

Transcriptomic Analysis of Vero Cell Adaptation to Suspension Cultivation and Its Association with Viral Receptor Expression

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Abstract

Vero cells represent an indispensable continuous cell lineage for large-scale viral vaccine manufacturing. To facilitate high-density industrial bioprocessing and overcome the spatial limitations of traditional adherent monolayers, transitioning these cells to suspension cultivation in bioreactors is a fundamental and highly sought-after strategy. However, the systemic transcriptomic alterations underlying this drastic physical and physiological adaptation process—particularly concerning their potential collateral impact on viral entry receptor expression and subsequent viral susceptibility—remain incompletely characterized. In this study, we performed comprehensive bulk RNA-sequencing to systematically delineate the global transcriptomic landscape of adherent and suspension-adapted Vero cells. Principal Component Analysis (PCA) and rigorous differential expression analysis ($|\log_2\text{FoldChange}| \geq 1$, adjusted $P < 0.05$) revealed a massive global transcriptomic reprogramming upon suspension adaptation, characterized by the widespread dysregulation of thousands of genes. To uncover the functional implications of these variations, comprehensive pathway analyses, including Gene Ontology (GO) and KEGG enrichment, were conducted. The results indicate that the differentially expressed genes are predominantly driven by cellular structural reorganization and extracellular matrix (ECM) interactions. Furthermore, Gene Set Variation Analysis (GSVA) and Gene Set Enrichment Analysis (GSEA) identified significant directional shifts. Most notably, we observed a pronounced repression in the Focal adhesion hallmark, perfectly mirroring the physical detachment from culture substrates, alongside distinct metabolic reprogramming characterized by significantly enhanced glycolysis to meet new energetic demands in suspension. Crucially, absolute expression quantification and Pearson correlation analysis demonstrated that this physiological adaptation concurrently and divergently modulates the expression landscape of key viral entry receptors. While receptors such as CD46 were significantly upregulated, others including ACE2, AXL, and PVR exhibited pronounced downregulation. These receptors established a robust co-expression matrix with core cellular adaptation signatures, implying a tightly linked regulatory environment. Overall, this study provides compelling evidence that the structural and metabolic reprogramming requisite for Vero cell suspension growth intrinsically alters their viral susceptibility profiles. These findings offer valuable molecular insights that can inform rational cell line engineering and targeted bioprocess optimization strategies, ultimately facilitating the efficient production of diverse viral vaccines.

Keywords

Vero Cells, Transcriptomics, Suspension Adaptation, Viral Entry Receptors, Vaccine Biomanufacturing