SOBRECARGA DE FERRO: HEMOCROMATOSE

Caracterização dos haplotipos AAT e GGG numa população de indivíduos homozigotos para a mutação C282y do gene HFE: contribuição para o estudo da penetrância da hemocromatose hereditária

A study of 147 extended haplotypes carryng the C282Y HFE mutation: A novel approach to explain the involvement of the MHC-CLASS I region in the setting of CD8+ T lymphocyte numbers in humans

Aluna da DIIC: Sandra Morais (Mestrado Integrado em Medicina; ICBAS/CHP)

Orientadores: Graça Porto (HSA/CHP, IBMC/UP e ICBAS/UP)

Background

The numbers of peripheral blood CD8+ T lymphocytes are known to be genetically determined in the context of genes at the MHC-class I region. The present study analyses, for the first time, the inheritance of CD8+T lymphocytes in the context of extended haplotypes defined between *HFE* and HLA-B by segregation analysis in families of Hereditary Hemochromatosis (HH) patients. With this novel approach we aimed to clarify the relative impact of the HLA specificities or the whole haplotype on the genetic transmission of CD8+T lymphocytes in humans.

Subjects and Methods

A total of 71 unrelated C282Y homozygous HH patients and 61 of their family members were studied for extended haplotype analysis, performed by segregation analysis for the SNP markers on PGBD1, ZNF193 and ZNF165 (defining the restricted SNP haplotypes AAT and GGG) and for the HLA-A and -B loci, all correlated with the numbers of CD8+T lymphocytes. In addition, 123 DNA samples from an independent population of C282Y homozygous subjects were tested to confirm the frequencies of the SNP markers in the Portuguese HH population.

Results

The relative frequencies of the AAT and GGG haplotypes in the population of C282Y homozygous HH patients was 94.3% and 4.9% respectively. We confirmed the strong association of the most common HLA-A*03, -B*07 and the A3B7-AAT ancestral haplotype with the inheritance of low CD8+T lymphocytes. The HLA-A*03 was the only HLA allele increased in frequency in patients with high lymphocytes. The definition of extended haplotypes allowed us to construct a model with all patients' chromosomes classified as carrying a "low" or "high CD8+ trait" and to compare the distribution of HLA alleles and haplotypes between the two groups. The results clearly showed a greater allelic and haplotypic variability in the "high" vs the "low CD8+ trait" group supporting the hypothesis of a different recombination history.

Conclusions

The study of extended haplotypes carrying the C282Y *HFE* mutation offers a new model to explain the contribution of the MHC region to the setting of CD8+T lymphocyte numbers. The results support the hypothesis of a putative still unidentified trait localized centromeric to HLA-A.