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Review

Metabolic Aspects of Hepatitis C Viral Infection: Steatohepatitis Resembling but Distinct from NASH

Running Title: Metabolic Aspects of HCV Infection

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Abstract

Although the target of hepatitis C virus (HCV) infection is the liver, it has become progressively more evident that HCV can induce diseases in numerous organs. Recently, much attention has been drawn to metabolic disorders in HCV infection. Initially, hepatic steatosis and disturbance in lipid metabolism have been found characteristic of HCV infection, and afterward a correlation has been noted between HCV infection and diabetes. It is now evident that HCV by itself can induce insulin resistance by way of disturbing the intracellular signaling pathway of insulin by the function of HCV core protein. Insulin resistance, caused by HCV infection, evolves to type 2 diabetes with the addition of high-fat diet and obesity. The fact that HCV infection induces insulin resistance by the virus itself may influence the progression of chronic hepatitis and open up novel therapeutic approaches. When hepatitis C is compared with non-alcoholic steatohepatitis (NASH), there are a number of similarities and several differences. In the metabolic aspects, hepatitis C resembles NASH in numerous features such as the presence of steatosis, serum dyslipidemia, and overproduction of oxidative stress in the liver, warranting hepatitis C is a steatohepatitis. In contrast, there are noticeable differences, between hepatitis C and NASH, that HCV modulates cellular gene expression and intracellular signal transduction including the activation of MAP kinase and transcription factor AP-1 while such details have not been known for NASH. This difference may explain the tremendously higher incidence of HCC development in chronic hepatitis C than that in NASH. HCV infection would need to be viewed not only as a liver disease but also a metabolic disease, which would be a clue to open up a novel way to the molecular understanding of pathogenesis of hepatitis C, as a virus-associated steatohepatitis (VASH).

Key Words: diabetes, hepatitis C virus, insulin resistance, steatohepatitis, hepatocarcinogenesis, lipid metabolism.

Introduction

Approximately 1.8 million people in Japan and 200 million people in the world are chronically infected with hepatitis C virus (HCV). Chronic HCV infection may lead to cirrhosis and hepatocellular carcinoma (HCC), thereby being a worldwide problem both in medical and socio-economical aspects [1]. In addition, chronic HCV infection is a multifaceted disease, which is associated with numerous clinical manifestations, such as type II mixed cryoglobulinemia, porphyria cutanea tarda and membranoproliferative glomerulonephritis [2]. Furthermore, a strong association of HCV infection with Sjögren's syndrome and lichen planus have been noted, which is validated in the animal model (Table 1) [3].

In addition, recently, there has been increasing lines of evidence to indicate metabolic disturbances in HCV infection, which would influence the pathogenesis of chronic hepatitis C. The discovery of HCV in 1989 enabled the comparison between chronic hepatitis C and the other chronic hepatitis, resulting in repeated reports that steatosis is significantly associated with chronic hepatitis C [4, 5]. Steatosis in HCV infection is reproduced in animal models [6] or cultured cells [7], strengthening a pathologic role of HCV in it. Furthermore, patients infected with HCV have abnormalities in serum lipids, such as hypocholesterolemia or abnormal levels of apolipoproteins in serum [8, 9]; they are corrected in sustained virological responders to antiviral treatment [9]. Thus, the association between HCV infection and disturbance in lipid metabolism has become increasingly strong both in patients and experimental systems including animals. Finally, patients with chronic hepatitis C accompanied by severe steatosis develop hepatic fibrosis more rapidly [10]. Thus, abnormal lipid metabolism in HCV infection would be deeply involved in the pathogenesis of hepatitis C.

Diabetes May Also Be a Manifestation of HCV Infection

The next character appearing as a metabolic aspect of HCV infection is type 2 diabetes. In 1994, Allison et al. [11] reported an epidemiological link between diabetes and HCV infection, but in a cirrhotic cohort. There was little impact, however, in view of well-known impaired glucose tolerance in advanced chronic liver disease. Several reports followed along this line from the same group and others. The trend to accept a positive association between diabetes and HCV infection seems to have been triggered by the population-based study in the United States [12], in which a solid association was found between them. The association between diabetes and HCV infection, however, is blemished by factors such as the development of cirrhosis, obesity and ageing common in patients with hepatitis C; they would make it difficult to prove this association as real. Hence there is a need to evaluate the association using experimental systems.

HCV Infection Induces Insulin Resistance In Vivo

We used mice transgenic for the HCV core gene [6, 13] to assess the association between HCV infection and diabetes. These mice carry the core gene of genotype 1b HCV, and express HCV core protein of an expected size in the liver, in levels comparable to those in patients with chronic hepatitis C (Fig. 1). They develop HCC late in life [13]. These transgenic mice were maintained and fed together with their normal littermates, and the glucose metabolism was studied [14]. Although the core gene transgenic mice did not develop overt diabetes, they had markedly elevated serum levels of insulin. Plasma glucose levels were somewhat higher in transgenic mice than their normal littermates control mice with no significant difference between them (Fig. 2B). In contrast, serum insulin levels were significantly higher in transgenic than normal control mice in both fasting and fed conditions (Fig. 2C). Since such a combination of normal glucose levels and hyperinsulinemia points to

the insulin resistance, then, we conducted glucose and insulin resistance. The core gene transgenic mice exhibited glucose levels a little higher than normal littermates without any significant differences between them (Fig. 2D). In insulin resistance tests, glucose levels were significantly higher in transgenic than normal control mice both 40 and 60 min after injection with insulin (Fig. 2E). These results indicate the presence of insulin resistance in the core gene transgenic mice. Since only the HCV core gene had been incorporated into these transgenic mice, the core protein of HCV would be able to induce insulin resistance *in vivo*.

By what mechanism, then, insulin resistance observed in the animal model would arise? The insulin resistance is considered to involve two factors. They are the central and peripheral insulin resistances (Table 2) [15]. The hyperinsulinemic-euglycemic clamp method was employed for differentiating between them. In this method, hepatic glucose production (HGP) is calculated on the basis of amounts of glucose required for keeping plasma glucose levels within a certain range at serum insulin levels higher than physiological ones. In normal control mice, HPG was suppressed by 60% by the administration of insulin, in contrast to core gene transgenic mice, in which there was only marginal suppression of HGP by insulin. These results indicate a hepatic (central) origin of insulin resistance in the transgenic mice. In further confirmation of this, uptake of glucose into the muscle was determined. There was no difference in the uptake in response to administration of insulin between transgenic and normal control mice. The insulin resistance in mice transgenic for the HCV core gene, therefore, is central and hepatic.

The Mechanism Underlying Insulin Resistance in HCV Infection

Next, we evaluated how insulin resistance emerges in the mouse model. For this purpose, liver homogenate was immunoblotted with anti-phosphotyrosine and anti-phosphserine antibodies after insulin receptor substrate (IRS)-1 and IRS-2 had been

immunoprecipitated. Tyrosines in IRS-1 were weakly phosphorylated both in normal and transgenic mice before they received insulin, with no differences between them. After the administration of insulin, however, the phosphorylation of tyrosines in IRS-1 increased in normal but not transgenic mice. Obtained results suggested disturbance in tyrosine phosphorylation as one of the factors for insulin resistance in the liver. There were no differences in phosphorylation of serines in IRS-1 or tyrosines in IRS-2 between transgenic and normal control mice. Overall, they provided experimental evidence for development of insulin resistance by the presence of HCV in the liver that would disturb the transduction of insulin signaling in hepatocytes (Fig. 3). There remains a possibility for the HCV core protein that would directly prohibit phosphorylation of tyrosines. Or else, it might inhibit tyrosine phosphorylation via certain cytokines.

In our extensive searches for the expression of cytokines in the liver of core gene transgenic mice, only TNF-α and IL-1β levels have been found increased [16]. For the purpose of evaluating the role of TNF-α in insulin resistance in transgenic mice, therefore, serum insulin was determined and insulin resistance test performed in them after they had received anti-TNF-α intraperitoneally. Pretreatment with anti-TNF-α partially restored insulin sensitivity in the core gene transgenic mice. Albeit a direct anti-insulin activity of the core protein cannot be excluded, high levels of TNF-α in the liver would be one of the factors for induction of insulin resistance in this mouse model.

Pathogenesis of Insulin Resistance in Hepatitis C Patients

Simultaneously with our report in experimental systems, Aytug et al. investigated insulin signaling in biopsied liver specimens from patients with chronic hepatitis C [17]. Specifically, they evaluated changes in IRS-1, IRS-2 and phosphatidyl-inositol (PI)3-kinase levels in the liver of patients. With insulin stimulation of biopsied liver samples,

insulin-receptor proteins and IRS-1 increased, while phosphorylation of tyrosines in IRS-1 decreased to one half the baseline value along with diminished activity for P13-kinase associated with IRS-1. The results of Aytug et al. [17] coincide with those of ours in analyzing the mechanism of insulin resistance with the experimental system in mice. Both implicate the impaired tyrosine phosphorylation in IRS-1 in the induction of insulin resistance by HCV infection. It struck us as a surprise, in a sense, that the mechanism of insulin resistance induced by HCV infection has been in agreement between clinical samples and experimental animals, in spite of hepatic IRS-2 that was preferred to IRS-1 for a role in development of insulin resistance in former studies [18]. HCV infection would be peculiar in that IRS-1 weighs heavier than IRS-2 in the induction of hepatic insulin resistance. Although our data strongly indicate a hepatic character of insulin resistance in HCV infection, they by no means exclude roles of the other factors in the induction of this resistance. There is little expression of the HCV core gene in muscles of our animal model; it is not known if HCV infects muscular cells in patients with chronic hepatitis C. Factors not intrinsic to the liver would have to be evaluated to sort this out, including dysfunction of mitochondria for induction of insulin resistance [19].

Insulin Resistance as a Risk Factor for Progression of Hepatic Fibrosis

Insulin resistance in HCV infection may have an additional significant clinical implication. In 260 patients with chronic hepatitis C, Hui et al. [20] have tried to establish the relationship between liver histology and indicators of glucose metabolism as well as insulin resistance represented by homeostasis model assessment of insulin resistance (HOMA-IR). They have found that insulin resistance already exists in hepatitis C patients with stage 0 or 1 fibrosis in the liver. This indicates that insulin resistance in HCV infection is not attributable to advanced liver disease. HOMA-IR was a significant and independent predictor for the stage

and velocity of hepatic fibrosis. The results of their study are important, because they implicate a role of hyperinsulinemia, and insulin resistance by inference, in promoting the progression of hepatic fibrosis. Insulin has been proven for an aggravating factor not only in atherosclerosis but also systemic inflammation and fibrosis. The liver would not be an exception in this respect.

Similarities and Differences between Hepatitis C and NASH: Hepatitis C Would Be a Virus-Associated Steatohepatitis

We have demonstrated that HCV *per se* induces insulin resistance in the animal model. High-fat diet and obesity superimposed on it lead to overt diabetes [14]. In view of the progression of chronic hepatitis C accelerated by insulin resistance [20], insulin resistance would naturally influence the development of HCC. Although the association has not been definite yet between non-alcoholic steatohepatitis (NASH) and development of HCC, it needs to be pursued energetically in view of histological resemblance of NASH to chronic hepatitis C.

When hepatitis C and NASH are compared, there are a number of similarities between these two medical settings (Table 3). Steatosis, which is one of the definitions of NASH, is a characteristic trait of chronic hepatitis C [4-6, 13]. Disturbances in the lipid metabolism are present in both settings, although phenotype may be distinct: hypo-β-lipoproteinemia in hepatitis C vs. hyperlipidemia in NASH. As described above, insulin resistance often arises in chronic hepatitis C, and is also a feature frequently observed in NASH, which is considered to be a basis for pathogenesis of NASH [21]. Some cytokines, such as TNF-α, are considered to be critical in the pathogenesis of both settings. TNF-α levels are increased in patients with chronic hepatitis C and are implicated in insulin resistance. TNF-α is also implicated in the pathogenesis of NASH [21]. Overproduction of

oxidative stress or reactive oxygen species (ROS) plays a pivotal role in the progression of hepatitis and development of HCC in both hepatitis C and NASH: in a mouse model for HCV infection, ROS is overproduced in the liver in the absence of inflammation, contributing, at least in part, to the development of HCC [13, 19, 22]. Presumably associated with ROS overproduction, a functional abnormality in the mitochondrion is suggested in the pathogenesis of liver diseases including HCC in hepatitis C and NASH. In an HCV mouse model, a functional disorder of the electron transfer system of mitochondrion has been implicated as an origin of ROS overproduction (Table 3).

Finally, HCC develops both in chronic hepatitis C and NASH. However, the association between NASH and HCC is not tight yet while there is a well-established connection in the case of HCV infection [1, 20]. Nevertheless, HCC develops in patients with NASH despite with a diverse rate of occurrence reported. Hence the underlying mechanism of hepatocarcinogenesis in NASH awaits further investigation. The analogy between chronic hepatitis C and NASH, as described above, may be a clue to solve a puzzle in the pathogenesis of NASH including hepatocarcinogenesis. Though not completely elucidated yet, the pathogenesis of HCC in HCV infection has been substantially understood by the analysis of animal models [23, 24]. For instance, in the MAPK intracellular signaling system, JNK, is activated in the liver by HCV. In the downstream of JNK, a transcription factor, AP1, and cell cycle machineries, CDK4 and cyclin D1, are subsequently activated, conferring an advantage for proliferation to hepatocytes (Fig. 4) [16, 23]. Such activations in cellular gene expressions and signaling systems have not been identified yet for NASH. The overproduction of ROS, together with the presence of hepatic steatosis, may be a common pathway to hepatocarcinogenesis in both hepatitis C and NASH (Fig. 5, upper half). However, the alterations in cellular gene expressions and/or intracellular signaling systems exist solely with hepatitis C in the presence of the viral protein(s), putting

chronic hepatitis C onto the fast track to the development of HCC (Fig. 5, lower half). This aspect observed in HCV infection is distinct from NASH, which may give a difference in the incidence of HCC in two settings. Based on the analogy in the metabolic pathways of hepatitis C and NASH but the distinction in cellular gene expressions and/or intracellular signaling systems, which are induced by the viral protein, we would like to propose to call hepatitis C as a "virus-associated steatohepatitis (VASH)" (Fig. 6).

Perspective for Therapeutic Strategies

We have demonstrated that HCV *per se* induces insulin resistance in the animal model. High-fat diet and obesity superimposed on it lead to overt diabetes. In view of the progression of chronic hepatitis C accelerated by insulin resistance, insulin resistance would naturally influence the development of HCC. Although the association has not been established between NASH and HCC, it needs to be pursued energetically in view of histological homology of NASH to chronic hepatitis C. Drugs for improving glucose metabolism and insulin resistance need to be kept in scope in treatment of hepatitis C patients who have failed to respond to antiviral, because they may well prevent progression of fibrosis and development of HCC in such patients. Traditional "high-protein and high-calorie" diet, advocated especially in Japan post-World War II, is obviously detrimental, except in some patients with advanced cirrhosis. Because hepatitis C is an infectious disease, the eradication of the virus is, naturally, the most efficient way to cure the disease. However, nearly one half of chronic hepatitis C patients who were treated with interferon/ribavirin combination therapy did not achieve eradication of the virus [25]. Therefore, besides anti-viral treatment to HCV, consultation on the dietary habit with hepatitis C patients should include iron restriction [26], as well as weight control, because high-calorie intakes are likely to accelerate hepatic fibrosis by aggravating insulin resistance in them.

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Table 1

Hepatitis C as a multifaceted disease

Hepatitis, cirrhosis and, eventually, HCC
Mixed cryoglobulinemia
MPGN
Sjögren's syndrome
Lichen planus
B-cell lymphoma
Disturbance in lipid metabolism
Diabetes or Insulin resistance

Table 2

Types of insulin resistance

Peripheral insulin resistance:	A shortage of insulin action in the muscle (deficit in the insulin-induced glucose uptake into the muscles)
Central insulin resistance:	A shortage of insulin action in the liver (deficit in the insulin-induced suppression of glucose production in the liver

Table 3

Comparison of hepatitis C and NASH

Hepatitis C	NASH
Steatosis	Steatosis
Hypo-β-lipoproteinemia	Hyperlipidemia
Insulin resistance	Insulin resistance
Cytokines (TNF-α, etc.)	Cytokines (TNF-α, etc.)
Oxidative stress	Oxidative stress
Mitochondrial abnormality	Mitochondrial abnormality
Obesity?	Obesity
HCC	HCC?

Figure Legends

Fig. 1

A mouse model for HCV-induced liver pathogenesis.

HCV core gene transgenic mice carry the core gene alone of genotype 1b HCV and express the core protein of an expected size in the liver, at levels comparable to those in human chronic hepatitis C patients. The mice eventually develop HCC late in life.

Fig.2

Altered glucose homeostasis in HCV core gene transgenic mice.

A, Body weight of 2-month-old mice.

B, Plasma glucose levels in fasting or fed mice.

C, Serum insulin levels in fasting or fed mice. The insulin level was significantly higher in the core gene transgenic mice than in control mice.

D, Glucose tolerance test. Animals were fasted overnight. D-Glucose (1 g/kg body weight) was administered by i.p. injection to conscious mice, and plasma glucose levels were determined at the time points indicated.

E, Insulin tolerance test. Human insulin (1 U/kg body weight) was administered by i.p. injection to fasted conscious mice and glucose concentrations were determined.

Values were normalized to the baseline glucose concentration at the time of insulin administration.

Values are means ± S.E.; *$p<0.05$; ***$p<0.001$; NS, statistically not significant; nTg, nontransgenic mice; Tg, transgenic mice.

Fig. 3

Insulin resistance and HCV infection.

HCV core protein or elevated intrahepatic TNF-α inhibits tyrosine phosphorylation of IRS-1 in the liver, suppresses insulin intracellular signal transduction and leads to insulin resistance. PKC, protein kinase C; PI3-kinase, phosphatidyl inositol 3 kinase; MAPK, mitogen-activated protein kinase; IRS, insulin receptor substrate.

Fig. 5

Molecular pathogenesis of liver disease in HCV infection.

Induction oxidative stress together with hepatic steatosis by the HCV core protein would play a pivotal role in the development of HCC. Alterations in cellular gene expressions, such as TNF-α or SOCS-1, and those in the intracellular signaling pathways including JNK would be co-accelerators to hepatocarcinogenesis in HCV infection. The latter pathway has not been found in NASH while the former may be common in the pathogenesis of hepatitis C and NASH.

HCC, hepatocellular carcinoma; TNF-α, tumor necrosis factor-α; SOCS-1, suppressor of cytokine signaling-1; NASH, non-alcoholic steatohepatitis.

Fig. 6

Virus-associated steatohepatitis.

HCV infection and NASH show a similar phenotype, steatohepatitis. However, in the case of HCV infection, the presence of the viral proteins, in particular, the core protein of HCV, confers alterations in cellular gene expression and intracellular signaling systems to hepatocytes, leading to the high-incidence of hepatocellular carcinoma.

HCV, hepatitis C virus; HCC, hepatocellular carcinoma; NASH, non-alcoholic steatohepatitis; VASH, virus-associated steatohepatitis.

Fig. 1

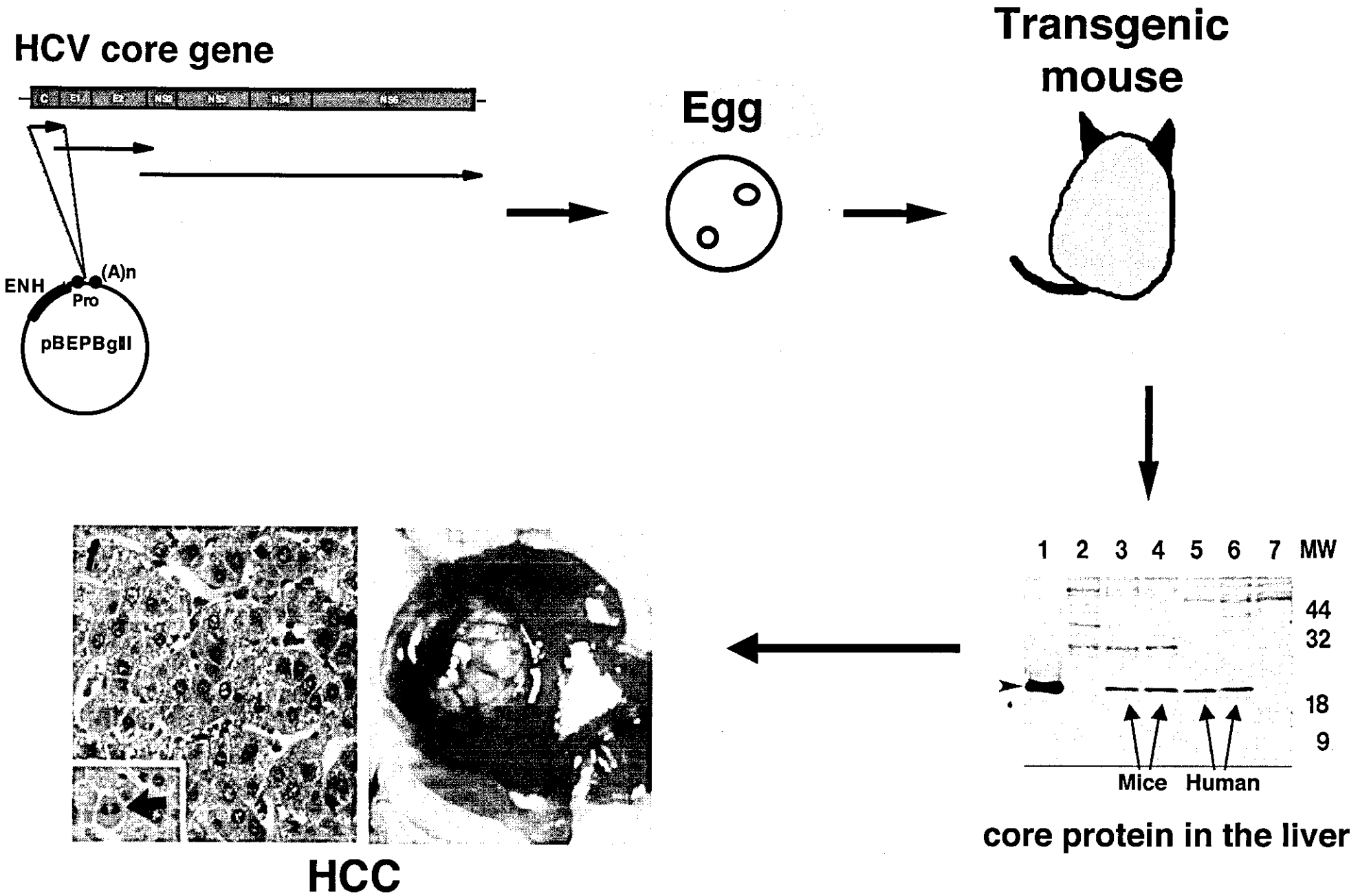
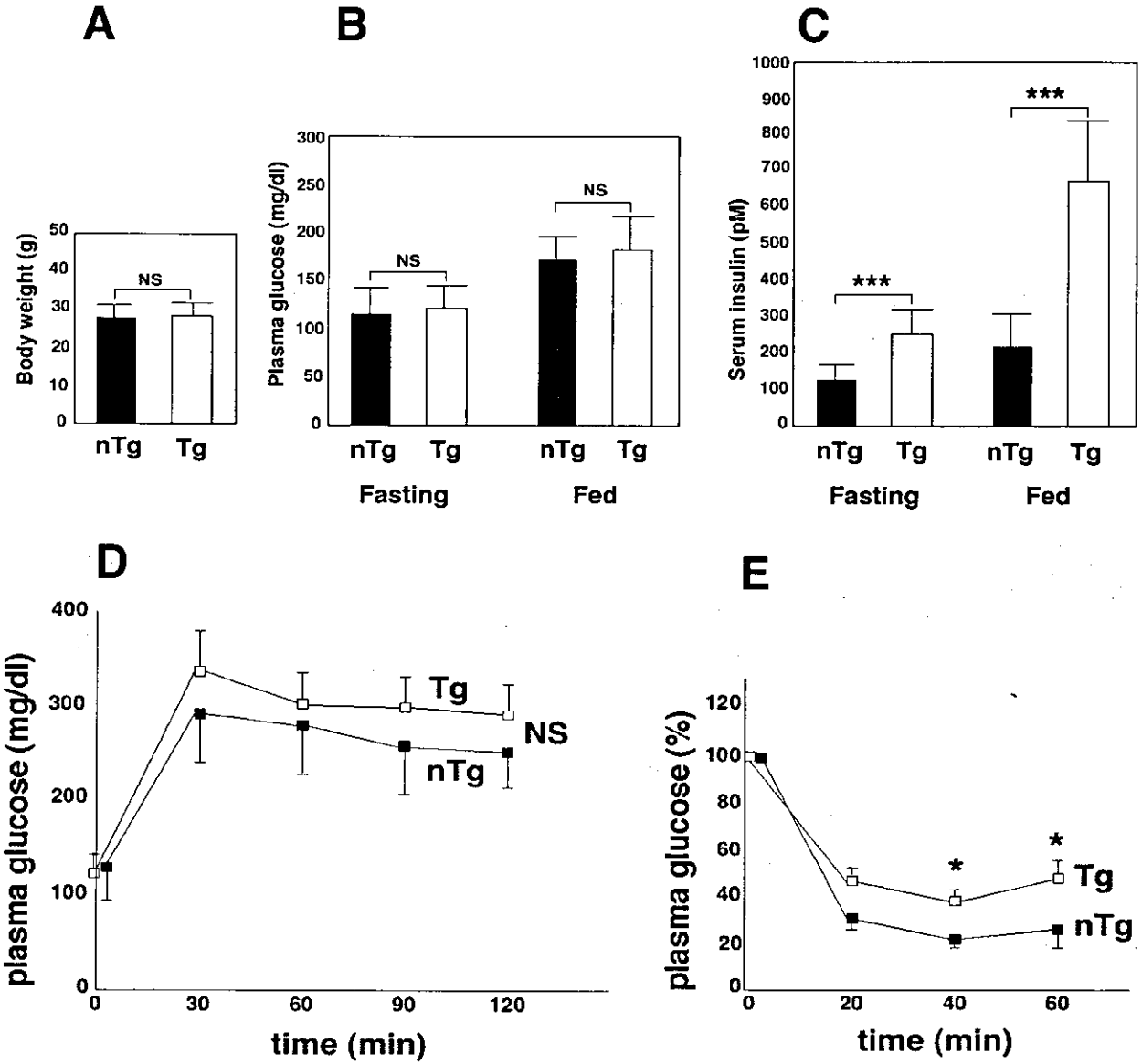

HCV core gene
C
E1
E2
NS2
NS3
NS4
NS5
ENH
Pro
(A)n
pBEPBglII
Egg
Transgenic mouse
1 2 3 4 5 6 7 MW
44
32
18
9
Mice
Human
core protein in the liver
HCC

Fig. 2


A
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Body weight (g)
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time (min)
plasma glucose (%)
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time (min)