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Efficacy Evaluation of Treatment of Psoriasis Via Narrow Band-Ultraviolet Radiation

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Abstract

Introduction: Psoriasis is a common autoimmune skin disease associated with genetically influenced chronic inflammation accompanied by remitting and deteriorating scaly skin. T-cell targeted biologics, IL-17 inhibitors, IL-12/IL-23 inhibitors, TNF-α inhibitors, PDE4 inhibitors, and ultraviolet (UV) radiation are applied to treat psoriasis. Efficacy evaluation of narrow band UVB (NB-UVB) radiation was the aim of this study.

Methods: Data were extracted from Gene Expression Omnibus (GEO) and were pre-evaluated via the GEO2R program. The significant differentially expressed genes (DEGs) were included in the protein-protein interaction (PPI) network analysis. The hubs, bottlenecks, and hub-bottleneck DEGs were introduced as central genes. Activation, inhibition, and expression relationship between central genes were assessed to explore the critical individuals.

Results: Among 513 analyzed significant DEGs, 22 hub-bottleneck genes were identified. Further analysis revealed that FN1, STAT3, HIF1A, IL1B, P4HB, SOD2, MMP2, and STAT1 were the crucial genes in psoriasis samples targeted by NB-UVB radiation.

Conclusion: In conclusion, NB-UVB radiation as a treatment targets critical genes in peri-lesion skin tissue biopsy of psoriasis patients via a complicated mechanism. This therapeutic method downregulates STAT3, HIF1A, IL1B, and P4HB to treat psoriasis but downregulates STAT1 and SOD2 and upregulates MMP2 and FN1 to develop disease.

Keywords: Psoriasis; NB-UVB; Treatment; Network analysis; Skin.

Introduction

Psoriasis is described as a genetically influenced chronic inflammatory skin disorder with remitting and deteriorating scaly skin.[1] This common autoimmune skin disease is associated with the hyperproliferation of keratinocytes via T cells.[2] It is estimated that 125 people have psoriasis around the globe. The most common type of psoriasis is plaque psoriasis which is accompanied by cardiometabolic diseases, psoriatic arthritis, and depression.[3] Advances in the treatment of psoriasis indicate that T-cell targeted biologics, IL-17 inhibitors, IL-12/IL-23 inhibitors, TNF-α inhibitors, PDE4 inhibitors, and UV radiation are used to treat psoriasis.[4]

An understanding of the molecular mechanism of treatment is an essential task in the application of an efficient method in therapy. The assessment of gene expression change is a suitable tool to explore the molecular mechanism of diseases. Since genomic approaches can provide a large number of data, bioinformatics is a powerful means to analyze gene expression profiles [5,6]. Network analysis is a common method for studying a set of genes or proteins to screen the queried individual and identify the crucial ones. Protein-protein interaction (PPI) network analysis is a useful technique that is used to

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evaluate some therapeutic methods.[7,8] Useful information about the effects of ultraviolet (UV) as a therapeutic tool is retrieved via PPI network analysis.[9]

The influential genes among a large number of genes can be detected via PPI network analysis. The nodes of a PPI network which have high values of degree (connections) with the first neighbors in the network are called hubs and are considered as a central node. The top nodes based on betweenness centrality are named bottlenecks, that is, the central nodes that play a critical role in the functions of the network. Common hubs and bottlenecks that are known as hub-bottlenecks are potent central nodes. Hub-bottleneck nodes are used frequently to describe the prominent molecular event in the studied system.[10-13] In the present study, the gene expression profiles of the peri-lesion skin tissue biopsy of psoriasis patients after and before narrow-band UVB (NB-UVB) therapy were extracted from Gene Expression Omnibus (GEO) and were analyzed via the PPI network to find the critical genes targeted by NB-UVB. Results can be used to improve therapeutic methods against psoriasis.

Methods

Data Collection

The high-throughput profiles (RNA sequencing) of the peri-lesion skin tissue biopsy of psoriasis patients after NB-UVB therapy versus before the treatment were extracted from GEO (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE179731). As it is reported by Boonpethkaew et al, the treatment started 2–3 times for 12 weeks with an initial dose of 200 mJ/cm^2. This dose was slowly amplified 10%–20% from the initial dose until the minimal erythema dose happened.[14]

Data Pre-evaluation

GSM5430057-9 related to after the condition versus GSM5430054-6 as the profiles of before the treatment were compared via the GEO2R program. The volcano plot, mean-variance trend plot, UMAP plot, and box plot were provided.

Gene Expression Analysis

The differentially expressed genes (DEGs) were determined via the GEO2R program. The significant DEGs were identified based on adjusted *P* value (P_{adj}). The uncharacterized genes were ignored.

PPI Network Analysis

The significant DEGs were included in the STRING database via Cytoscape software v 3.7.2. The recognized DEGs interacted via undirected links to form an interactome. The network was analyzed and visualized by the "Network analyzer" application of Cytoscape to explore centrality parameters. The top 10% of the nodes based on degree value and 5% based on betweenness centrality were determined as bottlenecks. The common hubs and bottlenecks were introduced as hub-bottlenecks. Activation, inhibition, and expression actions between hub-bottleneck nodes were identified by the CluePedia application of Cytoscape.

Statistical Analysis

The significant DEGs were determined based on adjusted *P* value (P_{adj}) less than 0.05. The PPI network was created by considering confidence score = 0.2.

Results

The data were assessed via pre-evaluation analyses; volcano plot analysis indicated that a large number of genes were significant DEGs including up- and downregulated individuals. Based on the mean-variance (Figure 1) trend plot, analyses were satisfactorily reliable. Based on the analyses, there were 543 DEGs among 18943 dysregulated genes. The results from UMAP assessment revealed that the treated samples were completely separated from the sample before using NB-UVB treatment by the studied DEGs. As depicted in the box plot diagram, the sample before and after treatment with NB-UVB are median-centric and can be compared statistically (Figures 2-4).

A total of 513 genes among the 543 significant DEGs were recognized by the STRING database and selected for more analysis. The PPI network including 5 isolated DEGs and a main connected component of 508 nodes and 7295 edges was formed. Fifty hubs and 25 bottlenecks were identified as the central nodes of the PPI network. As shown in Table 1, 22 common hubs and bottlenecks as hub-bottleneck genes (19 downregulated DEGs and 3 upregulated individuals) were explored. Action map analysis revealed that there were regulatory relationships between FN1, STAT3, HIF1A, IL1B, P4HB, SOD2, MMP2, and STAT1 (Figure 5).

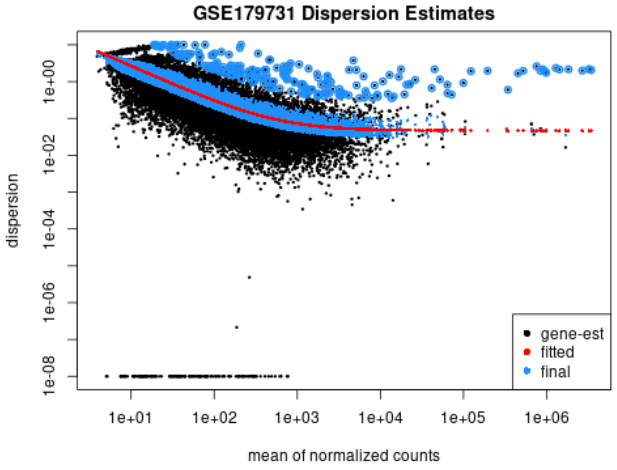

Figure 1. Mean-Variance Trend Plot of the Human Peri-Lesion Skin Tissue Biopsy of Psoriasis Patients After the Treatment With NB-UVB Versus Before the Condition.

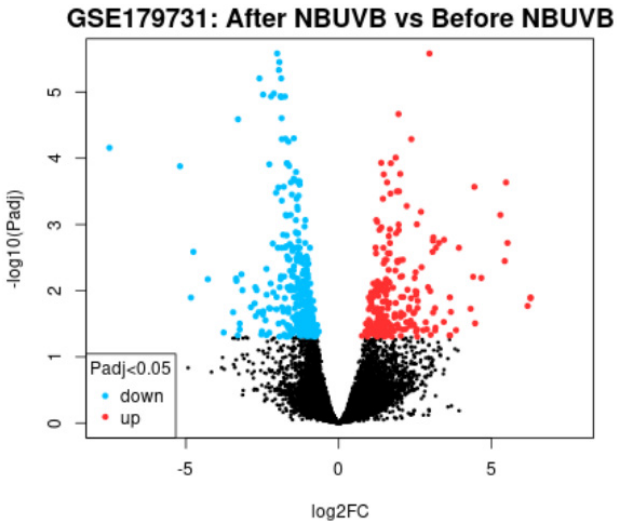

Figure 2. Volcano Plot of the Human Peri-lesion Skin Tissue Biopsy of Psoriasis Patients After the Treatment With NB-UVB Versus Before the Condition

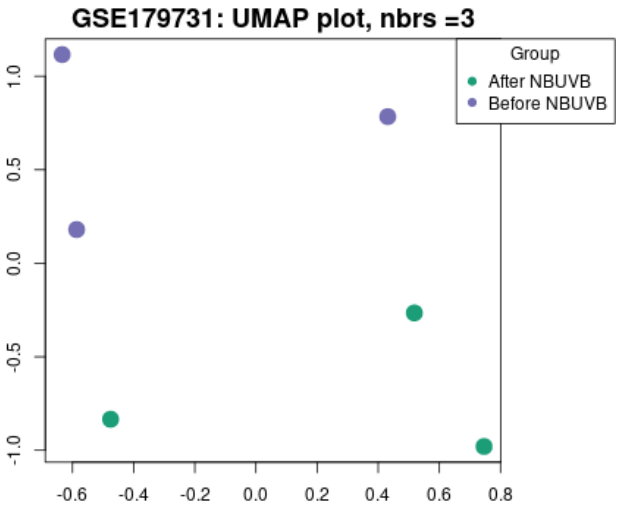

Figure 3. UMAP Plot of the Human Peri-lesion Skin Tissue Biopsy of Psoriasis Patients After the Treatment With NB-UVB Versus Before the Condition

Discussion

The role of the activation of several genes and the initiation and progression of psoriasis is reported and discussed in the literature. The activation of NF-κB initiates inflammation and it is associated with psoriasis.[15] Liu et al published a document about the possible biomarkers of psoriasis via the assessment of gene expression and PPI network analysis.[16] Since NB-UVB is applied to treat psoriasis, there are documents about the mechanism of therapy via transcriptomic analysis.[14,17]

In the present study, the transcriptomic results were evaluated via PPI network analysis to detect the efficacy and mechanism of psoriasis treatment by using NB-UVB radiation. As shown in Table 1, 22 hub-bottleneck genes are introduced as central nodes which are regulated by NB-UVB application as a therapeutic method. The action map result revealed that eight central genes were connected with regulatory connections. Here, the focus

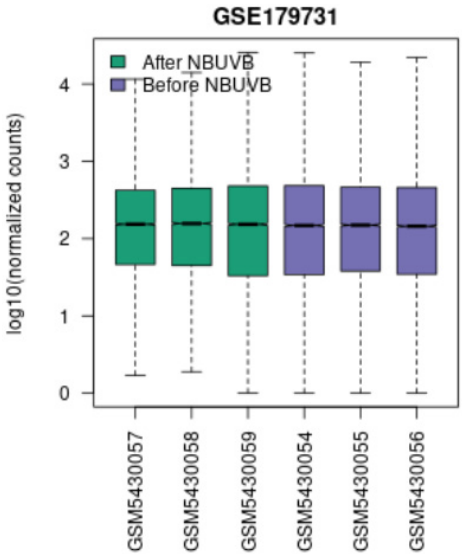

Figure 4. Box Plot of the Human Peri-lesion Skin Tissue Biopsy of Psoriasis Patients After the Treatment With NB-UVB Versus Before the Condition

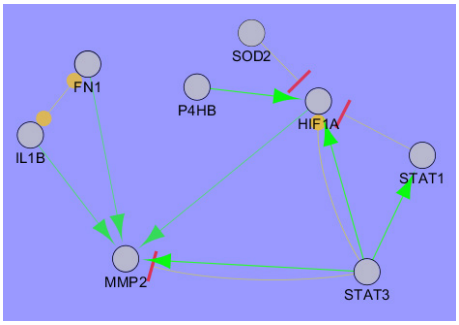

Figure 5. Action Map Illustration for the Introduced Hub-Bottlenecks. The isolated gens are excluded. Green and yellow refer to activation and expression relationships

was on the function and role of these eight crucial genes in the development or treatment of psoriasis.

Fibronectin 1 is the first ranked as hub and bottleneck. It is reported that FN1 levels increase in the epidermis of psoriatic lesions.[18] As it is shown in Table 1, FN1 is upregulated after UV treatment in patients' samples. UV therapy has not decreased FN1 expression, but it has increased its level. The other critical gene is IL1B which is downregulated about 9-fold after the treatment. On the basis of the literature, the suppression of IL1B production can lead to health improvement in psoriasis patients.[19] As shown in Figure 1, there is a positive correlation between the expression of both FN1 and IL1B. The results indicate that the downregulation of IL1B is consistent with the treatment of psoriasis, but the upregulation of FN1 is consistent with the development of the disease.

Investigations indicate that HIF1A overexpresses in psoriatic lesions. HIF1A, HIF2A, HIF3A, and HIF1B belong to the HIF family. HIF1A is the transcription factor that is involved in the biological processes that have changed in hypoxic conditions.[20] Based on researches, HIF1A and STAT3 are known as crucial transcription

Table 1. List of Hub-Bottleneck Genes

No.	Display Name	Gene Name	Degree	Betweenness Centrality	LogFC
1	FN1	Fibronectin 1	159	0.059	1.22
2	STAT3	Signal transducer and activator of transcription 3	123	0.030	-1.2
3	HIF1A	Hypoxia inducible factor 1 subunit alpha	115	0.026	-1.47
4	IL1B	Interleukin 1 beta	117	0.025	-3.24
5	KIF14	Kinesin family member 14	103	0.024	-2.28
6	HSPA8	Heat shock protein family a (hsp70) member 8	118	0.020	-1.04
7	ANLN	Anillin, actin binding protein	90	0.017	-1.36
8	CDK1	Cyclin dependent kinase 1	104	0.016	-1.69
9	EPRS	GLutamyl-prolyl-trna synthetase 1	80	0.016	-1.12
10	ASPM	Assembly factor for spindle microtubules	75	0.015	-1.59
11	NPM1	Nucleophosmin 1	102	0.015	-1.31
12	P4HB	Prolyl 4-hydroxylase subunit beta	89	0.014	-0.92
13	MKI67	Marker of proliferation ki-67	82	0.014	-1.3
14	YWHAZ	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein zeta	84	0.014	-0.99
15	ENO1	Enolase 1	95	0.013	-0.85
16	CCT2	Chaperonin containing TCP1 subunit 2	84	0.013	1.05
17	SOD2	Superoxide dismutase 2	79	0.013	-1.48
18	MMP2	Matrix metallopeptidase 2	96	0.013	1.46
19	CYCS	Cytochrome	87	0.012	-1.24
20	LMNB1	Lamin B1	77	0.012	-130
21	STAT1	Signal transducer and activator of transcription 1	84	0.011	-1.02
22	HSP90B1	Heat shock protein 90 beta family member 1	90	0.011	-1.1

FC; fold change.

factors which are involved in inflammation. It has been reported that both STAT3 and HIF1A are upregulated in psoriatic lesions. Experiments showed biologics treatments of psoriasis lead to the decrement of STAT3 and HIF1A.[21] STAT3 appeared as a critical DEG in our study (see Table 1). Both STAT3 and HIF1A are downregulated after the treatment with UV radiation. The activation and upregulation of HIF1A by STAT3 are illustrated in Figure 5. The suppression of HIF1A and STAT3 is consistent with the efficacy of NB-UVB in the treatment of psoriasis.

Starodubtseva et al published a document about the overexpression of matrix metalloproteinase MMP1 and MMP12 in psoriasis. It is reported that MMP1 and MMP12 are upregulated about 15-fold.[22] Fleischmajer et al have reported that MMP2 is overexpressed in the suprabasal layers of psoriatic epidermis.[23] As depicted in Figure 5, MMP2 is activated by FN1, IL1B, HIF1A, and STAT3. The upregulation of MMP2 after the treatment by NB-UVB is tabulated in Table 1. It can be concluded that the upregulation of MMP2 like the upregulation of FN1 is a side effect of UV therapy. The activation of HIF1A by P4HB is presented in Figure 5. P4HB is downregulated about 2-fold which supports NB-UVB as an efficient therapy. There is a negative correlation between SOD2 and STAT1 expression and HIF1A (see Figure 5). Both STAT1 and SOD2 are downregulated. This point does not support the treatment by UV radiation. However, both SOD2 and STAT2 are weak central genes.

Conclusion

In conclusion, NB-UVB radiation as a treatment targets critical genes including FN1, STAT3, HIF1A, IL1B, P4HB, SOD2, MMP2, and STAT1 in the peri-lesion skin tissue biopsy of psoriasis patients. The mechanism of treatment is complicated; while the downregulation of STAT1 and SOD2 and the upregulation of MMP2 and FN1 are the side effects of therapy, the downregulation of STAT3, HIF1A, IL1B, and P4HB supports the efficacy of treatment. It can be suggested that a combination of NB-UVB radiation and one of the other therapeutic methods may be a more efficient trend against psoriasis.

Authors' Contribution

Conceptualization: Reza M Robati, Mostafa Rezaei Tavirani.
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Resources: Fatemeh Montazer.

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Writing–review & editing: Babak Arjmand, Farideh Razi, Fatemeh Montazer.

Competing Interests
The authors declare they have no conflicts of interest.

Ethical Approval
This project was approved by Shahid Beheshti University of Medical Sciences with the ethical code of. IR.SBMU.LASER.REC.1402.010.

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