Interferome Profiling Links IFNα5-Mucin-1 Axis to HIV-1 Pathogenesis

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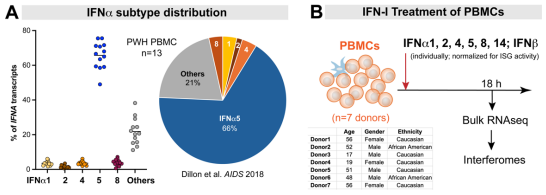
BACKGROUND

- Chronic HIV infection is linked to persistent immune activation that contribute to comorbidities among PWH.
- Type I interferons (IFN-I) are essential for antiviral immunity, but sustained IFN-I activity during chronic stages is associated with inflammation.
- IFN-I include 13 IFNα subtypes and IFNβ, but their relative contributions to HIV pathogenesis is unclear.
- Previously, we showed that IFN-I responses are *compartmentalized*: IFNβ is expressed highly in the gut but not in blood, where IFNα subtypes dominate instead.
- **Main question:** are there qualitative differences between IFNα subtypes in the blood, and if so, how do these differences impact HIV pathogenesis?

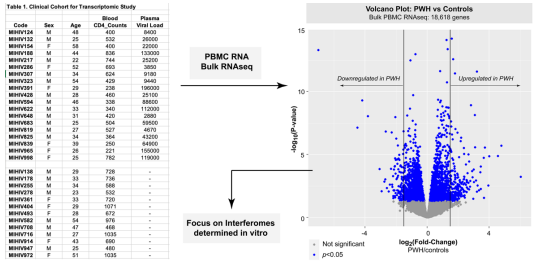
METHODS

We analyzed human peripheral blood mononuclear cells (PBMC) in 3 separate contexts:

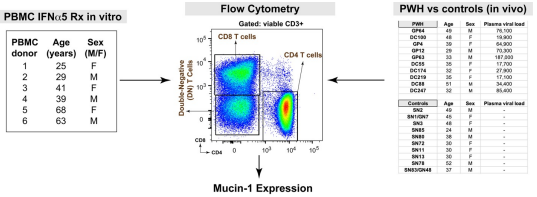
Study 1: IFNα-subtype Interferomes in PBMCs in vitro



Study 2: IFNα subtype interferomes in PWH PBMCs in vivo



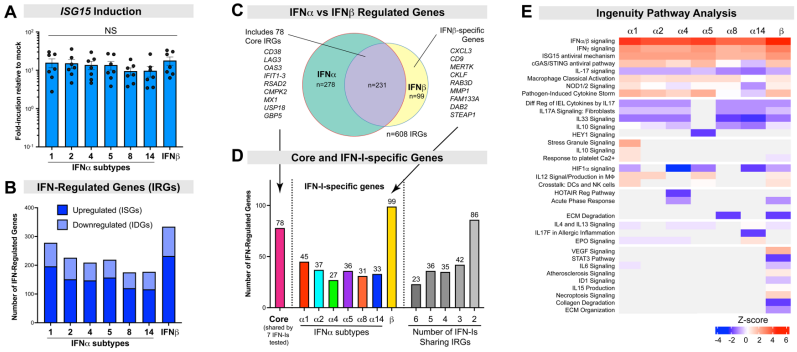
Study 3: Mucin-1 Expression in Immune Cells



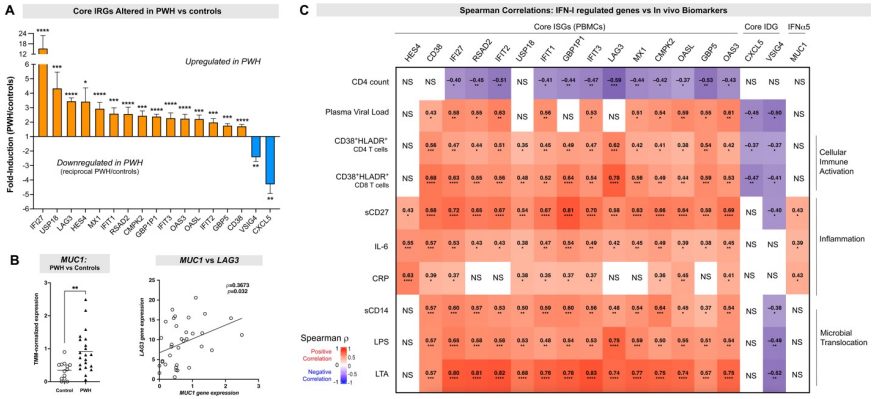
IFNα5, the dominant type I IFN in blood, induces *LAG3* and Mucin-1, T cell exhaustion markers linked to chronic inflammation among PWH.

RESULTS

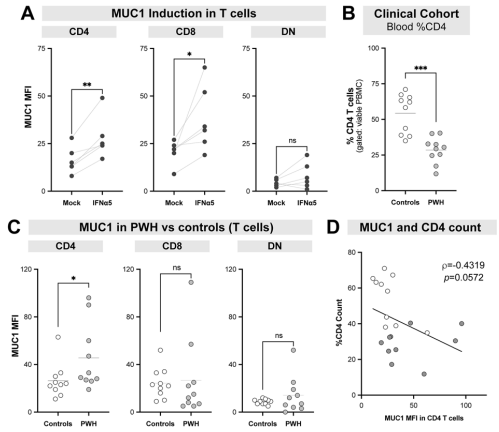
Study 1: Qualitative differences between IFNα subtypes inferred from PBMC interferomes



Study 2: A subset of Core and IFNα5-specific genes correlated with HIV pathogenesis biomarkers



Study 3: IFNα5 induces Mucin-1 in T cells, and Mucin-1 is upregulated in blood CD4 T cells of PWH



CONCLUSIONS

- IFNα subtypes can trigger distinct gene programs in bulk PBMC, confirming qualitative differences between them.
- Chronic IFNα signaling may promote pathogenesis by inducing immune activation (CD38), exhaustion (LAG3) and metabolic dysfunction (CMPK), while inhibiting protective immune mechanisms (CXCL5, VSIG4).
- IFNα5, the dominant IFN-I in blood, induced Mucin-1, a transmembrane glycoprotein linked to T cell exhaustion.
- Mucin-1 is elevated in CD4 T cells of PWH and correlated with heightened inflammation linked to the IL-6 pathway.
- The data demonstrate how a specific IFNα subtype may uniquely influence pathogenesis while pinpointing target effectors to restore immune function in PWH.

ADDITIONAL KEY INFORMATION

This work was supported by NIH R01 AI134220 and AI145428 (CCW and MLS), the University of Colorado CU-ASPIRE Program, and VAMC BX006270 (EMP, JHM).

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PLAIN LANGUAGE SUMMARY

A dominant antiviral immune signal in blood may contribute to HIV disease by driving persistent inflammation, revealing new potential targets to restore immune health among PWH.