Novel Biomarkers Link Inflammation, T-Cell Exhaustion, Bone Health, and Frailty in People With HIV

869

Michael L. Freeman[1], Wendy Fitzgerald[2], Brian M. Clagett[1], Leonid Margolis[3], Kristine M. Erlandson[4], Carey L. Shive[1,5]

[1]Case Western Reserve University, Cleveland, Ohio, USA, [2]Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, Maryland, USA, [3]Ilia State University, Tbilisi, Georgia, [4]University of Colorado, Denver, Colorado, USA, [5]Veterans Affairs Northeast Ohio Healthcare System, Cleveland, Ohio, USA

BACKGROUND

- Chronic inflammation in aging (inflammaging) is a critical driver of morbidities and geriatric syndromes such as frailty, a condition characterized by the accumulation of age-related functional decline and vulnerability to stressors.
- In people with HIV (PWH), persistently elevated plasma levels of inflammatory factors contribute to increased incidence and earlier onset of non-AIDS morbidities and geriatric syndromes, including frailty.

METHODS

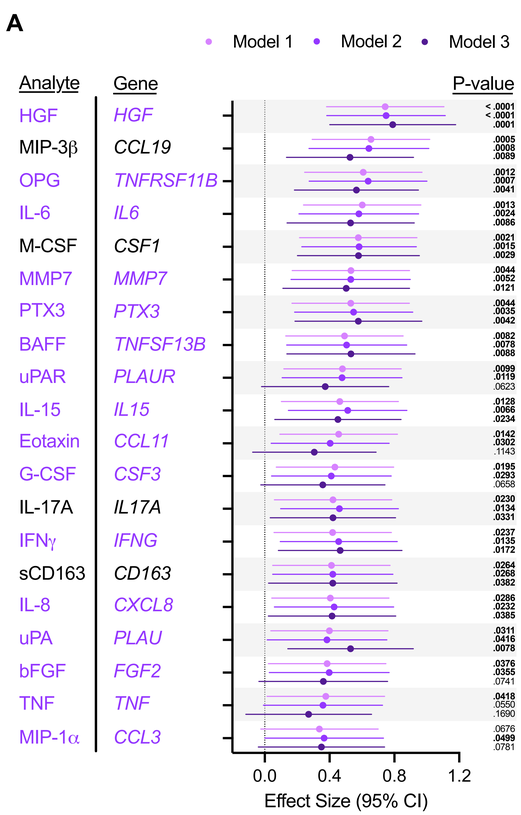
- Plasma analytes and T cell phenotypes from PWH without frailty (0 Fried score, n=60) and with frailty (≥3 Fried score, n=60) were measured by Luminex assay or flow cytometry, respectively.
- Multiple least-squares linear regression analysis was used to determine the association of each marker with frailty in unadjusted and adjusted models. Model 1: unadjusted; Model 2: adjusted for age, sex, race/ethnicity; Model 3: adjusted for age, sex, race/ethnicity, diabetes, hypertension, and cardiovascular disease
- Spearman correlations were used to determine the association of plasma analytes with T cell phenotypes.

PARTICIPANT INFORMATION

	Non-Frail	Frail	*P*-value
n	60	60	
Age (y); median (IQR)	58.0 (52.3-64)	59.6 (53.3-65)	ns
Sex at Birth; n (%)			ns
Male	48 (80)	42 (70)	
Female	12 (20)	18 (30)	
Race/Ethnicity; n (%)			ns
Black, Non-Hispanic	15 (25)	23 (38.33)	
White, Non-Hispanic	31 (51.67)	28 (46.67)	
Hispanic, Any Race	10 (16.67)	9 (15)	
Any Other Race	4 (6.66)	0 (0)	
Body Mass Index; median (IQR)	26.68 (23.14-29.06)	28.33 (23.88-32.07)	ns
CD4 T cell count (cells/uL); median (IQR)	637 (512-871)	645 (533-813)	ns
Plasma HIV RNA (copies/mL); median (IQR)	<40 (<40-<40)	<40 (<40-40)	ns
Substance Use			ns
Never, n (%)	18 (30)	10 (16.67)	
Prior, n (%)	30 (50)	30 (50)	
Current, n (%)	12 (20)	20 (33.33)	
Smoking			ns
Never, n (%)	20 (33.33)	10 (16.67)	
Prior, n (%)	17 (28.33)	35 (58.33)	
Current, n (%)	23 (38.33)	15 (25)	
Hypertension, n (%)	38 (63.33)	49 (81.67)	0.0400
Cardiovascular Disease, n (%)	6 (10)	16 (26.67)	0.0321
Diabetes, n (%)	5 (8.33)	18 (30)	0.0046

Osteoprotegerin links bone health, senescence, and T-cell exhaustion to **frailty** in PWH.

RESULTS



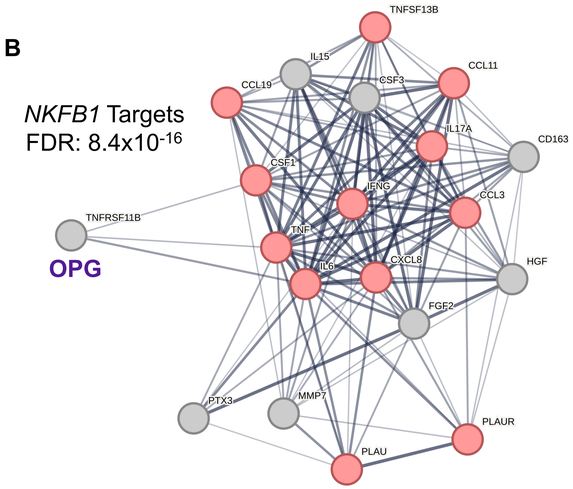


Figure 1. NF-κB-driven inflammation is associated with frailty in people with HIV. Soluble analytes in plasma were measured in people with HIV (PWH) without frailty (n=60) and PWH with frailty (n=59). **A)** Effect size and 95% confidence intervals of plasma analytes significantly related to frailty in at least one of the three models, as determined by multiple least-squares linear regression analysis. Analytes in purple are part of the senescence-associated secretory phenotype (SASP). **B)** STRING database visualization of 20 frailty-associated proteins. Targets downstream of *NFKB1* were determined using the TRRUST database and are highlighted in red. FDR, false discovery rate.

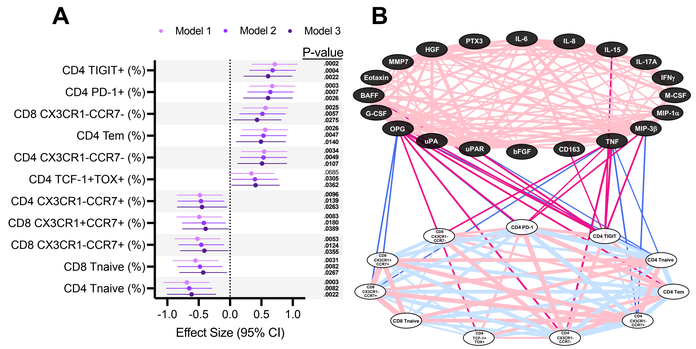


Figure 2. Association of T cell phenotypes with frailty in people with HIV. Peripheral blood T cell phenotypes were measured in PWH without frailty (n=60) and PWH with frailty (n=60). **A)** Effect size and 95% confidence intervals of T cell phenotypes significantly related to frailty in at least one of the three models, as determined by multiple least-squares linear regression analysis. **B)** The 20 soluble proteins associated with frailty (black nodes) were compared to the 11 frailty-associated T cell phenotypes (white nodes) by Spearman correlation analysis in PWH with frailty. Only significant correlations ($P \leq 0.05$) are shown. Correlations with a negative rho value are in red, correlations with a positive rho value are in blue. For emphasis, only correlations between soluble analytes and T cell phenotypes are in bold colors.

CONCLUSIONS

- We found a strong association of the SASP and NF-κB related inflammation with frailty in PWH.
- **Osteoprotegerin (OPG)**, a SASP component, can inhibit osteoclast formation and prevent bone resorption.
- Low proportion of naïve CD4 T cells and increased TIGIT and PD-1 expression were associated with both OPG levels and frailty, suggesting a link between inflammation, senescence, T cell activation, bone health, and frailty in PWH.

CONTACT

Michael L. Freeman, Ph.D.
Division of Infectious Diseases and HIV Medicine,
Case Western Reserve University School of Medicine,
Cleveland, Ohio, USA
MLF62@case.edu

FUNDING

New Works Concept Sheet 526 from the Advancing Clinical Therapeutics Globally for HIV/AIDS and Other Infections (ACTG) network [NIH AI068636] to MLF

ACKNOWLEDGMENTS

We thank Katelyn O'Hare, Vikhyath Jonalagadda, Brigid Wilson, Kunling Wu, Katherine Tassiopoulos, Paola Rodríguez-Nieves, Jeffrey Jacobson, Scott Sieg, and Michael Lederman for technical assistance and analysis, clinical samples and data, and helpful discussions.

CASE WESTERN RESERVE UNIVERSITY School of Medicine
Center for Global Health and Diseases
University Hospitals
RUSTBELT CFAR