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Integrated Bioinformatics Analysis Identifies Angiogenesis-Related Genes in Psoriasis

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Abstract

Background: Psoriasis is a chronic inflammatory skin disorder characterized by immune dysregulation and abnormal angiogenesis. Vascular remodeling plays a critical role in disease progression by facilitating immune cell infiltration and sustaining inflammation. However, the molecular mechanisms underlying angiogenesis in psoriasis remain incompletely understood.

Methods: Gene expression data from the GEO dataset GSE13355 were analyzed using GEO2R to identify differentially expressed genes (DEGs) between psoriatic lesional (PP) and non-lesional (PN) skin samples. Genes with an adjusted p-value < 0.05 and $|\log FC| > 1$ were considered significant. Angiogenesis-related genes were retrieved from Gene Ontology and intersected with DEGs to identify angiogenesis-associated genes. Functional enrichment analysis was performed using DAVID, focusing on Gene Ontology biological processes.

Results: A total of 1,061 DEGs were identified, of which 20 were associated with angiogenesis following intersection analysis. Among these, the majority of genes were upregulated, while 8 were downregulated. Key upregulated genes included CXCL8, HPSE, S100A7, and CCL2, whereas RORA, LEP, and GREM1 were among the downregulated genes. Gene Ontology enrichment analysis revealed significant enrichment in angiogenesis-related processes, including angiogenesis ($P = 9.00 \times 10^{-18}$), regulation of angiogenesis, and blood vessel morphogenesis. Functional annotation clustering further supported the involvement of coordinated vascular and cellular migration processes.

Conclusion: This study identified key angiogenesis-related genes and biological processes involved in psoriasis. The findings highlight the critical role of angiogenesis and its interaction with inflammatory pathways in disease pathogenesis. These genes may serve as potential therapeutic targets for future investigation.

Keywords: Psoriasis, Angiogenesis, Bioinformatics, Gene Expression, GEO, DAVID

Introduction

Psoriasis is a chronic immune-mediated inflammatory skin disorder affecting approximately 2–3% of the global population and is characterized by keratinocyte hyperproliferation, immune dysregulation, and marked vascular alterations within the dermis [1,2]. Among these pathological features, angiogenesis plays a central role in disease initiation and progression. Psoriatic lesions exhibit increased microvascular density, dilated and tortuous capillaries, and enhanced endothelial activation, which collectively contribute to erythema and facilitate immune cell trafficking into the skin [3,4].

Angiogenesis in psoriasis is driven by a complex interplay between inflammatory mediators and vascular growth factors. Vascular endothelial growth factor (VEGF) is a key regulator of neovascularization and is consistently upregulated in psoriatic lesions, promoting endothelial proliferation and vascular permeability [5]. Additionally, cytokines such as interleukin-17 (IL-17) and tumor necrosis factor-α (TNF-α) further amplify angiogenic signaling, highlighting the close link between inflammation and vascular remodeling [6]. Several additional regulators, including chemokines (CXCL8, CCL2), transcription factors (RORA, E2F8), and receptor tyrosine kinases (EPHA2, EPHB2, EFNB2), have also been implicated in endothelial activation and angiogenic processes [7,8].

Advances in high-throughput transcriptomic technologies and the availability of publicly accessible datasets, such as those in the Gene Expression Omnibus (GEO), have enabled systematic exploration of disease-associated molecular signatures [9]. Integrative bioinformatics approaches combining differential gene expression analysis with functional annotation provide a powerful strategy to identify key regulatory genes and biological processes underlying complex diseases. In particular, intersecting differentially expressed genes with curated angiogenesis-related gene sets allows for the identification of vascular-specific molecular drivers of psoriasis.

In the present study, we performed an integrated bioinformatics analysis using the GEO dataset GSE13355 to identify angiogenesis-related differentially expressed genes in psoriasis. By intersecting transcriptomic data with angiogenesis-associated genes, we identified key candidates, including RORA, LEP, GREM1, ANG, EFNB2, EPHB2, ID1, HMOX1, EPHA2, CCL2, CXCL8, and HPSE. These genes were further analyzed using functional enrichment and clustering approaches to elucidate their roles in vascular remodeling and disease pathogenesis. This study aims to enhance our understanding of angiogenesis-driven mechanisms in psoriasis and to identify potential molecular targets for therapeutic intervention.

Materials and Methods

Data acquisition

Gene expression data were obtained from the Gene Expression Omnibus (GEO) database. The dataset GSE13355, based on the Affymetrix Human Genome U133 Plus 2.0 Array platform, was selected for analysis. This dataset includes paired samples of psoriatic lesional (PP) and non-lesional (PN) skin, enabling controlled comparison within the same individuals [10].

Differential gene expression analysis

Differential gene expression analysis was performed using the GEO2R online tool. Samples were divided into two groups: lesional (PP) and non-lesional (PN) skin. Statistical analysis was conducted using the limma (Linear Models for Microarray Data) algorithm. Genes with an adjusted p-value (adj.P.Val) < 0.05 and absolute log fold change ($|logFC|$) > 1 were considered significantly differentially expressed genes (DEGs) [11].

Identification of angiogenesis-related genes

Angiogenesis-related genes were retrieved from the Gene Ontology (GO) database using the term “angiogenesis” (GO:0001525). The gene list was filtered for *Homo sapiens* to ensure species specificity. This curated list constituted the angiogenesis-related gene set (AngioGeneSet1) [12].

Intersection analysis

To identify angiogenesis-associated DEGs, an intersection analysis was performed between the DEG list and the angiogenesis-related gene set using Microsoft Excel. Genes common to both datasets were

selected and defined as angiogenesis-related differentially expressed genes (AngioGeneSet2), representing candidate genes involved in vascular processes in psoriasis.

Functional enrichment analysis

Functional enrichment analysis was conducted using the Database for Annotation, Visualization and Integrated Discovery (DAVID). The identified angiogenesis-related DEGs were uploaded, and Gene Ontology (GO) enrichment analysis was performed using the GOTERM_BP_DIRECT category to identify significantly enriched biological processes. A p-value < 0.05 was considered statistically significant [13].

Functional annotation clustering

To further explore the biological relationships among enriched terms, functional annotation clustering was performed using DAVID. This approach groups functionally related GO terms into clusters and assigns an enrichment score based on the geometric mean of p-values. Clusters with enrichment scores greater than 1.3 were considered biologically meaningful [13].

Results

Differential gene expression analysis

A total of 54,676 genes were initially retrieved from the GSE13355 dataset. Differential expression analysis was performed using GEO2R by comparing psoriatic lesional (PP) and non-lesional (PN) skin samples. After applying the filtering criteria of adjusted p-value < 0.05 and absolute log fold change (|logFC|) > 1, a total of 1,061 genes were identified as significantly differentially expressed genes (DEGs).

Identification of angiogenesis-related differentially expressed genes

To specifically investigate angiogenesis-associated molecular alterations, a total of 370 angiogenesis-related genes were retrieved from the Gene Ontology database. Intersection of this gene set with the identified DEGs resulted in 20 angiogenesis-related differentially expressed genes.

Among these, 8 genes were found to be downregulated, including **RORA**, **LEP**, **GREM1**, **RTN4**, **ANG**, and **EFNB2**, while the remaining genes were upregulated, including **EPHB2**, **ID1**, **HMOX1**, **E2F8**, **MICALL1**, **EPHA2**, **CCL2**, **HPSE**, **CXCL8**, and **S100A7**. Notably, certain genes such as **RORA**, **HPSE**, and **CXCL8** appeared multiple times due to the presence of multiple probe sets in the microarray dataset. For clarity and biological interpretation, duplicate entries were consolidated, and representative values were considered.

The final list of angiogenesis-related DEGs, along with their logFC values, adjusted p-values, and regulation status, is presented in **Table 1**. Among the upregulated genes, **CXCL8** (logFC = 4.03) and **HPSE** (logFC = 3.75) exhibited the highest fold changes, indicating strong upregulation in psoriatic lesions. Similarly, **S100A7** showed marked upregulation (logFC = 3.37). In contrast, **RORA** demonstrated consistent downregulation across multiple probes, suggesting a potential inhibitory role in angiogenesis-related pathways.

Gene Symbol	Adj p-value	log fc	Regulation
RORA	3.98E-34	-1.31	downregulated
LEP	2.09E-09	-1.2	downregulated
GREM1	7.91E-13	-1.16	downregulated
RTN4	3.55E-27	-1.14	downregulated
ANG	5.38E-30	-1.13	downregulated

RORA	3.02E-22	-1.11	downregulated
EFNB2	5.64E-32	-1.09	downregulated
RORA	3.67E-11	-1.05	downregulated
EPHB2	1.18E-28	1.03	upregulated
ID1	2.32E-26	1.06	upregulated
HMOX1	4.25E-23	1.08	upregulated
E2F8	2.42E-19	1.13	upregulated
MICALL1	2.68E-37	1.2	upregulated
EPHA2	2.05E-34	1.28	upregulated
CCL2	3.27E-19	1.44	upregulated
HPSE	4.06E-30	1.48	upregulated
CXCL8	4.04E-18	2.59	upregulated
S100A7	3.09E-34	3.37	upregulated
HPSE	1.32E-50	3.75	upregulated
CXCL8	1.55E-27	4.03	upregulated

Table 1: Angiogenesis-related differentially expressed genes identified in psoriasis, including logFC values, adjusted p-values, and regulation status.

Functional enrichment analysis

To explore the biological significance of the identified angiogenesis-related DEGs, Gene Ontology (GO) enrichment analysis was performed using the DAVID database. The results demonstrated significant enrichment in biological processes associated with angiogenesis and vascular development.

The most significantly enriched term was "angiogenesis" ($P = 9.00 \times 10^{-18}$), followed by "regulation of angiogenesis," "positive regulation of angiogenesis," "blood vessel morphogenesis," and "cell migration involved in sprouting angiogenesis." These processes are directly related to endothelial cell activation, migration, and vascular remodeling, indicating a strong angiogenic signature in psoriatic lesions.

The enrichment results are visualized in **Figure 1**, which presents the top Gene Ontology biological processes ranked by –log10(p-value). The prominent enrichment of angiogenesis-related terms further validates the biological relevance of the identified gene set.

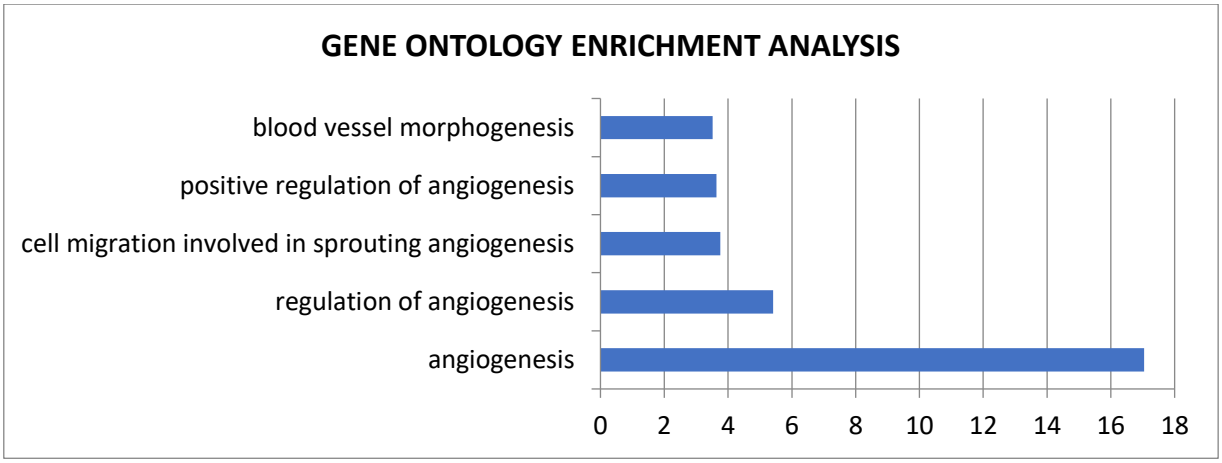

Figure 1: Gene Ontology enrichment analysis of angiogenesis-related differentially expressed genes showing significant enrichment in angiogenesis and vascular development-related biological processes.

Functional annotation clustering

To further understand the functional relationships among enriched biological processes, functional annotation clustering was performed. The most significant cluster (enrichment score = 1.96) included processes such as cell adhesion, cell migration, and signal transduction, all of which are essential for endothelial cell activation and angiogenesis. Another cluster highlighted angiogenesis-related processes, reinforcing the coordinated regulation of vascular pathways.

Overall findings

Collectively, these results demonstrate that angiogenesis-related genes are significantly dysregulated in psoriasis. The predominance of upregulated genes, along with strong enrichment of angiogenesis-associated biological processes, suggests active vascular remodeling and endothelial activation as key features of psoriatic lesions.

Discussion

In the present study, an integrated bioinformatics approach was employed to identify angiogenesis-related differentially expressed genes in psoriasis. By intersecting transcriptomic data with Gene Ontology-derived angiogenesis genes, a focused set of key regulators was identified. Functional enrichment analysis demonstrated that these genes are significantly associated with angiogenesis and vascular development, highlighting the importance of vascular remodeling in psoriasis pathogenesis.

Angiogenesis is a well-established feature of psoriasis, characterized by increased dermal vascularity, dilated capillaries, and enhanced endothelial activation. These vascular changes not only contribute to the characteristic erythematous appearance of psoriatic plaques but also facilitate immune cell trafficking and sustain chronic inflammation [14,15]. The significant enrichment of biological processes such as angiogenesis, regulation of angiogenesis, and blood vessel morphogenesis observed in this study further supports the central role of vascular remodeling in disease progression.

Among the identified genes, several key regulators of inflammation and angiogenesis were prominently upregulated. **CXCL8 (IL-8)**, one of the most highly upregulated genes in this study, is a potent chemokine known to promote neutrophil recruitment and angiogenesis through endothelial cell activation [16]. Similarly, **CCL2** plays a crucial role in monocyte recruitment and has been implicated in vascular inflammation and endothelial dysfunction [17]. The marked upregulation of these chemokines highlights the interplay between inflammation and angiogenesis in psoriasis.

Another significantly upregulated gene, **HPSE (heparanase)**, is involved in extracellular matrix degradation and facilitates endothelial cell migration and neovascularization [18]. Increased expression of HPSE has been associated with enhanced angiogenic activity in various inflammatory and pathological conditions. Additionally, **EPHA2** and **EPHB2**, members of the ephrin receptor family, are known to regulate endothelial cell adhesion, migration, and vascular assembly, further supporting their role in angiogenic processes [19].

S100A7, which showed strong upregulation in this study, is a psoriasis-associated protein that contributes to inflammation and has been linked to angiogenic signaling pathways [20]. Similarly, **HMOX1** plays a protective role in oxidative stress and has been reported to modulate angiogenesis through its effects on endothelial cells [21]. These findings suggest that multiple molecular pathways converge to promote angiogenesis in psoriatic lesions.

In contrast, several genes, including **RORA**, **LEP**, and **GREM1**, were found to be downregulated. **RORA** is a nuclear receptor involved in immune regulation and circadian rhythm, and its reduced expression may contribute to dysregulated inflammatory signaling [22]. **GREM1**, a known antagonist of bone morphogenetic proteins (BMPs), has been implicated in vascular development, and its downregulation may alter angiogenic balance [23]. The downregulation of these genes suggests a complex regulatory network involving both pro- and anti-angiogenic factors in psoriasis.

The functional annotation clustering analysis further revealed that angiogenesis-related processes are closely linked with cell migration, adhesion, and signal transduction pathways. These processes are essential for endothelial cell activation and vascular remodeling, reinforcing the concept that angiogenesis in psoriasis is a coordinated and multifactorial process rather than a single pathway-driven event.

Despite these findings, certain limitations should be acknowledged. The study is based on in silico analysis of a single dataset, and experimental validation is required to confirm the functional roles of the identified genes. Additionally, the presence of multiple probe sets for certain genes may introduce redundancy, although this was addressed during data interpretation.

In conclusion, this study identified key angiogenesis-related genes and biological processes associated with psoriasis. The results highlight the interplay between inflammation and angiogenesis and provide potential molecular targets for future therapeutic interventions. Further experimental studies are warranted to validate these findings and to explore their clinical relevance.

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