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Cytopathogenicity Modifies Antigenic Expression Profiles in Viral Hepatitis B-Infected Hepatocytes

Lawrence M. Agius
Department of Pathology, St Luke's Hospital, Gwardamangia,
University of Malta Medical School, Msida, Malta Europe

Abstract: A whole spectrum of consequence of viral hepatitis injury implicates directly a modulated antigenic profile expression that further modifies quantitatively the immune response to the infection. It is in terms of such consequence that cytopathic injury and cytotoxicity as induced by T lymphocytes induce an ongoing injury to hepatocytes. Persistence of injury is itself another parameter of activity in accounting for transformation of the expression profile of infected hepatocytes. The immune response would be sustained in the presence of persistent viral DNA in serum and tissues and in further allowing for transformation. The infected hepatocyte is indeed an expression consequence of injury that is precipitated by viral infection and driven by changing antigenic profile reactivity of the liver cells. The cytotoxic T lymphocytes would transcend aspects of targeting or pooling dynamics within the liver but would promote consequences of injury as quantitatively predetermined immunologic response in perinatal or adult studies. Derived consequence of hepatocyte injury ranges from clearance of virus to acute and chronic hepatitis to a persistent state of antigenicity that perhaps may culminate in hepatocellular carcinogenesis.

Key words: Modifies, hepatitis, consequences, infection

IMMUNE-MEDIATED INJURY

Immune-mediated injury to hepatocytes in viral hepatitis B infection appears to arise in terms of kinetics of activity of cytokines and of cytotoxic CD8 + T lymphocytes[1]. Homeostatic systems of control of viral antigen expression would prove a critical factor in eliciting immune reactivity[2]. Antigen presentation is itself a parameter of highly variable character in the evolution of an immune response.

The actual interactive exchange of viral particles with hepatocytes appears indicative of a number of possibly variable responses implicit to the genomic expression or of antigenic presentation of viral hepatitis B particles. One might view antigenicity of viral particle presentation as a variable reproduction of epitopes that evolves with progression of the hepatitis B infection. There would develop reactivity in the presentation and subsequent elicitation of the immune response that critically implicates inflammatory cytokine production.

The actual delivery of cytokine and other necroinflammatory endproducts including immune mediators would perhaps illustrate a complex interaction reflected particularly in the, at times, generation of neoplastic transformation as hepatocellular carcinoma[3].

It would be significant to consider the full reactivity pattern of hepatitis B infection critically dependent on an immune response as illustrated by a tendency for viral persistence in perinatally acquired infections.

Necroinflammatory progression of hepatitis B infection constitutes a particular inter-reactivity that dynamically integrates antigen presentation with cellular and cytokine stimulatory effects. E-selectin may play a role in pathogenesis in chronic hepatitis B[4]. In fact, a combination of inhibitory and stimulatory effects appears a critical kinetic mechanism in the evolution of a persistently active hepatitis viral infection, including cases in childhood[5]. It would be significant to consider the evolution of viral infection as critical to the outcome dynamics of liver injury or even as malignant transformation of hepatocellular carcinoma.

Persistence of viral infection proves a chief determinant not only of continuously active viral replication but particularly of a variably productive mechanism of antigenicity dynamics and reactive immune response. In severe immune suppression, chronic HBV patients may develop significant liver disease[6].

INFLAMMATORY REACTIVITY

The peculiar dynamics of conversion of inflammatory reactivity of viral hepatitis B to hepatocellular carcinoma

Corresponding Author: Lawrence M. Agius, 27 Ballarat Guzeppi Caruana Street, Tal-virtu, Rabat, RBT09 Malta Europe

indicate a reversion to an early evolutionary or developmental stage of modified antigenicity relative to immune response.

An immature immune response relates to a persistence of a viral antigenicity that further progresses subsequently with maturation of the immune response. In such terms an immature immune system further matures within an essential context of heavy dose viral hepatitis B antigenicity. In such a setting, the pre-existing presence of viral hepatitis B antigen presentation itself undergoes conversion in terms of an evolving critical form of antigenicity both as expression of the antigen and its presentation to the actively evolving immune system response[7].

Kinetics of development of hepatitis B viral infection appear integral to an evolving transformation of the immune reactivity both involving antigen presentation as expression systems. Serum cytokine values reflect pathological differences of the individual disease phases, with higher IL-10 and TNF-alpha on disease progression[8].

VIRAL LIFE-CYCLE

A life-cycle of viral infection would incorporate immunobiology particularly of chronic hepatitis with a tendency for hepatocellular carcinogenesis. Failure to mount a perinatal immune response appears a specific correlate of such hepatitis B viral infection within a context especially of dynamic risk of developing hepatocellular carcinoma.

A multispecific humoral immune response together with cellular immunity characterizes adult infection. Such diversity in immune reactivity would correlate with a distinct propensity for persistent or latent infection by hepatitis B virus. Biologic consequences of even the dominant mutations of hepatitis B virus have not been well-characterized[9].

Such persistent infection appears intrinsically coupled to suppression or inactivation of virus in an essentially non-cytolytic intracellular or intrahepatocyte series of mechanisms.

INFLAMMATORY CYTOKINES

Inflammatory cytokines liberated by lymphocytes and monocytes would hence influence immune reactivity and a host-cell-virus inter-reactivity based on suppression of viral antigen expression and presentation and also on inactivation of viral replication. A system relationship particularly between antigen expression by virus with active replication of virus and hepatocytes would correlate with the promotion of pathways of induced injury especially promoted by cytolytic T cell responses.

Mechanism of viral entry to within hepatocytes is linked to subsequent segregation of the DNA genome to the nucleus where the viral plus DNA is synthesized.

There is no evidence that HBV alone causes severe liver damage in individuals with "anti-HBc" alone[10].

Core antigen synthesis leads to viral capsid particles in the cytoplasm and nucleus of hepatocytes in a manner that correlates with genomic replication. Pregenomic RNA and reverse transcription to DNA and plus strand DNA are essential steps in the delivery of encapsulated circular DNA genomes for amplified recycling within the hepatocytes.

CYTOLYTIC LYMPHOCYTES

A particular propensity for delivery of cytolytic T lymphocytes to infected hepatocytes appears linked to onset dynamics of such amplified hepatitis virus B replication. Modulation of immune reactivity in addition would incorporate a role for injury to hepatocytes infected by hepatitis B virus and for an inactivation of systems of antigen expression and presentation by virus in other hepatocytes. Partial delipidation of HbsAg strikingly increases the T-cell antigenicity of this viral antigen[11].

In such a setting, a dual process evolves consisting of killing of infected hepatocytes and inactivation of antigenicity systems to modulate further the overall immune response to the hepatitis B virus infection.

ENDOPLASMIC RETICULUM

Endoplasmic reticulum participation in binding of the nascent precore protein would constitute a mechanism of preparation for subsequent secretion of viral particles and, in particular, would play an essential role in creation of the antigenicity induced by viral particles. Indeed, the ground-glass hepatocytes are particularly susceptible to the cytopathic effect of interferon gamma.

A concept of infected hepatocyte killing as a central mechanism in viral particle clearing and of the hepatitis B virus infection appears a result of ongoing kinetic evolution of incorporated viral genomes within the hepatocyte nucleus. After liver injury, parenchymal regeneration occurs through hepatocyte replication, with contributions in severe cases by oval cells and small hepatocyte like progenitor cells[12]. Indeed, such hepatocyte nuclear inclusion of viral genome appears integral in turn to various systems of viral antigen expression to further promote antigenicity of viral particles.

An interesting aspect of hepatitis B virus infection is a concept of latent infection that suppresses such antigenicity in a setting of ongoing injury to host hepatocytes. One might speak of a continuous process of passage of viral genome to the hepatocyte nucleus and of subsequent binding in the endoplasmic reticulum in an overall hyperplasia phenomenon.

Amplified hyperplasia of the endoplasmic reticulum would correlate with the possible future development of hepatocellular carcinogenesis[13].

IMMUNE SURVEILLANCE

Escape of viral antigen from immune surveillance would constitute in particular a manifestation of a considerable degree of acute infectivity of the viral particles.

Viral persistence appears integral to kinetics of evolution of a viral infection independent of essential antigen expression or presentation to the immune system. Hepatitis B viral mutants can emerge in patients due to selection pressure from immune response or treatment options[14].

In such a manner, essential dynamics of the relationship of the viral replicative process within host hepatocytes determines and sets the characteristic parameters of evolution of processes ranging from viral antigen expression to presentation of such antigenicity to the immune system.

MODULATORY EFFECT

An extensive and profound degree of modulatory effect appears to constitute an essential axial pathway in the evolution of an infection that incorporates clearance of hepatocytes as part of the antigenicity phenomenon.

In such terms, the actual killing of acutely infected hepatocytes correlates with ongoing modulation of the immune response to the virus. In a sense, the immune reactivity is directed more to the infected hepatocyte rather than specifically to the hepatitis B virus particle itself.

TRANSFORMATION OF THE ANTIGENIC PROFILE

The creation of the cytotoxic T lymphocyte response would implicate the transformation of the antigenic profile of the infected host hepatocyte. Identification and targeting of host hepatocytes appear primary determinants in the development of an immune response that transforms antigenic identity from the virus particle to the infected hepatocyte.

Such transfer would allow for disease pathogenesis that promotes also clearance of the virus as part of such progression of the liver pathology. Variability in pathogenesis of the liver injury would implicate persistence of the infection in terms of a transforming role of the viral particle in inducing a modulated immune response. Indeed, there might evolve an immunologic type of injury in the absence of cytopathic viral injury. Such a dual representation of hepatocyte injury ranging from viral cytopathic effect to modulated immune cytotoxic injury might characterize a broad spectrum of hepatitis B pathogenesis reflected in acute or chronic infective state or even hepatocellular carcinogenesis[15].

Coinfection with hepatitis B and C carries a significantly greater risk of fulminant liver failure, cirrhosis and hepatocellular carcinoma[16]. Further to such distinguishing features, it would appear that acute viral hepatitis B infection is also modulated significantly by an immune response that is cytotoxic to host hepatocytes specifically infected by the virus. Dynamics of clearance of the virus from infected host hepatocytes appear primarily determined by the degree of reactivity of the cytotoxic lymphocyte response that otherwise is cytopathic for the host hepatocyte. The possibility of HBV reactivation should be considered with advanced HIV infection[17].

TARGETING

Virus and hepatocyte cytotoxicity represent a dual targeting that cytopathically converts dynamics of a persistent viral infection to a full array of ongoing injuries including also acute pathogenesis and also carcinogenesis. Chronic carriers of hepatitis B infection often harbor virus strains with mutations in the precore region[18].

Acute infection is a significant consequence of the modulated lymphocyte response that resembles in part kinetics of a chronic infection that converts cytotoxicity of lymphocytes for the virus to a damaging clearance phenomenon involving loss of individual hepatocytes.

Persistence of very low levels of viral DNA would constitute the persistence of a viral presence in the absence of a previously acute viral hepatitis state. Viral persistence would provide for the basis of ongoing injury that transforms antigenicity of infected hepatocytes. Evolving antigenicity in the presence of injury to hepatocytes would allow for persistence of viral DNA that further promotes immunologic injury to other hepatocytes.

CHRONICITY OF INFECTION

Chronicity of the viral infection would constitute a transformed acute response that evolves typically more in terms of amplification of viral presence or persistence in serum and liver. Chronic HBV infection consists of four phases of immune tolerance, immune clearance, inactive carrier state and reactivation. HBV replication persists throughout the course of chronic HBV infection[19].

The immune response would allow for long term persistence of the virus beyond considerations of hepatocyte injury and in terms specifically implicating evasion of viral particles both systemically and intra-hepatically. Liver disease is a growing problem in HIV-infected patients[20].

Viral systemic evasion from the immune response would constitute a significant mechanism of disease pathogenesis based on inactivation of the antigenic reactivity pathways resulting from involvement of hepatocyte expression profiles.

EXPRESSION PROFILES

One might view complicity of hepatocyte expression profiles as masking the antigenicity of infected viral particles and thus allowing for persistence of the virus after an attack of acute hepatitis B. The development of cirrhosis in hepatitis B infection correlates strongly with the level of circulating virus[21].

Clearance of viral infection consists of an acute response that subsequently persists at low antigenic level and as low DNA level in serum. Serum HBV DNA level is a marker of viral replication[22]. Occult HBV infection is a frequent phenomenon[23].

Masking of antigenic viral profiles therefore would constitute an active mechanism of involvement of cytopathic lymphocyte response in cases recovering from an acute episode of viral hepatitis. The integral representation of chronically persistent high levels of viral particles in patients who are not immunoreactive constitutes a chronically indolent infectious state of the hepatocyte beyond considerations of dynamics of viral clearance.

MASKED ANTIGENIC PROFILES

All the hepatocytes would tend to be infected in terms of ongoing consequences of an injury that subsequently masks the antigenic viral profile.

Hepatocyte expression of viral consequence would allow for evolution of an injury that quantitatively varies from acute and fulminant to chronic and indolent[24]. Furthermore, persistence of viral DNA would constitute a stimulus for hepatocellular carcinogenesis linking hepatitis cases to a dynamic malignant transformation of the infected hepatocytes. Integration of viral DNA into chromosomal DNA may occur rarely during acute hepatitis B and might play a role in hepatocarcinogenesis[25].

A pooling of lymphocytes within the liver would determine dynamic hepatocyte clearance. Indeed, the vascular basement membrane and endothelium would constitute another mechanism of antigenic masking of infected hepatocytes. In this sense, a series of masking phenomena would allow for proliferation of hepatitis B virus in terms of inaccessibility of cytopathic lymphocytes to individual infected hepatocytes.

Activation induced cell death constitutes a further characterization of onset dynamics of the immune response based on amplification of cytopathic T lymphocyte response.

INTERPLAY

A complex interplay of effects of consequence involves acute hepatitis as manifested dynamics of a hepatocyte injury further promoting active masking of antigenicity. Antigenic profiles of derived consequence to the hepatocyte injury therefore would fluctuate quantitatively rather than qualitatively in terms of subsequent stimulation of the cytopathic T lymphocyte response.

Pathogenesis of the hepatitis state appears a derived result of injury to hepatocytes that tends to persist indefinitely. The necroinflammatory reactivity of hepatocyte injury involves consequences of such injury in terms of possible subsequent hepatocellular carcinogenesis. Macrophage migration inhibitory factor counteracts apoptotic activity of HBX and may contribute to hepatocellular carcinogenesis[26].

Virally encoded antigens are a recharacterization of the expression profile of infected hepatocytes. In such terms, a wide spectrum of fluctuating severity involves the infected hepatocyte and the immune response to it. The use of hepatitis B vaccine has reduced the incidence of new infection in many regions[27].

CONCLUSION

Inferred consequences of active viral hepatitis B relate particularly to a persistent modulation of expression systems of hepatocyte antigenicity and injury. Related development of acute and chronic hepatitis evolves in terms of an immune response conditioned in turn by antigenicity expression systems determining immune reactivity to injured hepatocytes. CD58 expression as an intercellular adhesion molecule correlates with severity of HBV infection and degree of liver injury[28]. Hepatocyte injury would prove a dominant determining factor in such modulated expression systems of antigenicity profiles.

Strict dynamics of definition of progression in Hepatitis B infection would implicate a particular tendency for masking of antigenic profiles. A transfer, in particular, of viral epitope determinants to the hepatocyte expression profile might entail a renewal process of viral replication and subsequent progression of clearance mechanisms.

Indeed, a full array of profiles expressed in terms of a basic transformation of ongoing dynamics of infection might be followed by the activation of cytotoxic CD8+ T lymphocytes[13].

Defining clearance mechanisms of virally infected hepatocytes might in fact evolve particularly due to the subsequent involvement of the endoplasmic reticulum. The ground-glass hepatocytes would indicate a predisposition for progression of the viral infection irrespective of binding kinetics of viral genome.

Recognition of specific characteristics of a putative masking phenomenon of antigenic profiles might allow for the definition of a process of transfer to hepatocyte endoplasmic reticulum in the overall process of progression of the infection. Positive anti-HBc may be related to T-lymphocyte activation and negative anti-HBc may imply immune tolerance in these patients[29].

An albumin intermediary role in the transfer entry of hepatitis B virus into the hepatocyte might perhaps further allow for definition of subsidiary factors in such antigenic masking. The parenteral spread of infection in hepatitis B would correlate with a long incubation period of 6 weeks to 6 months. Such dynamics of acquisition of the infection might entail an ongoing process of increasing susceptibility to the virus with increasing dose of exposure[30]. Hepatitis B virus is a classic process of clearance of the infected host cells that implicates hepatocytes as targeted onset of the inflammation and subsequent individual cell involvement.

One might indeed further redefine the hepatitis as a realized onset of inflammation with a particular propensity for persistence of the viral antigen within the host cells. Such antigenic persistence would further compromise the development of subsequent transformation to an integral representation of hepatocyte expression profiles that induce liver injury. Seroclearance of HbsAg confers favorable long-term outcomes in the absence of hepatocellular carcinoma or of decompensated liver cirrhosis[31].

The histopathologic features of viral hepatitis implicate the infiltration of the portal tract in a manner that may progress to destruction of the portal limiting plate. Fibrosis indicates a persistence of the viral antigen as a chronic infection in inducing viral replication. An essential difference between acute hepatitis B and chronic infection would allow for the development of dynamic injury that kinetically transforms the expression profile in antigen recognition. Escape of mutated hepatitis B virus may confer selective advantage to the virus in a given replicative environment[32].

One defining parameter is the destruction of the limiting plate that allows for the institution of chronic injury to the liver lobule.

In this sense, it is significant that lymphocytes are themselves possible targets in the subsequent increasing chronic injury to the liver. Lymphocytes appear to be vehicles of transfer of viral antigenicity that entails progression of expression profiles of hepatocytes.

The fibrosis and cirrhosis of chronic hepatitis B infection are particularly implicated in the malignant transformation[33]. Persistence of chronicity of the infection correlates with the long incubation period and would entail a particular susceptibility to hepatocellular carcinogenesis[34]. Indeed, fibrosis and disorganization of the hepatic lobule would further develop as regenerative nodules. Regeneration and implied injury to hepatocytes and possibly also to infiltrating lymphocytes appear a resolution of pathways that further define the infectious state in terms of the tendency for chronicity. Effective suppression of viral replication may reduce the risk for hepatocellular carcinoma[35].

The acute stage of the infection would further characterize dynamics of possible development of the chronic hepatitis stage in terms particularly of distribution of the ground-glass injury to individual hepatocytes that are associated with persistent necroinflammatory foci. Only insofar as progression allows for chronicity to result can there evolve a further redefinition of the hepatocyte injury integrally evolving as regenerative attempts of the lobule. It would appear that chronicity of the hepatitis B viral infection constitutes a recharacterization of infection and of expression antigen profiles; these would be primarily conducive to persistent targeting of the hepatocytes. Inflammation and lymphocyte response would induce ongoing transformation of antigenic representation of the infecting virus as injured hepatocytes.

REFERENCES

1. Boettler, T., E. Panther, B. Bengsch, N. Nazarova, H.C. Spangenberg and H.E. Blum *et al.*, 2006. Expression of theinterluekin-7 receptor alpha chain (CD127) on virus-specific CD8+ T cells identifies functionally and phenotypically defined memory T cells during acute resolving hepatitis B virus infections. J. Virol., 80: 3532-3540.

2. Huang, C.F., S.S. Lin, Y.C. Ho, F.L. Chen and C.C. Yang, 2006. The immune response induced by hepatitis B virus principal antigens. Cell. Mol. Immunol., 3: 97-106.
3. Chan, H.L and J.J. Sung, 2006. Hepatocellular carcinoma and hepatitis B virus. Semin Liver Dis., 26: 153-161.
4. Yan, M.X., H.T. Mao, Q. Liu, W.Q. Wang and Y.Q. Li, 2006. Elevated levels of serum soluble E-selectin in patients with chronic hepatitis B: Correlation with T lymphocyte subsets, NK cells and liver inflammation. Hepatol. Res., [Epub ahead of print].
5. Elisofon, S.A. and M.M. Jonas, 2006. Hepatitis B and C in children: current treatment in future strategies. Clin. Liver Dis., 10: 133-148, vii.
6. Meuleman, P., L. Libbrecht, S. Wieland, R. De Vos, N. Habib and A. Kramvis *et al*., 2006. Immune suppression uncovers endogenous cytopathic effects of the hepatitis B virus. J. Virol., 80: 2797-2807.
7. Villeneuve, J.P., 2005. The natural history of chronic hepatitis B virus infection. J. Clin. Virol., 1: S139-42.
8. Ayada, M., T. Ishikawa, A. Okumura, J. Tanabe, H. Ito and T. Ohashi *et al*., 2006. Alteration of serum cytokine balances among different phases of chronic hepatitis B virus infection. Hepatol. Res., [Epub ahead of print].
9. Tong, S., 2005. Mechanism of HBV genome variability and replication of HBV mutants. J. Clin. Virol., 1: S134-8.
10. Knoll. A., A. Hartmann, H. Hamoshi, K. Weislmaier and W. Jilg, 2006. Serological pattern "anti-HBc alone": Characterization of 552 individuals and clinical significance. World J. Gastroenterol., 12: 1255-1260.
11. Desombere, I., A. Willems, Y. Gijbels and G. Leroux-Roels, 2006. Partial delipidation improves the T-cell antigenicity of hepatitis B virus surface antigen. J. Virol., 80: 3506-3514.
12. Vig, P., F.P. Russo, R.J. Edwards, P.J. Tadrous, N.A. Wright and H.C. Thomas *et al*., 2006. The sources of parenchymal regeneration after chronic hepatocellular liver injury in mice. Hepatology, 43: 316-324.
13. Lin, S.M., J. Cheng, Y.Y. Lu, S.L. Zhang, Q. Yang and T.Y. Chen *et al*., 2006. Screening and identification of interacting proteins with hepatitis B virus core protein in leukocytes and cloning of new gene C1. World J. Gastroenterol., 12: 1043-1048.
14. Coleman, P.F., 2006. Detecting hepatitis B surface antigen mutants. Emerg. Infect. Dis., 12: 198-203.
15. D. Cougot, C. Neuveut and M.A. Buendia, 2005. HBV induced carcinogenesis. J. Clin. Virol., 1: S75-8.
16. Liu, C.J., J.M. Liou, D.S. Chen and P.J. Chen, 2005. Natural course and treatment of dual hepatitis B virus and hepatitis C virus infections. J. Formos. Med. Assoc., 104: 783-791.
17. Clark, S.J., S. Creighton, M. Horner, H.M. Smith, B. Portmann and C. Taylor *et al*., 2006. Reactivation of latent hepatitis B virus infection with HIV-related immunosuppression. Intl. J. STDAIDS, 17: 67-69.
18. Igman, M., B. Lindqvist and K. Kidd-Ljunggren, 2006. Novel mutation in hepatitis B virus preventing HbeAg production and resembling primate strains. J. Gen. Virol., 87: 307-310.
19. Yim, H.J. and A.S. Lok, 2006. Natural history of chronic hepatitis B virus infection: What we knew in 1981 and what we know in 2005. Hepatology, 1: S173-81.
20. Thomas, D.L., 2006. Growing importance of liver disease in HIV-infected persons. Hepatology, 1: S221-9.
21. Iloeje, U.H., H.I. S.U.J. Yang, C.L. Jen, S.L. You and C.J. Chen *et al*., 2006. Predicting cirrhosis risk based on the level of circulating hepatitis B viral load. Gastroenterology, 130: 678-686.
22. Chen, C.J., H.I. Yang, J. Su, C.L. Jen, S.L. You and S.N. Lu *et al*., 2006. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. JAMA., 295: 65-73.
23. Chemin, I. and C. Trepo, 2005. Clinical impact of occult HBV infections. J. Clin. Virol., 1: S15-21.
24. Hui, C.K. and G.K. Lau, 2005. Immune System and hepatitis B virus infection. J. Clin. Virol., 1: S44-8.
25. Kimbi, G.C., A. Kramirs and M.C. Kew, 2005. Integration of hepatitis B virus DNA into chromosomal DNA during acute hepatitis B. World J. Gastroenterol., 11: 6416-6421.
26. Zhang, S., R. Lin, Z. Zhou, S. Wen, L. Lin and S. Chen *et al*., 2006. Macrophage migration inhibitory factor interacts with HBX and inhibits its apoptotic activity. Biochem. Biophys. Res. Commun., 342: 671-679.
27. Ocama, P., C.K. Opio and W.M. Lee, 2005. Hepatitis B virus infection: Current status. Am. J. Med., 118: 1413.
28. Xie, M., X.L. Wang, Y.Q. Ji, J. Li, Z.J. Meng and L. Shi *et al*., 2005. Study on the relationship between level of CD58 expression in peripheral blood mononuclear cell and severity of HBV infection. Chin Med. J. (Engl), 118: 2072-2076.
29. Xiao, P., Q.F. Chen, Y.L. Yang, Z.H. Guo and H. Chen, 2006. Serum soluble interleukin-2 receptor levels in patients with chronic hepatitis B virus infection and its relation with anti-HBc. World J. Gastroenterol., 12: 482-484.

30. Wright, T.L., 2006. Introduction to chronic hepatitis B infection. Am. J. Gastroenterol., 1: S1-6.
31. Arase, Y., K. Ikeda, F. Suzuki, Y. Suzukin, S. Saitoh and M. Kobayashi *et al*., 2006. Long term outcome after hepatitis B surface antigen seroclearance in patients with chronic hepatitis B. Am. J. Med., 119: 9-16.
32. Pawlotsky, J.M., 2005. The concept of hepatitis B virus mutant escape. J. Clin. Virol., 1: S125-9.
33. Saini, N., A. Bhagat, S. Sharma, A. Duseja and Y. Chawla, 2006. Evaluation of clinical and biochemical parameters in hepatocellular carcinoma: Experience from an Indian center. Clin. Chin. Acta., [Epub ahead of print].
34. Zhang, X., H. Zhang and L. Ye, 2006. Effects of hepatitis B virus X protein on the development of liver cancer. J. Lab. Clin. Med., 147: 58-66.
35. Sherman, M., 2006. Optimizing management strategies in special patient populations. Am. J. Gastroenterol., 1: S26-31.