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EDITORIAL

Compartmentalization of hepatitis B virus: Looking beyond the liver

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Abstract

Hepatitis B virus (HBV) is classically considered to be hepatotropic, but accumulating evidences strongly support its extra-hepatotropic nature too. HBV nucleic acids and proteins have long been reported in a variety of extra-hepatic tissues. Of these, HBV has been studied in details in the peripheral blood mononuclear cells (PBMCs), due to its accessibility. From these studies, it is now well established that PBMCs are permissive to HBV infection, replication, transcription and production of infective virions. Furthermore, molecular evolutionary studies have provided definite evidences towards evolution of HBV genome in PBMCs, which is independent of evolution occurring in the liver, leading to the emergence and selection of compartment specific escape variants or drug resistant strains. These variants/resistant strains of HBV remain restricted within the PBMCs and are rarely detected in the serum/plasma. In addition, HBV infected PBMCs have been reported to be directly transmitted through intrauterine modes, and this infection does not correlate significantly with serum HBV surface antigen or HBV DNA markers. This editorial briefly reviews the current knowledge on this topic, emphasizes and delineates the gaps that are required to be filled to properly understand the biological and clinical relevance of extrahepatic tropism of HBV.

Key words: Lymphotropism; Compartmentalization; Hepatitis B virus; Peripheral blood mononuclear cell; Genotype

Core tip: This editorial discusses the phenomenon of compartmentalization of hepatitis B virus (HBV) in the peripheral blood mononuclear cells, their clinical relevance in emergence of escape mutants/drug resistant strains and also in transmission of infection through intrauterine routes. Referring to findings reported in some of the recently published articles on this topic, possible implications of compartmentalization is discussed with a focus on knowledge gaps that need to be filled to better understand HBV biology and pathology.

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TEXT

Hepatitis B virus (HBV) belongs to the family Hepadnaviridae of enveloped, partially double-stranded DNA viruses and is classically considered to be a hepatotropic virus[1]. However, HBV proteins and nucleic acids (both DNA, RNA) have been documented in a variety of extrahepatic sites, including peripheral blood mononuclear cells (PBMCs), lymph nodes, spleen, bone marrow, brain, cerebro-spinal fluid[2-7]. As compared to other tissues, extrahepatic tropism of HBV has been studied in considerable details in the PBMCs, due to their easy access. These cells have been reported to be permissive to HBV infection, replication, production of replicative intermediates and biologically competent virion particles[8-10] strongly supporting the lymphotropic nature of HBV. HBV DNA has also been found to infect bone marrow cells *in vitro*, express HBV antigens, produce virion - like particles containing HBV genome attesting to the fact that progenitor cells are also potential targets for HBV infection[11-13]. Despite the insufficiency of evidences to prove histo-pathological changes due to extrahepatic HBV infection[3,14], the significance of such tropism is enormous from the perspective of long persistence and parallel evolution of the viral genome and its transmission. Two previous case studies among liver transplant patients clearly suggested the restricted persistence of immune escape variants of HBV in PBMCs that acted as a source of re-infection[15,16].

Systematic studies on woodchuck hepatitis virus (WHV, an animal model of hepadnaviral infection), have revealed a number of unique and important facets of lymphotropism of Hepadnaviruses[17-19]. These studies have clearly demonstrated that Hepadnaviruses are strongly lymphotropic in nature and that lymphoid cells serve as an important non-hepatic reservoir for occult persistence of the virus[17,18]. Furthermore, challenge experiments with low doses of WHV was shown to induce primary occult infection, restricted within the lymphatic system, that rarely engaged the liver[18]. Such lymphoid cell restricted infection was transmissible to virus naive hosts as an asymptomatic, occult infection specifically within the lymphoid cells[18]. Interestingly, it was also demonstrated that woodchuck mothers with lymphoid cell restricted occult hepadnaviral infection transmit infection to their offspring, inducing an occult infection, that too remain restricted within the lymphatic system of the offsprings[19]. These evidences indicate a fascinating biology of lymphoid restricted Hepadnaviruses, that is distinct from hepatic infections.

Subsequently, findings resembling the WHV animal model, were found in human HBV occult infections too. A previous study from our research group reported asymptomatic, persistent occult HBV infection, specifically in the peripheral blood leukocytes (PBL), and its possible transmission within members of a family, that lacked HBV DNA in serum, clearly signifying the involvement of lymphatic cells in occult HBV infection[20]. Based on the analysis of HBV sequences isolated from the PBLs, it was observed that despite the presence of two different subtypes of HBV, namely *"ayw"* and *"adw"* (genotypes D and A, respectively) in the family, only subtype *adw* with an immune escape mutation of HBV surface antigen (HBsAg) (G145R) was present in the PBLs of all the family members, that possible acquired HBV by non-sexual intrafamilial modes[20]. The results of this study also suggested the different modes of transmission of HBV subtypes, *i.e.*, possible sexual transmission for *"ayw"* and restricted persistence of *"adw"* with G145R within the PBL and its transmission through non-sexual modes. Later, we demonstrated the PBL specific persistence of HBV subgenotype Ae/A2 with G145R even in unrelated individuals within our study population[8]. Using multiple clonal analyses of HBV DNA from serum and PBL from the same individuals, we detected diverse HBV subgenotypes (D1, D2, D3, D5, Cs/C1 and Aa/A1) in the serum, but could not detect subgenotype Ae/A2 sequences in any of the serum samples analyzed. On the other hand HBV subgenotype Ae/A2 with G145R was exclusively present in the PBL of majority of the subjects, signifying the compartmentalization of a typical HBV type with immune escape variants across a population of unrelated individuals, as previously reported for other viruses too[21-23]. It has long been recognized that HBV interacts with cell receptors present on the hepatocytes and lymphocytes through its preS envelope protein, and amino acid residues 21-47 are crucial for this interaction[24]. Interestingly, from the analysis of HBV multiple amino acid sequences, it has been observed that the length of the preS region vary among HBV genotypes, and also that the preS region is remarkably conserved within genotypes in relation to its marked inter-genotype variability[25]. These facts suggest the HBV genotype specific differences in attachment efficiency to cellular receptors present on diverse cell types, and might be responsible for genotype specific compartmentalization of HBV. Despite being discovered much later than HBV, in sharp contrast to HBV, compartmentalization have been well studied for many other DNA and RNA viruses, including human immunodeficiency virus (HIV), HCV, epstein barr virus[26-29].

In the recent years, studies on genetic variability of HBV in PBMCs and in paired liver/plasma from different groups of HBV infected individuals, have provided strong evidences in support of compartmentalized evolution of HBV within the PBMCs[30,31]. In these studies, researchers have investigated the HBV genetic variability, drug resistance and immune escape mutation patterns in plasma and PBMCs from patients in different phases of the chronic hepatitis B (CHB). Interestingly, in one

study on 22 patients, only 3 patients had identical HBV genotype profiles in plasma and PBMCs[7]. Moreover, the occurrence of immune escape mutations was also found to be mostly compartment specific, being frequently detected in the PBMCs of immune-active CHB patients[7]. Similarly, in another recent study on HIV-HBV co-infected individuals, researchers documented compartment-specific evolution of HBV, as evident by distinct resistance mutation profiles in the plasma and cerebro-spinal fluid, signifying independent evolution of HBV in the central nervous system[32]. Infection of immunologically privileged sites by different viruses, evolution of escape variants is known to be a well recognized immune evasion or immune modulation strategy, well recognized in case of other viruses such as HCV[33] and HIV[34-37].

Apart from providing a privileged site for viruses to persist and evolve, PBMCs also play an important role in virus transmission, through trafficking of maternal PBMCs to the fetal blood[38]. More specifically, recent studies have demonstrated *in utero* transmission of HBV (including vaccine escape mutants) *via* PBMCs, crossing the placental barrier[39,40]. In a recent study on PBMC HBV DNA positive subjects, the authors observed that HBV infected PBMCs from the mothers are able to cross the placental membrane, and infect the fetus[40]. Very recently, a similar study, reported mother-to-infant PBMC trafficking activity in 63% of the study subjects and intrauterine transmission of HBV through this trafficking of infected PBMCs was evident in 71.4% of the neonates[41]. The intrauterine infection rate was much higher in neonates born to PBMC HBV DNA-positive mothers, as compared to PBMC HBV DNA-negative mothers. The results of this study clearly demonstrated that mother to fetal PBMC traffic significantly increased the risk of PBMC HBV infection in newborns. However, surprisingly, no noteworthy association was found between mother to fetal HBV positive PBMC transfer and detection of serum HBsAg and/or HBV DNA positivity in the newborns[41] signifying that mother to fetus transfer of HBV positive PBMCs is not frequently reflected in serum. Additionally, the response to therapeutic approaches has been shown to be different in PBMC restricted HBV, as compared to HBV persisting in the liver[30,31]. Thus, there remains a serious concerns regarding the use of therapeutic approaches for prevention of vertical transmission of HBV, since serum marker based evaluation studies might not represent the actual incidences of transmission of HBV infected PBMCs or the efficacy of therapeutic interventions in containing such transmissions.

From the accumulating data, it is gradually becoming apparent that infection of lymphocytes is an inevitable phenomenon in a number of viral infection, including HBV. Interestingly, this also raise a serious question, if HBV is really a classical hepatotropic virus. Perhaps, further studies in this direction might lead to the answer in future. Nevertheless, persistence of HBV in PBMCs have important implications in long term persistence, emergence of immune escape/drug resistant variants and also in transmission. It is thus extremely essential to study the phenomenon in details to properly understand the mechanisms involved. Further deliberations might be necessary to recommend testing of PBMCs for routine diagnosis of HBV infection, particularly in studies related to monitoring of transmission or therapeutic efficacy. Taking into account the significance of PBMCs in transfusion, transplantation, therapeutics, vaccination, and intrauterine transmission, a comprehensive understanding of HBV infection in these cells is imperative for designing effective strategies to reduce the burden of HBV and other viral infections.

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