Autoantibodies Targeting FCHSD2 In PLWH with Diabetes: A Link to Metabolic Dysfunction

Laventa M. Obare[1], Samuel Bailin[1], Xiuqi Zhang[1], Kisyua Nthenge[1], Mona Mashayekhi[1], Curtis Gabriel[1], Simon A. Mallal[1], John R. Koethe[1], Wyatt McDonnell[2], Celestine N. Wanjalla[1]

[1]Vanderbilt University Medical Center, Vanderbilt University, [2]Infinimmune, Alameda, CA

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HIV-driven immune activation induces anti-FCHSD2 autoantibodies, linking immune dysregulation to metabolic diseases

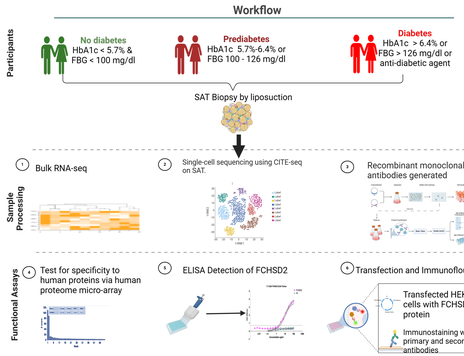
BACKGROUND

- Persons living with HIV (PLWH) experience a **1.5–2-fold** higher incidence of cardiovascular disease (CVD) not solely attributable to traditional risk factors.
- Subcutaneous adipose tissue (SAT) regulates metabolic health, but inflammation and insulin resistance can shift its secretome to a pro-inflammatory, pro-atherogenic state.
- B cells have been associated with cardiometabolic disease in the general population and are present in SAT.
- FCHSD2 is an adapter protein involved in insulin secretion and has been implicated in the pathogenesis of diabetes.
- HIV and diabetes contribute to chronic inflammation, immune dysfunction, and molecular mimicry, potentially promoting autoantibody production against FCHSD2.

OBJECTIVE

This study investigates B cell subsets in SAT and clonal B cell populations in PLWH with diabetes.

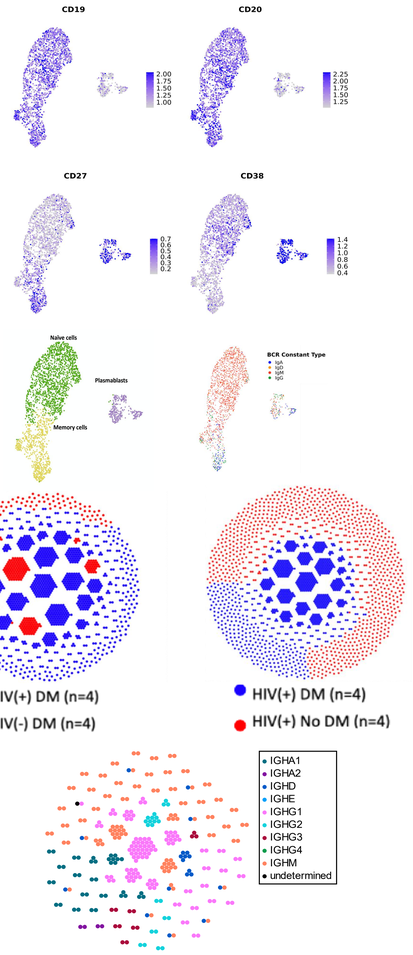
METHODS



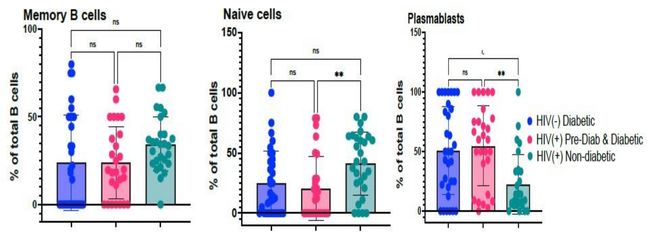
- Cohort: N=87
- Single-cell sequencing of the stromal vascular fraction from SAT using CITE-seq, followed by B cell receptor (BCR) sequencing.
- BCR sequences were analyzed using the 10X enclone program.
- Generated recombinant human monoclonal antibodies from clonal BCRs from PLWH with diabetes and PWoH with diabetes.
- Verified the specificity of a clonal antibody orphan antibody and identified its target antigen as FCHSD2.
- Used immunofluorescence to stain 293K cells after transient transfection with plasmids expressing FCHSD2
- ELISA detection of FCHSD2.

RESULTS

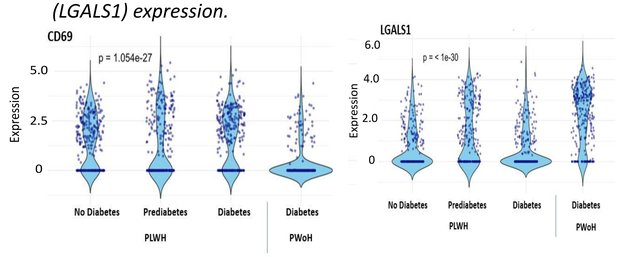
A ***Figure 1 : Characterization of B cell subsets.*** *B cells in the adipose tissue were identified using CITE-seq combined with 10x Genomics single-cell RNA sequencing.*



B ***Figure 2: Adipose tissue B cells.*** *Projection plot shows plasmablasts, memory B cells, and naïve cells from PLWH and PWoH and the distribution of cell subsets.*



C ***Figure 3:Transcriptional signatures of B cells****. B cells from PLWH are more pro-inflammatory based on CD 69 and Galectin 1 (LGALS1) expression.*



E ***Figure 5: Anti-FCSHD2 identified from specificity testing of orphan antibodies made from clonal BCRs in SAT of PLWH.*** *This was identified using the CDI Labs Human Protein Microarray v4*

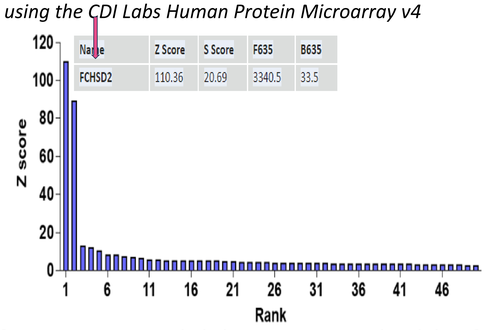


Figure 4: BCR clonality in the adipose tissue of participants*. BCRs from participants with diabetes were more clonal than from those without diabetes, irrespective of HIV status. Dots depict individual BCRs. Clonal B cells (more than two dots clustered indicate identical receptors). The largest clusters are in the center. Top Left: BCRs from diabetic PLWH (blue) are more clonal than diabetic PWoH (red). Top Right: BCRs from PLWH without HIV (red), are less clonal. IgG from PLWH are shown in the bottom image, color-coded based on the subtype.*

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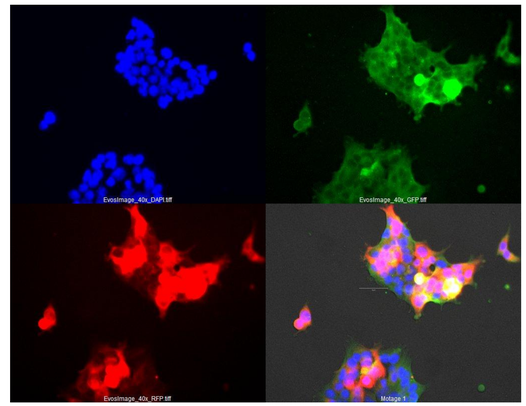


Figure 6: Immunofluorescence. *(Clone #5 binds to FCHSD2 expressed in HEK293 cells transfected with FCHSD2 plasmid that also expresses the mCherry marker.*

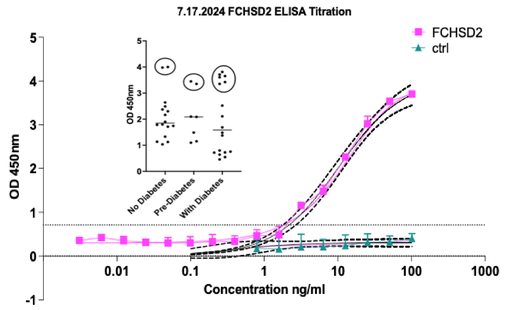


Figure 7 :ELISA EC50 curve. *Anti-FCHSD2 [#5] has an EC50 of 12.69 ng/ml. Inset dot plots show ten PLWH (without diabetes, pre-diabetes, and diabetes) with high titers of anti-FCHSD2 in their plasma.*

CONCLUSIONS

- Clonal B cells accumulate in adipose tissue with cardiometabolic disease, regardless of HIV status, and plasmablasts largely contribute to this accumulation.
- Antibodies made by clonal B cells against human proteins may be associated with autoimmune responses and are important in the development of DM and its progression in PLWH.
- Anti-FCHSD2 Abs will offer important insight into novel therapeutic targets.

FUTURE DIRECTIONS

- Exploration of the functional implication, therapeutic or diagnostic potential of anti-FCHSD2 abs in PLWH.

ACKNOWLEDGEMENTS

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Contact Information*: Laventa Obare, Department of Medicine, Division of Infectious Diseases, Vanderbilt University Medical Center, Nashville, TN, 37232-2582. Email: laventa.m.obare@vumc.org*