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Molecular Mechanism of DNA Damage Response Pathway During Hepatic Carcinogenesis

Yasunobu Matsuda¹ and Toshifumi Wakai²

¹*Department of Medical Technology,
Niigata University Graduate School of Health Sciences*

²*Division of Digestive and General Surgery,
Niigata University Graduate School of Medical and Dental Sciences
Japan*

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide. The prevalence of HCC is still increasing in Asia and Africa, and represents a leading cause of death among patients with chronic liver diseases in industrial countries including Europe and North America (Llovet et al., 2003). The prognosis of HCC is considerably poor for following reasons: (1) aggressive treatment for HCC is not usually possible because most of the patients have impaired liver function, (2) hepatoma cells are refractory to standard chemotherapy drugs and radiation, and (3) HCC frequently recurs even after curative resection (Poon et al., 2009). Moreover, owing to the lack of reliable clinical HCC markers, fewer than 20% of patients are diagnosed at a stage where curative treatment can be performed (Llovet et al., 2003).

HCC is unique among the various types of malignancies, in that it frequently arises in individuals with hepatitis B virus (HBV)- and C virus (HCV)-related liver cirrhosis. Although the precise mechanism of the relationship between the hepatitis viruses and hepatocarcinogenesis is unknown, recent studies have suggested that an aberrant response against DNA damage might be involved in HBV- and HCV-induced carcinogenesis, as observed in many types of cancer cells. Therefore, for future development of treatments against HCC, understanding the functional role of the DNA damage response (DDR) in HCC-prone individuals would be of value.

2. Impact of oxidative DNA damage during hepatocarcinogenesis

Many previous studies have indicated a close relationship between metal overload and oxidative DNA damage (Imlay et al., 1988). For example, when DNA is exposed to hydrogen peroxide with iron, the Fenton reaction, in which hydrogen peroxide (H₂O₂) is catalysed to hydroxyl radicals (OH•) by iron (II) (Lloyd et al., 1998), causes the production of carcinogenic malondialdehyde, 4-hydroxynonenal (4-HNE) and other exocyclic DNA

adducts including 8-hydroxy-2'-deoxyguanosine (8-OHdG) (Jomova et al., 2011). Among these products, 8-OHdG is considered to be an oxidative DNA marker produced by reactive oxygen species (ROS), because the numbers of 8-OHdG-positive hepatocytes are significantly increased with progression of the severity of chronic hepatitis activity (Kitada et al., 2001; Ichiba et al., 2003) with iron content (Tanaka et al., 2008). Kato et al. (2001) investigated whether therapeutic iron reduction by phlebotomy with a low-iron diet could decrease the risk of HCC development in patients with chronic HCV. They found that patients treated with phlebotomy for 6 years showed significantly decreased levels of 8-OHdG in the liver, with improved severity of chronic hepatitis. Interestingly, all the patients who received phlebotomy did not develop HCC, suggesting a strong correlation between oxidative DNA damage and hepatocarcinogenesis. Subsequent studies reported that the level of hepatic 8-OHdG can be a predictive factor for the risk of recurrence in HCC patients after surgery (Matsumoto et al., 2003; Tanaka et al., 2008) and for individuals with naive chronic HCV infection (Chuma et al., 2008).

Intracellular ROS not only induce DNA damage but also regulate various types of intracellular signaling. In hepatoma cells, ROS potentiate cell growth by activating the signaling pathways of the stress kinases Akt, extracellular signal-regulated kinase (ERK) and Jun N-terminal kinase (JNK) (Liu et al., 2002). On the other hand, ROS accelerate tumor invasiveness in many types of cancers. In the case of hepatoma cells, Lim et al. (2008) reported tight correlations among ROS induction, E-cadherin downregulation, Snail upregulation and E-cadherin promoter methylation (Lim et al., 2008). Since E-cadherin is a master regulator of the epithelial-to-mesenchymal transition in HCC cells, it is plausible that tumor invasiveness is significantly accelerated by ROS. Importantly, recent studies have revealed that hepatitis viruses might have the property of producing ROS, supporting the idea that oxidative DNA damage might be directly induced in viral hepatitis.

2.1 Causative risk for HCC and ROS

2.1.1 HBV and ROS

Chronic HBV infection is still prevalent in Asia and Africa, and is one of the most important risk factors for HCC. HBV encodes HBV X (HBx), surface (HBs), core (HBc) and pol genes, and among these, HBx is widely considered to be a potent inducer of HCC. Many studies have reported that HBx transactivates the host genome (Tsu et al., 1989; Feitelson et al., 1999), leading to deregulation of the cell cycle checkpoints. Intriguingly, a crucial role of HBx in oxidative DNA damage has recently been reported. Lee et al. (2004) reported that HBx downregulates the mitochondrial enzymes involved in electron transport in oxidative phosphorylation. They found that HBx increases the levels of mitochondrial ROS and lipid peroxide production, suggesting that HBx-induced mitochondrial dysfunction might be one of the main reasons for HCC development. A close relationship between iron metabolism and the ROS level in HBx-expressing cells was reported by Gu et al. (2008), who showed that HBx decreases transferrin receptor 1 expression through downregulation of iron regulatory protein 1 and upregulation of ferritin heavy chain expression with ROS production. Intriguingly, HBx-mediated ROS induction also causes DNA hypermethylation. HBx of genotype D HBV causes hypermethylation of the gene promoter of glutathione S-transferase GSTP1, which is a candidate enzyme for protecting cells against ROS with

related toxic products (Niu et al., 2009). In turn, ROS stimulate HBx expression (Ha et al., 2010), suggesting that ROS may be an autocrine transducer of HBx-mediated carcinogenesis. Very recently, HBX was shown to activate the transcriptional activity of Forkhead box class O 4 (Foxo4) via JNK, leading to enhancement of the resistance to oxidative stress-induced cell death (Srisuttee et al., 2011).

2.1.2 HCV and ROS

HCV infection is a leading cause of HCC development throughout the world. Several lines of evidence have suggested that HCV plays a critical role in the state of oxidative stress in the liver. HCV is constructed of core, E1, E2 and nonstructural (NS2, NS3, NS4A, NS4B, NS5, NS5A, NS5B) proteins, and each of these encoded proteins has been shown to be essential for the pathogenesis of HCV. HCV core protein plays a role in cell proliferation, while NS5A interacts with the double-stranded RNA-dependent PKR to promote viral replication. Many studies have revealed that chronic HCV infection leads to double-stranded DNA breaks and enhances the mutation frequency of whole cellular genes (Machida et al., 2004). Okuda et al. (2002) reported that HCV core protein localizes to mitochondria, leading to redistribution of cytochrome c from the mitochondria to the cytoplasm. Their data clearly indicate that HCV can be a direct source of ROS production. Moreover, HCV core protein has been shown to be strongly associated with the outer membrane of mitochondria to increase Ca^{2+} uptake, leading to oxidation of the glutathione pool and a decrease in the NADPH content in vivo (Korenaga et al., 2005). Recently, the mechanism by which hepatic iron overload develops in patients with HCV-associated chronic liver disease has been elucidated. Miura et al. (2008) reported that hepcidin, which plays a pivotal role as a negative regulator of iron absorption, was significantly decreased in HCV replicon cells and HCV core-expressing cells. Their findings should be important, because the decreased level of hepcidin may lead to increased duodenal iron transport as well as macrophage iron release, thereby causing hepatic iron accumulation. Since increased activity of histone deacetylase (HDAC) was found to be the main reason for the decreased levels of hepcidin (Miura et al., 2008), HDAC may play a critical role in HCV-related hepatocarcinogenesis.

2.1.3 Alcohol consumption and ROS

It is widely known that ethanol is a strong inducer of DNA damage. The ethanol derivative acetaldehyde causes DNA damage by directly binding to DNA and inhibiting DNA repair systems (Seitz et al., 2006). Furthermore, ethanol treatment increases the production of intracellular ROS and lowers the levels of antioxidants, leading to enhancement of oxidative stress (Wu et al., 2009). Ethanol-induced oxidative stress plays a critical role in the pathogenesis of DNA damage as well as liver injury, and mitochondrial dysfunction is also induced by oxidation of various mitochondrial proteins (Suh et al., 2004). One of the most well-known mediators of alcohol-induced ROS is cytochrome P450 2E1 (CYP2E1) (Lu et al., 2008; Wu et al., 2009; Beier et al., 2010). CYP2E1 is an important enzyme for the conversion of ethanol to acetaldehyde and acetate, and is involved in the metabolism of xenobiotics. Ethanol intoxication increases CYP2E1 not only in the endoplasmic reticulum but also in mitochondria, leading to oxidative stress in these compartments (Robin et al., 2005). Intriguingly, Wang et al. (2009) reported that both protein-bound 4-HNE and etheno-DNA

adducts were strongly correlated with cytochrome P450 2E1 (CYP2E1) expression in patients with alcoholic liver diseases. More importantly, Tsutsumi et al. (2003) reported the mechanism of the synergic enhancement of ROS production by HCV infection and alcohol consumption. They reported that HCV core protein cooperates with ethanol for activation of ERK and p38 mitogen-activated protein kinase (MAPK) pathways, leading to a decreased level of glutathione S-transferase (GST). Since GST plays a key role in protecting cells against oxidative stress, it is plausible that ethanol consumption would worsen the pathogenesis of the liver disease in HCV-infected patients. Thus, there is no doubt that alcohol consumption enhances DNA damage and is a strong promoter of hepatocarcinogenesis in individuals with chronic viral hepatitis.

2.1.4 Nonalcoholic steatohepatitis and ROS

To date, the prevalence of nonalcoholic fatty liver disease (NAFLD), including its aggressive type nonalcoholic steatohepatitis (NASH), has been increasing in developed countries. NASH may account for a large proportion of idiopathic or cryptogenic cirrhosis, as well as HCC in individuals with non-B non-C hepatitis (Mori et al., 2004; Starley et al., 2010). It has been suggested that ROS induced by mitochondrial dysfunction may play a key role in the mechanism of NAFLD (Pérez-Carreras et al., 2003), and growing evidence suggests that the ethanol-inducible cytochrome CYP2E1 is involved in the pathological conditions of NASH (Lieber, 2004). CYP2E1 expression and activities are frequently increased in the livers of NASH patients (Weltman et al., 1998; Chalasani et al., 2003), indicating that CYP2E1 may promote cellular injury (Robertson et al., 2001). However, since CYP2E1 is an ethanol-inducible enzyme, the reason why this enzyme is induced in NAFLD patients remains unknown. In this regard, Baker et al. (2010) reported that the genes for alcohol dehydrogenase, catalase and aldehyde dehydrogenase were elevated in the liver of NASH patients. They suggested that these genes may be partly induced by certain intestinal bacteria, especially in obese individuals. Further studies are awaited for more understanding of the mechanism of the cancer development in NASH patients.

3. DDR machinery

As mentioned above, intracellular ROS are potent inducers of oxidative DNA damage. ROS are produced by a variety of types of environmental stimuli, including ultraviolet light, ionizing radiation and chemical agents (Bertram et al., 2008). When organisms are exposed to such stimuli during cell division, genomic instability and DNA replication errors are easily caused, which may be the first step for cancer development or premature aging. To prevent such errors of DNA replication, a strict DDR system is highly conserved among mammals and induces cell cycle arrest or apoptosis. The DDR is mainly regulated by two phosphatidylinositol-3-related kinases, ataxia telangiectasia mutated (ATM) and ATM-Rad3-related (ATR), and the cell cycle checkpoint kinases Chk1 and Chk2 (Poehlmann et al., 2010). ATM is exclusively activated by DNA double-strand breaks induced by ionizing irradiation, whereas ATR is mainly stimulated by disrupted DNA replication forks caused by stimuli such as ultraviolet light and hydroxyurea (Abraham, 2001). During the process of DDR or stalled DNA replication, the ATM and ATR-mediated pathways interact with each other to phosphorylate histone H2AX, and MDC1, 53BP1, BRCA1 and MRE11 are recruited for phosphorylation. The Chk1 and Chk2 kinases are activated to regulate

Cdc25, Wee1 and p53, and finally cyclin-dependent kinases (Cdks) are inactivated to induce cell cycle arrest (Kawabe, 2004; Iliakis et al., 2008). To date, there have been many studies showing that these DDR-associated proteins are functionally deregulated in cancer cells. Of note, recent studies revealed that hepatitis viruses are considerably involved in the regulation of the DDR machinery.

3.1 HBV and the DDR

It is well known that HBx has the capacity to transform cells both in vitro and in vivo (Shirakata et al., 1989; Kim et al., 1991). Although the precise mechanism of HBx-mediated carcinogenesis is unclear, recent studies have suggested that HBV directly interferes with the DDR (Groisman et al., 1999; Matsuda et al., 2009). Zhao et al. (2008) reported that HBV infection stimulates the steady state of ATR with downstream targets including Chk1, p53 and gamma-H2AX, while the activity of ATM-Chk2 signaling is unchanged. Along with the ATR-mediated response to the replication stress, HBV-infected cells may acquire survival potential toward DNA damage. Wang et al. (2008) reported that HBx activates p38 MAPK and its Cdk4 and Cdk2, leading to phosphorylation of Rb and transcription of ARF. Accordingly, HBx-mediated p38 MAPK signaling sensitizes the cells to p53-mediated apoptosis by activating ATR, which leads to phosphorylation of p53. Wu et al. (2008) reported that HBx-transformed cells show defective S-phase arrest and consequent G2/M arrest after DNA damage induced by mitomycin C. Importantly, they also found that HBx impairs the ATR-dependent phosphorylation of Chk1 and monoubiquitination of FANCD2, suggesting that the defect in the intra-S-phase checkpoint may be the reason for genomic instability. Studach et al. (2009) reported that HBx-induced polyploid cells showed continued DNA damage after long repopulation, which was associated with loss of p53 function. They suggested that polo-like kinase 1 (Plk1), which is frequently overexpressed in human HCC, might play an important role in the acquisition of HBx-induced DNA damage. Interestingly, HBx-mediated Plk1 activation reduces claspin, an adaptor of ATR-mediated Chk1 phosphorylation, leading to inactivation of Chk1 and finally allowing the propagation of DNA damage (Studach et al., 2010). These lines of evidence may explain why Chk1 is inactivated in the presence of ATR activation in HBV-infected cells. Interestingly, Zheng et al. (2011) reported that HBV exploits the activated DDR, and that ATR and ATM kinase inhibitors, such as theophylline, significantly reduce the yield of HBV DNA. Collectively, HBx and DDR are closely linked in a tight loop, not only from the viewpoint of hepatocarcinogenesis but also from the viral life cycle.

When normal cells are exposed to stimuli that cause DNA damage, the well-known tumor suppressor p53 is transcriptionally activated to stimulate DNA damage repair proteins or induce apoptosis. Prost et al. (1998) suggested that HBx might inhibit the p53-dependent DNA repair system, since the efficiency of DNA repair is decreased in HBx-expressing p53-wild-type cells to the level of p53-null hepatocytes. Jia et al. (1999) reported that HBx functionally binds to p53 as well as p53-associated DNA repair factors, leading to impaired p53-downstream signaling. They also found that HBx not only binds to p53 but also to p53 partners, and TFIIH transcription-nucleotide excision repair factors such as the DNA helicases XPB and XPD. Since HBx strongly induces DNA damage via multiple pathways (Fig. 1), it is plausible that other DNA-damaging agents could significantly promote the tumorigenesis in individuals with chronic HBV infection (Lee et al., 2005).

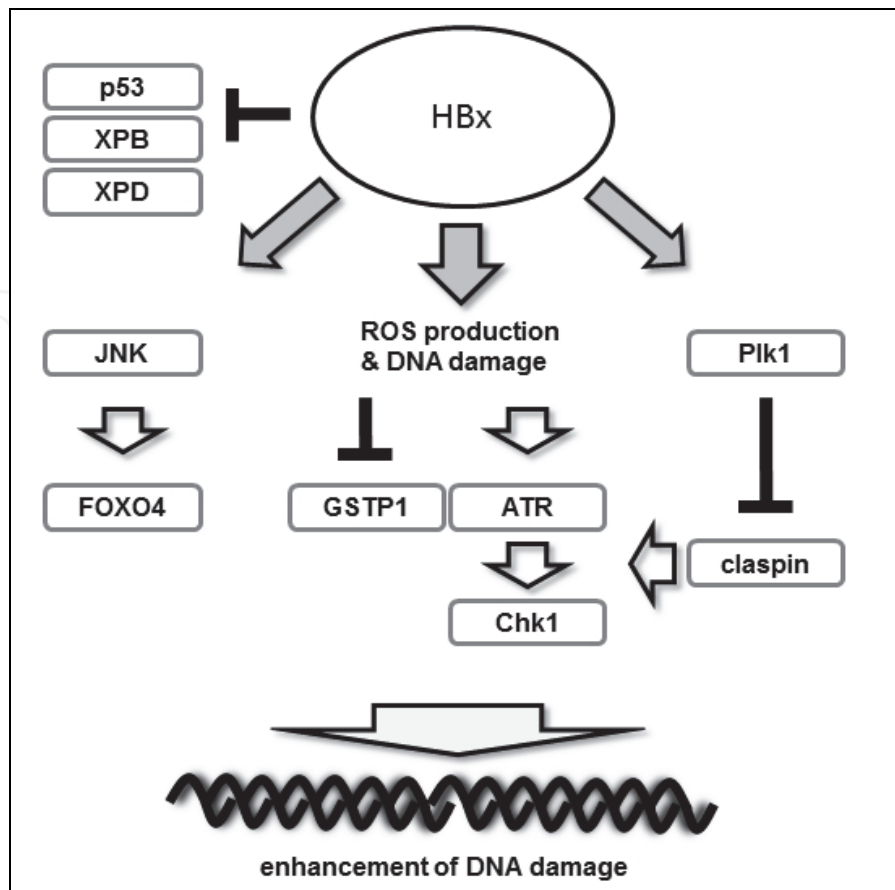


Fig. 1. Functional role of HBx in the DNA repair machinery.

HBx induces mitochondrial ROS production, followed by oxidative DNA damage. HBx inactivates claspin via Plk, modulates the GSTP1 gene promoter and activates FOXO4, thereby weakening the DNA damage repair response. Moreover, HBx binds to p53, leading to inhibition of p53-mediated antitumor activity.

3.2 HCV and the DDR

Recently, the functional role of HCV in DNA repair processes has been clarified, and its mechanism appears to be more complex than that of HBV. Lai et al. (2008) reported that HCV nonstructural proteins NS3 and NS4A translocate ATM into the cytoplasm. In the presence of DNA damage, NS3A and NS4A were shown to delay the dephosphorylation of activated ATM and gamma-H2AX. As a result, ATM-mediated DNA repair might be impaired in HCV-infected cells, leading to an increase in double-stranded DNA breaks. Similarly, Machida et al. (2010) reported that peripheral blood mononuclear cells from HCV-infected patients show frequent chromosomal aberrations with impaired nonhomologous end-joining repair, suggesting that HCV NS3 might be partly responsible for the inhibition of DNA repair. Taken together, HCV may directly inhibit the DNA repair processes not only in hepatocytes but also in monocytes, where HCV-associated lymphoma could develop. On the other hand, HCV core protein was shown to bind to the DNA repair protein NBS1 to inhibit the formation of the Mre11/NBS1/Rad50 complex, a keystone complex connecting the ATM-mediated DNA repair machinery (Machida et al., 2010). Intriguingly, Ariumi et al. (2008) reported that replication of HCV RNA was suppressed in ATM- or Chk2-knockdown

cells, suggesting that the ATM signaling pathway is critical for HCV RNA replication. These lines of evidence strongly indicate that a tight relationship between HCV and the ATM-mediated DDR machinery may exist.

Although the mechanism of HCV-DNA damage is unclear, some studies have suggested that this might be partly caused by aberrant function of p53. Nishimura et al. (2009) reported that HCV induces overexpression of 3beta-hydroxysterol Delta24-reductase (DHCR24), which causes accumulation of the MDM2-p53 complex in the cytoplasm and inhibits the acetylation and activation of p53 in the nucleus. Their findings may explain how HCV-infected cells acquire resistance to oxidative stress-induced apoptosis. Recently, HCV-encoding proteins were shown to independently interact with p53. One of the most potent candidates for p53 inactivation is HCV NS5A. NS5A physiologically associates with p53, leading to localization of the p53-NS5A complex in the perinuclear membrane. In this setting, the NS5A-p53 complex inhibits p53-mediated transcriptional activation from a synthetic promoter containing multiple p53-binding sites, leading to transcriptional repression of the p21/waf1 gene (Majumder et al., 2001). Moreover, NS5A forms a heteromeric complex with TATA box binding protein (TBP) and p53. The binding of NS5A to p53 and TBP may abrogate their interaction with the DNA consensus, and the formation of p53-TBP and p53-excision repair cross complementing factor 3 (ERCC3) protein-protein complex would be impaired (Qadri et al., 2002; Gong et al., 2004). Similar to NS5A, the HCV core was also shown to colocalize with p53 in subnuclear granular structures and in the perinuclear area, and to repress the activity of p53 (Smirnova et al., 2006). It has been suggested that the HCV core can interfere with p53-mediated signaling in several ways, such as physical interactions, modulation of p53 gene regulatory activity and post-translational modification (Kao et al., 2004). Collectively, HCV should be regarded as a direct inhibitor of DNA repair by inducing intracellular ROS, abrogating the ATM-mediated DDR and inhibiting p53 activity (Fig. 2).

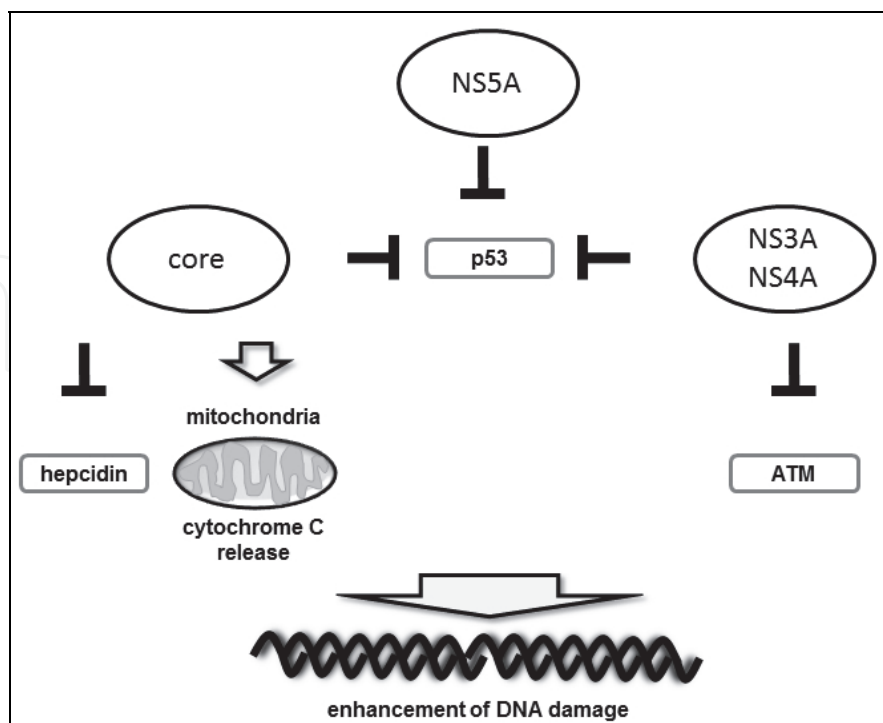


Fig. 2. Functional role of HCV in the DNA repair machinery.

HCV-encoded proteins independently interfere with the DNA damage repair machinery. The NS3A and NS4A proteins inhibit ATM signaling through cytoplasmic sequestration, while the NS5A protein binds and inhibits p53. The core protein induces mitochondrial ROS, while inhibiting hepcidin, leading to an increased iron load. ATM, ataxia telangiectasia mutated.

4. Conclusions

To date, newly developed antiviral drugs, such as nucleotide analogs and interferon, have been introduced in the management of individuals with chronic HBV or HCV infection. Unfortunately, the clinical evidence suggests that their therapeutic efficacy is still less than satisfactory. Many patients have to discontinue the antiviral therapy owing to side effects or lower efficacy of the treatment, implying that they face the risk of cancer development. Even when not infected with hepatitis viruses, some obese individuals have a high risk of HCC development induced by NASH. Since there are no useful curative treatments for HCC, the need to prevent the early step of hepatocarcinogenesis is inevitable. Many studies have shown that the DNA damage repair system might be considerably involved in HCC development, irrespective of the different etiologies. Novel treatments for preventing DNA damage and/or potentiating the cellular capacity of DNA damage repair are under investigation and the results are awaited.

5. References

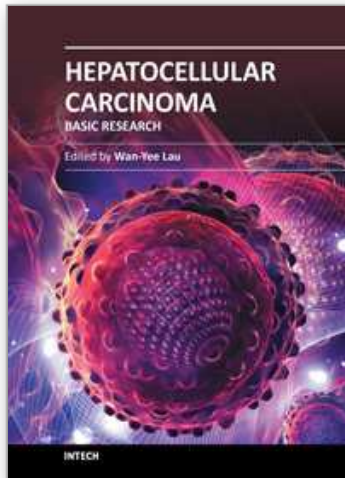
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Hepatocellular Carcinoma represents a leading cause of cancer death and a major health problem in developing countries where hepatitis B infection is prevalent. It has also become increasingly important with the increase in hepatitis C infection in developed countries. Knowledge of hepatocellular carcinoma has progressed rapidly. This book is a compendium of papers written by experts to present the most up-to-date knowledge on hepatocellular carcinoma. This book deals mainly with the basic research aspect of hepatocellular carcinoma. The book is divided into three sections: (I) Biomarkers / Therapeutic Target; (II) Carcinogenesis / Invasion / Metastasis; and (III) Detection / Prevention / Prevalence. There are 18 chapters in this book. This book is an important contribution to the basic research of hepatocellular carcinoma. The intended readers of this book are scientists and clinicians who are interested in research on hepatocellular carcinoma. Epidemiologists, pathologists, hospital administrators and drug manufacturers will also find this book useful.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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