Identification of CD3⁺CD14⁺ Immune Complexes as Integrated Markers of Insulin Resistance & Chronic Inflammation in HIV

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708

BACKGROUND

- People living with HIV (PLWH) face a significantly higher risk of developing comorbidities like diabetes and cardiovascular disease compared to the general population (PMID: 24138880).
- CD3⁺CD14⁺ T cell–monocyte complexes are stable, functionally active immune synapses that serve as dynamic markers of immune activation across various inflammatory contexts (PMID: 31237234).
- Our previous studies have shown that these complexes are increased in PLWH with insulin resistance compared to PLWH without diabetes (PMID: 37162990).

OBJECTIVE

Investigate how antigenic stimulation influences the abundance and inflammatory profile of CD3⁺CD14⁺ T cell–monocyte complexes and to determine their relationship with longitudinal glycemic control in PLWH.

METHODS

The study cohort was drawn from the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS, Table 1). The study was approved by the Vanderbilt and UAB Institutional Review Boards (IRB).

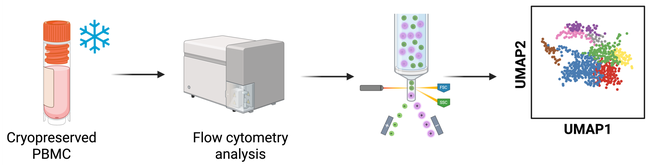


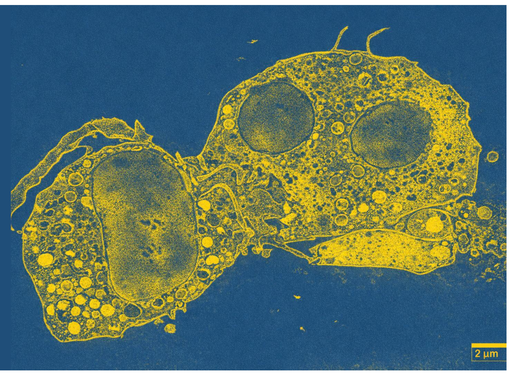
Figure 1. Workflow

	Diabetes, A1C >9 N=20	Diabetes, A1C <7 N=12	No-Diabetes N=15	Pre-Diabetes N=15	p-value
Age, Years	55.0 [48.0, 57.0]	54.0 [47.8, 57.0]	54.0 [49.5, 56.5,	55.0 [50.5, 55.0]	0.99[2]
Sex : % Male	0.85 $^{17}/_{20}$	1.00 $^{12}/_{12}$	1.00 $^{15}/_{15}$	1.00 $^{15}/_{15}$	0.085[1]
Race : % Black	0.55 $^{11}/_{20}$	0.50 $^{6}/_{12}$	0.47 $^{7}/_{15}$	0.40 $^{6}/_{15}$	0.85[1]
Viral load, copies/mL	1 [1, 20]	23 [20, 31]	20 [20, 20]	1 [1, 20]	0.033[2]
CD4 T cell at enrollment (cells/ml)	670 [428, 790]	558 [448, 743]	642 [488, 817]	605 [479, 770]	0.88[2]
Hemoglobin A1C, %	10.30 [9.07, 11.30]	6.70 [6.60, 6.82]	5.10 [5.00, 5.30]	5.80 [5.75, 6.05]	**0.001**[2]
Blood glucose, mg/dL	206.5 [171.5, 250.0]	112.5 [104.8, 140.5]	94.0 [81.0, 95. 0,	95.0 [89.5, 96.5]	**0.001**[2]

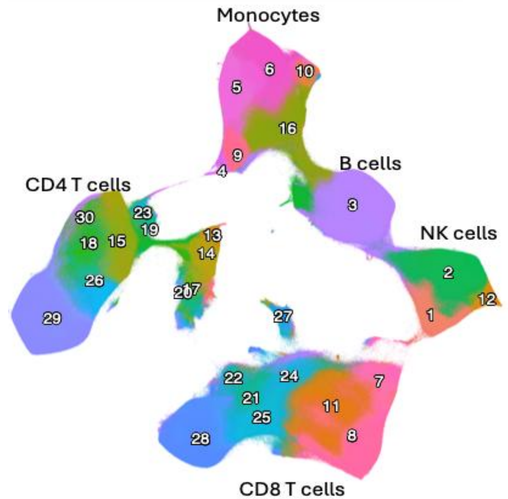
B [a, c] represent the lower quartile a, the median b, and the upper quartile c for continuous variables.
Tests used: [1]Pearson test; [2]Kruskal-Wallis test .

Table 1 . Patient demographics

Some immune cells travel through the blood already bound together, and these "paired" cells are associated with inflammation. By studying them, we may learn more about what drives ongoing inflammation in people with HIV.



RESULTS



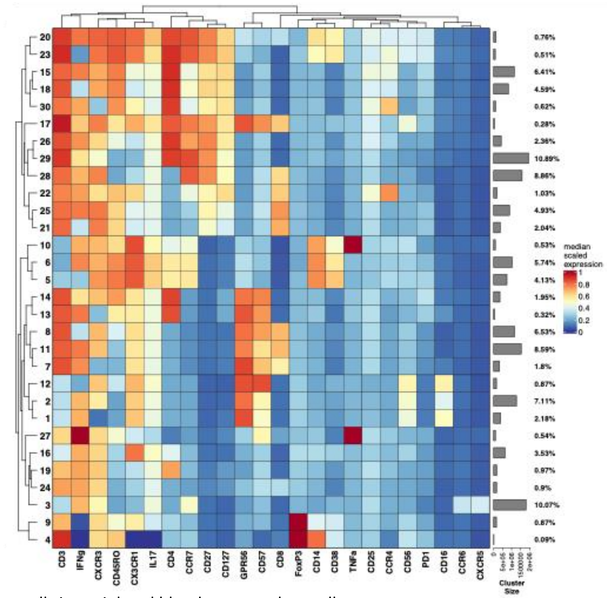


Figure 2. UMAP clustering and heatmap identifying clusters of immune cells in peripheral blood mononuclear cells.

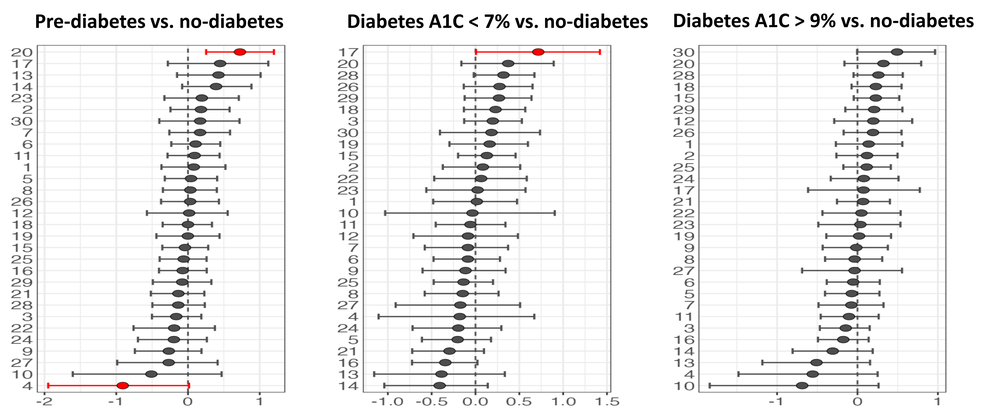


Figure 3. Forest plots showing Bayesian posterior estimates for associations between immune cell clusters and glycemic status relative to no diabetes. Cluster 20 and Cluster 23 are clusters with CD3⁺ T cell: CD14⁺ Monocyte complexes.

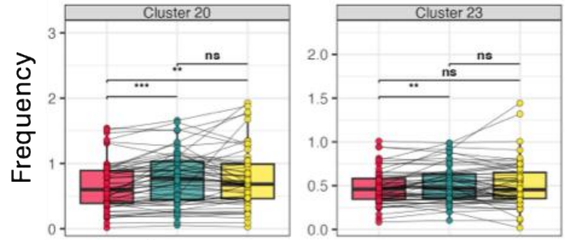


Figure 4. Complex clusters 20 and 23 decreased significantly with γ-irradiated Mycobacterium Tuberculosis (gRV) stimulation, but not CMV peptide stimulation.

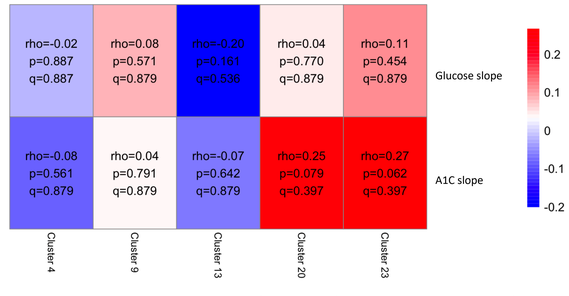


Figure 5. Partial Spearman correlations (adjusted for status, age, and race) showing associations between longitudinal metabolic slopes and molecular clusters.

CONCLUSIONS

- In this clinical cohort of patients, we identified two CD3⁺ T cell-CD14⁺ monocyte complexes (Clusters 20 and 23) that increased with insulin resistance.
- Antigenic stimulation with gRV decreased the frequency of clusters, but not with the CMV pp65 peptide. This may be due to the ability of whole-cell Mtb antigens to trigger specific phagocytic pathways or TLR-mediated internalization in monocytes, which may prioritize individual cell activation over the formation of stable complexes.
- The correlation between the complex clusters and longitudinal metabolic slopes was stronger for A1C but was not statistically significant.

FUTURE DIRECTIONS

- A larger, long-term study investigating these immune complexes in the context of HIV and aging is underway to elucidate antigenic drivers of diseases of aging.

ACKNOWLEDGEMENTS

R01-AG094488-01 (CNW), K23 HL156759 (CNW), Doris Duke CSDA 2021193, Burroughs Wellcome Fund 1021480 (CNW), and the Gilead Research HIV Scholars Award.

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