3′ untranslated region A>C (rs3212227) polymorphism of Interleukin 12B gene as a potential risk factor for Hodgkin's lymphoma in Brazilian children and adolescents

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Introduction

Natural Killer (NK) cells represent a key component of the innate immune system against cancer. It was observed that patients with Hodgkin's Lymphoma (HL) exhibit inactivated peripheral NK cells due to high serum levels of MHC class I ligands for the Natural Killer Group 2D (NKG2D) protein. According to the literature, inactivation of NK cells may be associated with NKG2D blockade by these ligands, and consequently may interfere on your antitumor function. On the other hand, expression of NKG2D can be regulated by cytokines, such as IL-12. IL-12 plays an important role in immunoregulation between the Th1/Th2 helper lymphocytes and in the antiviral and antitumor immune response. The aim of the present study was to investigate the possible association between the interleukin 12B polymorphism rs3212227 and the risk to develop HL in childhood and adolescents.

Methods

A total of 100 patients with Hodgkin's lymphoma and a group of 181 healthy controls aged 0 to 19 years were selected. DNA extraction from peripheral blood was performed by the ''Mini Salting out'' method. Genotyping was determined using Polymerase Chain Reaction–Restriction Fragment Length Polymorphism (PCR-RFLP). The 118 bp PCR product was digested by the enzyme TaqI (10 U/mL) for 4h at 65°C. Data analysis was performed using the BioEstat 5.0 program. The associations were considered significant when $p<0.05$.

Results

The AA genotype was the most frequent in the controls (53.04%) and the AC genotype was the most frequent in the patients (54%). The AC genotype showed an association with the development of HL (OR = 2,091, 95% CI = 1,240-3,523, $p = 0.007$). When AC + CC genotypes were analyzed together, an increase in risk of 1.9 times more chances for HL development could be observed (OR = 1,923, 95% CI = 1,166-3,170, $p = 0.014$). However, there was no association between the AC and CC genotypes of the *IL-12B* polymorphism with the clinical risk group ($p = 0.992$, $p = 0.648$, respectively).

Conclusion

Our results suggest that the presence of the C allele may be contributing to the development of HL in children and adolescents. Thus, the identification of this
polymorphism may help in the stratification of patients with HL according to the risk for the disease. This is the first study to analyze this type of association in children and adolescents with HL in Brazil. However, other studies in other populations are important to investigate this association, since the antitumor mechanisms of this interleukin are not yet fully understood.

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References

[1] Gonzalez S, Lopez-Soto A, Suarez-Alvarez B, et al. NKG2D ligands: key targets of the immune response. Trends Immunol 2008; 29: 397–403.
[2] Zhou L, Yao F, Luan H, et al. Functional polymorphisms in the interleukin-12 gene contribute to cancer risk: evidence from a meta-analysis of 18 case-control studies. Gene 2012; 510(1): 71–77.
[3] Sun L, He C, Nair L, et al. Interleukin 12 (IL-12) family cytokines: role in immune pathogenesis and treatment of CNS autoimmune disease. Cytokine 2015; 75: 249–255.
[4] Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease Staging Classification. Cancer Res 1971; 31: 1860–1861.
[5] Kuppers R, Engert A and Hansmann M-L. Hodgkin lymphoma. J Clin Invest 2012; 122: 3439–3447.