Impact of PERK Genetic Variants on the Serum Cytokine Profile of People with HIV on Antiretroviral Therapy: An Ancestry-Stratified Analysis

Khalifah A[1], Akay-Espinoza C[2], Omolehinwa T[2], Jordan-Sciutto KL[2]

[1] Department of Periodontology, School of Dental Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States; [2] Department of Oral Medicine, School of Dental Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, United States

Rationale: Despite advances in antiretroviral therapy (ART), immune dysregulation remains a challenge in people with HIV (PWH). PERK, encoded by *EIF2AK3*, plays a crucial role in endoplasmic reticulum stress and inflammatory pathways; yet, its impact on systemic cytokine expression in PWH remains unclear. We previously that minor PERK genetic variants, resulting from three single-nucleotide variants (SNVs) of *EIF2AK3*, were associated with global cognitive deficits and elevated IL-6 levels in PWH. In this study, we evaluated the serum cytokine profiles of PWH on ART stratified by PERK genetic variants and ancestry to identify potential inflammatory patterns.

Materials and Methods: Clinical data, including sociodemographic information, were collected from 96 PWH on ART. DNA extracted from saliva was used to determine *EIF2AK3* variant status for the three SNVs that define the two most common PERK haplotypes (rs867529, rs1805165, and rs13045) using real-time polymerase chain reaction. Participants were stratified as those with the major PERK haplotype PERK*A and those with the minor haplotype PERK*B. Serum cytokine levels were determined using Olink® Target 48 Cytokine Proteomics proximity extension assay. Statistical analyses were conducted using the Mann–Whitney *U* test with Stata SE (v16), and a p-value of <0.05 was considered statistically significant.

Results: Among PWH with European ancestry, β-NGF, caspase 8, CCL25, CCL28, CSF2, FGF-19, and interferon-γ levels were higher in those with PERK*B than in those with PERK*A. Among PWH with African ancestry, CXCL9, FGF-19, IL-15RA, IL-17C, IL-18, IL-6, MMP-10, and TNFSF10 levels were higher in those with PERK*B than in those with PERK*A.

Conclusions: The PERK*B haplotype was associated with distinct cytokine and chemokine signatures in PWH on ART with European and African ancestry, suggesting ancestry-associated inflammatory signatures in PWH. These findings underscore PERK's role in immune and inflammatory responses and emphasize the need for further research into genetic factors influencing ART-related immune regulation and the contribution of ancestry background.

Clinical Significance: This study supports the integration of genetic and inflammatory profiling into the clinical assessment of PWH on ART. Characterization of PERK-associated immune dysregulation may contribute to the development of personalized interventions, ultimately improving long-term health outcomes for this population.

Support: This study was supported by the NIDCR/NIH/DHHS grant R01-DE029648-01 and the NIMH/NIH grant P30MH097488.