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Peer Review

Review of: "Thrombospondin Regulation Differentiates HIV Patients with Natural and Therapy-Mediated Control of Plasma Viremia: A Genome-Wide Transcriptomic Analysis"

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Reviewer Comments

Title:

The manuscript's title, "Thrombospondin Regulation Differentiates HIV Patients with Natural and Therapy-Mediated Control of Plasma Viremia: A Genome-Wide Transcriptomic Analysis," clearly captures the study's essence. It specifies the core finding—thrombospondin regulation—and the methodology—genome-wide transcriptomics—highlighting the difference between natural and therapy-mediated HIV control. This precise phrasing helps readers immediately grasp the focus and novelty.

Abstract

The abstract offers a clear, structured summary of the study, covering the rationale, methods, key findings, and implications. It is balanced, includes relevant data (e.g., correlation coefficients, p-values), and uses accessible language, making it readable across disciplines. The closing sentence could better highlight future relevance, for example, by highlighting THBS1 as a biomarker. Overall, it's a well-crafted summary setting the tone for the manuscript.

Introduction

The introduction provides a firm overview of HIV infection biology and the clinical features of elite controllers and LTNPs. It contextualises the research within existing gene-expression studies of immune cells. The choice of whole PBMCs is justified, given the limitations of the archived sample. The authors

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link their previous work, showing a logical progression. The introduction highlights a gap in understanding natural versus HAART-mediated viremia control at the transcriptomic level. To enhance clarity, adding a brief paragraph summarising the study's aims in bullet or numbered format would help readers grasp the objectives more easily.

Objective

While the study doesn't have a dedicated section outlining its objectives, they are explained throughout. The authors aim to differentiate LTNPs' transcriptomic signatures from HAART-treated patients, identify key genes and pathways, and validate some targets using proteomics. These clear, measurable objectives provide a strong research framework. Explicitly stating them in a dedicated section or box could improve clarity and organisation, enhancing readability.

Methods

The methods section effectively highlights careful experimental design, using whole PBMCs to capture immune responses. It employs tools like Bead-Studio for microarray, MetaCoreTM for pathways, and validation techniques such as qRT-PCR, confocal microscopy, and flow cytometry, demonstrating a thorough multi-method approach. Including ethical approval details (IRB, consent) would increase transparency. A workflow diagram could also improve clarity.

Results:

The results are comprehensive and highly informative. The authors identify hundreds of differentially expressed genes (DEGs) between LTNPs and therapy-treated groups, using robust bioinformatics tools to highlight significant pathways like BCR signalling and apoptosis regulation. Hierarchical clustering and pathway enrichment analyses clearly show a distinct transcriptomic profile for LTNPs. The authors effectively use visual aids, such as figures and tables, to present their findings clearly. qRT-PCR validations are detailed and show high agreement with microarray data, especially for the THBS1 gene, which serves as a strong disease phenotype marker. Flow cytometry and microscopy data further confirm these findings at the protein level. A notable strength is the triangulation of results across three validation methods. The study could be improved by summarising the key quantitative findings in bullet points or a table at the end of the results section for quick reference.

Discussion:

The discussion integrates the study's findings with previous research, correctly interpreting unique immune pathways and downregulation of apoptosis genes in LTNPs as markers of a distinctive immune

profile. The role of THBS1 as a potential biomarker is well-supported and explained. The manuscript notes that patients on HAART do not fully reconstitute their immune system despite viral suppression, which is well contextualised. However, the discussion could be more balanced by acknowledging limitations such as small sample size, lack of single-cell resolution, and issues with archived samples. Mentioning possible confounders such as age, gender, or co-infections would improve the analysis. Including alternative interpretations and future research directions would strengthen the section.

Conclusion

The conclusions align with the research aims, noting LTNPs' unique transcriptomic and immunological profile and identifying THBS1 as a promising biomarker. They avoid exaggeration and new data, maintaining consistency. Highlighting practical applications of THBS1, such as clinical use or patient grouping, could enhance impact. Using bullet points for main conclusions might improve clarity for diverse audiences.

Appendices and supplementary material

The supplementary data are well organised and include valuable details. Supplementary Table 1 provides clinical information, such as drug regimens and T-cell counts, while Supplementary Tables 13 and 14 support flow cytometry analysis. These are properly cited, enhancing transparency. To improve clarity, adding a brief explanation or legend for flow cytometry data would help readers less familiar with the technique. Uploading raw transcriptomic datasets to public repositories such as GEO or ArrayExpress would also promote open science and reproducibility.

Declarations

Potential competing interests: No potential competing interests to declare.