A genetic variation in Fucosyltransferase 8 accelerates HIV-1 disease progression indicating a role for N-glycan fucosylation

Lisa van Pul, Karel A. van Dort, Brigitte Boeser-Nunnink, Irma Maurer, Neeltje Kootstra
Amsterdam UMC location University of Amsterdam, Experimental Immunology, Meibergdreef 9, Amsterdam, Netherlands
Amsterdam Institute for Infection and Immunity, Infectious diseases, Amsterdam, The Netherlands

Background
Fucosyltransferase 8 (FUT8) is an enzyme that is uniquely responsible for a process known as N-glycan core fucosylation and is involved in post-translational modification of glycoproteins. Changes in core fucosylation can affect the immune response. For instance, mutation of immuneglobulin G (IgG) alters the antibody binding to Fc receptors. In addition alterations in T-cell receptor (TCR) fucosylation have been shown to influence TCR conformation, TCR signaling, T-cell development and function. Moreover, low level of core fucosylation is associated with the progression of HIV-1 disease and thereby improves T-cell responses. We hypothesise that genetic variations in FUT8 may affect fucosylation and thus the immune response against HIV-1.

Methods
SNPs in FUT8 were analysed in HIV-1 infected participants of the Amsterdam Cohort Studies (ACS) on HIV-1 and AIDS. Cox regression and survival analysis was performed to determine the effect of the SNPs on the outcome of untreated infection. Using flow cytometry, the effect of a SNP in FUT8 on T cell surface marker expression was determined 1 year before HIV-1 infection and 3 and 5 years after seroconversion (SC). In a set of blood donors additional flow cytometry analysis was performed to assess T cell surface marker expression. The effect of the SNP on T cell function was analyzed by proliferation assay using CellTrace Violet staining in blood donor PBMC.

Results: Survival analysis
Genome wide association study (GWAS) in the ACS identified 92 SNPs in the FUT8 gene region. SNPs in FUT8 were defined as the percentage CD4 or CD8 T cells co-expressing HLA-DR and CD38 at different time points: before seroconversion (pre), 1 year and 5 years post seroconversion. No significant differences in CD4 or CD8 T cell activation were seen at any time point between individuals homozygous for the major variant of rs4131564 and individuals carrying the minor allele. Regression analysis (indicated by the line) revealed an overall significant increase in T cell activation over time in major individuals in both CD4 and CD8 populations (p<0.0001 and p=0.0006 respectively) and not in minor. However, there was no significant difference in the slopes when comparing individuals carrying the minor variant of rs4131564 and individuals carrying the major variant both in the CD4 and CD8 compartment.

Results: Proliferation marker expression in HIV-1 infected individuals
In order to assess the effect of SNP rs4131564 on T cell exhaustion and senescence, surface marker expression of CD0-1, CD57 and CD27 & CD28 was determined in PBMC of blood donors. T cell exhaustion was defined as expression of CD0-1 and T cell senescence was defined as CD57 expression or absence of expression of both CD0-1 and CD27. No significant differences in expression of exhaustion or senescence markers were found on the CD4 T cells of donors homozygous for the major allele of rs4131564 (n=27) and donors hetero/homozygous for the minor allele (n=12). CD57 expression on CD8 T cells was significantly lower in individuals carrying the minor allele of the SNP.

Conclusions
• We observed a naturally occurring genetic variation in the FUT8 gene was associated with accelerated HIV-1 disease progression independent of CCR5a22 and HLA-B*57 genotype.
• The SNP was not associated with differences in IgG fucosylation.
• T-cell activation, exhaustion, TCR signaling and T-cell proliferation were also not significantly different between individuals with the minor or major variant of rs4131564.

However, these assays were unable to detect minor or combined effects of the SNP on the immune response that might accumulate over time. Our data show that glycoprotein fucosylation plays a role in HIV-1 infection by a yet unknown mechanism.

Acknowledgements: Special thanks to the participants of the Amsterdam Cohort Studies (ACS). Correspondence: lvanpul@amsterdummc.nl

Amsterdam Institute for Infection and Immunity