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MEETING ABSTRACTS Open Access

Elevated serum levels of heat shock protein 70 precede the development of AIDS-non-Hodgkin lymphoma in carriers of the common and highly conserved HLA-B8-DR3 haplotype

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Background

Polymorphisms in the tumor necrosis factor (*TNF*) and lymphotoxin alpha (*LTA*) genes, by themselves or in combination with nearby specific human leukocyte antigen (*HLA*) loci, have been associated with classical and AIDS-related non-Hodgkin lymphoma (NHL). However, whether those gene variants represent true etiologic factors remains uncertain because they are part of the conserved and extended HLA-B*08-containing AH8.1. Building on recent observations linking the MHC-encoded heat shock protein 70 (Hsp70) to lymphomagenesis, we hypothesized that concomitant carriage of presumably high TNF and Hsp70 producing gene variants on AH8.1 may predispose HIV-infected individuals to AIDS-NHL. To test this hypothesis, we have compared Hsp70 serum levels in the years preceding the diagnosis of AIDS-NHL in carriers vs. non-carriers of AH8.1.

Materials and methods

A Caucasian case-control sample (n=169 pairs) was nested in the Multicenter AIDS Cohort Study (MACS). Cases are participants diagnosed with AIDS-NHL prior to April 2002, matched 1:1 with HIV+ NHL-free controls on duration of HIV infection and availability of serum samples at time points 3-5 years; 1-3 years; and <1 year prior to NHL diagnosis. Typed loci are HLA-B, HLA-DRB1, and 6 MHC class III single nucleotide polymorphisms (SNPs) from *TNF* and complement factor gene clusters. Hsp70 levels were measured by an ultra-sensitive ELISA. Extended MHC haplotypes were estimated via the EM-algorithm and were modeled as fixed main and interaction (with time) effects in a mixed linear model with adjustment for the CD4+ counts at the time of NHL diagnosis separately in cases and controls. A random model was fitted to account for the different levels of Hsp70 at the earliest time point.

Results

No MHC haplotype was associated with a change in Hsp70 levels in cases or controls during the 5 years preceding NHL. However, when the study was restricted to the subset of cases who developed NHL as their AIDS-defining condition (vs. NHL subsequent to another AIDS-defining condition), carriage of AH8.1 haplotypes was significantly (p=0.0002-0.006) associated with increasing Hsp70 levels in the cases but not in the matched controls. Conversely, the common HLA-B7-DR15 haplotype appears to be protective and associated with decreasing Hsp70 levels.

Conclusion

An altered level of Hsp70 may be a component of the AH8.1-mediated pathogenetic pathway in AIDS NHL, perhaps through the action of Hsp70 as a B-cell stimulatory molecule. Investigation of *Hsp70* promoter variants in AIDS-NHL is a worthy undertaking, especially if the association can be replicated in larger studies.

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