HLA antigens in Brazilian patients with paracoccidioidomycosis

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Abstract

Eighty patients with paracoccidioidomycosis were typed for 43 HLA specificities from loci A, B, C and DR. A highly significant increased frequency of HLA-B40 (relative risk 29.2) and HLA-Cwl (relative risk 8.8) were found in patients compared to control subjects. The frequencies HLA-A2, B7 and B21 were also increased in patients and haplotypes-B40-Cwl and -A2-B40 were positively correlated with the disease. DR antigen frequencies were not significantly altered in the patients and evidence of a protective effect was not found for any of the 43 antigens tested. These findings further support the involvement of the HLA system in the genetic susceptibility to paracoccidioidomycosis and the importance of ethnic variability in this association.

Introduction

Paracoccidioidomycosis is a systemic mycosis caused by the dimorphic fungus Paracoccidioides brasiliensis (Pb). The disease is endemic in Latin American countries, especially Brazil, Venezuela, Colombia and Argentina. Many factors that probably determine the course of the disease have been investigated such as the virulence of different strains of Pb, the route of infection, the inocula used, the general state of health of the host and genetic background [1, 2, 3, 4].

Previous studies on HLA antigens in paracoccidioidomycosis have shown different correlations. Restrepo et al. [5] demonstrated an association of HLA-A9 and HLA-B13 in Colombian patients with the disease. In another investigation, Gonzales et al. [6] found that the occurrence of paracoccidioidomycosis is positively correlated to the presence of HLA-B13 in Venezuelan patients. In Brazil, Lacerda et al. [7] described the association of HLA-B40 with paracoccidioidomycosis.

The objective of this study was to establish which of these antigens are primarily involved in our population with paracoccidioidomycosis and their correlation with clinical forms of the disease. Since the previous studies of HLA in this disorder have tested only alleles at the A and B loci and 2 alleles in the locus C, we also typed antigens related to the loci C and DR in order to establish other possible correlations.

Methods

We studied 80 patients (65 males and 15 females) with mycologically and histopathologically proven paracoccidioidomycosis in an endemic area of Brazil (Ribeirão Preto – State of São Paulo).
There were 8 blacks, 13 mullatos and 59 whites who ranged in age from 5 to 84 years. There were 33 patients with the subacute form and 47 patients with the chronic clinical form classified according to Franco et al. [8].

The control group comprised 100 healthy individuals from the same geographic area and a similar ethnic background.

Lymphocytes were separated by Ficoll–Hypaque gradient from heparinized venous blood and HLA typing was carried out using the standard microcytotoxicity test described by Terasaki et al. [9]. The cells were typed for 43 specificities for loci A, B, C and Dr: A1, A2, A3, A9, A11, Aw19, A23, A24, A28, A29, A30, B5, B7, B8, B12, B13, B14, B15, B17, B18, B21, B27, B35, B37, B38, B39, B40, B51, B52, Cw1, Cw2, Cw3, Cw4, Cw5, Cw6, Cw7, DR1, DR2, DR3, DR4, DR5, DR6 and DR7. The HLA typing antisera were obtained for France Transplant. At least two antisera were used to analyse each specificity.

Antigen frequencies in the paracoccidioidomycosis group were compared with those of the control by Chi-squared analysis. The p values were corrected by multiplying the p value by 43, i.e., the total number of antigens investigated. The relative risk was determined for the statistically significant antigens and haplotypes in order to estimate the strength of the association according to Sveggaard et al. [10].

Results

Statistical analysis of HLA antigens frequencies demonstrated a highly significant increase in the incidence of HLA-B40 and HLA-Cw1 in the patient population (corrected $p < 0.001$) compared to the controls (Table 1). The relative risk of occurrence of paracoccidioidomycosis was 29.2 and 8.8 in patients with HLA-B40 and HLA-Cw1 respectively. We also observed significantly increased frequencies of HLA-A2, HLA-B7 and HLA-B21 in the patient population (corrected $p < 0.05$). The haplotype analysis revealed statistically significant correlations of both HLA-B40-Cw1 and HLA-A2-B40 with paracoccidioidomycosis (corrected $p < 0.001$) (Table 2). On the other hand, no DR antigen was increased in patients and none of the 43 antigens tested had a significantly decreased frequency in patients with paracoccidioidomycosis.

The correlations of the HLA phenotypes with disease manifestations was studied by comparing antigen frequencies in two clinical forms of the disease. There was no significant differences for any phenotype (data not shown).

Discussion

The involvement of the HLA region has been found in many fungal diseases such as coccidioidomycosis. The presence of HLA-B40 and HLA-Cw1 in patients with paracoccidioidomycosis suggests a possible role in the immune response against the pathogen. Further studies are needed to elucidate the mechanism of this association and its implications in the development of the disease.