti LG, Eggers CM, Raney A, Chi SY. In vivo regulation ofhepatitis B virus replication by peroxisome proliferators. J of Virology 1999;50:10377-86.

11. Vergani D and Vergani GM. Viral hepatitis: virus/host interaction. J Hepatol 2004;19:S307-S310.

12. Van nunen AB. Pontesilli O, Uytdehaag F, Osterhaus ADME and De man RA. Suppression ofhepatitis A-induced cytokine production. Liver 2001;21:45-9.

13. Hu KQ, Kyulo NL, Esrailian E, Thompson K, Chase R, Hillebrand DJ and Runyon BA. Overweight and obesity, hepatic steatosis, and progression of chronic hepatitis C: a retrospective study on a large cohort of patients in the united states. J Hepatol 2004;40:147-54.

14. Tilg H and Hotamsligil OS. Nonalcoholic fatty liver disease: cytokine-adiponectin interplay and regulation of insulin resistance. Gastroenterology 2006;131:934-45.

15. Chandran M, Phillips SA, Ciaraldi T, and Henry RR. Adiponectin: more than just another fat cell hormone? Diabetic Care 2003;26:2442-50.

16. Sanyal AJ. Insulin resistance and tissue repair: a "foto-logical" phenomenon. Gastroenterology 2001;125:1886-8.

17. Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, and Tobe K. Adiponectin andadiponectin receptors in insulin resistance, diabetes, and the metabolic syndrome. J Clin Invest 2006;1156:1784-92.

18. Yang B, Brown KK, Chen L, Carrick KM, Clifton LG, McNulty J A, Winegar DA, Strum JC. Serum adiponectin as a biomarker for in vivo PPARgamma activation and PPARgamma agonist-induced efficacy on insulin sensitization/ lipid lowering in rats. BMC Pharmacology 2004;4:23-32.

19. Neels JG and Olefsky JM. Inflamed fat: what starts the fire? J Clm Invest 2006;116:33-5.

20. Petit JM, Minello A, Joeste V, Bour JB, Galland F, Duvillard L, Verges B, Olsson NO, GambertP, and Hillon P. Decreased plasma adiponectin concentration are closely related to steatosis in hepatitis C virus-infected patients. J Clin Endocrinol Metab 2006;90:2240-3.

21. Lonardo A, Adinolfi LE, Loria P, Carulli N. Ruggiero G, and Day CP. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. Gastroenterology 2004;126:586-97.

22. Hollinger FB and Emerson SU. Hepatitis A virus. In: Hollinger FB, PureeII RH, Gerin JL. Ganem DE and Feinstone SM, editors. Viral Hepatitis. Philadelphia: Lippincott Williams & Wilkins; 2002.p. I -42.

23. Kowdeley KV and Pratt DS. Adiponectin-tipping the scales from NAFLD to NASH? Gastroenterology 2005;128:511-3.

24. Welltn KE and Hotamsligil GS. Inflammation, stress and diabetes. J Clin Invest 2005; 115:1111-9.

25. Rudin E and Barzilai *H.* Inflammatory peptides derived from adipose tissue. Immunity & Ageing 2005;2:1-3.

26. Brakenhielm E, Veitonma Id N, Cao R, Kihara S, Matsuzawa Y, Zhivotovsky B, Funahashi T, and Cao Y. Adiponectin-induced antiangiogenesis and antitumor activity involve caspase-mediated endothelial cell apoptosis. PNAS 2004;101:2476-81.

27. Meier U and Gressner AM. Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspect of leptin, ghrelin, adiponectin, and resistk Clinical Chemistry 2004;50:1511 -25.