

Shared Inflammatory and Stress-response Transcriptomic Alterations in Irritant Contact Dermatitis

Yahya Asemani¹, Fatemeh Ezzatifar^{2,3}, Mohammad Kamalinejad⁴, Ali Anissian⁵, Masoud Tohidfar⁶, and Forouzan Karimi¹

¹ Department of Immunology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

² Cancer Research Center, Semnan University of Medical Sciences, Semnan, Iran

³ Department of Immunology, Faculty of Medicine, Semnan University of Medical Sciences, Semnan, Iran

⁴ Department of Pharmacognosy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

⁵ Department of Veterinary, Abhar Branch, Islamic Azad University, Abhar, Iran

⁶ Department of Cell and Molecular Biology, Faculty of Life Sciences and Biotechnology, Shahid Beheshti University, Tehran, Iran

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ABSTRACT

Irritant contact dermatitis (ICD) is a common inflammatory skin disorder characterized by epidermal barrier disruption and dysregulated inflammatory responses, yet its molecular basis remains incompletely understood.

To identify conserved transcriptional alterations associated with ICD, we performed an integrated cross-species transcriptomic analysis of human and murine Gene Expression Omnibus datasets generated using microarray and RNA sequencing platforms. Genes were prioritized using a π -value-based ranking strategy integrating expression effect size and statistical significance, followed by orthology mapping, functional enrichment, and protein-protein interaction network analyses.

A total of 174 prioritized genes were shared across all datasets, forming a conserved cross-species transcriptomic signature associated with ICD. The shared signature comprised increased expression of inflammatory and barrier-associated genes, including *S100A8*, *S100A9*, *SERPINB3* and *SERPINB4*, *KRT6A*, and *GJB2*, together with mitotic regulators, such as *CDK1*, *CDC20*, and *AURKB*, whereas differentiation- and homeostasis-associated regulators, including *GATA3*, *RORA*, and *LRP4*, were consistently reduced. Functional enrichment identified mitotic cell-cycle processes, chromosome segregation, and Aurora kinase-related pathways, as the dominant biological themes, together with cornified envelope formation, while network analysis prioritized *CDK1*, *CDC20*, *AURKB*, and *BIRC5* among the principal hub genes.

Collectively, these findings identify a conserved ICD-associated transcriptomic program consistent with keratinocyte hyperproliferation, impaired epidermal differentiation, barrier remodeling, and innate inflammatory responses. Although requiring independent experimental

Corresponding Authors: Forouzan Karimi, PhD;
Department of Immunology, School of Medicine, Shahid Beheshti
University of Medical Sciences, Tehran, Iran. Tel: (+98 21) 2243
9970, Email: fkarimi@sbmu.ac.ir

Masoud Tohidfar, PhD;
Department of Cell and Molecular Biology, Faculty of Life
Sciences and Biotechnology, Shahid Beheshti University, Tehran,
Iran. Tel: (+98 21) 2990 5952, Email: m_tohidfar@sbu.ac.ir

validation, this conserved signature provides a framework for future mechanistic studies and for the development of candidate biomarkers in irritant-induced skin inflammation.

Keywords: Dermatitis, Irritant; Gene expression profiling; Immunity, Innate; Keratinocytes; Species specificity; Transcriptome

INTRODUCTION

Irritant contact dermatitis (ICD) is a prevalent inflammatory skin disorder resulting from direct exposure to chemical or physical irritants, leading to epidermal barrier disruption, keratinocyte stress responses, and activation of innate inflammatory pathways.^{1,2} Unlike allergic contact dermatitis, which is mainly characterized by T-cell-mediated hypersensitivity, ICD is primarily driven by keratinocyte stress responses, epidermal barrier disruption, and innate immune signaling, with emerging evidence suggesting the involvement of metabolic and stress-response alterations.^{1,3} As a major occupational health concern, ICD accounts for nearly 80% of contact dermatitis cases, imposing substantial healthcare and economic burdens.⁴ Despite its widespread prevalence, a detailed molecular characterization of ICD remains elusive, limiting the development of mechanism-informed diagnostic and therapeutic strategies.

Historically, ICD was considered a largely nonspecific inflammatory response to irritants. However, emerging transcriptomic analyses indicate that ICD involves a coordinated inflammatory program characterized by activation of pattern-recognition receptors, inflammasomes, cytokine/chemokine signaling, and altered epidermal differentiation.⁵ Inflammatory mediators, such as interleukin-1 β (IL-1 β), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α), along with chemokines CXCL2 and CXCL5, play key roles in leukocyte recruitment and amplification of innate inflammatory responses.⁶ Moreover, ICD pathogenesis may extend beyond immune activation to include alterations in keratinocyte metabolic and stress-response pathways, potentially contributing to sustained epidermal inflammation.⁷

With the advent of high-throughput transcriptomic profiling, bioinformatic re-analysis of publicly available datasets has substantially advanced our understanding of inflammatory skin diseases by enabling systematic reuse of existing data to identify disease-associated molecular signatures.⁸ Repositories, such as the Gene Expression Omnibus (GEO), provide a valuable resource for

investigating differentially expressed genes (DEGs), enriched biological pathways, and regulatory networks associated with conditions such as ICD.^{9,10} Integrating data across independent studies, transcriptomic platforms, and species helps identify robust, conserved transcriptional changes while reducing study-specific noise, an approach that has repeatedly revealed conserved human-mouse signatures and candidate hub genes in inflammatory conditions.^{11,12} Despite this potential, integrative analyses directly comparing human and murine ICD transcriptomes remain scarce, leaving shared molecular signatures with translational relevance largely undefined.

To address this, we employed a comparative bioinformatics strategy integrating human and murine ICD datasets from GEO, through functional enrichment and protein-protein interaction (PPI) network analyses to identify shared DEGs, enriched biological processes and pathways, and candidate hub genes implicated in ICD. By integrating cross-species transcriptomic data, this study systematically characterizes conserved molecular alterations associated with ICD and provides a framework for future mechanistic studies and candidate biomarker discovery.

Dataset Selection Strategy

A systematic search was conducted in the GEO database to identify transcriptomic datasets related to ICD and irritant-induced skin inflammation. Search terms included "irritant contact dermatitis" and "contact dermatitis." Both microarray- and RNA sequencing (RNA-seq)-based studies were considered. Human and murine skin datasets were included to facilitate identification of conserved molecular responses across species. Heterogeneous datasets were intentionally integrated to identify transcriptional alterations conserved across species, transcriptomic platforms, and irritant models.

RNA-seq Data Acquisition

RNA-seq data were retrieved from the GEO database under accession number GSE95317,² with raw sequencing reads linked to the Sequence Read Archive

(SRP100651) and downloaded in FASTQ format. The original dataset comprised 12 samples, including wild-type and knockout mice with or without benzalkonium chloride (BKC) exposure. The murine ICD model was established by 7-day BKC exposure to induce irritant-mediated epidermal inflammation. To avoid potential confounding effects introduced by gene knockout, only wild-type untreated control samples (GSM3091589, GSM3091590, and GSM3091591) and wild-type BKC-treated samples (GSM3091595, GSM3091596, and GSM3091597) were included in the present analysis.

Quality Control, Read Alignment, and Quantification

RNA-seq data were processed using the Galaxy platform. Initial quality assessment was performed with FastQC, followed by trimming of low-quality bases ($Q < 20$) and adapter sequences using Trimmomatic. Cleaned reads were aligned to the *Mus musculus* reference genome (GRCm38) using HISAT2, achieving a mapping efficiency exceeding 95%. Gene-level read counts were generated with HTSeq-count and subsequently analyzed for differential expression using DESeq2. To assess sample quality prior to downstream analyses, boxplots and expression-density plots were generated from normalized expression values, and principal component analysis (PCA) was performed to evaluate sample clustering and overall transcriptomic variation.

Normalization and Statistical Processing of RNA-seq Data

Normalization and differential expression analysis were performed using DESeq2 on the Galaxy platform. DESeq2 shrinkage estimation was applied to stabilize dispersion estimates and $\log_2$ fold changes ($\log_2FC$), improving the stability of differential expression estimates. For visualization and quality assessment, normalized read counts were $\log_2$ -transformed to facilitate comparison of gene expression patterns across samples.

Microarray Datasets

To complement the RNA-seq analysis, microarray datasets GSE18206 and GSE168735 were retrieved from GEO for subsequent analysis.^{13,14} GSE18206, generated on the GPL570 platform ([HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array), comprised skin biopsy samples collected from healthy

volunteers following exposure to sodium lauryl sulfate (SLS) or nonanoic acid at multiple time points. Only baseline control samples collected before irritant exposure (0 h, $n=18$) and samples collected on day 11 following cumulative irritant exposure ($n=6$) were included to evaluate cumulative irritant-induced transcriptional changes. GSE168735, profiled on the GPL29838 platform ([PrimeView] Affymetrix Human Gene Expression Array), comprised skin biopsy samples collected following exposure to irritants or allergens. To specifically evaluate irritant-induced transcriptional responses, only samples exposed to SLS ($n=11$), nonanoic acid ($n=4$), or cantharidin ($n=7$), together with the corresponding vehicle-treated or reference control samples, were included, whereas allergen-exposed samples were excluded. Additional methodological details for both datasets are provided in Supplementary Table S1.

Microarray Data Analysis

Differential expression analysis between irritant-exposed and control samples was performed using GEO2R (<https://www.ncbi.nlm.nih.gov/geo/geo2r/>), an integrated analytical tool within the NCBI GEO platform.¹⁵ GEO2R uses the GEOquery and limma (v3.60.4) R packages to process normalized microarray expression data and identify DEGs. Analyses were performed using the default GEO2R settings, including automatic $\log_2$ transformation and Benjamini–Hochberg false discovery rate (FDR) adjustment. The resulting expression data were used for downstream ranking and enrichment analyses. To evaluate sample quality and overall sample relationships, expression-density plots, boxplots, and PCA were generated using the complete normalized expression matrices.

Differential Expression Analysis and π -value-based Gene Prioritization

For each dataset, probe-level measurements were collapsed to unique genes, yielding a single value per gene. Differential expression between ICD and control samples was assessed for all genes, and the results were visualized using volcano plots. Genes with a nominal $p < 0.05$ were considered significantly differentially expressed and were designated as up- or down-regulated according to the sign of the $\log_2FC$ ($|\log_2FC| > 0$). Gene prioritization for cross-dataset integration was performed on all unique genes, independently of the DEG classification described above. Specifically, π -

values were calculated for all unique genes in each dataset using the π -value metric,¹⁶ defined as:

$$\pi = |\log_2 FC| \times (-\log_{10} p)$$

where $|\log_2 FC|$ is the absolute $\log_2 FC$ and p is the nominal (unadjusted) p value. Because transcriptomic alterations in ICD are often modest, no fold-change threshold was imposed. Instead, all unique genes were ranked by π -value, which integrates effect size and statistical significance into a single metric, thereby retaining genes with modest but biologically relevant expression changes. Within each dataset, genes with π -values at or above the 90th percentile of the dataset-specific distribution (top 10%) were selected for downstream analyses. The 90th-percentile threshold was chosen to enrich for highly ranked genes while maintaining sufficient overlap across datasets for cross-species integration. Nominal (unadjusted) p values were used at this prioritization step because the objective was to rank candidate genes for cross-dataset comparison rather than to define a final list of statistically confirmed DEGs; the robustness of this strategy was subsequently evaluated using alternative percentile thresholds (85th and 95th percentiles). All statistical analyses were performed in R (v4.4.1), and data processing was conducted using the dplyr package (v1.1.4).

Hierarchical Clustering and Heatmap Analysis

For heatmap visualization, DEGs (nominal $p < 0.05$) were separated into up- and down-regulated groups and ranked independently by π -value. The top 25 genes from each group were selected for visualization. $\log_2$ -transformed expression values were transformed to row-wise z-scores, and hierarchical clustering of genes and samples was performed using Euclidean distance and complete linkage. Prior to visualization, mitochondrial genes, pseudogenes, and unannotated loci were excluded.

Orthology Mapping and Identification of Shared Genes

Murine genes with π -values at or above the 90th percentile of the dataset-specific distribution in GSE95317 were mapped to human orthologs using the g:Orth module in g:Profiler (<https://biit.cs.ut.ee/gprofiler>), based on Ensembl Compara orthology annotations. One-to-many ortholog relationships were retained, whereas many-to-one relationships were resolved by retaining the murine gene with the highest π -value, thereby assigning a single

value to each human ortholog. Genes without a human ortholog were excluded. Human genes and orthology-mapped murine genes were subsequently harmonized to human Ensembl gene IDs, and shared genes among GSE18206, GSE168735, and GSE95317 were identified in R (v4.4.1) and visualized using Venn diagrams. Genes common to all three datasets were retained for downstream enrichment and PPI analyses.

Functional Enrichment Analysis

Functional enrichment analyses were performed on the shared prioritized genes to identify overrepresented biological functions and pathways. Integrated pathway and process enrichment was performed using Metascape (<https://metascape.org>),¹⁷ which integrates multiple ontology and pathway resources (GO, KEGG, Reactome, WikiPathways, and canonical pathways) and clusters redundant terms into non-redundant functional groups, with the best-scoring term selected as the representative of each cluster. Transcriptional-regulator enrichment was additionally assessed using the integrated TRRUST library; terms with $p < 0.01$, an enrichment factor > 1.5 , and ≥ 3 genes were considered significant. GO enrichment across the biological process (BP), cellular component (CC), and molecular function (MF) categories was further performed using ShinyGO v0.85.1 (<http://bioinformatics.sdstate.edu/go/>),¹⁸ using an FDR-adjusted $p < 0.05$ as the significance threshold.

PPI Network Analysis

To investigate molecular interaction networks among the shared prioritized genes, a PPI network was constructed using the Search Tool for the Retrieval of Interacting Genes/Proteins (STRING). The shared prioritized genes were mapped to the STRING database using a medium-confidence interaction threshold of 0.4. The resulting network was subsequently analyzed in Cytoscape (v3.7.1) using the CytoHubba plugin for hub-gene prioritization. Five topological algorithms—Maximal Clique Centrality (MCC), Degree, Betweenness, Closeness, and Stress—were applied to identify candidate hub genes. Each gene was ranked independently by all five algorithms, and the mean rank across the five methods was calculated. Genes with the lowest mean ranks were considered the highest-priority consensus hub genes within the network. The top-ranked genes identified by this integrated ranking strategy were selected for downstream analyses. As a sensitivity analysis, the PPI network was additionally reconstructed

using higher STRING confidence thresholds (0.7 and 0.9) to evaluate the robustness of network topology and hub-gene prioritization across different interaction-confidence levels. Disconnected nodes were excluded from network visualization.

RESULTS

Quality Assessment and Sample Clustering

Boxplots and expression-density plots showed comparable distributions of normalized expression values across samples in all datasets, consistent with successful normalization and minimal technical bias (Supplementary Figures S1 and S2). PCA revealed no obvious outliers and an overall separation between ICD and control samples, although partial overlap was observed in some datasets (Supplementary Figure S3).

Differential Gene Expression in ICD

Volcano plots for each dataset are shown in Figure 1A–C. Initial differential expression analysis (nominal $p < 0.05$) identified 6440 up-regulated and 5155 down-regulated genes in GSE18206, 4834 up-regulated and 3807 down-regulated genes in GSE95317, and 3306 up-regulated and 3391 down-regulated genes in GSE168735. π -value-based prioritization yielded 2085 genes in GSE18206, 1864 genes in GSE168735, and 4951 genes in GSE95317. Following orthology mapping and harmonization to human Ensembl gene IDs for cross-species comparison, 2016, 1850, and 3677 unique genes were retained for GSE18206, GSE168735, and GSE95317, respectively, and used for overlap analysis (Figure 1D). Among these, 174 genes were shared across all three datasets (Supplementary Tables S2–S4).

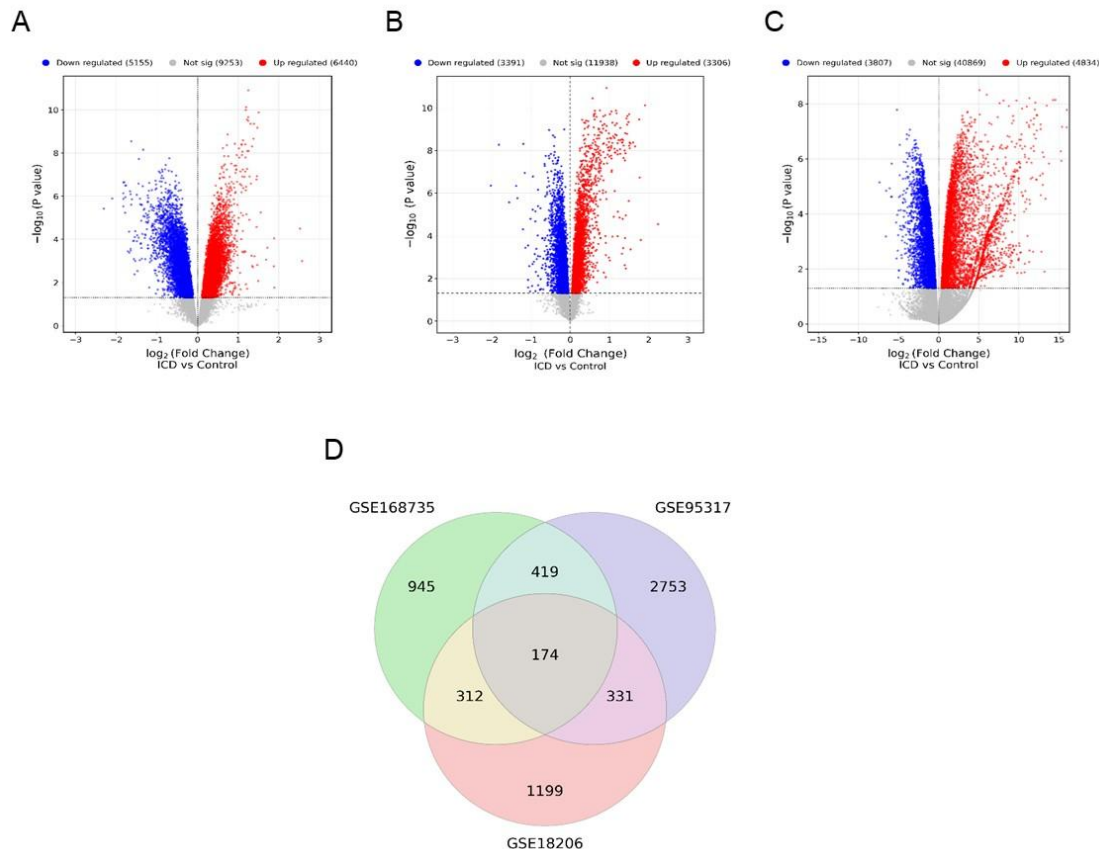


Figure 1. Differential expression analysis and identification of shared prioritized genes across the three GEO datasets. A–C. Volcano plots showing differential gene expression in A. GSE18206, B. GSE168735, and C. GSE95317. Red and blue points represent significantly up- and down-regulated genes, respectively (nominal $p < 0.05$), whereas gray points represent non-significant genes. D. Venn diagram illustrating the overlap of prioritized genes across the three datasets following orthology mapping. DEG, differentially expressed gene; GEO, Gene Expression Omnibus; $\log_2\text{FC}$, $\log_2$ fold change.

Hierarchical Clustering of Top-ranked Differentially Expressed Genes

Hierarchical clustering of the top 25 up- and top 25 down-regulated genes showed largely distinct clustering of ICD and control samples across all three datasets (Figure 2 and Supplementary Figures S4 and S5). In GSE18206, ICD samples were characterized by increased expression of *CDC20*, *AURKB*, *BIRC5*, *UBE2C*, *NDC80*, *KIF20A*, *CCNB2*, *NUSAP1*, *S100A9*, and *S100A2*, together with reduced expression of *CLDN23*, *MUC15*, *SUSD2*, *SCEL*, and *EPPK1*. Likewise, GSE168735 was characterized by increased expression of *CDK1*, *CCNB1*, *TOP2A*, *UBE2C*, *PRC1*, *RRM2*, *NCAPG*, *SERPINB3/B4*, *SPRR1B*, and *S100A9*, accompanied by reduced expression of *CD207*, *FCGBP*, *LCE5A*, *CLDN8*, *SUSD2*, and *IL37*. The murine dataset (GSE95317) showed a comparable expression pattern, with increased expression of *S100a8*, *S100a9*, *Il1b*, *Ccl3*, *Ccl4*, *Cxcl2*, *Spr1b*, *Spr2d*, *Spr2i*, *Lce3a*, *Lce3b*, *Lce3d*, *Lce3f*, *Krt6b*, and *Krt16*, together with decreased expression of *Mylk2*, *Mylk4*, *Actn3*, *Cyp2e1*, and *Il20ra*.

Cross-Species Enrichment Analysis

The 174 shared genes were subjected to integrated cross-species enrichment analysis using Metascape. The most significantly enriched functional clusters corresponded to mitotic cell-cycle processes ($p=8.5 \times 10^{-46}$), chromosome organization, Aurora B signaling, cell cycle, PLK1 signaling, DNA metabolic process, and S phase. Enriched terms also included epidermal differentiation-related processes, such as formation of the cornified envelope (Figure 3; Supplementary Figure S6). Transcriptional-regulator analysis (TRRUST) identified E2F1, SP1, E2F3, YBX1, and MYC as the highest-ranked predicted upstream regulators of the shared gene set, followed by E2F4, IRF1, STAT3, and KLF5 (Supplementary Figure S7).

To further characterize the shared signature, GO enrichment analysis was performed separately for the BP, CC, and MF categories. Consistent with the integrated Metascape results, BP enrichment further resolved the mitotic signature, with the shared genes predominantly enriched in attachment of spindle microtubules to the kinetochore, microtubule cytoskeleton organization involved in mitosis, and sister chromatid segregation, highlighting a central role in chromosome segregation and mitotic cell-cycle

progression (Figure 4A). At the CC level, the shared signature was localized to key structural elements of the mitotic machinery, with significant enrichment in cyclin-dependent protein kinase holoenzyme complexes, spindle microtubules, kinetochores, and condensed chromosomal regions (Figure 4B). At the MF level, the genes were enriched for microtubule binding, cyclin-dependent protein serine/threonine kinase regulator activity, and protein kinase binding, consistent with the mitotic and cytoskeletal program. Less significant enrichment was observed for Toll-like receptor 4 (TLR4) binding and receptor for advanced glycation end products (RAGE) receptor binding, suggesting a potential link with inflammatory signaling that requires experimental validation (Figure 4C).

PPI Network Analysis and Key Hub Gene Discovery

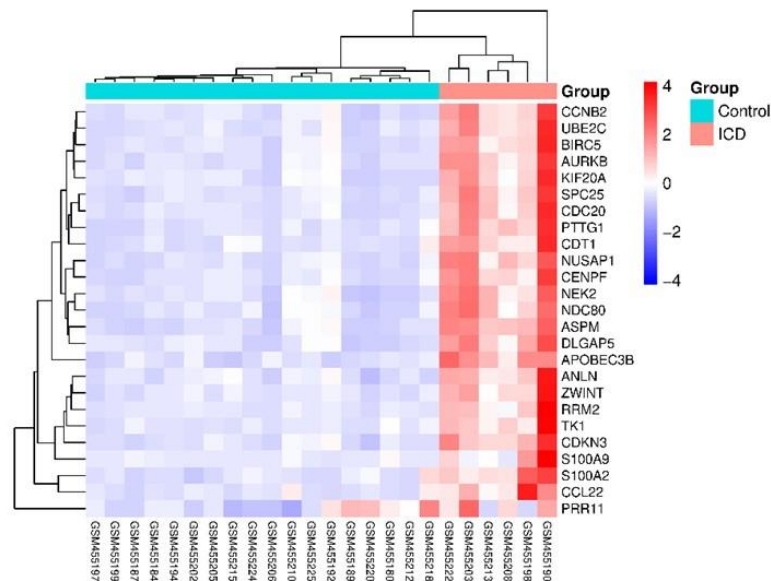
The PPI network comprised 174 nodes and 1939 edges, with an average node degree of 22.3 and significant PPI enrichment ($p < 1.0 \times 10^{-16}$), indicating that the network was more interconnected than expected by chance (Figure 5). Consensus hub-gene analysis identified *CDK1*, *CDC20*, *CCNA2*, *AURKA*, *CCNB1*, *BIRC5*, *CCNB2*, *TOP2A*, and *AURKB* as the highest-ranked hub genes. Hub-gene prioritization remained consistent across different STRING confidence thresholds and ranking algorithms, with 15 of the top 20 genes retained at all three thresholds, supporting the robustness of the network-based prioritization (Figure 6; Supplementary Tables S5–S7).

Robustness of Gene Prioritization and Sensitivity Analysis

Sensitivity analysis using alternative prioritization thresholds identified 397, 174, and 62 shared genes at the 85th-, 90th-, and 95th-percentile cutoffs, respectively. Functional enrichment results were consistent across all three thresholds, with mitotic cell cycle remaining the top-ranked term and with persistent enrichment of epidermal differentiation-related terms, including formation of the cornified envelope and keratinocyte/epidermal cell differentiation, as well as core cell-cycle pathways, including Aurora B signaling, regulation of mitotic nuclear division, and cell-cycle phase transition. The highest-ranked hub genes were retained in the most stringent 62-gene set, supporting the stability of hub-gene prioritization across thresholds (Supplementary Figure S8 and Table S8).

Cross-species Molecular Signatures in ICD

A



B

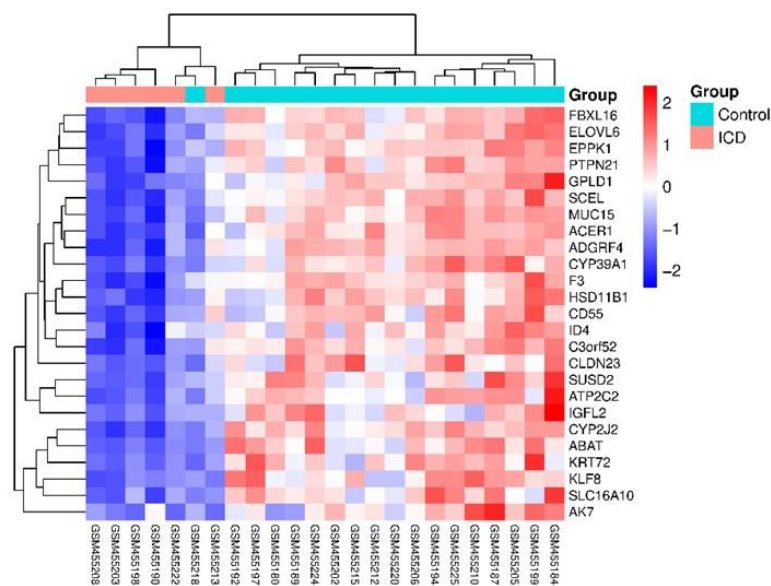


Figure 2. Hierarchical clustering heatmaps of top-ranked genes in the GSE18206 dataset. Heatmaps show the 25 highest-ranked up-regulated A. and down-regulated B. genes in ICD and control samples. Rows represent genes and columns represent samples. Expression values are displayed as row-wise z-scores, with red indicating relatively higher expression and blue indicating relatively lower expression.

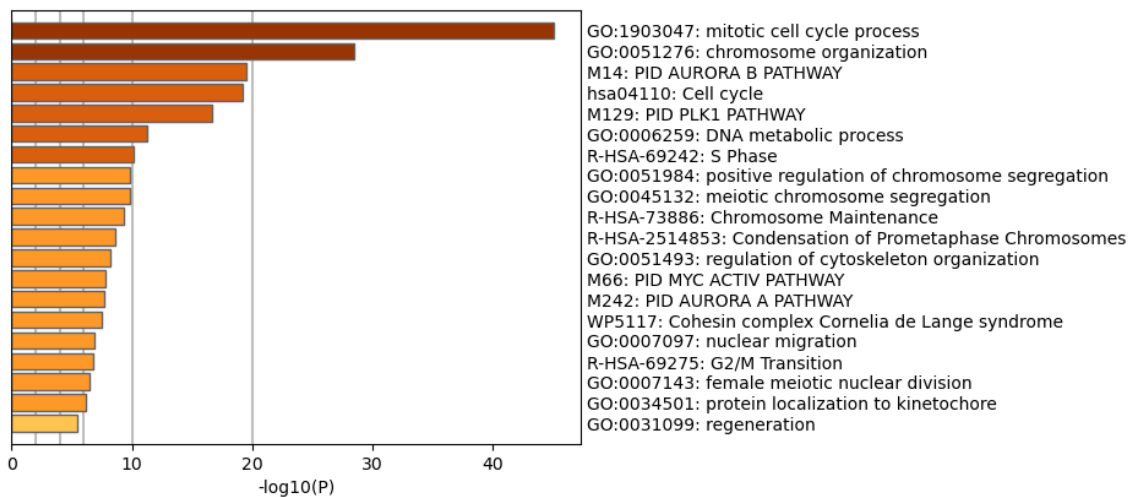
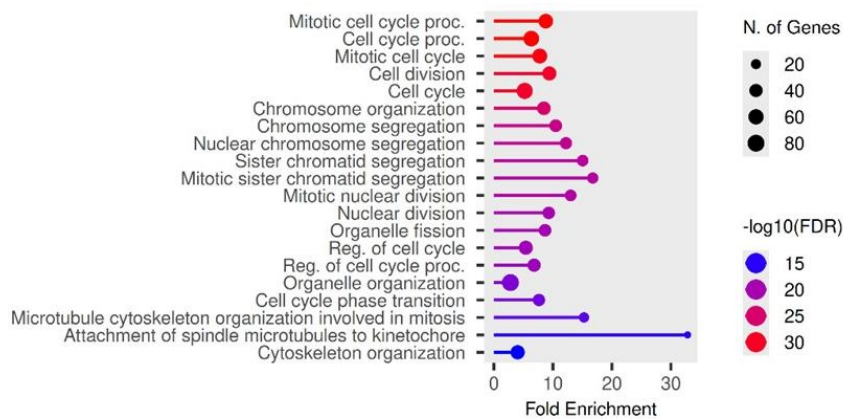
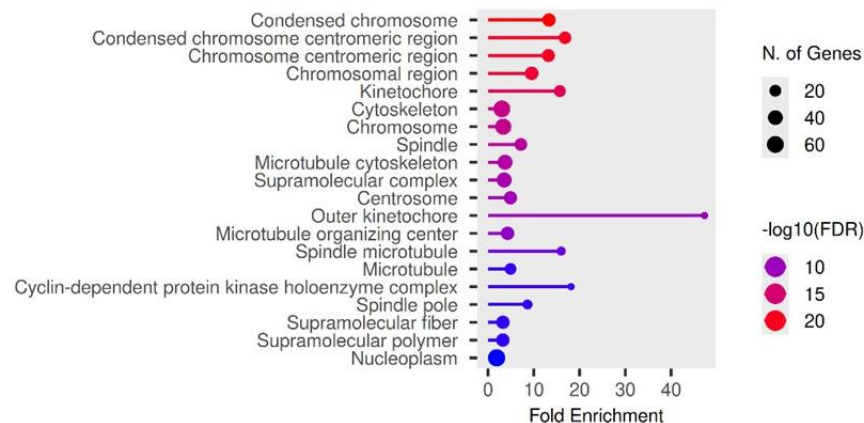


Figure 3. Integrated enrichment analysis of the shared prioritized genes using Metascape. The top 20 non-redundant enrichment clusters are shown, with bars representing the best-scoring term per cluster and colored by statistical significance ($-\log_{10}p$).

A



B



C

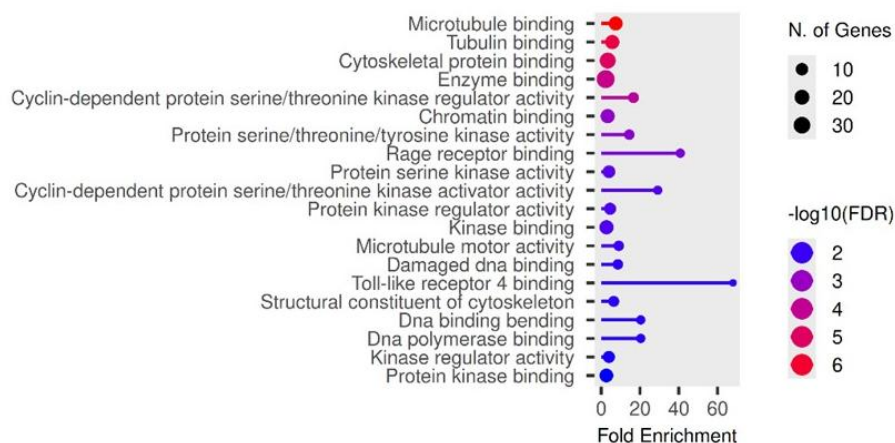


Figure 4. Gene Ontology enrichment analysis of the shared prioritized genes. The most significantly enriched categories are shown for A. BP, B. CC, and C. MF. BP, Biological Process; CC, Cellular Component; MF, Molecular Function.

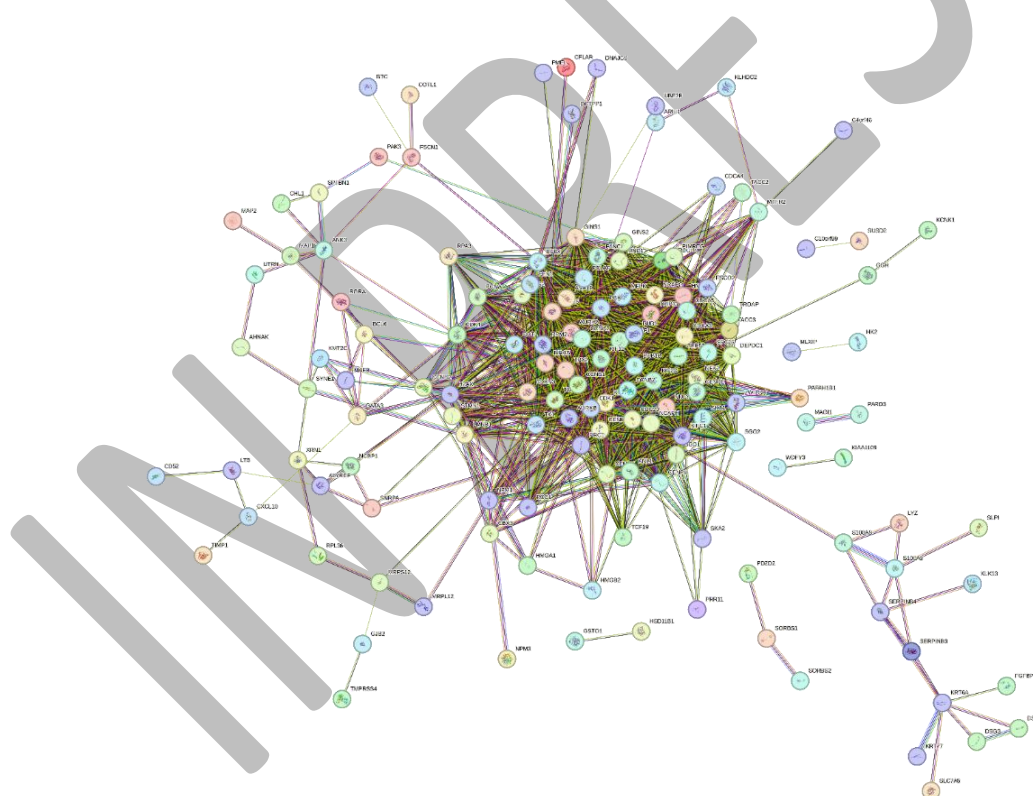


Figure 5. PPI network of the 174 shared genes constructed using STRING. Nodes represent proteins encoded by the shared genes, and edges indicate known or predicted interactions. PPI, protein–protein interaction; STRING, Search Tool for the Retrieval of Interacting Genes/Proteins.



Figure 6. CytoHubba analysis of the PPI network showing the top 20 hub genes identified by five topological algorithms: A. Maximal Clique Centrality (MCC), B. Closeness, C. Betweenness, D. Degree, and E. Stress. Node colors indicate the relative ranking of genes within each algorithm, with red representing higher-ranked genes and yellow representing lower-ranked genes. MCC, Maximal Clique Centrality.

DISCUSSION

The present study identifies a conserved cross-species transcriptomic signature associated with ICD. By integrating human and murine datasets generated using different transcriptomic platforms, we identified 174 shared prioritized genes that were nominally differentially expressed between ICD and control skin in all datasets. Despite differences in species, irritants, and experimental platforms, this conserved signature remained stable across alternative prioritization thresholds, suggesting that ICD is associated with a common epidermal stress-response program rather than predominantly compound-specific transcriptional changes. These findings extend previous bioinformatic studies, which have largely analyzed individual datasets without cross-species integration.¹⁹ By prioritizing genes using the π -value, which jointly considers fold change and statistical significance, the analytical framework retained biologically relevant transcriptional signals that may be overlooked when ranking genes by either metric alone. Together, these findings provide a robust transcriptomic foundation for investigating conserved molecular responses to irritant-induced epidermal injury.

Beyond the statistical overlap, the shared transcriptomic signature was characterized by two interconnected biological programs: epidermal hyperproliferation and innate inflammatory responses. Core mitotic regulators, including *CDK1*, *CDC20*, and *AURKB*, together with genes governing spindle assembly, chromosome segregation, DNA replication, and repair, were concurrently up-regulated and formed a dense interaction network in the PPI analysis, reflecting concerted regulation of mitotic progression rather than isolated changes in individual cell-cycle genes.^{20,21} This transcriptional program is consistent with accelerated keratinocyte proliferation accompanying epidermal barrier repair and is supported by enrichment of cell-cycle- and microtubule-organization-related pathways, including Aurora B and PLK1 signaling, as well as by the characteristic histopathological features of ICD, including acanthosis and epidermal thickening.^{2,22,23} Importantly, this regenerative mitotic program complements, rather than contradicts, the established inflammatory nature of ICD, suggesting that epidermal proliferation and innate inflammatory responses represent complementary components of a common

epidermal stress response. Consistent with this interpretation, increased expression of *NEK2* and *PBK*, two kinases implicated in proliferative and stress-associated signaling, is compatible with the regenerative transcriptional program observed in ICD.^{24,25} Notably, enrichment of terms related to the meiotic cell cycle and neoplastic gene sets most likely reflects the widespread conservation of core mitotic machinery across cell types rather than tissue-specific biological processes. Accordingly, these enrichments are best interpreted as reflecting shared cell-cycle machinery rather than activation of meiotic or neoplastic biological processes.

Complementing the regenerative mitotic program, the conserved transcriptomic signature also contained a coherent damage-associated molecular pattern (DAMP)/alarmin module that more directly reflects the inflammatory component of ICD. Its core comprised the calprotectin subunits S100A8 and S100A9—among the most strongly and consistently up-regulated transcripts across all datasets—together with the chromatin-associated alarmin HMGB2.^{26–28} Previous studies have shown that S100A8/S100A9 function as endogenous danger signals released by stressed keratinocytes and can engage TLR4 and RAGE, consistent with enrichment of the "TLR4/RAGE binding" molecular-function term in the present analysis.^{29–31} This DAMP-associated signature was accompanied by induction of *TIMP1*, previously implicated in tissue remodeling and injury responses,³² and the interferon-inducible chemokine *CXCL10*, a mediator of leukocyte recruitment during cutaneous inflammation,³³ together with increased expression of *LYZ*, *LTB*, and *CD52*, and reduced *BCL6*. Collectively, this transcriptional pattern is consistent with previous reports linking these molecules to epithelial danger sensing, innate host defense, immune-cell recruitment, and inflammatory regulation.^{34,35} As these findings are derived from bulk transcriptomic data, part of the observed signal—particularly *LYZ* and *CD52*—may reflect changes in immune-cell composition rather than altered keratinocyte expression. The coexistence of this DAMP-associated module with the regenerative mitotic program suggests that irritant-exposed epidermis simultaneously engages tissue-repair and innate inflammatory transcriptional responses, potentially contributing to the characteristic combination of epidermal hyperplasia and inflammation observed in ICD lesions.³⁶

Beyond inflammatory signaling, the shared signature also suggested coordinated metabolic and structural adaptation. Up-regulation of the solute carriers *SLC7A5* and *SLC20A1*, together with the redox-regulating enzyme *GSTO1*, is consistent with previous studies implicating these molecules in nutrient transport, oxidative-stress adaptation, and metabolic support of proliferating cells.^{37–41} In parallel, increased expression of *FGFBP1*, *FSCN1*, *COTL1*, and *TMPRSS4*—genes previously associated with cytoskeletal remodeling, epithelial migration, and wound repair—suggests transcriptional programs compatible with structural reorganization during epidermal regeneration.^{42–44} Notably, these metabolic and cytoskeletal alterations were directionally consistent across both human and murine datasets, supporting their conservation across species. Collectively, these findings extend the transcriptomic landscape of ICD beyond inflammatory responses, suggesting that metabolic adaptation and tissue remodeling accompany the regenerative response to epidermal injury.

A further epidermis-specific component of the conserved signature reflected structural remodeling of the epidermal barrier and intercellular communication. The keratin cytoskeleton exhibited a characteristic switch, with up-regulation of the stress-responsive keratin *KRT6A* and reciprocal down-regulation of the terminal-differentiation keratin *KRT77*, consistent with altered keratinocyte differentiation during epidermal regeneration.^{45,46} This pattern was accompanied by increased expression of the desmosomal cadherins *DSG3* and *DSC2* and the gap-junction protein *GJB2* (connexin 26), suggesting coordinated remodeling of cell–cell adhesion and intercellular communication. Previous studies have shown that connexin 26 participates in feed-forward responses to epidermal barrier disruption and has been associated with persistent epidermal activation and inflammatory cell recruitment.⁴⁷ Together with the stress-responsive serpins *SERPINB3/B4*, these transcriptional changes are consistent with coordinated reorganization of keratin networks, intercellular junctions, and barrier architecture, providing a plausible link between epidermal remodeling and the innate inflammatory responses observed in ICD.

In parallel with these activation-associated programs, a coordinated set of down-regulated genes suggested impaired epidermal differentiation and homeostatic maintenance. Reduced expression of the

transcription factors *GATA3* and *RORA*, both implicated in epidermal maturation and skin homeostasis, is consistent with previous studies linking these regulators to keratinocyte differentiation and barrier integrity.^{48,49} This pattern was accompanied by decreased expression of *BTC* and *SUSD2*, which have been associated with epithelial maturation, together with reduced *MAGI1*, *LRP4*, and *CHL1*, genes involved in cell adhesion and tissue organization.^{50–52} In addition to their established roles in epidermal homeostasis, two consistently down-regulated genes, *RORA* and *LRP4*, have also been implicated in hair follicle biology. *RORA* is expressed in the suprabasal epidermis, sebaceous glands, and hair follicles, and its epidermal deletion has been reported to exacerbate cutaneous inflammation and impair barrier function in experimental atopic dermatitis.⁵³ Likewise, *LRP4*, a co-receptor of the Wnt signaling pathway, is required for hair follicle placode formation and skin appendage development.⁵¹ However, because bulk transcriptomic data cannot distinguish follicular from interfollicular contributions, these findings suggest that chronic irritant exposure may also influence follicle-associated homeostatic pathways. Collectively, these transcriptional changes are consistent with attenuation of differentiation and homeostatic programs accompanying the regenerative and inflammatory responses, and may contribute to impaired barrier stability during persistent irritant exposure.⁵⁴

When placed in the context of prior literature, our results reinforce and extend existing observations. Previous studies have independently implicated several genes identified in the conserved signature, including *S100A8/S100A9* in inflammatory skin disorders, *KRT6A/KRT16* in keratinocyte activation following epidermal injury, and *SERPINB3/B4* in experimental models of epidermal inflammation and barrier dysfunction.^{55–58} However, these findings were largely confined to individual genes, specific disease settings, or single experimental models and lacked cross-species or cross-irritant validation. The present integrative analysis extends these observations by demonstrating that these stress-responsive genes constitute part of a conserved transcriptomic program shared across multiple irritants, transcriptomic platforms, and species.

PPI analysis further resolved the conserved signature into a highly interconnected mitotic core comprising *CDK1*, *CDC20*, *CCNA2*, *AURKA*, *AURKB*, *CCNB1*, *CCNB2*, *BIRC5*, and *TOP2A*, consistent with previous studies identifying *CDK1*, *CCNB1*, and *CDC20* as

central regulators of the proliferative phase of cutaneous wound healing.²¹ Transcriptional-regulator enrichment further identified E2F family members (E2F1, E2F3, and E2F4), together with SP1, YBX1, and MYC, as candidate upstream regulators of this cell-cycle module. Previous studies have also shown that *AURKB* is co-expressed with *FOXMI* in psoriatic keratinocytes, where *FOXMI* has been linked to NF- κ B-associated inflammatory signaling,²⁰ while pro-inflammatory cytokines, such as IL-17A, can promote keratinocyte proliferation.⁵⁹ Together, these observations suggest that proliferative and inflammatory transcriptional programs may be functionally linked during epidermal stress. Because these inferences are based on network topology, co-expression, and enrichment analyses rather than direct functional evidence in ICD, this model should be regarded as hypothesis-generating and requires experimental validation.

From a translational perspective, the conserved cross-species signature provides a framework for prioritizing candidate biomarkers and therapeutic targets for future investigation. In particular, the S100A8/S100A9–TLR4/RAGE axis, together with regulators of keratinocyte proliferation (*CDK1*, *AURKA/B*, and *MELK*), emerged as prominent candidates for experimental validation because of their consistent dysregulation across datasets and their established roles in epidermal stress and inflammatory responses. Likewise, genes involved in barrier remodeling (*GJB2*), epidermal differentiation (*GATA3* and *RORA*), and metabolic adaptation (*SLC7A5*, *FSCN1*, and *FGFBP1*) may represent complementary molecular entry points for studies aimed at restoring barrier integrity and epidermal homeostasis. Beyond therapeutic implications, the reproducible conservation of these transcriptional modules across human and murine datasets suggests that combined signatures encompassing proliferative, DAMP-associated, and barrier-remodeling components may also provide a useful foundation for biomarker development and future studies evaluating anti-irritant therapies or distinguishing irritant from allergic contact dermatitis.

Although this study provides an integrative cross-species framework for ICD, some limitations should be acknowledged. The analyzed datasets represent static snapshots rather than temporal progression, limiting inference about the sequence of events linking barrier disruption, inflammation, and tissue repair. Biological heterogeneity arising from differences in irritant type,

exposure duration, experimental design, and transcriptomic platform may also have contributed to variability across datasets, as reflected by the partial overlap between ICD and control samples in the PCA. Although dataset-specific analysis and an intersection-based strategy were used to reduce these effects, residual heterogeneity cannot be excluded.

More broadly, the findings are subject to the inherent limitations of bulk transcriptome-based *in silico* analyses. Bulk profiling averages signals across heterogeneous cell populations and measures transcript abundance rather than protein expression or biological activity. Consequently, the identified DEGs, enriched pathways, and hub genes should be interpreted as transcriptomic associations rather than direct evidence of altered protein expression, pathway activation, or biological function. Additional limitations include the exclusion of genes lacking reliable mouse–human orthologs and the intentional focus on genes conserved across species and irritant models, which may have overlooked biologically relevant dataset- or species-specific responses. Furthermore, because nominal rather than multiple-testing-adjusted *p* values were used during the initial gene-prioritization step, some false-positive candidates may have been retained; however, the consistent enrichment patterns observed across the 85th, 90th-, and 95th-percentile thresholds support the robustness of the principal biological conclusions. Therefore, the conserved molecular signature and candidate hub genes identified here should be regarded as hypothesis-generating findings requiring independent experimental validation rather than evidence of causal involvement in ICD.

Future studies should validate the conserved molecular signature by confirming the principal hub genes and the S100A8/S100A9–TLR4/RAGE axis at both the transcript and protein levels and by determining their functional relevance using appropriate *in vitro* and *in vivo* models. Single-cell, spatial, and longitudinal transcriptomic approaches will further help resolve the cellular and temporal dynamics of this conserved response. Such studies will clarify the biological significance of the identified molecular modules and their potential utility as candidate biomarkers and therapeutic targets for ICD.

By integrating human and murine transcriptomic datasets across diverse irritants and experimental platforms, this study identifies a conserved cross-species transcriptomic signature of ICD characterized by epidermal hyperproliferation, innate inflammatory

signaling, barrier remodeling, keratin-network reorganization, and attenuated differentiation. Within this framework, the S100A8/S100A9–TLR4/RAGE danger axis is identified as a candidate link between the inflammatory and regenerative components of the epidermal response, together with barrier- and differentiation-associated regulators (*GJB2*, *GATA3*, and *RORA*) that reflect impaired epidermal homeostasis. Although these findings are based on bulk transcriptomic associations and require independent experimental validation, they provide a framework for future mechanistic studies and for the development of candidate biomarkers in irritant-induced skin inflammation.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of [Shahid Beheshti University of Medical Sciences, Tehran, Iran] (Approval No. [IR.SBMU.AEC.1403.013]).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

All datasets analyzed in this study are publicly available in the Gene Expression Omnibus (GEO) database under the accession numbers reported in the Materials and Methods section. Additional data supporting the findings of this study are available from the corresponding author upon reasonable request.

AI ASSISTANCE DISCLOSURE

No artificial intelligence (AI) tools were used in the preparation of this manuscript.

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