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KIR and specific HLA-C gene are associated with occult HBV infection and spontaneous HBV clearance in blood donors with ANTI-HBC-ONLY profile

Patricia

Colsan, Brazil

Abstract

In a previous study, we observed that blood donors with an anti-HBc -only serologic profile with detectable HBV DNA had decreased NK cell activity. However in the absence of HBV DNA these blood donors had increased NK cell activity. The antiviral activity of NK cells is regulated partially through inhibitory and activating killer cell immunoglobulin-like receptors (KIR) interacting with human leukocyte antigen C (*HLA-C*) ligands. The highly polymorphic nature of *HLA-C* and KIR genes, along with diverse *HLA-C*/KIR combinations, may contribute to susceptibility to, or protection against viral infection. **Aim:** The aim of this study was to investigate the role of the different KIR/*HLA-C* combinations on susceptibility or protection against HBV in blood donors with anti-HBc-only profiles. **Methods**. We analysed the genes encoding KIR receptors and HLA-C ligands using commercial SSO (sequence specific oligonucleotides) genotyping tests (One Lambda,CA, USA). HLA-C/KIR combinations were analysed in 20 healthy donors negative to HBsAg, anti-HBc, HBcAg-specific T cell response and undetectable levels of HBV DNA; 42 HBV carriers positive for HBsAg, anti-HBc, HBcAg-specific T cell response and with detectable HBV DNA; 33 donors with occult hepatitis B infection (OBI) positive for anti-HBc, anti-HBs, HBcAg-specific T cell response and with detectable HBV DNA; and 17 donors showing spontaneous HBV clearance, positive for anti-HBc, HBcAg T cell response and with undetectable HBV DNA. All samples were tested for HBsAg, anti-HBs, and anti-HBc using fluorometric tests (BioMérieux). NK cells were tested for cytotoxicity against K562 cells and for HBcAg-specific T cell response by lymphoproliferation. **Results.** There was higher NK cytotoxic activity in spontaneous HBV clearance (95+3.5%) when compared to HBV carriers (56+2.7%), healthy donors (20+1.1%) and OBI (61+2.1%). When we analysed HLA types, we observed that *HLA-C1C2* was present in all studied groups. However, the frequency of blood donors with two copies of *HLA-C1* alleles (*HLA-C1C1*) was higher in OBI (50,6%0%) when compared with spontaneous HBV clearance (35.8%) (OR=1.40, IC95%, 1.07-1.84, *P*=0.01). The reciprocal association of two *HLA-C2* alleles (*HLA-C2C2*) with spontaneous HBV clearance (92% in resolved *versus* 80.2% in persistent infection) was also observed (OR=0.67, IC95%, 0.47-0.95, *P*=0.02). The presence of KIR2DL1 and KIR2DL2 (both inhibitory receptors) was observed in all studied groups. On the other hand, we found a high frequency (92.8%) of the KIR2DS1- activation receptor in spontaneous HBV clearance. We hypothesized that the KIR2DS1-*HLA-C2C2* interaction could be protective against HBV infection because this interaction was associated with HBV resolution (OR=1.65, IC95%, 1.20-12.42, *P*=0.001) and high NK cell activity (OR=1.74, IC95%, 1.10-2.55, *P*=0.001). The interaction between KIR2DL3 and *HLAC1C1* (high affinity) was related to persistent infection, because we observed an association with HBV carrier (OR=1.48, IC95%, 1.02-1.90, *P*=0.001) and OBI (OR=1.56, IC95%, 1.20-2.12, *P*=0.001*P* = 0.001; OR = 1.56) and low NK cell activity (OR=1.61, IC95%, 1.06-1.86, *P*=0.001*P* = 0.001; OR = 1.61). **Conclusion**. The data suggest that KIR/HLA interactions are important in determining antiviral immunity and contributed to protection or susceptibility to HBV infection.

Biography

Patricia Araujo has completed her Ph.D in Infection Diseases from University of Cambridge-United Kingston. She is the manager of Infection diseases Laboratory from Colsan-Associação beneficente de Coleta de Sangue, São Paulo, Brazil. Collaborator of HBV save group in Brazil.