Whole-Blood Transcriptomic Profiling Unveils An HERV-Interferon Axis as A Novel Immunological Signature in Latent Autoimmune Diabetes in Adults (LADA)

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Abstract. Latent Autoimmune Diabetes in Adults (LADA) is characterized by progressive autoimmune beta-cell destruction, yet its upstream molecular triggers remain elusive. In this study, we utilized whole-blood RNA sequencing to investigate the global transcriptomic and endogenous virome landscapes of LADA patients. Principal Component Analysis revealed a robust systemic separation driven by both host immune gene remodeling and a distinct human endogenous retrovirus (HERV) expression signature. Differential expression profiling uncovered widespread host immune dysregulation coupled with a highly targeted and bidirectional modulation of specific HERV loci, including the profound upregulation of distinct viral elements alongside the significant downregulation of others. Crucially, functional enrichment demonstrated a profound "viral mimicry" state, characterized by overwhelming antiviral innate immune activation and Type I interferon (IFN) signaling, despite the absence of exogenous viral infection. Gene Set Variation Analysis (GSVA) further confirmed the Type I IFN storm as the singular, significantly upregulated systemic module in peripheral circulation. Finally, a highly stringent Spearman co-expression network and node degree analysis directly linked specific upregulated HERV hubs (e.g., loci 1371) to core IFN pathway integrators and molecular switches (e.g., IFI27, USP18, ISG15, IFITM3). Together, our findings provide compelling bioinformatic evidence that specific HERV activation serves as a crucial upstream trigger orchestrating the pathogenic interferon cascade in LADA.

Keywords: LADA, ERV, Type 1 Interferon, Autoimmune, Transcriptome.

1. Introduction

Human Endogenous retroviruses (HERVs) are genomic elements derived from ancient retroviral infections in which viral genetic material became permanently integrated into the DNA of host germline cells and was subsequently inherited across generations. Retroviruses infect cells by fusing with the host cell membrane and releasing a capsid into the cytoplasm that contains enzymes required for genome integration; their RNA genome is reverse-transcribed by viral reverse transcriptase into double-stranded DNA, which is then transported into the nucleus and inserted into host chromosomes, where it is termed a provirus (Bannert & Kurth, 2004; Griffiths, 2001). Complete proviruses include genes encoding viral proteins, a primer-binding site, and long terminal repeats (LTRs) at both ends that contain transcription-factor binding motifs, allowing the virus to exploit the host's transcriptional machinery (Griffiths, 2001). If integration occurs in germline cells, the viral sequence can be inherited by future generations. Across millions of years of primate evolution, repeated retroviral infections have deposited proviral sequences into the human germline. These sequences accumulated mutations, deletions, and recombination events that disabled their ability to produce infectious particles or undergo further retrotransposition, effectively fixing them at specific genomic locations (Bannert & Kurth, 2004; Griffiths, 2001). When such proviral sequences accumulate mutations or deletions that disable normal viral replication yet remain embedded in the genome, they are classified as human endogenous retroviruses (HERVs). In humans, these elements are called human endogenous retroviruses and collectively account for approximately eight percent of the genome — a proportion far greater than the roughly one to two percent that encodes protein-coding genes — highlighting their substantial evolutionary and biological footprint (Jakobsson & Jern, 2022; Lander et al., 2001; Stein, 2023; Yi, 2004). Most HERV loci are transcriptionally repressed through epigenetic

mechanisms such as DNA methylation and histone modifications, and dysregulation of these mechanisms can permit HERV reactivation (Hurst & Magiorkinis, 2017; Leung & Lorincz, 2012).

Beyond their "fossil" status, HERV-derived sequences—particularly LTRs—can function as regulatory modules that shape host transcriptional networks by acting as promoters or enhancers, sometimes dispersing binding sites for immune-related transcription factors and influencing innate immune programs (Chuong, Elde, & Feschotte, 2016; Fuentes et al., 2018). This regulatory potential is increasingly relevant to autoimmunity, where aberrant HERV expression has been discussed as a contributor to immune dysregulation through mechanisms including molecular mimicry, "viral mimicry," and innate immune receptor engagement (Grandi & Tramontano, 2018; Jin & Zhang, 2023). In type 1 diabetes, aberrant expression of HERV-W envelope proteins has been detected in patients and shown to promote pro-inflammatory responses and β-cell dysfunction via innate immune pathways such as TLR4 signaling (Levet et al., 2017; Richardson et al., 2014). This supports the broader view that HERV activity may intersect with inflammatory circuits central to autoimmune endocrinopathies (Levet et al., 2019).

Latent autoimmune diabetes in adults (LADA) is a slowly progressive form of autoimmune diabetes diagnosed in adulthood that is frequently misclassified as type 2 diabetes at onset because insulin is not immediately required; however, unlike type 2 diabetes, LADA is defined by the presence of pancreatic islet autoantibodies—most commonly against glutamic acid decarboxylase (GAD65)—and progressive β-cell failure, placing it immunologically closer to type 1 diabetes (Fourlanos et al., 2005; Hawa et al., 2013). Individuals with LADA often carry HLA class II susceptibility alleles associated with autoimmune diabetes and demonstrate T-cell–mediated β-cell destruction, albeit at a slower rate than classic childhood-onset type 1 diabetes (Buzzetti et al., 2020; Hawa et al., 2013). Although direct causal evidence linking HERV activation specifically to LADA remains limited, the overlap in autoimmune mechanisms between LADA and type 1 diabetes makes HERV-mediated immune dysregulation a plausible upstream or amplifying factor worth investigating using modern genomic and computational approaches (Grandi & Tramontano, 2018; Jakobsson & Jern, 2022).

In this study, we performed a comprehensive transcriptomic investigation to evaluate whether abnormal HERV activity contributes to the molecular pathology of LADA. By using publicly available RNA-sequencing datasets from LADA patients and healthy controls, we systematically quantified both host gene expression and locus-specific HERV transcription across the human genome. Through integrated bioinformatic analyses, we determined that the reactivation of specific HERV loci is associated with the immune activation in autoimmune diabetes. By jointly analyzing the host transcriptome and the endogenous retro-virome, our study provided insights into the distinct HERV expression signatures that are present in LADA while exploring their potential mechanistic links to autoimmune pathology.

2. Methods

2.1. HERVmap Database and RNA Sequencing Datasets

The exact locus information for each HERV was extracted from previously published studies (Tokuyama, 2018). We obtained the following RNA sequencing datasets through ENCODE: LADA (SRR10005264, SRR10005265, SRR10005266, SRR10005268, SRR10005269, SRR10005271).

2.2. RNA-seq Data Processing and HERV Quantification

Raw Illumina sequencing reads from LADA patients and healthy controls were first processed to remove sequencing adaptors and low-quality regions using fastp. For standard cellular gene expression analysis, the high-quality trimmed reads were mapped to the human reference genome (GRCh38) using HISAT2 with default parameters. Read counts for each host gene were generated based on the Ensembl genome annotation using HTSeq.

To accurately quantify human endogenous retrovirus (HERV) expression, we applied a highly stringent alignment and filtering strategy to account for the repetitive nature of these elements. Trimmed reads were aligned to the GRCh38 assembly, and uniquely mapped reads or those passing strict edit-distance thresholds were retained using SAMtools. Specifically, reads were evaluated based on the CIGAR string and alignment scores to exclude those with excessive soft-clipping or mismatches. The resulting high-confidence BAM files, along with the curated BED file containing comprehensive HERV coordinates in the human genome, were used as input for the BEDtools coverage function to quantify read counts at each HERV locus. To correct for sequencing depth and compositional biases, HERV read counts were subsequently normalized using the size factors derived from the host cellular genes within the identical sample, as calculated by the DESeq2 normalization algorithm.

2.3. Statistical Analysis and Visualization

All statistical analyses and bioinformatic visualizations were performed in the R programming environment. The raw read counts of host cellular genes and human Endogenous retroviruses (HERVs) were merged into separate expression matrices. For host genes, ENSEMBL IDs were mapped to official Gene SYMBOLs using BioMart; in cases of duplicated symbols, the feature with the highest total expression (rowSums) was retained. To avoid compositional bias introduced by the repetitive nature of HERVs, size factors were primarily estimated from the host cellular gene count matrix using the DESeq2 algorithm, and these identical size factors were subsequently applied to normalize the HERV count matrix.

Differential expression analysis for both host genes and HERVs was conducted using the DESeq2 package. Statistical significance was defined by an adjusted p-value (padj) < 0.05 (Benjamini-Hochberg procedure) and an absolute $\log_2$ fold change > 1.0. For downstream clustering and visualization, raw counts were subjected to Variance Stabilizing Transformation (VST). Principal Component Analysis (PCA) was performed to explore global transcriptomic patterns, and unsupervised hierarchical clustering heatmaps of the top differentially expressed features were generated using the heatmap package with Z-score scaling. Volcano plots were visualized via the Enhanced Volcano package.

Gene Ontology (GO) enrichment analysis focusing on Biological Processes (BP) was performed using the cluster Profiler package with a p-value cutoff of 0.05. Redundant GO terms were removed using the simplify function (similarity cutoff = 0.7). To evaluate the systemic immune landscape, Gene Set Variation Analysis (GSVA) was executed using the GSVA package with a Poisson kernel applied to normalized counts. Predefined core immune pathway modules were scored, and statistical differences between the LADA and Control groups were assessed using the two-tailed Student's t-test.

Finally, to interrogate the direct regulatory relationships between HERV reactivation and the interferon storm, a Spearman co-expression network was constructed. VST-transformed expression profiles of significantly differentially expressed HERVs and core genes within the "response to type I interferon" pathway were extracted. Only highly robust correlations with an absolute Spearman's rank correlation coefficient ($|R|$) > 0.8 were retained. The resulting hub-and-spoke bipartite network was built using the graph package and visualized with the Fruchterman-Reingold layout algorithm via the graph package.

3. Results

3.1. Global Transcriptomic and HERV Signatures Distinguish LADA from Healthy Controls

To explore the overarching molecular alterations in Latent Autoimmune Diabetes in Adults (LADA)—a complex disease with high pathological heterogeneity (Maruyama, 2011)—we first performed Principal Component Analysis (PCA) on both host gene and HERV expression profiles. The global transcriptomic PCA demonstrated a clear and robust separation between LADA patients

and healthy controls, with the first principal component (PC1) explaining a substantial 57% and the second (PC2) explaining 15% of the total variance (**Figure 1A**). This high degree of inter-group separation indicates that the onset of LADA is accompanied by a systemic remodeling of immune and metabolic transcriptional networks, rather than random expression fluctuations. Remarkably, when we constructed a PCA based solely on the expression profiles of human Endogenous retroviruses, we also observed distinct clustering along the primary axes (PC1: 36%, PC2: 23%) (**Figure 1B**). These results not only confirm host-level transcriptomic shifts but also provide the first line of evidence that LADA is characterized by a distinct endogenous virome signature. This suggests that under disease conditions, the expression of HERVs is not merely widespread genomic noise, but rather undergoes non-random, specific alterations tightly linked to the disease state.

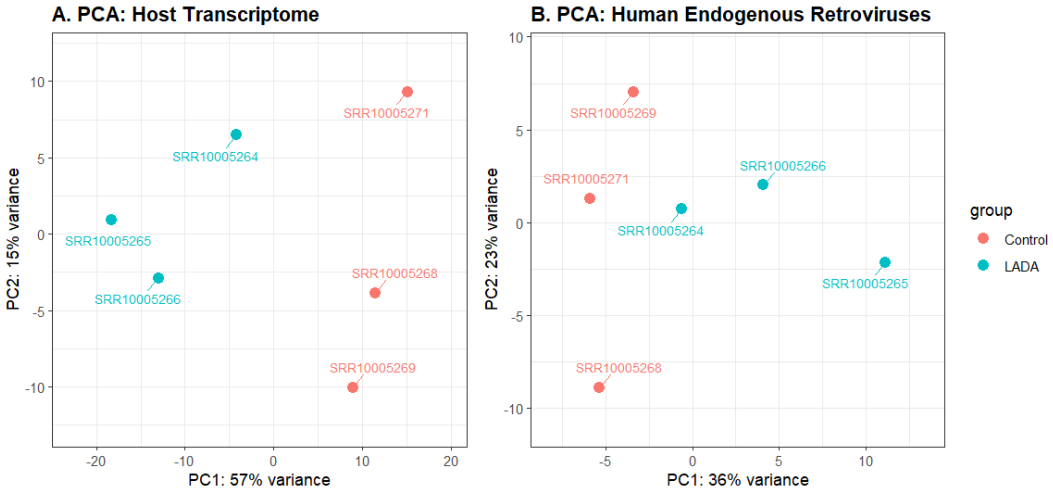

Figure 1. Global transcriptomic and HERV expression patterns distinguish LADA from healthy controls. PCA plots based on the normalized expression profiles of **(A)** host genes and **(B)** human Endogenous retroviruses (HERVs). Each dot represents an individual sequencing sample (Cyan: LADA patients; Salmon: Healthy controls). The percentages on the x- and y-axes indicate the proportion of total variance explained by Principal Component 1 (PC1) and Principal Component 2 (PC2), respectively. The robust clustering highlights distinct transcriptional remodeling in the disease state.

3.2. Widespread Host Gene Dysregulation Accompanied by Specific HERV Reactivation

We next conducted differential expression analysis to quantify the magnitude of these transcriptomic shifts and pinpoint key pathogenic molecules. Volcano plot analysis of the host transcriptome revealed massive and widespread gene dysregulation in LADA patients, with a substantial number of immunity-related genes (e.g., the classical interferon-stimulated gene ISG15) exhibiting highly significant differential expression levels (**Figure 2A**). The corresponding Z-score heatmap of the top 50 differentially expressed host genes confirmed highly consistent expression modules within groups, clearly illustrating a robust and systemic upregulation of immune-responsive elements in the LADA microenvironment (**Figure 2B**).

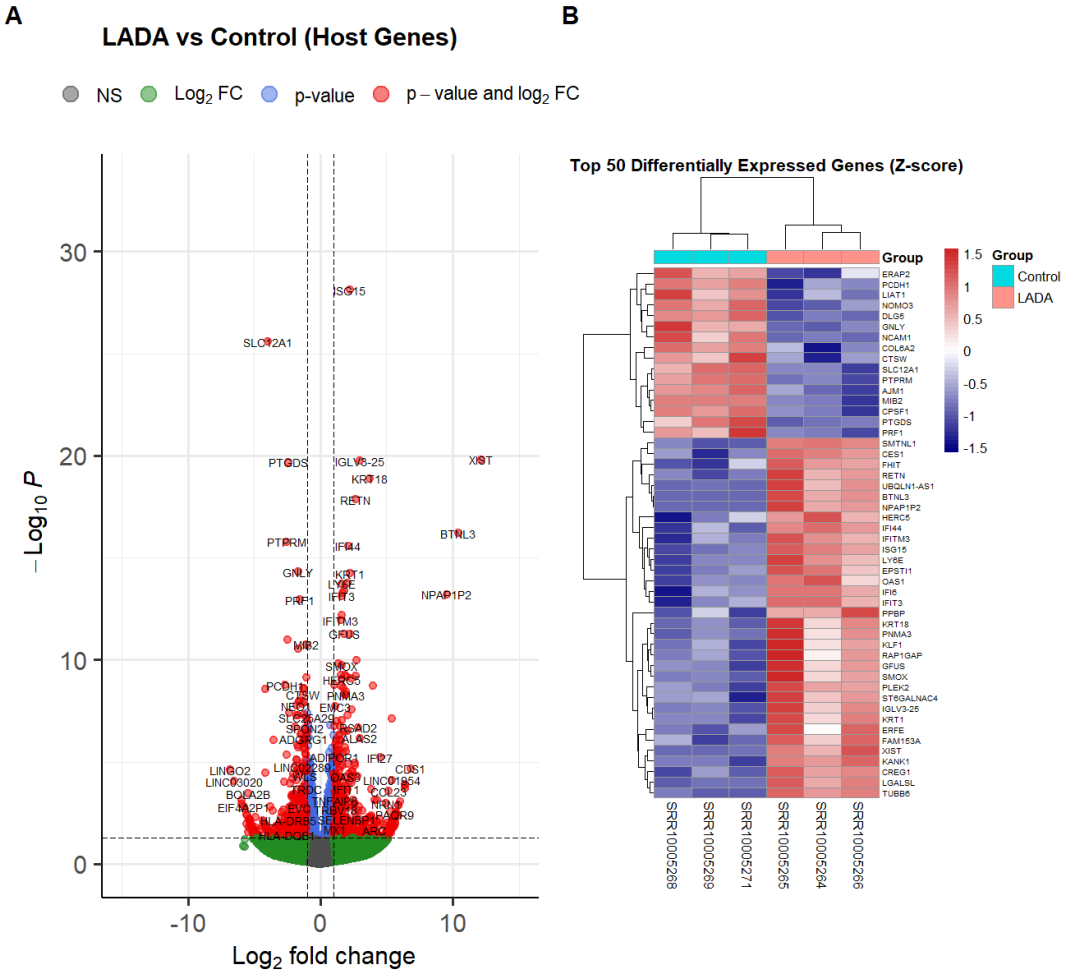

Figure 2. Widespread dysregulation of host genes and targeted reactivation of specific HERVs in LADA. (A) Volcano plot illustrating the global differential expression of host genes between the LADA and control groups. Red dots represent significantly dysregulated genes meeting the stringent thresholds of an adjusted p-value < 0.05 and an absolute log2 fold change > 1.0. **(B)** Z-score normalized heatmap of the top 50 differentially expressed host genes, demonstrating perfect unsupervised hierarchical clustering of samples by disease status.

In stark contrast, the differential analysis of the HERV repertoire displayed a much more targeted and selective pattern of reactivation. Specifically, we observed a distinct cluster of profoundly upregulated HERV loci (e.g., loci 1371, 1474, 3508, and 565), which are hypothesized to actively contribute to the viral mimicry state and the downstream interferon cascade. Conversely, a substantial subset of HERV loci (such as 4780, 3692, 4329, and 3247) was significantly downregulated in LADA patients.

This bidirectional and highly selective modulation confirms that the disease state does not simply trigger a global "pan-activation" or chaotic transcription of all dormant retroelements.

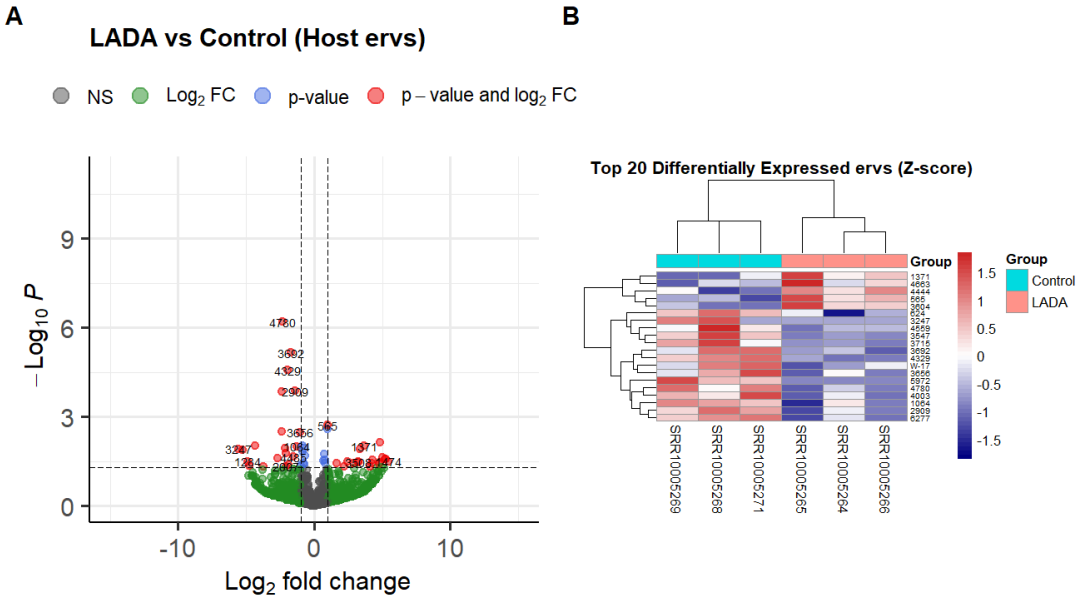

Figure 3. Targeted reactivation of specific HERVs in LADA. (A) Volcano plot depicting the restricted pattern of differentially expressed HERV loci, highlighting a selective awakening rather than pan-activation. **(B)** Z-score heatmap of the top 20 most significantly differentially expressed HERVs across all samples, identifying specific viral elements highly expressed in LADA patients.

3.3. Functional Enrichment Highlights Antiviral and Type I Interferon Responses

To further delineate the specific biological functions and downstream consequences of the dysregulated host genes, we performed Gene Ontology (GO) enrichment analysis. **Figure 4** showcases the top enriched Biological Process (BP) terms for all significantly dysregulated genes as well as those specifically upregulated in LADA. These enrichment results provide compelling direct evidence for the recently highlighted "viral mimicry" hypothesis in autoimmune pathogenesis (Suliman, 2024). Despite the absolute clinical absence of exogenous viral infections in these patients, the top enriched pathways among the upregulated genes were overwhelmingly dominated by antiviral defense mechanisms, including "response to virus," "humoral immune response," and "viral genome replication". Crucially, the "response to type I interferon" was also highly significantly enriched. This strongly suggests that double-stranded RNA (dsRNA) or DNA species generated by HERVs may be recognized by cytosolic nucleic acid sensors, thereby "tricking" the host immune system into mounting a potent and potentially tissue-destructive antiviral interferon storm. Furthermore, the significant enrichment of the humoral immune response pathway perfectly aligns with the classical pathological phenotype of LADA, which is clinically characterized by the sustained positivity of islet autoantibodies (Yang, 2019).

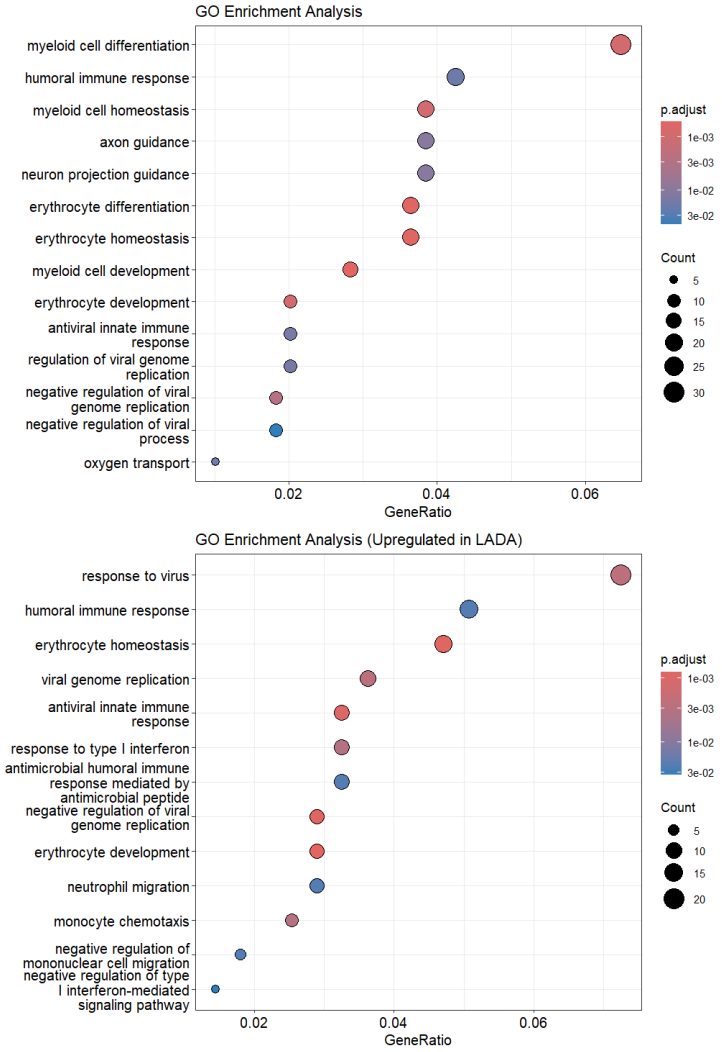

Figure 4. Functional enrichment reveals robust antiviral and humoral immune activation in LADA. Gene Ontology (GO) enrichment analysis dot plot highlighting the top Biological Process (BP) terms enriched among the significantly upregulated host genes in LADA. Dot size corresponds to the number of enriched genes within each pathway (Count), while the color gradient represents the adjusted p-value (p.adjust). Notably, pathways such as "response to virus," "viral genome replication," and "response to type I interferon" emerged as the top biological signatures.

3.4. GSVA Confirms Type I Interferon Storm as the Core Systemic Signature

To gain deeper mechanistic insights at the pathway level and to overcome the limitations of single-gene analysis, we performed Gene Set Variation Analysis (GSVA). We systematically evaluated a predefined set of six functional modules representing the chronological progression of 'viral mimicry'-induced autoimmunity (**Figure 5**). Strikingly, the Type I Interferon Response emerged as the singular molecular signature reaching strict statistical significance for upregulation in the peripheral blood of LADA patients ($p = 0.013$). This robust systemic interferon signature provides critical quantitative validation for the theory that HERV reactivation leads to downstream immune cascade amplification. Interestingly, while pathways associated with downstream adaptive immunity and tissue infiltration—such as Antigen Processing and Presentation ($p = 0.34$) and Chemokine Signaling Pathway ($p = 0.28$)—displayed noticeable median upward trends in LADA, they did not reach statistical significance in the peripheral blood sequencing data. We hypothesize that this reflects the highly organ-specific and localized nature of the adaptive autoimmune attack. During disease progression, highly active effector T cells and antigen-presenting cells are likely actively recruited and infiltrated into the pancreatic islet target tissues, meaning that the highly soluble and systemically

diffusible Type I interferon storm remains the primary detectable signal in the circulating peripheral blood.

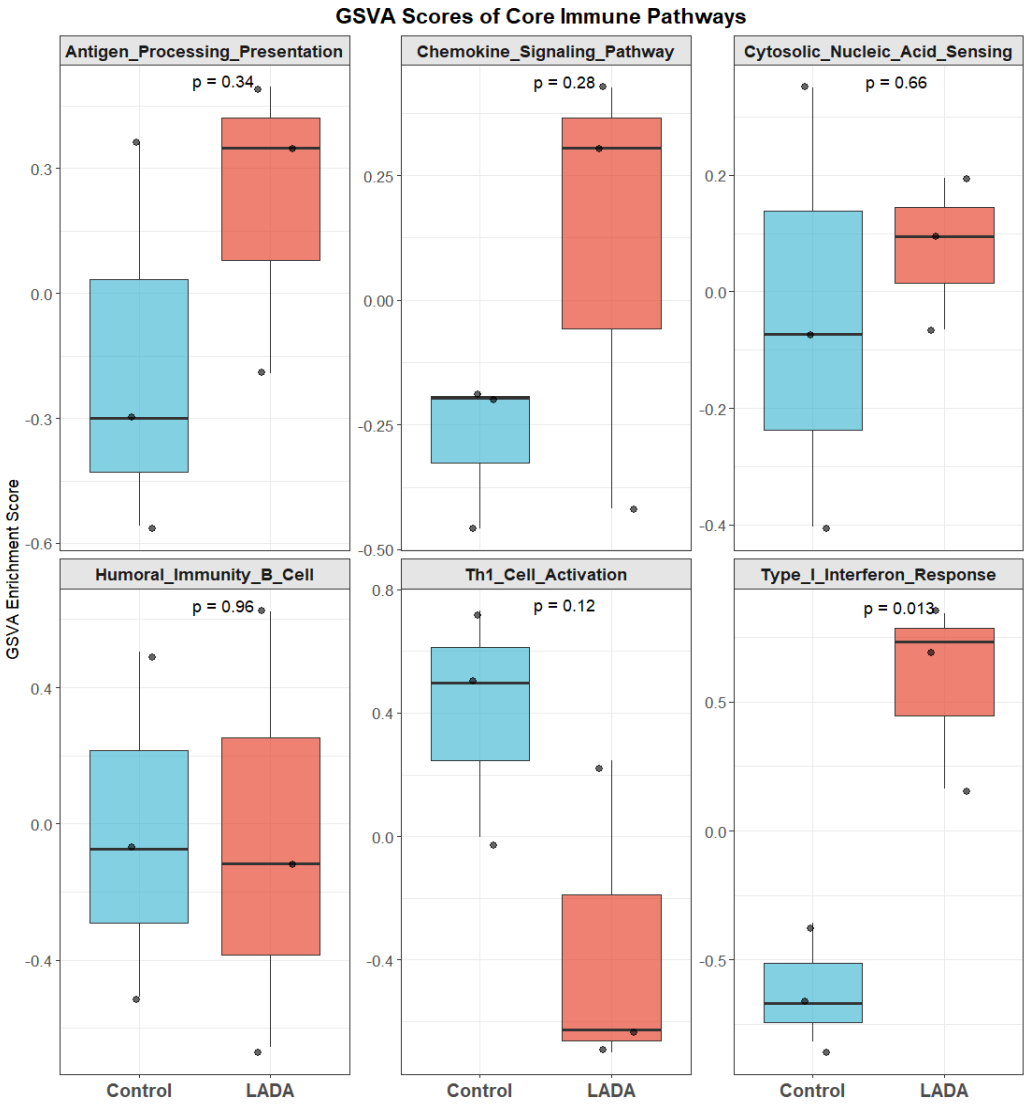

Figure 5. GSVA reveals Type I Interferon pathway hyperactivation in LADA. Faceted boxplots illustrating the Gene Set Variation Analysis (GSVA) enrichment scores across six core customized immune modules. The Type I Interferon Response module exhibits a statistically significant upregulation (p = 0.013, calculated via Student's t-test) in LADA patients (Salmon boxes) compared to healthy controls (Cyan boxes). Individual points represent the specific pathway score for each sample.

3.5. Co-expression Network Links HERV Hubs Directly to the Interferon Cascade

To establish a direct, quantitative link between the targeted reactivation of HERVs and the clinically observed interferon storm, we constructed a highly stringent Spearman co-expression network (filtering for a correlation threshold of $|R| > 0.8$). Crucially, we specifically mapped differentially expressed HERVs (red nodes) exclusively to the core effector genes belonging to the Type I Interferon signaling pathway (cyan nodes) (**Figure 6**). The resulting network exhibited a highly interconnected, dense topology, structurally and intuitively visualizing how targeted HERVs may act as the upstream triggers for the immune cascade.

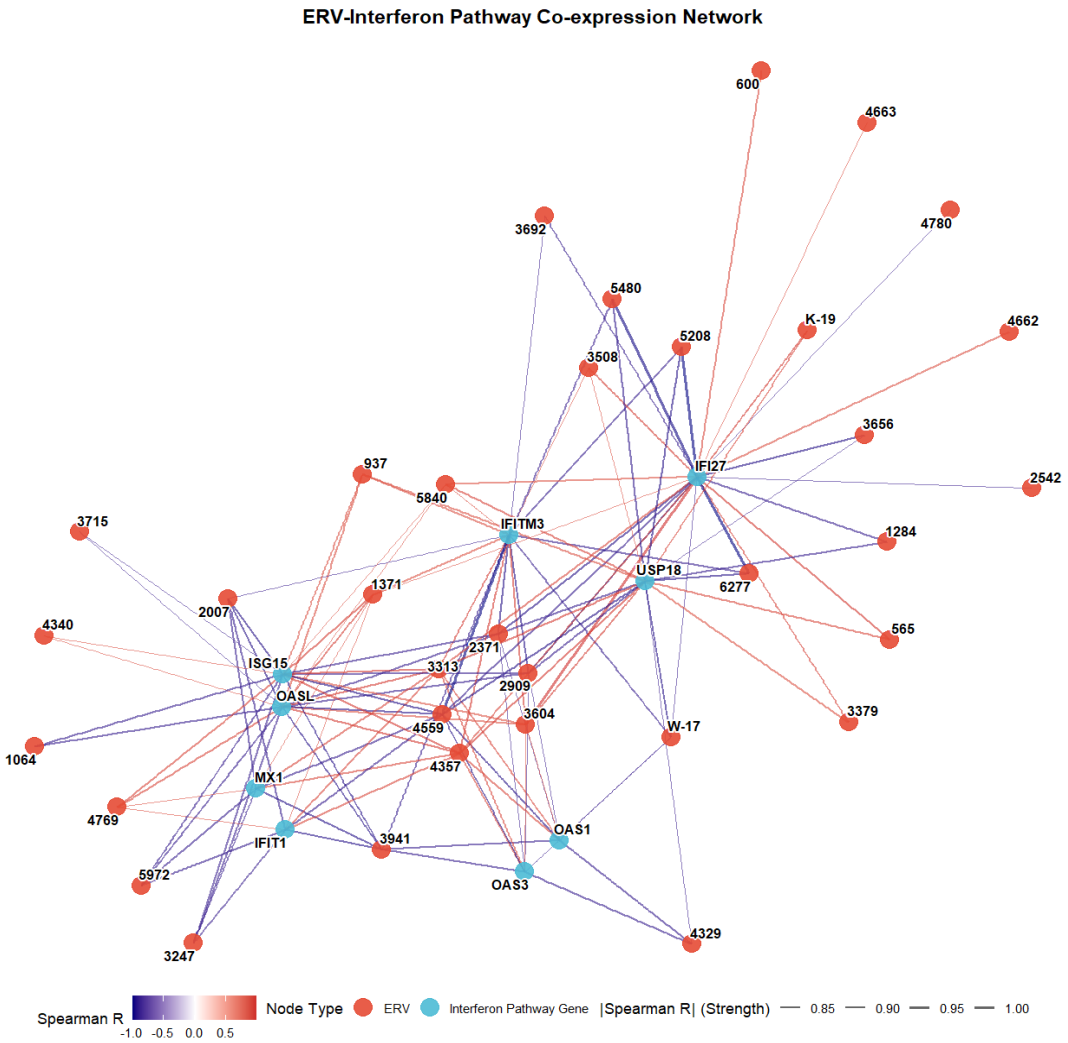

Figure 6. Targeted co-expression network between reactivated HERVs and Type I Interferon pathway core genes. A highly stringent Spearman co-expression network structurally illustrating the direct interactions between differentially expressed specific HERV elements (Salmon nodes) and key Interferon Pathway effector genes (Cyan nodes). Edges represent statistically significant correlations ($|R| > 0.8$), with the thickness and color intensity explicitly denoting the strength of the correlation (Red gradient: positive correlation; Blue gradient: negative correlation). The topology highlights central hub integrators such as USP18, ISG15, and IFITM3 densely coordinated with anomalous HERV loci.

To quantitatively pinpoint the core drivers within this topological structure, node degree analysis was performed. Specifically, major interferon-stimulated genes (ISGs) acting as central integrators and molecular switches—including IFI27 (degree = 24), the immune regulator USP18, the ubiquitin-like modifier ISG15, and the viral restriction factor IFITM3—were identified as the absolute master hubs of the host response. On the viral side, the network revealed dense, synergistic co-expression modules tightly linking these ISGs to multiple specific HERV elements (e.g., top degree hubs 4559, 4357, and 3313). Crucially, locus 1371, which our prior differential analysis identified as one of the most profoundly upregulated HERVs in LADA patients, emerged as a critical viral driver (**Figure 7**). The network explicitly captures strong positive correlations (thick red edges) between this highly expressed 1371 locus and key antiviral effectors like ISG15 and IFITM3. This structural interplay between explicitly upregulated upstream ERV hubs and downstream immune effectors provides robust bioinformatic evidence that the anomalous transcriptional activity of these specific endogenous retroelements serves as a direct molecular engine driving the pathogenic interferon cascade. The overwhelming presence of strong positive correlations (thick red edges) between these specific HERV nodes and key antiviral effectors provides robust and specific bioinformatic evidence, further

substantiating that the anomalous transcriptional activity of these endogenous retroelements serves as the direct molecular engine driving the pathogenic interferon cascade in LADA.

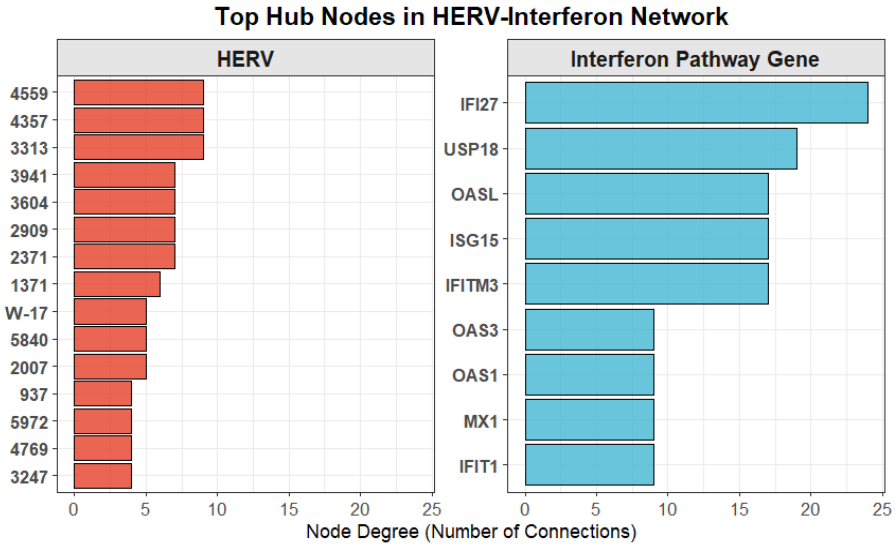

Figure 7. Quantitative identification of core hub nodes in the HERV-Interferon network. Faceted bar plots quantifying the node degree (number of significant connections) for the top hub elements within the network. The analysis is stratified by node type (Salmon: HERVs; Cyan: Interferon Pathway Genes), quantitatively identifying the most densely connected viral triggers and downstream immune integrators driving the pathogenic cascade.

4. Discussion

Latent Autoimmune Diabetes in Adults (LADA) represents a complex phenotypic intersection between Type 1 and Type 2 diabetes (Hu et al., 2022; Ravikumar et al., 2023). While the progressive autoimmune destruction of pancreatic beta cells in LADA is well-documented, the upstream molecular triggers initiating this autoimmune cascade have remained largely elusive (Hu et al., 2022). Our study provides compelling transcriptomic evidence that the aberrant reactivation of specific human Endogenous retroviruses (HERVs), coupled with a robust "viral mimicry" state, may serve as a crucial pathogenic driver in LADA (Zhao et al., 2024; Wang, 2025). Notably, our PCA demonstrated a robust separation between LADA and controls not only in the global host transcriptome but uniquely within the endogenous virome. This suggests that aberrant HERV expression is not merely background genomic noise, but a distinct, non-random signature of the disease state.

A hallmark finding of our analysis is the overwhelming enrichment of antiviral innate immune responses and Type I interferon (IFN) signaling pathways in LADA patients, despite the absence of exogenous viral infections (Li et al., 2024; Liu et al., 2025). Our differential expression analysis revealed a striking contrast: massive dysregulation of host immune genes was accompanied by a highly targeted and bidirectional modulation of specific HERV loci. Specifically, we observed the profound upregulation of distinct viral elements (e.g., loci 1371, 1474), alongside the significant downregulation of others (e.g., loci 4780, 3692). This precise, bidirectional mobilization implies a specific epigenetic derepressing mechanism rather than general genomic instability (Zhao et al., 2024). When normally silenced HERVs are epigenetically derepressed, their bidirectional transcription can generate double-stranded RNAs (dsRNAs) (Chen et al., 2021; Wang, 2025). These endogenous dsRNAs are recognized by cytosolic sensors (such as RIG-I and MDA5), tricking the host immune system into mounting a potent antiviral response (Rehwinkel & Gack, 2020). The resulting Type I interferon storm acts as a pleiotropic catalyst, driving the "humoral immune response" and "monocyte chemotaxis" observed in our GO analysis, which collectively culminate in the breakdown of peripheral tolerance and the generation of islet autoantibodies (Li et al., 2024).

Our Gene Set Variation Analysis (GSVA) further solidified this hypothesis by evaluating chronologically defined immune modules. The Type I Interferon Response emerged as the singular significantly upregulated systemic signature in the peripheral blood (Li et al., 2024). Interestingly, while adaptive immunity modules (such as antigen processing and chemokine signaling) trended upward, they lacked statistical significance in the blood compartment. We propose that this reflects the "blood-tissue paradox" inherent to organ-specific autoimmunity (Li et al., 2024). Highly active effector T cells and antigen-presenting cells are likely actively recruited to the pancreatic islets, leaving the highly soluble and systemically diffusible Type I interferon storm as the primary detectable biomarker in circulation (Hu et al., 2022).

Crucially, our co-expression network and node degree analysis successfully pinpointed specific HERV elements—such as the top-degree hubs 4559, 4357, and 3313, as well as the profoundly upregulated locus 1371—as upstream regulatory hubs. These viral hubs were structurally linked to central ISG integrators (IFI27, USP18, ISG15, IFITM3) and key antiviral effectors (OAS1, MX1) (Wang, 2025; Zhao et al., 2024). This is a striking alignment with recent breakthroughs in neuroimmunology and diabetology, where HERV elements have been implicated in the pathogenesis of Multiple Sclerosis and classical Type 1 Diabetes (Zhao et al., 2024). Furthermore, our topological network explicitly visualizes that these specific HERV hubs are strongly correlated with master interferon cascade regulators and molecular switches. This structurally implies that the activation of specific HERV loci in LADA is not merely a bystander effect of inflammation, but rather a driving force that actively coordinates the downstream innate immune effector pathways and interferon storms.

Several limitations of this study should be noted. Firstly, the use of bulk whole-blood RNA-sequencing introduces cellular heterogeneity, and transcriptomic noise from erythrocytes and other blood components required stringent computational filtering. Second, the co-expression correlations, while statistically robust, do not definitively prove causality. Future investigations utilizing single-cell RNA sequencing (scRNA-seq) combined with spatial transcriptomics are warranted to pinpoint the exact immune or pancreatic cell populations harboring these reactivated HERVs. Furthermore, in vitro mechanistic assays are needed to validate whether targeted inhibition of these specific HERV hubs can abrogate the downstream interferon response.

5. Conclusion

In conclusion, our profiling unveils a novel HERV-driven immunological landscape in LADA. The identification of the HERV-Interferon axis not only advances our understanding of the etiology of delayed-onset autoimmune diabetes but also highlights the potential of HERV-targeted therapies or interferon-blockade as novel clinical intervention strategies for LADA patients.

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