Journal of Lasers in Medical Sciences

J Lasers Med Sci 2026;17:e51694

Original Article

https://journals.sbmu.ac.ir/jlms

doi:10.34172/jlms.51694

Down-Regulation of IL6 Plays a Critical Role in Red Light Radiation Against UVB-Induced Damages

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Received: February 16, 2026
Accepted: August 5, 2026
ePublished: October 27, 2026

Abstract

Introduction: UVB is a sub-spectrum of the UV spectrum which induces immunological responses in human skin. On the other hand, the protective effect of red light on human skin is highlighted in the literature. The detection of the key molecular point of this protective effect via protein-protein interaction (PPI) network analysis is the aim of this study.

Methods: RNA-seq data of normal human dermal fibroblast cells treated with UVB in the absence and presence of red light radiation were retrieved from the Gene Expression Omnibus (GEO) database and evaluated with the GEO2R program to find the significant differentially expressed genes (DEGs). The identified DEGs were assessed via directed protein-protein interaction (PPI) network analysis and the key targeted genes via red light exposure were determined and discussed.

Results: A total of 703 significant DEGs were assessed to find the key genes which differentiated the two compared groups of the fibroblast cells. IL6 as the top critical gene and FOS, DNAJA1, DNAJA4, EGR1, and PTGS2 as the critical individuals were highlighted as the targeted genes by red light radiation in normal human dermal fibroblast cells treated with UVB exposure.

Conclusion: It can be concluded that red light protects normal human dermal fibroblast cells against UVB-induced damages. This effect of red light is accompanied by down-regulation of IL6 and attenuation of PTGS2 and FOS activity. Reduction of inflammation progression is the consequence of red light radiation.

Keywords: Red light, UVB, Gene, Network analysis, IL6

Introduction

One part of the ultraviolet (UV) spectrum that affects human skin and induces immunological responses followed by possible carcinogenesis activity in skin is UVB.[1] To assess skin sensitivity to UVB, the minimal erythema dose was evaluated. Based on this finding, total blood flow, blood flow peak, and blood flow depth significantly increased in the irradiated samples.[2] Photoaging is another well-known effect of UVB radiation.[3] An investigation indicates that associated pyroptosis with gasdermin E plays a preventive role in the damaged skin from UVB radiation. This effect results from the inhibition of extreme employment and the activation of neutrophils in the irradiated inflamed skin.[4]

On the other hand, red light with a 600-700 nanometer wavelength is another part of the electromagnetic spectrum which is characterized with low-level energy (about 1.8-2.1 electron volt) and high capacity to penetrate the skin. Stimulatory effects of red light on the skin have demonstrated this radiation as a suitable light-based therapy.[5] Reverse skin aging signs via light-therapy (photobiomodulation) is investigated by researchers.[6] A field that focuses on controlling cellular functions via light-activated proteins is known as optogenetics. Experiments demonstrated that opsins (the heptahelical transmembrane

Please cite this article as follows: Hossein-Khannazer N, Arjmand B, Razzaghi Z, Razi F, Bandarian F, Rezaei-Tavirani M et al. Down-regulation of IL6 plays a critical role in red light radiation against UVB-induced damages. J Lasers Med Sci 2026;17:e51694. doi:10.34172/jlms.51694

proteins) are suitable tools in optogenetic investigations. There are several publications about red light-activated opsins in optogenetics. Based on the literature, the skin-derived cells, such as fibroblasts, melanocytes, and keratinocytes, express opsin.[7,8]

The gene expression analysis of biological samples is a beneficial way to explore the molecular mechanism of the studied event in physiological and pathological conditions. Many diseases and therapeutic methods are studied via gene expression evaluation. Since genomics is a high throughput method, the integration of bioinformatics and genomics appears as a necessary tool in biological and medical investigations.[9-12] PPI network analysis as a bioinformatics tool can be used to detect the relationship between a set of genes or proteins. The queried genes are included in an interactome, and each one demonstrates its central properties. Degree is one of the important central parameters that refers to the number of the first neighbors of a certain node in the constructed PPI network. In-degree and out-degree values for a node in the network refer to the number of directed links that enter or exit from the node, respectively.[13-15] In the present study, the gene expression profiles of normal human dermal fibroblast cells treated with UVB and UVB + red light radiation are extracted from the GEO database and are assessed via directed PPI network analysis to explore the key genes that demonstrate the possible preventive effects of red light against damages of UVB exposure. Findings can provide a new perspective on the application of red light in human lifestyles.

Methods

Data collection

Three RNA-seq datasets from normal human dermal fibroblast cells treated with UVB (312nm) in the absence of red light (660nm) exposure and three profiles of the mentioned cells which were exposed to UVB after red light radiation were extracted from the GEO database (https://www.ncbi.nlm.nih.gov/geo/geo2r/?acc=GSE116968). GSM3265437-9 and GSM3265434-6 were selected as the cells that received UVB + red light and red light radiation, respectively.

GEO2R analysis

The gene expression profiles were analyzed using the GEO2R program (Version info: R 4.2.2, Biobase 2.58.0, GEOquery 2.66.0, limma 3.54.0) to find the possible DEGs. Separation of the gene expression profiles of the cells that were exposed to UVB and profiles of the cells which received additional red light were assessed via the Uniform Manifold Approximation and Projection (UMAP) plot. The significant DEGs were identified based on an adjusted P value < 0.05 and a fold change > 2. The significant DEGs versus total DEGs were visualized via a Venn diagram. The determined significant DEGs were cleaned via deletion of the uncharacterized genes and microRNAs.

PPI network analysis

The significant DEGs were assessed via a directed PPI network to find the critical actors and controlled genes. The studied genes were included in an interactome using CluePedia v 1.5.10, an application within Cytoscape software v 3.10.1. Activation, inhibition, and expression actions between nodes of the constructed network were extracted from CluePedia_STRING.ACTIONS_v11.0_9606_27.02.2. For more investigation, the sub-networks of the PPI network were constructed and evaluated based on each action. The nodes of the sub-networks which were characterized with out-degree and in-degree values > 2 were selected for more evaluation. If one of the out-degree or in-degree values were more than 2, the node was pointed out as a significant node in the network.

Key genes identification

To identify the key genes that play critical roles in the analyzed PPI network, the out-degree and in-degree values of nodes in the sub-networks were determined and the distribution of the crucial genes based on the total value of degree amounts for a node in all sub-networks was provided. Also, R^2 statistical parameter was evaluated to find a suitable cutoff to determine the key genes. The possible top key gene and its first neighbors were included in a sub-network to explore more details of its role in the PPI network.

Results

As depicted in Figure 1 (UMAP plot), red light exposure separated the treated normal human dermal fibroblast cells which received UVB radiation. A total of 703 significant DEGs differentiated the two compared groups of the fibroblast cells (see Figure 2). After cleaning the data, 538 significant DEGs remained for further investigation.

PPI network analysis

Among 538 query DEGs, 535 individuals were recognized by ClueGO and were connected with 250 activation, inhibition, and expression connections. Since there were no considerable numbers of inhibition links, the nodes were assessed separately via activation and expression connection. The main connected components of the two sub-networks of the PPI network are presented in Figures 3 and 4. The significant nodes of the studied sub-networks are demonstrated in Table 1. As depicted in Table 1, there are 30 significant genes that play crucial roles in the PPI network of red light against UVB radiation. IL6 is the top crucial gene, which is characterized with a total degree of 28.

Key genes identification

Distribution of nodes based on total degree value is shown in Figure 5. Total degree value ranges from 4 to 28. To find the key genes; the linear alteration of total degree values was considered a suitable statistic criterion. As depicted in Figure 6, the R^2 values of 0.73, 0.90, and 0.96 refer to the lines, including total degrees of all genes, all genes except IL6, and other individuals. It means IL6 is a critical player

in the network, and FOS, DNAJA1, DNAJA4, EGR1, and PTGS2 can be considered key genes related to the effect of red light radiation. Since IL6 appeared as the top key gene, a sub-network, including this gene and its first neighbors, were included in an interactome (see Figure 7). As demonstrated in Figure 7, both FOS and PTGS2 are first neighbors of IL6.

Discussion

Kim et al.'s investigation showed that red light radiation effects on UV-induced DNA oxidative damage in normal human dermal fibroblast cells. This effect is accompanied by "growth arrest and DNA damage inducible, alpha" changes and "base excision repair" to promote DNA renovation. It was explored that red light increases the physical activity of apurinic/apyrimidinic endonuclease 1 (APE1) and GADD45A. The significant role of APE1 in reducing DNA damages resulting from UV radiation via red light treatment was pointed out in this research.[16] In the present study, two classes of genes including IL6 as the top class and FOS, DNAJA1, DNAJA4, EGR1, and PTGS2 as the second cluster of the genes appeared as the key genes that were affected by red light in the UVB irradiated normal human dermal fibroblast cells. DNAJA1 and DNAJA4 are members of heat shock protein 40 (HSP40).[17]

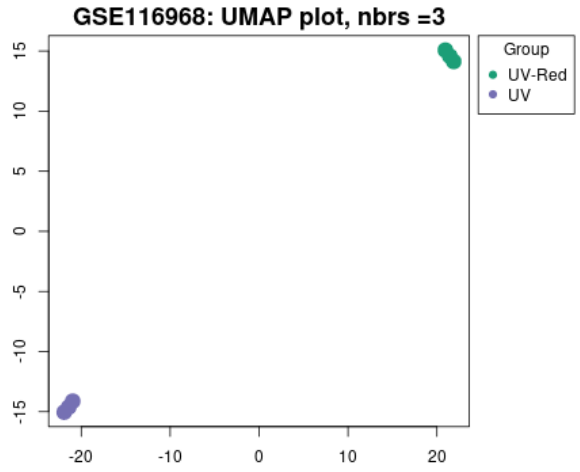


Figure 1. Uniform Manifold Approximation and Projection plot for comparing the gene expression profiles of the normal human dermal fibroblast cells irradiated with UVB and UVB + red light. Nbrc refers to the compared neighbors of the studied profile

Interleukin 6 (IL-6) cytokine is involved in various functions, such as effects on blood brain permeability, acute phase reactant pathways, synovial inflammation, B and T lymphocytes function, embryonic development, transition between innate and adaptive immune responses, hematopoiesis, and employment of macrophages and lymphocytes to the sites of infection or injury.[18] Investigations have confirmed that following tissue injury, the expression of IL6 is up-regulated about 63.3-fold.[19] Here, IL6 is down-regulated by red light radiation in UVB-irradiated normal human dermal fibroblast cells, which refers to the skin protective effect of red light against UVB-

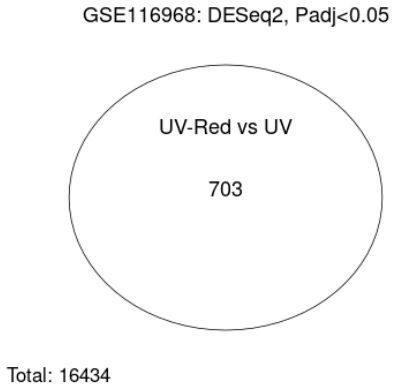


Figure 2. Venn diagram for visualizing the significant DEGs which differentiate the two treated groups of fibroblast cells by UVB and UVB + red light. A total of 703 significant DEGs are identified

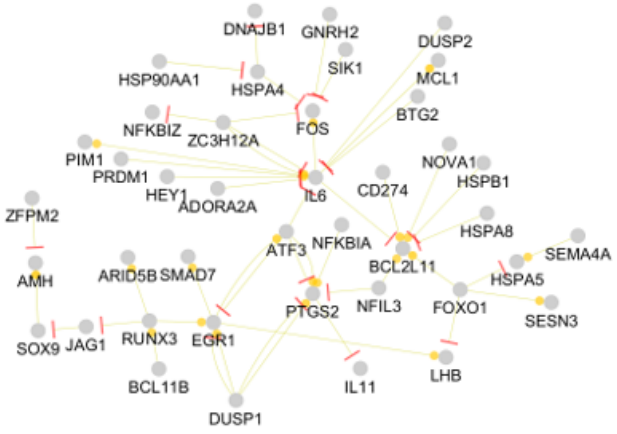


Figure 4. Main connected component of the sub-network of the directed PPI network which is formed via expression action

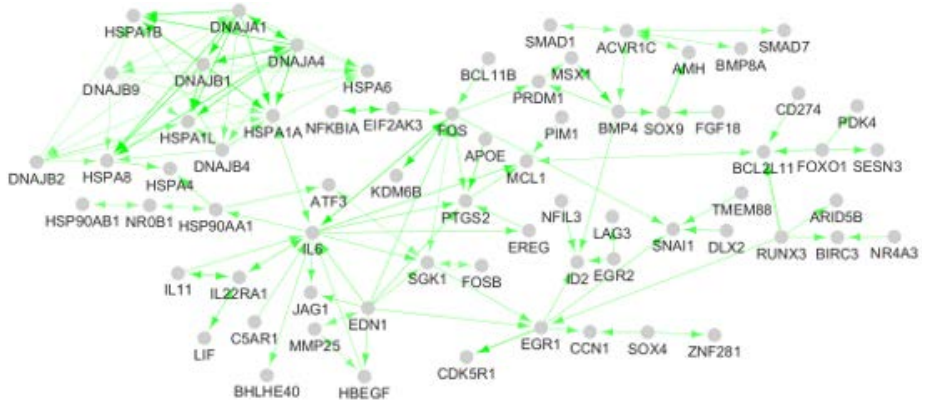


Figure 3. Main connected component of the sub-network of the directed PPI network which is formed via activation action

induced damages. As depicted in Figure 7, IL6 activates FOS and PTGS2, the two key genes in the introduced second cluster of genes. Therefore, the down-regulation of IL6 is accompanied by the decrement of the activity of PTGS2 and FOS genes.

Based on the literature, Fos proto-oncogene, AP-1 transcription factor subunit (FOS), and FOSB proto-oncogens play significant roles in a widespread variety of tumourigenic processes. Rearrangement of these genes is detected in pseudomyogenic haemangioendothelioma, epithelioid haemangioma, proliferative myositis/fasciitis, and osteoid osteoma/osteoblastoma/cementoblastoma.[20] It can be concluded that, the down-regulation of IL6 is accompanied by the decrement of the mentioned

Table 1. The significant nodes of the main connected component of the constructed sub-networks. The central properties of nodes, including outdegree, indegree, and total degree for the subnetworks which are formed via activation and expression, are presented

No.	Action	Activation		Expression		Total degree
	Gene	Out degree	In degree	Out degree	In degree	
1	IL6	10	6	4	8	28
2	DNAJA1	10	5	-	-	15
3	DNAJA4	10	5	-	-	15
4	EDN1	8	1	-	-	9
5	DNAJB2	7	2	-	-	9
6	DNAJB4	7	2	-	-	9
7	DNAJB9	7	2	-	-	9
8	DNAJB1	7	2	-	-	9
9	FOS	6	6	0	5	17
10	ACVR1C	5	5	-	-	10
11	BMP4	5	3	-	-	8
12	EGR1	4	3	3	4	14
13	RUNX3	4	0	3	1	8
14	SGK1	4	5	-	-	9
15	FOXO1	3	0	4	0	7
16	HSP90AA1	3	2	-	-	5
17	IL22RA1	3	3	-	-	6
18	PTGS2	2	5	1	6	14
19	MCL1	1	4	-	-	5
20	HSPA8	1	6	-	-	7
21	HSPA1A	1	7	-	-	8
22	BCL2L11	0	4	0	7	11
23	ID2	0	4	-	-	4
24	SNAI1	0	4	-	-	4
25	HSPA6	0	6	-	-	6
26	HSPA1B	0	6	-	-	6
27	HSPA1L	0	6	-	-	6
28	ZC3H12A	-	-	4	0	4
28	ATF3	-	-	4	1	5
30	DUSP1			4	1	5

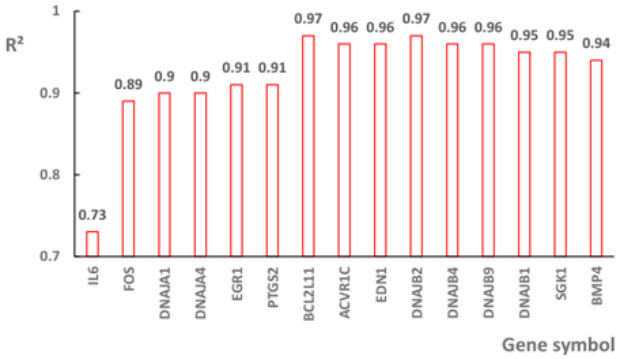


Figure 6. Square of correlation coefficient (R^2) for the lines from ZC3H12A to the pointed out gene in the Figure 5

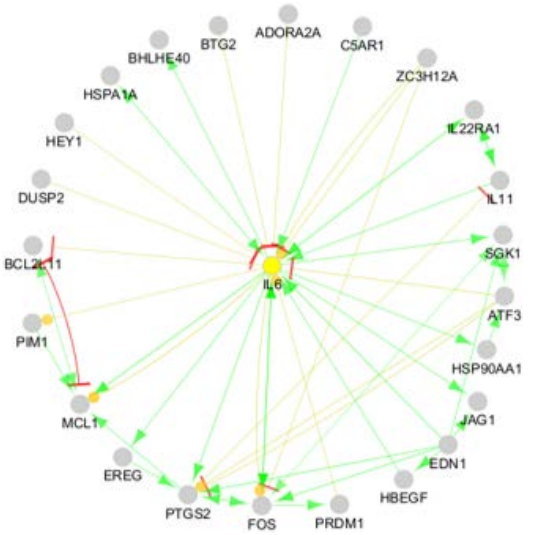


Figure 7. A sub-network of the main connected component of the directed PPI network, including IL6 and its first neighbors. The expression and activation actions are shown in yellow and green, respectively

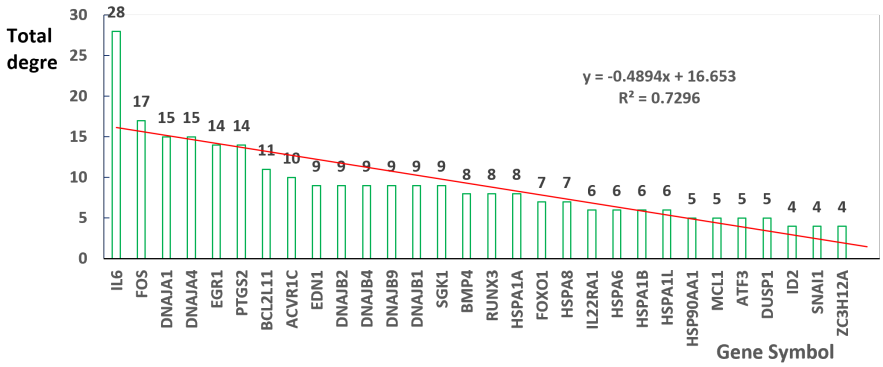


Figure 5. Distribution of total degree value for the crucial 30 genes. The fitted line is presented in red

tumorigenic processes via the attenuation of the positive effect of IL6 on FOS gene activity.

Prostaglandin-endoperoxide synthase 2 (PTGS2) (COX2) is the second activated gene by IL6. Investigations have demonstrated that PTGS2 is a critical regulator of inflammation. Elevated levels of PTGS2 mRNA in adenoma tissue in colorectal cancer have been explored by researchers.[21] Like the effect of IL6 on the activation of FOS, the interaction between IL6 and PTGS2 leads to the promotion of inflammation and cancer progression. Therefore, the down-regulation of IL6 by red light refers to its protective property against UVB-induced damages via the decrement of PTGS2 activity.

Early growth response 1 (EGR1) is a transcription factor that is down-regulated by red light radiation. The role of EGR1 in the progression of prostate cancer,[22] fibrosis, immune response, tissue injury, initiation and progression of cancer, tumor angiogenesis, metastasis, and tumor cell proliferation[23] has been reported by researchers. In accordance with the aforementioned findings, the down-regulation of EGR1 by red light radiation represents an additional defensive effect of this mode of exposure against UVB-induced damages.

The HSP40 members (DNAJA1 and DNAJA4) are the other down-regulated genes due to red light radiation. HSP40 members act as cochaperone proteins and affect complex formation between the patron proteins and HSP70 chaperone.[24] It has been reported that nitric oxide mediated apoptosis is inhibited via HSP70 and HSP40.[25] It seems that the down-regulation of DNAJA1 and DNAJA4 under the effect of red light refers to the attenuated effect of UVB exposure on normal human dermal fibroblast cells.

Conclusion

In conclusion, the most important protective effect of red light against UVB-induced damages in normal human dermal fibroblast cells is the down-regulation of IL6. However, the attenuation of PTGS2 and FOS activity is highlighted as another defensive property of red light radiation. The inhibition of inflammation progression is pointed out as the positive effect of red light on health care of the irradiated normal human dermal fibroblast cells by UVB exposure.

Authors' Contribution

Conceptualization: Nikoo Hossein-Khannazer, Farideh Razi Fatemeh Bandarian Mostafa Rezaei-Tavirani
Data Curation: Nikoo Hossein-Khannazer
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Investigation: Nastarn Asri
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Project Administration: Zahra Razzaghi, Babak Arjmand, Fatemeh Bandarian
Resources: Nastarn Asri
Software: Nikoo Hossein-Khannazer
Supervision: Mostafa Rezaei-Tavirani
Validation: Zahra Razzaghi, Farideh Razi
Visualization: Zahra Razzaghi
Writing–Original Draft: Nikoo Hossein-Khannazer, Zahra Razzaghi
Writing–Review & Editing: Mostafa Rezaei-Tavirani, Babak Arjmand, Farideh Razi

Competing Interests

There is no Competing interests.

Ethical Approval

This project is confirmed with IR.SBMU.LASER.REC.1404.046 ethical code.

Funding

This project is supported by Shahid Beheshti University of Medical Sciences.

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