Cellular immunity driving HIV-1 evolution
Navis, M.

Citation for published version (APA):
Chapter 7

The relation between HLA B*5701, HCP5 and HIV-infection

Marjon Navis*, Daniëlle van Manen*, Neeltje A. Kootstra, Angélique B. van ‘t Wout and Hanneke Schuitemaker

Dept Experimental Immunology, Sanquin Research, Landsteiner Laboratory, and Center for Infectious Diseases and Immunity Amsterdam (CINIMA) at the Academic Medical Center of the University of Amsterdam, Amsterdam, the Netherlands

* These authors contributed equally to this work

Manuscript in preparation
Abstract
Recently, Fellay et al. reported an association between a low HIV-1 viral load set point and a minor allele of the HLA complex P5 (HCP5). However, high linkage disequilibrium between this HCP5 allele and the protective HLA B*5701 allele prevented resolution of the effect. In the Amsterdam Cohort, all individuals with HLA B*5701 carry the minor HCP5 allele, even those with a progressive disease course. Moreover, nonprogressors with protective HLA B*5801 or B*5703 alleles, which present the same viral epitopes as HLA B*5701, did not carry the minor HCP5 allele. These observations support a major dominant role for HLA restricted cellular immunity in nonprogressive HIV-infection.

Human leukocyte antigen (HLA) B*5701, HLA B*5703 and the closely related HLA B*5801 have been consistently associated with a more benign clinical course of HIV-1 infection 1-4. HLA B*5701 and HLA B*5801 alleles are highly overrepresented in HIV-1 infected Caucasians with a long-term nonprogressive disease course 2 while the HLA B*5703 allele has been associated with slower disease progression in HIV-1-infected Africans 5.

The underlying mechanism for the association between HLA B57/5801 and a nonprogressive disease course is not fully understood. It has been suggested that HLA B57/5801 restricted cytotoxic T lymphocytes (CTLs) are more potent. Moreover, certain escape mutations in HLA B57/5801 restricted CTL epitopes would come at a fitness cost to the virus implying that the net effect of CTL activity and viral escape would still be a low HIV-1 load 6.

Recently, Fellay et al. reported a whole-genome association study of major determinants for host control of HIV-1 7. They identified the minor allele of a single nucleotide polymorphism (SNP) within the HLA complex P5 (HCP5) gene (SNP database number rs2395029, major allele T and minor allele G) associated with a low viral load set point. The HCP5 gene is located 100kb centromeric from HLA B on chromosome 6, and the associated SNP is known to be in high linkage disequilibrium (LD) with the protective HLA B*5701 allele. Therefore, Fellay et al. hypothesized that the association between this polymorphism in HCP5 and a low viral load set point could in fact be due to the protective effect of HLA B*5701. The authors suggested, however, that as a human endogenous retroviral element (HERV) with sequence homology to retroviral pol genes 8, HCP5 itself could additionally interfere with HIV-1 replication through an antisense mechanism. This could be enhanced through the associated polymorphism which would result in an amino acid substitution in one of the two proteins encoded by the HCP5 gene.

To test this idea, we determined the HCP5 rs2395029 genotype in participants from the Amsterdam Cohort Studies who despite an HLA B57 or the closely related HLA B*5801 typing (n=20), were highly variable in their viral load set point and HIV-1 disease course 9 (Table I). All individuals with HLA B*5701 typing (n=20), were highly variable in their viral load set point and HIV-1 disease course 9 (Table I). All individuals with HLA B*5701 carried the minor HCP5 allele, confirming the high LD between polymorphisms (r²=1 in our data set). Interestingly, the 9 individuals who despite the expression of the HLA B*5701 allele had a progressive clinical course all carried the minor HCP5 allele. Thus, disease progression occurred despite the presence of both HLA B*5701 and the minor HCP5 allele.
Conversely, certain alleles of the HLA B58 supertype (HLA B*5701, HLA B*5801, and HLA B*5703) have been associated with nonprogressive HIV-1 infection, yet only individuals with HLA B*5701 carry the minor HCP5 allele. Considering the fact that these 3 alleles belong to the HLA B58 supertype presenting identical sets of CTL epitopes, it is tempting to speculate that it is the HLA type rather than HCP5 that is associated with protection from HIV-1 disease progression. Whether this protection is mediated through constant CTL pressure, through viral attenuation due to CTL escape mutations in conserved epitopes, through the association between HLA B*5701 and certain protective KIR alleles, or even through a currently unknown mechanism, remains to be established.

Acknowledgements

We thank all participants from the Amsterdam Cohort Studies for their continuous participation. The Amsterdam Cohort Studies on HIV infection and AIDS is a collaboration between the Amsterdam Health Service, the Academic Medical Center of the University of Amsterdam, Sanquin Blood Supply Foundation and the University Medical Center Utrecht and part of the Netherlands HIV Monitoring Foundation.

This study was financially supported by the Landsteiner Foundation for Blood Transfusion Research (LSBR; grant 0317) and Netherlands Organization for Scientific Research (NWO; grant 9120.6046). The Amsterdam Cohort Studies receive financial support from the Netherlands National Institute for Public Health and the Environment.
Reference List