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Hbc Alone Profile: Susceptibility versus Protection against *Hepatitis B Virus* could be associated with TNF Production

Araujo Patricià[1,2]*, Gonçalves Giovanna[1,2], Latinni Flavia[1], Barreto Jose Augusto[1] and S Diaz Ricardo[2]

[1]*Colsan - Associação Beneficente de Coleta de Sangue, São Paulo, SP, Brazil*
[2]*Retrovirology Laboratory, Infectious Diseases Division, Federal University of São Paulo (UNIFESP), São Paulo, Brazil*

Abstract

Background: Donors with occult HBV (*Hepatitis B virus*) infection, defined as those who lacked detectable HBsAg but whose exposure to HBV infection was indicated by a positive anti-HBc (HBc alone) profile and the presence of HBV DNA, are a potential source of HBV infection. The aim of this study was to evaluate HBcAg-specific T cell responses, NK cell activity and cytokine levels in blood donors with HBc alone profiles with and without detectable viral DNA.

Methods: From January 2010 to December 2012, a total of 4,252 HBc alone donations were obtained. Of the 4,252 donors, 681 donors had spontaneous HBV clearance (Co/s >10,0 by chemiluminescent assay, undetectable HBV DNA and reactivity to anti-HBc in subsequent donations), 3,097 were classified as false-positive for anti-HBc (Co/s<6,0 in chemiluminescent assay, undetectable HBV DNA and no reactivity to anti-HBc in subsequent donations), 438 were classified as having chronic HBV infection (Co/s>10,0 in chemiluminescent assay, detectable HBV DNA and reactivity to anti-HBc in subsequent donations) and 36 were OBI (anti-HBc positive and detectable HBV DNA). There were 500 healthy blood donors and 434 HBV carriers (HBsAg, anti-HBc positive and detectable HBV DNA). NK cells were tested for cytotoxicity against K562 cells, serum levels of specific cytokines (IL-8, IL-1, IL-10, IL-12, IL-6 and TNF) were assayed by flow cytometry and HBcAg-specific T cell responses were assessed by lymphoproliferation reported in stimulation index (SI) units.

Results: The IL-8 and IL-12 serum levels increased significantly ($p<0.001$) in HBV carriers and OBI, whereas the TNF-α serum levels increased significantly ($p<0.001$) in spontaneous HBV resolvers compared to HBV carriers and OBI. The serum levels of IL-1 and IL-10 were similar in HBV carrier, OBI and spontaneous HBV resolvers. Higher NK cytotoxic activity was observed in spontaneous HBV resolvers compared to HBV carriers, healthy donors and OBI. TNF-α correlated with NK cell activity in spontaneous HBV resolvers. A low intensity of HBcAg-specific T cell responses was observed in healthy donors (SI<3.0) and OBI (SI=8.0 to 10.0) compared to spontaneous HBV resolvers (SI>22.0). TNF-α was correlated with HBcAg-specific T cell responses in spontaneous HBV resolvers.

Conclusion: Our results suggest that TNF-α production may be associated with protection against *hepatitis B virus* through increased NK cell activity and HBcAg-specific T cell responses in HBc alone blood donors.

Introduction

Hepatitis B virus (HBV), as a member of the *hepadnavirus* family, is a small, enveloped, partially double-stranded circular DNA virus that primarily infects hepatocytes. HBV causes acute and persistent liver diseases, which are among the most critical human health problems in high-prevalence regions, such as Brazil [1-7].

Consequently, the pathogenesis of HBV has been the focus of HBV research for years. However, the precise pathogenic mechanism responsible for the various forms of associated liver diseases are poorly defined, especially in regards to occult HBV infection due to its low frequency of occurrence [8-10].

Most studies indicate that the host immune response to the virus has a critical role in determining pathogenesis, as HBV itself is not cytopathic to hepatocytes [11]. The T cell response to viral antigens is essential for both clearance and pathogenesis in HBV infection [11-17]; the specific adaptive cellular immune response to HBV-encoded proteins, principally HBc (core of *hepatitis B virus*), is decisive in determining the out-come of the infection [18]. In a recent study by our group, we observed that spontaneous HBV resolvers showed a strong peripheral blood mononuclear cell (PBMC) response to HBcAg when compared with HBV carriers and occult HBV infection (OBI) corroborating data in the literature [19].

Another important defense against viruses, including HBV, is the natural killer (NK) cell response. Similar to T cells, NK cells can produce high levels of cytokines when these cells are activated and thereby kill infected cells directly or indirectly through cell-cell contacts. NK cells not only have antiviral effects, but they also have regulatory effects on other lymphocytes such as T cells via cytokine production [20,21]. For example, INF-γ can induce MHC class I expression and promote Th1-type T cell responses, and TNF-α can promote the differentiation and maturation of monocytes/macrophages and dendritic cells [22].

In an animal model, it has been shown that NK cell activity, T cells and cytokines (e.g., interleukin-12) can inhibit HBV replication in transgenic mice, thus implying a role for innate immunity in controlling HBV infection in this model [23].

One of the challenges in understanding HBV pathogenesis is elucidating the full repertoire of immune responses that controls viral replication, especially in spontaneous HBV clearance. Additionally, insight into the control of the HBV infection in these individuals could clarify the mechanism of HBV persistence. The goal of this study was

***Corresponding author:** Patrícia Araújo, Associação Beneficente de Coleta de Sangue, Retrovirology Laboratory, Infectious Diseases Division, Federal University of São Paulo (UNIFESP), Avenida Indianópolis, 1260, Indianópolis, São Paulo, Brazil, Tel: 55-1150556588; E-mail: rba.patricia@gmail.com

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