Oral Abstract Session 4: Immunology and persistence

OA4-1

Trancriptomics and Metabolomics identify inflammatory profiles that segregate subjects with High and Low inducible HIV reservoir

Ghneim K.[1], Ahlers J.[2], Fourati S.[1], Shive C.[1], Cameron M.[1], Mukerjee P.[1], Ghannoum M.[1], Rodriguez B.[1], Deeks S.[3], Lederman M.[1], Sekaly R.[1]

[1]Case Western Reserve University, Pathology, Cleveland, United States, [2]VGTI-FL, Port Saint Lucie, United States, [3]University of California San Francisco, San Francisco, United States

Background: To identify mechanisms that control immune reconstitution and the size of the inducible HIV reservoir, we performed whole blood transcriptional and metabolic profiling of subjects from the CLIF and UCSF SCOPE cohorts. These cohorts included subjects who increased CD4 counts post cART (IR) or stayed < 350/mm3 after 3 years of cART (INR).

Methods: We performed unsupervised analysis of gene expression data using hierarchical clustering to identify class and supervised analysis using statistical filtering to identify gene signatures and pathway activity differentially expressed between classes. Multivariate analysis based on Sparse Partial Least Regression was used to determine if Group membership correlated with plasma metabolites measured by LC-MS/GC-MS. A gene-based classifier was developed to identify INR groups using the pamr package.

Results: Two groups of INR subjects were identified by whole blood gene expression and pathway analysis. INR-A had the highest levels of IL-6, sCD14, FOXO3 and STAT1 expression, and highest levels of oxidative stress and mitochondrial dysfunction. Pathway analysis showed that INR-A failed to activate the NF-κB pathway, TLR- MyD88 signaling, and proinflammatory modules yet upregulated expression of the p38 MAPK pathway, IRF-3, IRF-4, and IL-10 associated with a tolerogenic myeloid response. In contrast, INR-B was characterized by an unrestrained proinflammatory response including the upregulation of multiple TLRs, STAT1, IRF1, and IRF8 associated with Type I/II IFN responses. Plasma metabolites including carnitines, bacterial metabolites and cholesterol also segregated between the 2 INR groups and correlated with gene expression including FOXO3A and STAT-1. TILDA, a measure of the inducible HIV reservoir; revealed that INR-A subjects had higher levels than INR-B and IR's. As CD4 counts and plasma biomarkers of inflammation/immune activation fail to distinguish the two INR groups, we developed a 352 gene-based classifier that accurately identified patient groups (AUC of 0.81 by ROC analysis) in an independent test cohort (UCSF SCOPE) including those that had the highest levels of HIV reservoir.

Conclusions: Identifying pathways that control immune reconstitution and the size of the inducible HIV reservoir paves the way to the development of therapeutic strategies that can lead to eradication of HIV.

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