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SHORT COMMUNICATION

KIR and a specific *HLA-C* gene are associated with susceptibility and resistance to hepatitis B virus infection in a Brazilian population

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BRIEF REPORT

The activity of natural killer (NK) cells is partially regulated by killer cell immunoglobulin-like receptors (KIRs) interacting with human leukocyte antigen C (HLA-C) ligands.[1] The ligands of several inhibitory (2DL and 3DL) and activating (2DS and 3DS) *KIR* have been described.[2] Clinical observations of hepatitis B virus (HBV) infection reveal that some cases progress to liver failure, fibrosis, cirrhosis and hepatocellular carcinoma, whereas infection resolution occurs in other cases. However, the mechanisms involved in the susceptibility or resistance to HBV are not completely understood.

Study subjects were recruited from a blood bank, COLSAN-Associação Beneficente de Coleta de Sangue (São Paulo, Brazil), during the period between January 2010 and December 2010. We selected 20 occult HBV infection (OBI) cases and 40 spontaneous HBV resolvers (SHRs). As control subjects, we enrolled 80 healthy blood donors and 42 HBV carriers ($HBsAg^+$, anti-HBc^+ and detectable HBV DNA). The study was approved by the Ethics Committee of the Federal University of Sao Paulo, Brazil, and all study participants signed an informed consent. Sera were screened for anti-HBc and HBsAg using a commercial chemiluminescent microparticle immunoassay (Abbott, Wiesbaden, Germany). A commercial test was used for the detection of HBV DNA (HBV Monitor; Roche, Nutley, NJ, USA). An HBcAg-specific T-cell response, *ex vivo* NK cell activity assay and enzyme-linked immunospot assay for interferon-gamma were performed as previously described.[3] The cytokines tumor-necrosis factor-alpha (TNF-α), IL-1, IL-6, IL-8, IL-10 and IL-12 were evaluated using cytometric bead array assays (human Th1/Th2 cytokine kit; BD Biosciences, San Diego, CA, USA). IL-2, IL-4 and IL-18 assays were performed using an enzyme immunoassay (BioLegend, San Diego, CA, USA). *HLA-C* and *KIR* genotyping was performed using a Luminex MultiAnalyte profiling system (One Lambda, Inc., Canoga Park, CA, USA) with the LABType SSO OneLambda typing kit (One Lambda, Inc.). *KIR* locus typing was performed to detect the presence or absence of 15 known *KIR* genes, including 2DL1-5, 2DS1-5, 3DL1-3, 3DS1 and the pseudogene *KIR*3DP1.

The T-cell response is thought to be a key factor determining the outcome of infection, and it has been shown that chronic HBV is associated with the presence of dysfunctional immune responses.[4] Within this context, we observed that SHRs presented a higher magnitude of HBcAg-specific T-cell responses (SI=62.3, $P<0.0001$) in comparison to HBV carriers (SI=25.4) and OBI cases (SI=26.2).

The role of NK cells in viral clearance during acute HBV infection is also supported by previous reports showing that early high interferon-gamma production by NK cells may contribute to initial control of the infection and allow the timely development of an adaptive immune response.[1] In this study, INF-γ production by T cells was measured to observe the regulatory effect of T cells on NK cell activity *via* INF-γ. Higher NK cell activity (93%±3.1%, $P=0.005$) was observed in SHRs compared to HBV carriers (58%±2.5%) and OBI cases (57%±2.3%), and INF-γ production by T cells was higher in SHRs (1852±2.2 ISCs/10^6 PBMCs, $P<0.0001$) compared to OBI cases (653±2.0 ISCs/10^6 PBMCs) and HBV carriers (685±2.3 ISCs/10^6 PBMCs). Higher T-cell responses and INF-γ production correlated with higher NK cell activity ($P<0.0001$). However, the opposite scenario was observed in cases of HBV persistence: low T-cell responses, INF-γ production and NK cell activity ($P<0.0001$).

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