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Assessment of NB-UVB Effects on Skin of Atopic Dermatitis Patients: A Network Analysis

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Abstract

Introduction: Atopic dermatitis is a common inflammatory skin disease which is treated with narrowband ultraviolet B (NB-UVB). Exploring the critical targeted genes in patients by UV radiation is the main aim of this study.

Methods: Gene expression profiles of lesional and non-lesional skin samples of atopic dermatitis patients after treatment with NB-UVB and the non-irradiated samples were extracted from the Gene Expression Omnibus (GEO) database and analyzed via protein-protein interaction (PPI) network analysis to find the critical targeted genes.

Results: A total of 357 significant differentially expressed genes (DEGs) were included in the PPI network. CTNNB1, SRSF1, YWHAB, SMC3, GNB2, ARF3, UBL7, RAB2A, YWHAE, EIF5B, SNRPE, PPIG, RC3H2, CFL1, SMARCB1. LAPTM5, PRPF40A, and RBBP4 were introduced as hub-bottlenecks.

Conclusion: In conclusion, five central genes including SMC3, ARF3, EIF5B, SMARCB1, and LAPTM5 were highlighted as the critical genes in response to NB-UVB radiation in the skin of the treated atopic dermatitis patients. The introduced crucial genes are involved in essential cellular functions such as apoptosis, cell cycle, cell proliferation, and inflammation. It seems that applied NB-UVB radiation is a suitable therapeutic method for atopic dermatitis disease.

Keywords: Atopic dermatitis; Human; Skin; Gene; Network.

Introduction

Atopic dermatitis is one of the skin disorders which is common in infants and children, and it frequently appears during the first 6 months of life.[1] This disease, also known as atopic eczema, is a chronic inflammatory skin condition which threatens patients' health.[2] It has been reported that atopic dermatitis has a complex and multifactorial pathophysiology. The disease includes an imperfection in the epidermal barrier, genetic disorders, and altered immune response. This disorder is associated with the disruption of the microbial stability of the skin.[3] Corticosteroids, calcineurin inhibitors ultraviolet A (UVA) and ultraviolet B (UVB) radiation, azathioprine, cyclosporine, and methotrexate are introduced as therapeutic methods for atopic dermatitis disease.[4]

The assessment of the efficacy of therapeutic methods requires the exploration of the molecular mechanism of cellular and tissue events. Bioinformatics as a suitable tool is applied to discover different aspects of treatments in medicine. Network analysis is a common technique that has attracted researchers' attention to exploring the critical genes, proteins, or metabolites that are targeted during the treatment of diseases. In such a study, large numbers of genes interact to form a network, and since each gene plays its unique role in the network, the genes can be clustered as the central genes and others.[5,6]

Two types of central nodes of protein-protein interaction (PPI) networks are introduced as critical elements of the

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studied networks: the hubs and bottlenecks. Hubs are the elements of the network which are connected to the most first neighbors. The hubs are characterized by high values of degree. The bottleneck nodes are the genes that are characterized by higher values of betweenness centrality. The common hub and bottleneck nodes that are known as hub-bottlenecks are the potent central nodes which are involved in the major function of the constructed network.[7-9] In the present study, the skin gene expression profiles of the patient with atopic dermatitis, treated with narrowband ultraviolet B (NB-UVB), were extracted from the GEO database, and they were compared with controls via network analysis to find the molecular event relative to the therapeutic method.

Materials and Methods

Data Collection

Eighteen gene sets of lesional and non-lesional skin samples of atopic dermatitis patients after treatment with NB-UVB versus 17 non-treated samples were extracted from GSE27887 of GEO. The samples were exposed to NB-UVB three times weekly for up to 12 weeks. Details of the methods are described by Tintle et al in a published document entitled "Reversal of atopic dermatitis with narrow-band UVB phototherapy and biomarkers for therapeutic response".[10]

Data Pre-evaluation

Data were pre-evaluated via GEO2R to find the significant differentially expressed genes (DEGs). The Volcano plot was applied to visualize the differential expressed genes. Box plot analysis was considered to find possible statistical matching between the samples. The significant DEGs were determined via the Venn diagram.

Network Analysis

The significant DEGs were screened to find the characterized genes, and then the characterized significant DEGs were evaluated via PPI network analysis. The recognized significant DEGs by the STRING database were included in the network via Cytoscape software v3.7.2 to form an interactome. The main connected component of the PPI network was analyzed via the "Network Analyzer" application of Cytoscape, and 10% of top nodes based on degree value were identified as hubs. To find the bottleneck nodes, we selected 5% of the top nodes based on betweenness centrality for further analysis. The common hubs and bottlenecks were identified as hub-bottlenecks.

Statistical Analysis

To find the significant DEGs, we considered adjusted p-value less than 0.05; however, fold changes above 1.5 were applied to limit the number of significant DEGs. The PPI network was formed based on a confidence score = 0.2.

Results

The Volcano plot of the analyzed data is shown in Figure 1. Based on the results, there are many significant DEGs which differentiate the treated samples from the samples before radiation. To compare samples, we provided a box plot. As shown in Figure 2, the samples are median centric and are comparable statistically. More assessment revealed that among 54 100 affected genes, 575 individuals were significant DEGs. Results are shown in Figure 3.

The PPI network was created from 357 recognized significant DEGs including 12 isolated nodes and a main connected component of 345 genes and 2210 edges (the network is not shown). Thirty-five top nodes based on degree value were introduced as hubs and 18 genes were identified as bottleneck nodes. Results indicate that all bottleneck nodes are hubs. Therefore, 18 hub-bottleneck nodes are introduced in Table 1.

Discussion

Pre-evaluation analysis showed that there are many significant DEGs that differentiate the irradiated samples from controls. As it is depicted in Figures 1-3, there are 575 significant DEGs which can be assessed as the affected genes by NB-UVB radiation. Further investigation revealed that 357 genes among the significant DEGs are eligible to form the PPI network. Since hubs and bottleneck nodes, especially hub-bottlenecks, are the critical elements of a PPI network,[11,12] the hub-bottleneck genes were determined (see Table 1).

As it is depicted in Table 1, the fold change of the most introduced hub-bottlenecks is below 1.5. Therefore, it was decided that logFC = 0.6 as a cutoff be applied to screen the central nodes. Based on this selection rule, SMC3, ARF3, EIF5B, SMARCB1, and LAPTM5 were candidates as the critical targeted genes.

Based on the investigation of Rivas et al, the dosage

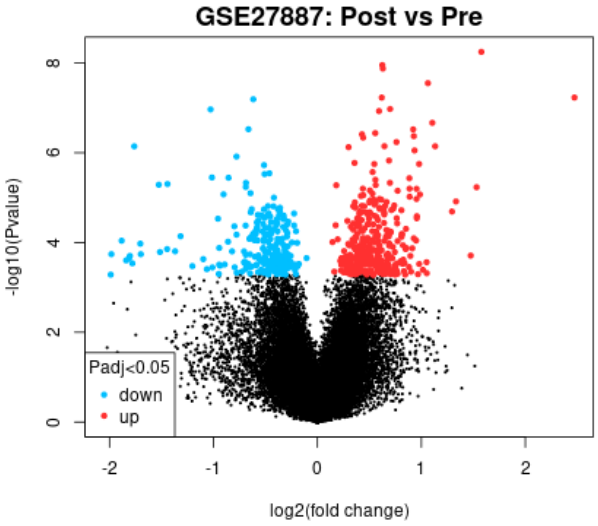

Figure 1. Volcano Plot of Gene Expression Profiles of Treated Skin Samples with NB-UVB Versus Non-exposed Individuals

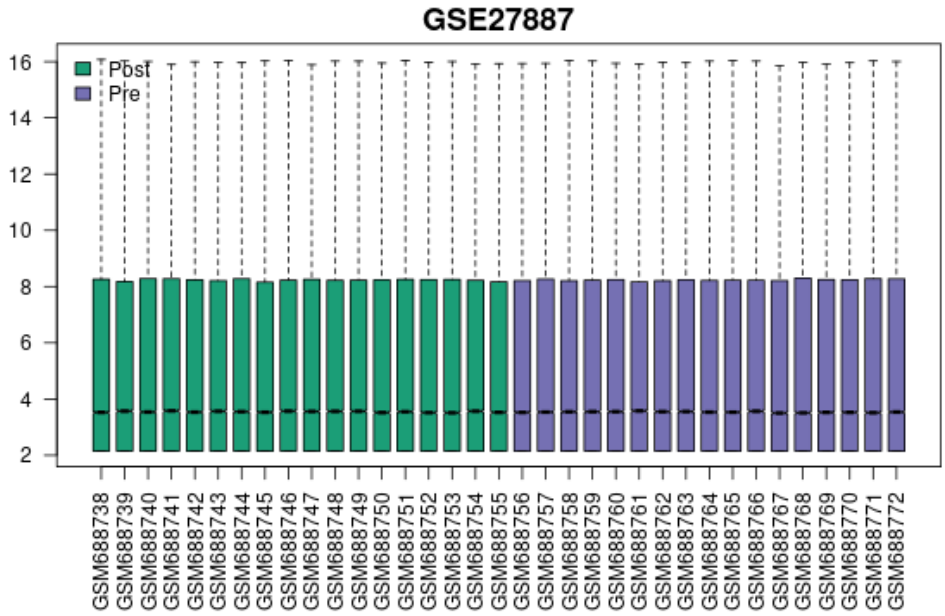

Figure 2. Box Plot of Gene Expression Profiles of Treated Skin Samples with NB-UVB Versus Non-exposed Individuals

Table 1. List of Hub-Bottleneck Genes of the Main Connected Component of the PPI Network

No.	Display Name	Description	Degree	BC	LogFC
1	CTNNB1	Catenin beta 1	82	0.106	0.363
2	SRSF1	Serine and arginine rich splicing factor 1	53	0.046	0.312
3	YWHAB	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein beta	45	0.031	-0.485
4	SMC3	Structural maintenance of chromosomes 3	31	0.026	-1.76
5	GNB2	G protein subunit beta 2	34	0.025	-0.360
6	ARF3	ADP ribosylation factor 3	39	0.024	-0.893
7	UBL7	Ubiquitin like 7	37	0.023	-0.308
8	RAB2A	RAB2A, member RAS oncogene family	32	0.023	-0.330
9	YWHAE	Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein epsilon	40	0.021	-0.379
10	EIF5B	Eukaryotic translation initiation factor 5B	37	0.021	0.771
11	SNRPE	Small nuclear ribonucleoprotein polypeptide E	31	0.020	0.377
12	PPIG	Peptidylprolyl isomerase G	29	0.019	-0.400
13	RC3H2	Ring finger and CCCH-type domains 2	34	0.019	-0.471
14	CFL1	Cofilin 1	32	0.019	-0.302
15	SMARCB1	SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1	39	0.019	-0.644
16	LAPTM5	Lysosomal protein transmembrane 5	23	0.018	-1.01
17	PRPF40A	Pre-mRNA processing factor 40 homolog A	33	0.018	-0.313
18	RBBP4	RB binding protein 4, chromatin remodeling factor	34	0.017	0.370

BC, betweenness centrality; FC: fold change.

of structural maintenance of chromosomes 3 (SMC3) regulates the transit of B cells through germinal centers and limits their malignant transformation.[13] As it is shown in Table 1, SMC3 is downregulated extensively in response to NB-UVB radiation. Previous studies indicated that SMC3 downregulation in the MCF7 cell line led to inducing apoptotic cell death and inhibition of cell proliferation and cell cycle progression at G_1.[14] ADP ribosylation factor 3 (ARF3) mainly works at the trans-Golgi network.[15] Results indicate that ARF3 is downregulated after NB-UVB radiation in the studied samples. The significant role of ARF3 in the inhibition of proliferation and development of apoptosis in gastric cancer has been reported by researchers.[16]

The third central gene is eukaryotic translation initiation factor 5B (EIF5B). A published document indicates that initiation factor eIF5B plays a role in eukaryotic translation initiation.[17] The upregulation of EIF5B is shown in Table 1. Lee and colleagues' study showed that EIF5B upregulation controls cell-cycle arrest

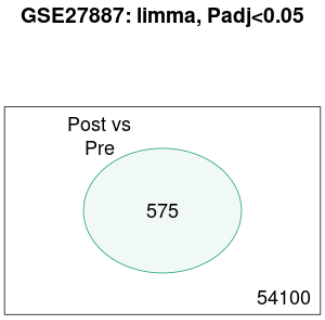

Figure 3. Venn Diagram Related to Gene Expression Profiles of Treated Skin Samples with NB-UVB Versus Non-exposed Individuals. The significant DEGs are shown versus 54100 dysregulated genes.

and exact progressive stages.[18] SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily b, member 1 (SMARCB1) is the 4th central gene that is downregulated in response to UV treatment. The role of SMARCB1 as a critical gene in the regulation of an enhancer is highlighted in previous studies.[19] The last downregulated central node is lysosomal protein transmembrane 5 (LAPTM5). Glowacka et al published a document about the positive role of LAPTM5 in the regulation of proinflammatory signaling pathways in macrophages.[20] Chen et al showed that the downregulation of LAPTM5 leads to the suppression of cell proliferation and viability in bladder cancer cells.[21] It seems the targeted central genes are involved in essential biological processes in the irradiated samples.

Conclusion

In conclusion, SMC3, ARF3, EIF5B, SMARCB1, and LAPTM5 were pointed out as the crucial genes in response to NB-UVB radiation in treated atopic dermatitis patients. Evaluations showed the introduced critical genes are associated with the control of apoptosis, cell cycle, cell proliferation, and inflammation. It can be concluded that the applied NB-UVB radiation can be considered an efficient method for treating atopic dermatitis disease. Gene ontology analysis as a suggested complementary investigation can provide useful information about the dysregulated pathways and biological processes. A comparative study about the effects of drugs and UV radiation on the treatment of patients is the next suggested project.

Authors' Contribution

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Investigation: Mohammad Rostami Nejad, Fatemeh Bandarian.
Methodology: Zahra Razzaghi.
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Resources: Fatemeh Bandarian.
Software: Mostafa Rezaei Tavirani.
Supervision: Mostafa Rezaei Tavirani, Mohammad Rostami Nejad.
Validation: Zahra Razzaghi.
Visualization: Fatemeh Bandarian.
Writing–original draft: Mostafa Rezaei Tavirani, Zahra Razzaghi.
Writing–review & editing: Babak Arjmand, Farideh Razi, Fatemeh Bandarian.

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.RETECH.REC.1402.033.

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