Comprehensive Characterization of LEDGF/p75 in an HIV-1 infected Patient Cohort

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BACKGROUND:
Lens epithelium derived growth factor interaction inhibitors (LEDGInS) form an emerging class of allosteric integrase inhibitors, targeting the cellular co-factor of integrase, i.e. LEDGF/p75. Only few data are available on LEDGF/p75 expression and its genetic variability in HIV infected patients. The present study evaluated whether genetic variation in the LEDGF/p75 gene and mRNA/protein expression levels influence HIV disease progression.

METHODS & RESULTS:
Patients: Samples were derived from a therapy-naive patient cohort from Ghent University Hospital and from long-term non-progression patients as kindly provided by the HIV Biobank (Spanish AIDS Research Network, RIS). Elite controllers are defined as therapy-naive long-term non-progressors (LTNP) with undetectable viral load. LTNP viremic controllers have a viral load below 2000 copies/ml without therapy in 75% of the progressors (LTNP) with undetectable viral load, LTNP viremic controllers all patients

SNP detection: A genomic scan of the coding region (including intronic regions near the exon-intron boundary and 3’UTR) of LEDGF/p75 was performed with high resolution melting (HRM) curve analysis and Sanger sequencing to identify single nucleotide polymorphisms (SNPs). 24 SNPs were identified, of which 5 in the coding region, 17 in the non-coding regions and 3’UTR. In addition to these, two known tagSNPs were included. Only the SNPs that were correlated with disease progression, average viral load or CD4 slope are described (Fig. 1).

Association of LEDGF/p75 SNPs with disease progression
The SNPs in the coding region were low-abundant and did not correlate with disease progression nor with LEDGF/p75 expression. For most of the intronic and 3’UTR SNPs found, no correlation could be determined with either CD4 slope, viral load or LEDGF/p75 expression. However, for three SNPs, a possible association between SNP presence and HIV disease were found, i.e. rs2737828, rs2737835 and rs16933270.

rs2737828
This intronic SNP was under-represented in Caucasian HIV patients (P<0.0001) compared to healthy Caucasians as published in HapMap. In addition, the presence of this SNP tends to correlate with lower LEDGF/p75 expression (P=0.053), but not with disease progression markers.

rs2737835
This SNP tends to be associated with slower CD4 decline in Caucasian non controllers (P=0.058).

rs16933270
This SNP, mainly present in Africans was correlated with CD4 decline (P= 0.020).

DISCUSSION:
This is the first report on SNP profiling in the entire coding region of the LEDGF/p75 gene in HIV infected patients. The results reveal that the coding region contains little variation. Certain rare variants of LEDGF/p75 intronic or 3’UTR region can be associated with HIV disease susceptibility or disease progression.

The variant rs2737835, present in Caucasian patients, tends to associate with slower CD4 decline. rs16933270, mainly present in African patients significantly correlated with CD4 decline. These data indicate that genetic variations in LEDGF/p75 can influence disease progression.

The finding that SNP rs2737828 was significantly underrepresented in Caucasian HIV patients in relation to the expected frequency according to HapMap, suggests that this SNP might influence disease susceptibility.

Interestingly, except for rs2737828, there was no correlation between the presence of these variants and differential expression at the mRNA and protein levels. The high variety of protein expression that is not correlated with slower CD4 decline (P=0.058) is an emerging class of allosteric integrase inhibitors, targeting the cellular co-factor of integrase, i.e. LEDGF/p75. On

LEDDInS
This study supports the hypothesis that genetic variation in the host factors LEDGF/p75 can influence HIV disease progression.

CONCLUSIONS:
This study supports the hypothesis that genetic variation in the host factors LEDGF/p75 can influence HIV disease progression.