抄録

Current antiviral therapy for chronic hepatitis in Japan

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HBV and HCV infection are major risk for liver cancer. Patients should acquire hepatitis quiescent status by timely appropriate antiviral therapies. Recent advance for each HBV and HCV treatment, we need to refer to guidelines issued by domestic or international society/organization based on the evidence from various clinical studies. Standard antiviral therapies are differed by country because of the difference of viral characteristics, biological host factors and social factors including economic status.

In Japan, hepatitis treatment guidelines are issued by Japanese Society of Hepatology (JSH) and updated every year, of course, referred to WHO, AASLD, EASL, APASL guidelines. For HBV antiviral therapy, nucleos(t)ide analogue or interferon should be selected according to age, HBV-DNA and ALT values. These HBV-DNA values are configured from clinical studies regarding the risk of advanced liver diseases or liver cancer. HCV antiviral therapies are selected after evaluating HCV viral status. For example, combination of DAAs (direct-acting antiviral agents) are selected according to viral mutation status of Y93 or L31 in NS5A or the degree of renal dysfunction for genotype 1 HCV patients. Recent updated JSH guideline includes therapies for special population such as HBV or HIV coinfection, renal dysfunction, after liver transplantation patients.

However, successful antiviral therapy does not result in the complete cure for liver disease, some cases exhibit liver cancer. We need to use and investigate biomarker predicting chronic liver disease progression and incidence of liver cancer.

Hepatitis B virus X protein stimulates HBV replication through regulating transcription factors associated with DNA or Histone methylation

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Background: Hepatitis B virus (HBV), a small enveloped DNA virus, chronically infects more than 350 million people worldwide and causes liver diseases from hepatitis to cirrhosis and liver cancer. HBx is a multifunctional protein encoded by the HBV genome; HBx stimulates HBV replication and is thought to play an important role in the development of HBV-associated HCC. Previously, we found that HBx has an important role in stimulating HBV transcription and replication and that the transcriptional transactivation function of HBx may be critical for its augmentation effect on HBV replication. However, the molecular mechanism of HBx in transcriptional coactivation remains unclear. In this study we show the new insight of coactivator mechanism and possibility of new treatment target for HBV replication and HBV-related hepatocarcinogenesis.

Methods: We used a retrovirus vector to introduce HBxwt or empty vector (EV) into HepG2 cells. Gene expression profiling was carried out on Affymetrix GeneChip Human U133A2.0 ver.2.0 arrays according to the manufacturer's protocol. Unsupervised hierarchical clustering analysis and Class Comparison analysis were performed by BRB-Array Tools software Version 4.2.2. Transcription factor analysis was performed using Ingenuity Pathway Analysis (Ingenuity Systems) to identify a potential upstreme transcription factors. We used 244 chronic hepatitis B patients' array data and evaluate identified transcription factors are related to HBV infection status in clinical cases.

Results: Unsupervised hierarchical clustering analysis of HepG2-HBxwt or HepG2-EV cells revealed that gene expression of these cell lines was significantly different. 803 HBx related genes were identified by class comparison between these two cells. Six transcription factors (TFs) were identified for HBx related activated TFs which affected HBV replication by IPA, siRNA and inhibitor analysis. Three of these six TFs control HBV replication through modifying DNA or Histone methylation. By the analysis of 244 Hepatitis B patients, these three TFs were significantly highly expressed in HBeAg(+)HBeAb(-) cases than HBeAg(-)HBeAb(+) cases. Moreover, these TFs up-regulated stemness markers (EpCAM, AFP, SOX9) and EMT markers (ZEB1, ZEB2, VIM) and associated with poor prognosis of HCC.

Conclusions: HBx upregulated three TFs associated with DNA or Histone methylation.

Moreover, HBx stimulates HBV replication and hepatocarcinogenesis through modifying DNA or Histone methylation. Our study suggests that transcription factors which activated by HBx will be an important therapeutic target against both virus replication and CLD aimed at the prevention of HCC.

Symposium in China, June 2016

Title:

Role of scaffold protein JSAP in cancer

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Abstract

Proper cell cycle regulation is essential for normal cell function, and its dysregulation is often associated with cellular transformation and tumorigenesis. We previously showed that JSAP1 (also known as JIP3) and its family member JSAP2 (also known as JLP and SPAG9) play a role in cytokinesis, the final stage of cell division, with functional redundancy. On the other hand, increasing evidence identifies JSAP2 as a novel marker for various types of cancer. In addition, recently several groups have reported that overexpression of JSAP2 is correlated with poor prognosis in hepatocellular carcinoma and non-small cell lung cancer. To date, however, functional role of JSAP in cell division control and cancer remains largely unknown. Here we examined the effect of high expression of JSAP on cultured cells. Overexpression of wild-type (WT) JSAP1 or JSAP2, but not their mutants lacking kinesin-1 heavy chain-binding domain (KBD), caused nuclear morphological abnormalities. Furthermore, prolonged mitotic phase without chromosome segregation, and increased cell death were observed in cultured cells overexpressing JSAP_WT, but not JSAP_ΔKBD. Together, these findings suggest that overexpression of JSAP may lead to impairment of the spindle assembly checkpoint in cooperation with kinesin-1. In this symposium, I will discuss a potential role of JSAP in cancer development and progression.

Effectiveness and safety of sofosbuvir/ledispavir 90/400 mg treatment For monoinfected HCV patients in Mongolia

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Key words: Viral eradication, Rapid viralresponse(RVR), Sustained viral response (SVR), Nucleotide polymerase inhibitor, NS5A inhibitor, Direct acting antivirals(DAA), HCV

Background: Ledipasvir and Sofosbuvir combined Direct Acting Antiviral drugs (DAAs) have been proven to eradicate 94-97% of Chronic HCV infection cases. Results ofRapid virologic response(RVR)and End of treatment(EOT) are essential for predicting the final outcome of HCV treatment regimen. One of the new treatment regimen drugs discovered recently are rightfully the new DAAs used for HCV eradication treatments.

In 2014, NS5A inhibitor Ledipasvir and nucleotide polymerase inhibitor Sofosbuvir combination therapy was introduced into clinical use. While the interferon based treatment had an eradication rate of 50% with many side effects including flu like symptoms, depression and cytopenia syndrome. However the new treatment regimen had an effective outcome of 94-99% with mild side effects registered[1].

Liver diseases have been classified as a serious health issue by the Government of Mongolia. Primary and secondary prevention methods have been implemented in public health sectors to increase healthy population and early diagnosing of chronic HCV patients. Tertiary prevention methods were also funded and implemented by the Government by a National program named "Prevention of viral hepatitis, decreasing fatality and mortality".

In the National statistics of cancer book on the year 2014: 1907 HCC new cases , 2792 patients and 1405 death were registered due to HCC. Unfortunately, 81.2% of newly found liver cancer (HCC) cases were diagnosed in III,IV stages and effectiveness of treatment options for these patients are limited with a 5 year survival rate of 19.5%.

A sustained viral response(SVR) is when Real time PCR results are <15IU/ml in patients who have taken the antiviral treatment at the 12th and 24th week after End of treatment(EOT).Not enough data has been accumulated for this new treatment to throughly define guidelines for special and rare conditions. The Rapid viral response(RVR) and EOT, real- time PCR results are especially helpful in predicting the SVR 12 week and 24 weeks outcomes with a prediction value of more than 96%[2,3].

Not enough studies have been done on using the RVR predictive values to manipulate the treatment regimens for each patients' conditions. Since December 2015 the Mongolian Expanded Access Programm has provided DAAs for patients with hepatitis and liver cirrhosis, using sofosbuvir (SOF) combined with ledipasvir (LDV).

The aim of present work was to study virological and liver functional outcomes in 4th and 12th weeks during sofosbuvir/ledispavir 90/400 mg antiviral treatment using data of 6 medical hospitals in order to evaluate safety and efficacy of this regimen.

Patients and Methodology: The prospective study subjects were chosen with a targeted sampling method from patients who received antiviral treatment from Dec.2015 to June 2016 at UB Songdo hospital of Ulaanbaatar as a part of the Access program. A total of n=86 patients with a mean age 52.95±11.62 were included in our research. From these patients n=32 were male and n=54 were women. Four (4.65%) patients were the treatment experienced and n=82(95.34%) were naïve patients.

HCV-RNA PCR (Roche Molecular System) tests were performed at the start of treatment, 4th week and End of Treatment. Also a Common Blood Count (WBC , HGB , PLT,etc) and LFT, KFT(Creatinine, T.Bil, D.Bil, ALT, AST , ALP, GGT, Alb, T.Prot,) tests were taken at the respective treatment dates. The Abdominal ultrasound results were acquired from the BIT system of UB Songdo hospital. The APRI and FIB-4 scores were calculated from the above tests and statistical data was processed with STATA 12 program. The patients filled their consent of approval.

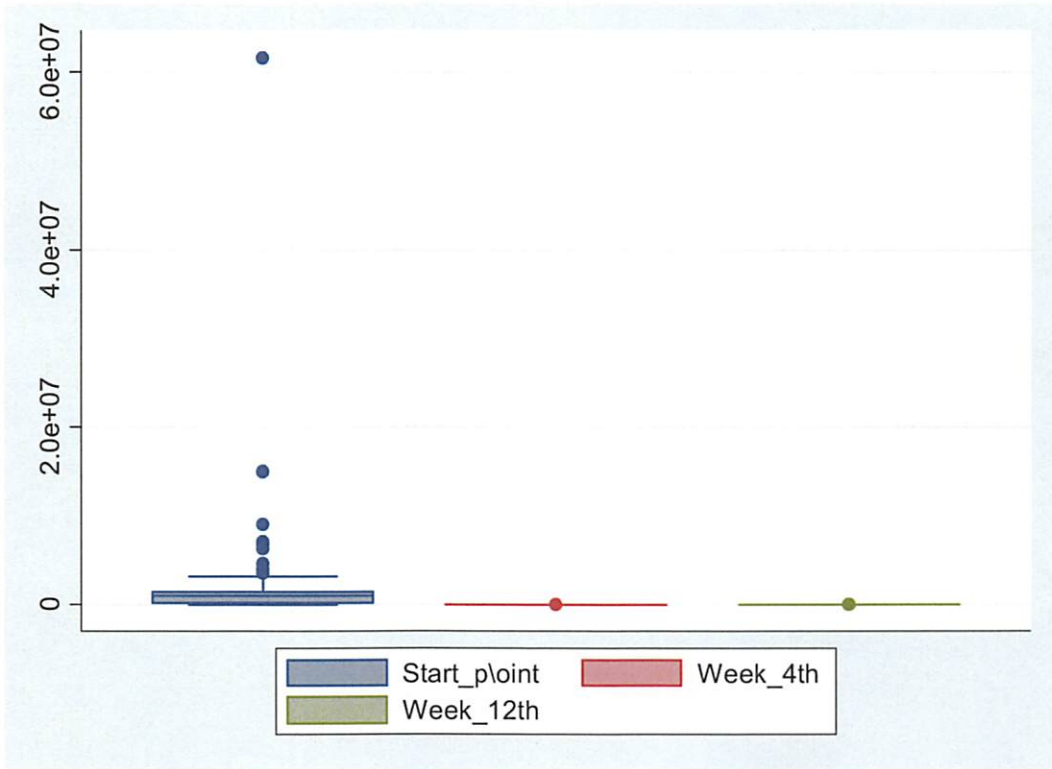
Unified treatment data were prospectively collected from clinics to show a comparison of other results. The 628 patients included had LED/SOF 90/400 mg DAA without ribavirini (RBV) from December 2015 to May 2016; 252(40%) male, 376(60%) female, mean age 52.77+-11, diagnostic percentage: hepatitis 458(72%), Liver cirrhosis 163(26%),HCC 7(2%) cases.

Results: At the 4th week of treatment, RVR was achieved with 83.72% of patients, RNA positive cases were 16.28%. End of treatment results with elimination of HCV RNA were in 97.67% but RNA positives remained in 2.33% of patients who had the treatment.The RVR and End of treatment results of HCV RNA were not related to the demographic structure or the predictive scores of APRI and FIB-4 (p=0.0034).

The liver fibrosis predictive scores APRI and FIB-4 decreased after the 12 week combination therapy relatively(p=0.0001). The mean platelet numbers at the EoT increased $16.2\pm19.07*10^9$/L(p=0.0001).

93% of the patients that had a HCV genotype test had either 1a or 1b genotype and this correlates with the 97% and above treatment end results. The main adverse effects noted were headache, fatigue, nausea and dry skin. These adverse effects seemed to be more common with patients who had a progressed liver disease and older age.

Table 1: Virological response of treatment/UB Songdo hospital (n=86)/



Mean /at the start of treatment/ = 99 000 **IU/ml (HCV RNA) real-time PCR**

Mean /End of treatment 12 weeks/ = 0 IU/ml p= 0.0001

Conclusion:

In this prospective study of patients treated with LED/SOF, it was concluded that sofosbuvir/ledispavir 90/400 mg treatment for single HCV infected patients were effective and safe with an End of treatment success rate of more than 97%. Also, the APRI, FIB-4 scores and platelet counts show the treatment

had positive outcomes on the overall liver disease progression. Further tests to determine SVR 12 and 24 are being awaited.

Reference

1.Journal of hepatology, Abstract Book 2016, EASL
2."Diagnosis " Mongolian GI Journal. GI week 2016 , p107-114
3. EASL recommendations on treatment of Hepatitis C 2016.

Strategy for Checkups for Hepatitis Patients in Ishikawa, Japan

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In Japan, approximately 2% of the population is estimated to be infected with hepatitis C virus (HCV) or B virus (HBV). It is believed that, within this 2%, many do not know they are infected. It is vital to find, diagnose and correctly treat HBV/ HCV infected people because, if left untreated, these viruses can cause death from liver disease. Fortunately, effective anti-viral therapies have become available, therefore, the Japanese Government is strongly suggesting that all people get hepatitis tests for HBV and HCV at least once in their life.

To encourage hepatitis testing, the Japanese national and local government provide free hepatitis testing, at five year intervals, for people aged 40 – 70 from 2002-2006. To support identification, proper diagnosis and treatment for hepatitis virus infected people, the Ishikawa Prefectural Government started its own follow-up check-up program in 2002.

The 2002 program's main points were:

1. Local governments got personal information consent from hepatitis applicants allowing direct contact by local government health care workers (LGHCWs).
2. LGHCWs did checkups for hepatitis-positive people yearly.
3. Standard protocols for liver imaging at detailed examinations were established.

Even after 2006, local governments have continuously provided people several chances to get free hepatitis test, and unique subsidies for hepatitis treatment costs have been started from 2009.

In 2009, Kanazawa University Hospital (KU), became a regional core institution and took over annual checkups of hepatitis patients from local governments and created Ishikawa Hepatitis Network.

The 2009 program's main point is:

1. Both local government and KU do checkups testing for Hepatitis-positive people.
2. Previously, only local governments were allowed to possess individuals' private information. Now, based on signed consent from citizens, local governments will share certain Hepatitis-related information with Ishikawa Hepatitis Network administered by KU.

So far, 1402 out of 3028 hepatitis virus-infected patients have agreed to

participate in this program. KU directly contacts consenting patients and checkup to confirm they annually see specialized doctors in addition to primary doctors. Local governments continue to contact people who do not respond or accept direct contact with KU.

In conclusion, the condition of all hepatitis-infected patients found by local governments can be checked annually by the local government or KU. This kind of checkups system for hepatitis patients in Ishikawa has been distributed throughout Japan as a promising model system.

WHO guidelines for the screening, care and treatment of persons with hepatitis C infection

Azumi Ishizaki, WHO, Global Hepatitis Programme

Globally, the morbidity and mortality attributable to hepatitis C virus (HCV) infection continues to increase. Approximately 700 000 persons die each year from HCV-related complications, which include cirrhosis and hepatocellular carcinoma (HCC). HCV infection can be cured by antiviral treatment; however, due to the asymptomatic nature of the disease, most infected persons are unaware of their infection and, for those who are diagnosed, access to treatment remains low in many settings.

The World Health Organization (WHO) issued the first Guidelines for the screening, care and treatment of persons with hepatitis C infection in 2014. Since then, several new medicines for the treatment of HCV infection have been introduced. Of these, daclatasvir, ledipasvir, and a combination of ombitasvir, paritaprevir and dasabuvir were added to the WHO Model List of Essential Medicines in 2015. These medicines are transforming the treatment of HCV, enabling the use of regimens that can be administered orally, are shorter in duration (as short as eight weeks), result in cure rates higher than 90%, and are associated with fewer serious adverse events (SAEs) than the previous interferon-containing regimens.

The objectives of these 2016 updated WHO Guidelines are to provide evidence-based recommendations for the treatment of persons with HCV infection using, where possible, all-oral combinations of these new medicines, direct-acting antivirals (DAAs). The Guidelines also provide recommendations on the preferred regimens based on a patient's HCV genotype and clinical history, and assess the appropriateness of continued use of the existing medicines. The Guidelines are appropriate for all countries, from low-, middle- and high-income countries.

The WHO guidelines on HCV treatment, HBV treatment and other key documents are all available at the following link: http://www.who.int/hepatitis/en/

Co-infection of HIV and hepatitis viruses

Azumi Ishizaki, WHO, Global Hepatitis Programme

HIV and viral hepatitis, HBV and HCV have common routes of transmission. It is estimated that , globally, 2.3 million persons are coinfected with HCV and HIV and 2.6 million persons are coinfected with HBV and HIV. With the widespread use of antiretroviral therapy (ART), which reduces the risk of HIV-associated opportunistic infections, liver related-disease has started to overtake AIDS-defining illnesses as a leading cause of death in some high-income countries.

Treatment and management of HIV/HCV co infection

Outcomes of HCV therapy with DAAs in persons with HIV coinfection are comparable to those with HCV monoinfection. There are fewer drug-drug interactions (DDIs) between DAAs and antiretroviral (ARV) medicines. For these reasons, all persons with HIV/HCV coinfection should be considered for HCV treatment. It is advisable to first initiate treatment for HIV and achieve HIV suppression before starting HCV treatment, except some circumstances where it may make sense to treat HCV infection first and then initiate therapy for HIV.

Persons coinfected with HIV are at higher risk of developing side-effects of HCV therapy, and should be monitored more closely for hepatotoxicity and haematological suppression if they are on interferon-based regimen. The concentration of tenofovir will be increase when used with Ledipasvir/sofosbuvir or increased in efavirenz-containing regimens and should be used with frequent renal monitoring if other alternatives are not available.

Treatment and management of HIV/HBV co infection

HBV screening and vaccination: All persons newly diagnosed with HIV should be screened for HBsAg and anti-HBs to identify those with chronic hepatitis B infection, and vaccinated if non-immune.

When to initiate ART in HBV/HIV-coinfected persons: The 2015 WHO ARV guidelines recommends to treat all HIV-infected persons. HIV/HBV-coinfected persons should be simultaneously treated for both HIV and HBV infection, and receive ART that is active against both viruses. A tenofovir-based regimen is the recommended therapy. To date, no viral resistance to tenofovir in vivo has been described, although resistant strains have been identified in vitro. If tenofovir is absolutely contraindicated, entecavir may be an option, as part of an active ART regimen.

Other considerations: An increase in ALT will be the result of HIV-related opportunistic infections, ARV medicines, alcohol used, flares of hepatitis B due to ART-associated

immune reconstitution, HBV reactivation and so on. Increased drug levels of efavirenz which increases the risk for central nervous system toxicity may occur in advanced liver disease. Renal function (and possibly bone function) should be monitored at least annually because of their impact on renal and bone metabolism.

Children: In children under the age of 12 years, tenofovir cannot be used, and some children do not require treatment for their HBV infection. In these children, use of a standard ART regimen (that may include the use of lamivudine) may be advisable with subsequent modification to a tenofovir-based regimen when the child is 12 years of age.

HBV x gene integration and HBV/HDV double infection in HCC patients in Mongolia

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Hepatocellular carcinoma (HCC) is very high correlation to HDV and HBV coinfections. HDV infection is closely associated with HBV infection. According to WHO report, newly HDV-infected person who are chronically infected with hepatitis B carrier (superinfection).
HDV superinfection is causes of acute and chronic hepatitis, it is often progressive to cirrhosos.

The aim of our study was to determine HDV and HBx gene integration in human liver genomic DNA of HBV-related HCC patients and in Mongolia.

The genomic DNA isolated from liver biopsy samples of 56 patients with HBV and HCC, as well as one healthy liver sample as a control. For detection of HBx gene PCR method was used.

In the results HBx gene integration was detected in 78,5% of HBV-related HCC patients' liver DNA. HDV and HBV coinfected cases are 25,7%; triple infection with HDV, HBV, HCV cases are 16,9% of HCC patients in Mongolia. This result indicates that HDV infection and HBx gene integration may have a role for HCC development in patients with HBV infection. To clarify the integration sites of HBV X gene and its molecular role of HCC development further studies and international collaboration are needed.

Research on Hepatitis B Virus X protein (HBx): Overview and Recent Progress

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After since the cloning and sequencing technology had applied to the HBV genome research, HBV and the related viruses of animals have been classified as *Hepatdnaviridae*. The fourth unidentified ORF, X-ORF, was found to be conserved among human (HBV) and rodent (WHV and GSHV) but not in avian hepadnaviruses (DHBV). The possible oncogenic role of X protein was focused since the tight association of chronic hepatitis and HCC incidence has been etiologically established and HCC incidence happens in the experimental WHV-infected woodchuck but not in the DHBV-duck model.

During exploring the properties of X-protein, it became evident that X-protein has no counter part in hosts, and no ability to bind DNA. Therefore the reports that HBx activates host and HBV genes related to cancer and inflammation seemed promising to unveil its putative oncogenic property. However, its molecular mechanism is in enigma since no specific target transcription factor(s) could not be assigned and any kind of strong promoters respond to HBx. Transforming ability of HBx, then HCC incidence in HBx-transgenic mice seemed to support the oncogenic property of HBx, although the latter result could not be reproduced by other groups except one. It is accepted at present that HBx alone may not be oncogenic but retain tumor-promoting ability in the presence of weak carcinogenic stimulus.

The many reports on the molecular function of HBx exhibited a wide variety of modulating activities of HBx in cytoplasm and nucleus, such as kinase signaling cascades, mitochondrial function, protein degradation and transcription, with or without specifying its direct interacting partner(s). These results were obtained with transient overexpression or transgenic expression systems, and HBx exhibited promiscuous binding to many host target proteins, then the concept is accepted in the HBx research fields that "HBx is a multifunctional viral regulator" (1, 2). The plasmid construct harboring 1.3 or 1.1 genome-length of HBV genome afforded the chance to examine the possible role of X-ORF on HBV replication. Three reports in J. Virol, 2005 shows the strong augment, but not essential effect of HBx in transient replication transfected with HBV replicon (3,4). Tang H et al demonstrated the augmentation effect of HBx might be due to the transcriptional co-activator function by scanning with a clustered alanine substitution library of HBx (3). Leupin O et al showed the augmentation of HBx requires the HBx-DDB1 binding with mutants HBx defective in the DDB1-binding. A definitive

answer on the virological role of HBx must be addressed with HBV virions harboring wild or X(-) HBV genome. Lucifora J et al clearly demonstrated the essential role of HBx at the step of pgRNA transcription, thus replication, neither at infection, cccDNA production nor assembly in human primary hepatocytes and HepaRG cell line (5). Supporting this result, several groups reported the recruitment of HBx to the minichromosome of HBV cccDNA together with chromatin remodeling proteins and transcriptional coactivators which make the cccDNA chromatin structure in active state.

Recently Strubin's group opened a new paradigm on the essential role of HBx by identifying a new HBx-interacting player after their deployment of the research on the HBx-DDB1 interaction (6). The Smc5/6 complex, the critical factors to resolve contorted replicated chromosome, was recruited to HBx, then subjected to degradation by the DDB1-containing E3 ubiquitin ligase that HBx hijacked. They demonstrated the downregulation of Smc5/6 in wild HBV-infected humanized liver, and also resolved the enigma that HBx specifically activates pgRNA synthesis of episomal form (cccDNA) but not integrated one. These results by his group provides a testable scenario to unveil the biological role of HBx, buy several basic and clinical questions remain elusive; how the Smc5/6 complex represses pgRNA transcription, whether HBx has additional roles to augment pgRNA transcription after when Smc5/6 was degraded, whether clinically genetic variation of Smc5/6 is associated to hepatic inflammation and/or HCC incidence.

References.

1. Seishi Murakami. (2001) Hepatitis B Virus X protein: A multifunctional regulatory protein. J Gastroenterol. 36:651-660.
2. Tang H et al. (2006) The Molecular functions and the biological roles of Hepatitis B Virus X protein (HBx). Cancer Sci., 97: 977-983.
3. Tang H et al. (2005) The transcriptional transactivation function of HBx protein is important for its augmentation role in hepatitis B virus replication. J. Virol., 79: 5548-5556.
4. Leupin O et al. (Strubin M) (2005) Hepatitis B Virus X protein stimulates viral genomic replication a DDB1-dependent pathway distinct from leading to cell death. J. Virol., 79: 4238-4245.
5. Lucifora J et al. (Protzer U) (2011) Hepatitis B virus X protein is essential to initiate and maintain virus replication after infection. J Hepatol, 55: 996-1003.

6. Decorsiere A et al (Strubin M) (2016) Hepatitis B virus X protein identifies the Smc5/6 complex as a host restriction factor. Nature, 531: 386-389.

ABSTRACT: HBV and HCV infected patient treatment in VietNam

In some survey, the prevalence of HBV in Việt Nam is 10-20% population especially in pregnant women (10-16%) and in children (2-6%). Safe and effective vaccines against HBV infection have been popular in VietNam since 1997. Antiviral treatment is the only way to reduce morbidity and mortality from chronic HBV infection, Peg IFN and Tenofovir, Entacavir have been the primary treatments to date in VietNam. Peg IFN produces a durable response in a moderate proportion of patients but has undesirable side-effects. Tenofovir, Entacavir monotherapy or in combination with nucleoside analogs are options for patients who have developed resistance to other therapies for chronic HBV, including lamivudine and adefovir. APRI, FIB4, FibroScan were simple, available and non invasive biochemical marker to predict the presence or absence of liver fibrosis and cirrhosis with AUROC >0,7 in VietNam. There is a correlation between concentrations of HBsAg and HBV DNA in serum and it can be used as a marker widely for monitoring of HBV treatment in Việt Nam.

Prevalence of hepatitis C infection in Viet Nam is low in the general population (4-6%) but concentrated among people who inject drugs. Up to 97% of people who inject drugs, 26,6% dialysis patients have been infected with hepatitis C virus. HCV-1 (30,4%), HCV-6 (54,4%) are the most common in Vietnam. Treatment for chronic HCV is based on National guidelines propose that PegIF with RBV is the current standard of care in VietNam since 2013. Health insurance pay 50% price of PegIFN since 2014. Treatment is taken place in large cities such as Ha noi, Hue, Ho Chi Minh city.Vietnamese patients also appear to have a higher likelihood of achieving a SVR than Caucasians who receive the corresponding regimen. Rapid virological response (RVR) is the single best predictor of treatment response, such as lower body weight and higher doses of RBV, can help ensure the achievement of SVR in Vietnamese pantients. The first protease inhibitor indicated for use in HCV infection, boceprevir, sofosbuvir, telaprevir in case HCV-1 have failed standerd regiment. The combination of ombitasvir/paritaprevir/ritonavir and dasabuvir for the treatment of genotype 1 chronic hepatitis C infection in adults, including patients with compensated cirrhosis. This all-oral regimen can be used with or without ribavirin. The treatment duration is 12 weeks for patients without cirrhosis and 24 weeks for those with cirrhosis. We hope that with national strategy for viral hepatitis control till the year 2020 can reduce new hepatitis B,C, and increase access to appropriate management and care for the HBV, HCV.

Innate immunity during HCV infection

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Treatment of hepatitis C virus (HCV) infection has experienced a major advancement with the advent of the new direct acting antivirals (DAA). Current HCV infection cure rates exceed 90%. However, an unexpected high rate and pattern of tumor recurrence coinciding with HCV clearance has been reported, though based in a very small cohort of patients (Reig M et al. J Hepatol. 2016). Moreover, reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection has been reported. These findings are probably due to the loss of endogenous IFN signaling during the DAA treatment against HCV.

We previously showed interferon stimulated genes (ISGs) were up-regulated in liver of treatment resistant IL28B genotype (TG/GG: rs8099917) and were down-regulated in liver of treatment sensitive IL28B genotype (TT: rs8099917) (Gastroenterology 2011, Hepatology 2014). We investigated the association between the IL28B genotype and the biology and clinical outcome of HCC patients receiving curative treatment. Genotyping of 183 HCC patients with CH-C who were treated with hepatic resection or radiofrequency ablation (RFA) was carried out. Multivariate Cox proportional hazard analysis demonstrated that the IL28B TT genotype was significantly associated with HCC recurrence ($p = 0.007$; hazard ratio, 2.674; 95% CI, 1.16-2.63). Histological findings showed that more lymphocytes infiltrated into tumor tissues in the TG/GG genotype (Clin. Cancer Research 2013). Thus, endogenous IFN signaling could be associated with HCC recurrence and IL28B TG/GG with high ISGs, therefore, prevented the recurrence of HCC.

To stimulate innate immune reaction, we found a unique gene, LECT2, a secretary protein mainly expressed in hepatocytes. LECT2 was specifically induced by IL28B. We found LECT2 enhanced IFNβ induction 5–10 fold and increased induction of ISGs through the activation of IRF3, IRF7, and JAK/STAT pathway. Interestingly, the expression of LECT2 in HCC tissues were substantially repressed compared with non-tumor liver tissues. Our data suggest that LECT2 plays a potentially important role in the innate immune system in hepatocytes and might be a therapeutic target for preventing and treatment of HCC.