Peripheral blood DNA methylation markers are associated with HIV progression

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**Background:** Veterans Aging Cohort Study Index (VACS Index) is predictive for disease progression and mortality in HIV-infected population. Using the VACS index as an indicator of HIV outcome, our goal is to identify DNA methylation (DNAm) in blood for HIV progression. The findings may reveal molecular profile to predict HIV outcomes.

**Methods:** The VACS index includes information on age, CD4+ count, HIV-1 viral load, hemoglobin, FIB-4, eGFR and hepatitis C infection. DNAm in epigenome for 1,266 HIV-infected men was profiled using the Infinium Human Methylation 450K BeadChip (N=586) or the Infinium Human MethylationEPIC BeadChip (N=680). Epigenome-wide association study (EWAS) for two platforms was separately performed using linear model, adjusting for multiple confounders. Meta-analysis of the shared CpG sites between 450k and EPIC data was conducted using METAL. Gene enrichment analysis was performed using DAVID.

**Results:** EWAS revealed 8 CpGs in 450K and 81 CpGs in EPIC significantly associated with the VACS index. Meta-analysis identified 131 significant CpG sites for the VACS index. The highlights of genes are related to antiviral effects and immune response such as MX1 (cg26312951, Z=-8.2, p = 2.3 10^-16; cg22862003, Z=-7.014, p=2.31 10^-12; cg21549285, Z =-6.119, p= 9.43 10^-10), PSMB8 (cg01309328, Z=-7.397, p=1.39 10^-13; cg08099136, z=-7.169, p=7.54 10^-13) and PARP9 (cg08122652, Z = -7.263, p= 3.79 10^-13; cg22930808, z = -7.005, p= 2.47 10^-12). Gene enrichment analysis identified significant pathways in response to type I interferon (FDR = 3.73 10^-17) and defense response to virus (FDR= 1.78^-13).

**Conclusion:** The results suggest that DNAm on genes involving immune and inflammation may contribute to HIV progression.