Proteomic Correlates of Depressive Symptoms – Insights from the RV254/SEARCH010 Acute HIV Thai Cohort

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BACKGROUND

- Depressive disorders occur nearly 3 times more often among people with HIV (PWH) compared to demographically similar people without HIV.
- Proteomics enables identification of molecular signatures linked to symptom trajectories.
- Are exploratory plasma proteomic markers during acute HIV infection associated with longitudinal depressive symptom trajectories following ART initiation?

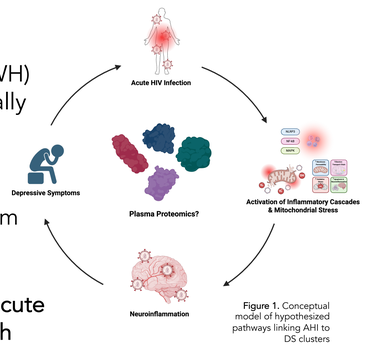

Figure 1. Conceptual model of hypothesized pathways linking AHI to DS clusters

METHODS

- Proteomic analysis of plasma from N = 150 participants in the RV254/SEARCH010 Cohort using SomaLogic's aptamer-based SomaScan Assay
- Curated assay of 100 proteins associated with inflammation, mitochondrial dysfunction, immunometabolism, metabolic reprogramming and oxidative stress. Ten proteins were excluded due to variance.
- Depressive symptoms (DS) were classified in 3 clusters from ART initiation through 96 weeks: Cluster 1 (persistently high DS), Cluster 2 (remitting DS) and Cluster 3 (persistently low DS) using machine learning methods.

Figure 2. Depressive symptom trajectories over 96 weeks

- Protein–DS cluster associations were evaluated using linear models implemented in limma, adjusting for relevant covariates, including age, viral load and amphetamine type stimulant use (ATS).

Exploratory proteomic analyses revealed preliminary associations between **depressive symptom clusters** and proteins implicated in **inflammation** and **metabolic reprogramming, independent of age, viral load** and **stimulant use.**

RESULTS

Table 1. Participant Demographic Information

	Cluster 1 Persistently High Depressive Symptoms (n = 61)	Cluster 2 Remitting Depressive Symptoms (n = 28)	Cluster 3 Persistently Low Depressive Symptoms (n = 61)	Overall (N = 150)
Age (M, SD)	26.3 (6.10)	28.0 (8.50)	29.1 (9.36)	27.8 (8.06)
Plasma viral load [log10] (M, SD)	6.34 (0.879)	5.76 (0.925)	5.91 (1.16)	6.06 (1.03)
Amphetamine type stimulant use (n, %)	25 (41.0)	2 (7.1)	8 (13.1)	35 (23.3)

Table 2. Proteins significant before adjusting for age, viral load and ATS use ($p < 0.05$)

Mitochondrial	Inflammation	Immunometabolism	Metabolic Reprogramming	Oxidative Stress
ACADM ↑	CXCL7[a] ↑	KMO ↓	LPL[a] ↓	PARP1[b] ↑
Malate dehydrogenase ↑	CSF1 ↓	CD25/IL-2[a] ↑	PDK1[a] ↑	Glutathione reductase[b] ↑
TFAM ↑	S100A12 ↓	Adiponectin[a] ↓	LDHA[b] ↑	
Citrate synthase ↑	IL-18 ↓	sCD14[b] ↓	CYP2E1 ↑	
		CD27[b] ↓	CYP2D6[b] ↓	
			Alpha enolase ↑	
			GAPDH ↑	

[a]only in cluster 1 vs cluster 3; [b]only in cluster 2 vs cluster 3

Table 3. Proteins significant after adjustment ($p < 0.05$)

Protein	Pathway	Log2FC	FDR q
Cluster 1 versus Cluster 3			
GAPDH	Metabolic reprogramming	+0.56	4.89×10^{-7}
Alpha enolase	Metabolic reprogramming	+0.67	6.23×10^{-5}
IL-18	Inflammation	-0.33	1.00×10^{-3}
Cluster 2 versus Cluster 3			
GAPDH	Metabolic reprogramming	+0.86	2.04×10^{-11}
Alpha enolase	Metabolic reprogramming	+1.07	1.00×10^{-8}
IL-18	Inflammation	-0.38	1.37×10^{-3}

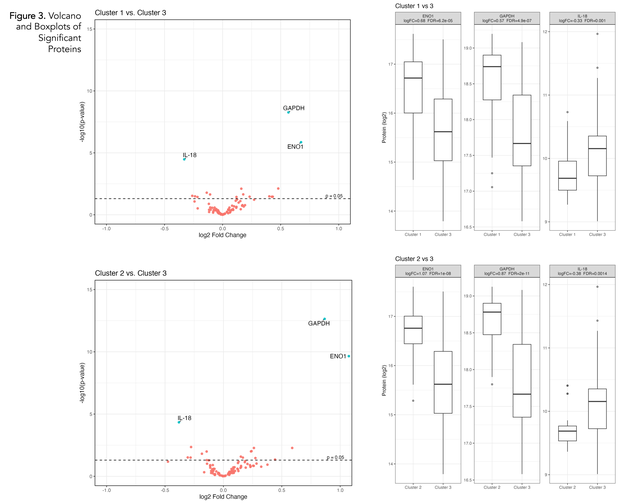

Figure 3. Volcano and Boxplots of Significant Proteins

CONCLUSIONS

- Persistently high and remitting DS clusters differed from persistently low DS cluster by proteomic signatures related to inflammation and metabolic reprogramming.
- Most robust differences were observed in proteins related to glycolytic pathways and upstream mitochondrial markers (GAPDH and alpha enolase), as well as a marker of innate inflammation (IL-18).
- Proteins implicated in mitochondrial dysfunction, immunometabolism, oxidative stress and inflammation were differentially expressed at a nominal significance – supporting broader immunometabolic and mitochondrial remodeling across the DS clusters.
- Proteomic differences were independent of age, plasma viral load and stimulant exposure, indicating that DS-linked proteomic and biological changes are not necessarily explained by HIV disease severity or substance use.

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PLAIN LANGUAGE SUMMARY

People with different patterns of depressive symptoms showed differences in blood proteins related to how the body uses energy and regulates the immune system. These differences were not related to age, HIV viral load or stimulant use, which suggests that these proteins may be modified by depressive symptoms rather than HIV alone.