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Introducing BDNF and SNAI1 as the Crucial Targeted Genes by UV Radiation

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Abstract

Introduction: Due to widespread penetration of UV radiation in human life, the biological effect of UV radiation is studied through many investigations in the field of medicine. There are many assessments about UV radiation which are concerned with protein-protein interaction (PPI) network analysis. In the present study, a network analysis associated with the complementary evaluation of UV radiation on human primary melanocytes is presented.

Methods: The gene expression profiles of the irradiated human primary melanocytes and the control cells were extracted from Gene Expression Omnibus (GEO) and were evaluated via PPI network analysis and action map assessment.

Results: 69 significant differentially expressed genes (DEGs) were included in the main component of the PPI network. Brain-derived neurotrophic factor (BDNF), SNAI1, and SOCS1 were highlighted as the top dysregulated and hub genes. Results indicate that BDNF and SNAI1 participate in the regulatory unit including the total hubs and top dysregulated genes.

Conclusion: Considerable down-regulation of BDNF and up-regulation of SNAI1 as the two critical targeted genes by UV radiation are accompanied by gross alteration in cell functions.

Keywords: Human; UV-radiation; Gene; Network; Expression change.

Introduction

Natural UV radiation has attracted scientists' attention during the last decades. Besides the sun's UV radiation, human-made UV has been used in different fields of human life. Many instruments are equipped with UV rays. Penetration of UV radiation in medical fields is considerable.[1-3] Application of UV laser radiation in medicine implies serious investigation into the molecular mechanism of biological effects following radiation.[4,5] UV effects on human health are studied via different methods and techniques. Chih-Hung Lee et al published a document about the effects of UV radiation on the immune system. Effects of the UV/Visible boundary region on the skin which leads to damage have been investigated by Lawrence et al.[5,6]

Genomics, proteomics, and bioinformatics are useful methods for studying the molecular mechanism of biological effects. There are many studies concerned with gene expression evaluation in the field of radiation.[7,8] Protein-protein interaction (PPI) network analysis is a method for evaluating a set of genes, proteins, or metabolites via the construction of a network from the queried elements. The genes as nodes interact with each other to form a network with different properties.[9,10] A node in the network is characterized by its centrality properties. The well-studied central property is the degree which corresponds to the connections that the node made with the first neighbors. The nodes with a high value of degree are called hubs. Hub nodes play a crucial role in the functions which are related to the elements of the studied network.[11,12]

The biological effects of radiation are studied via network analysis, and different aspects of the molecular mechanism have been discussed by researchers. Vafaee et al reported the analysis of the reversible effects of UV radiation on *Saccharomyces cerevisiae*, the data of which resulted from PPI network analysis. They pointed to the results that refer to the repairment of biological

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effects after 60 minutes of radiation.[13,14] In the present investigation, the gene expression profiles of human primary melanocytes that are irradiated by UV are extracted from Gene Expression Omnibus (GEO) and are analyzed via PPI network analysis and complementary methods to explore the important affected genes. It seems that the results of the present research can provide a new perspective on the molecular mechanism of UV radiation on the cellular level of human life.

Methods

Data of GSE157824 from GEO (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE157824) were extracted to be evaluated. As it is reported in the published data, the human primary melanocytes were irradiated by direct UV (91 mJ/cm^2) and were analyzed after 2-hour incubation. The gene expression profiles of the four radiated cell samples (GSM4775518-GSM4775521) were compared with the control individuals. The gene expression profiles were compared by the GEO2R program to find the pattern of the gene expression rate as a function of UV effects. The top 250 differentially expressed genes (DEGs) based on |LogFC| were retrieved for more analysis. Since the logarithm of the expression change of queried DEGs was above |2| and p-values were less than 0.05, the 250 genes were characterized as the significant DEGs.

The gene names of the significant DEGs were presented as gene IDs. Since the gene name is required for network analysis, the IDs of the 250 queried genes were searched in the "Expression Atlas" (https://www.ebi.ac.uk/gxa/home). The top 10 down-regulated and up-regulated DEGs (20 genes in total) as the most affected genes were selected for further analysis.

The identified significant DEGs were included in a PPI network via the STRING database by Cytoscape software. The network was constructed by using undirected edges and a default condition of a confidence (score) cutoff of 0.4. The network was analyzed by the "Network Analyzer" to explore the properties of the connected nodes. The nodes of the main connected component were assessed by degree value.

Considering the alteration of fold change and degree value, the 20 top dysregulated DEGs and the nodes with the highest values of degree were evaluated by action plot analysis via the CluePedia application of Cytoscape software. Three actions including activation, inhibition, and expression actions of the investigated genes were assessed via action map examination. Finally, the crucial affected genes were determined and discussed.

Results

Since UV radiation induced gene expression change in many genes, the meandiff plot analysis was done to find the genes which were dysregulated significantly. As it is depicted in Figure 1, the |LogFC| value for many genes is above 2. It means that a wide spectrum of genes is dysregulated significantly. The gene display name of 150 DEGs among the 250 searched significant DEGs in "Expression Atlas" were identified. To find the most affected genes, the top dysregulated genes are shown in Figure 2. SOCS1 as the top up-regulated gene and TAF5L as the top down-regulated individuals were identified.

Among the 150 queried DEGs, 133 individuals were recognized by the STRING database. The network including 52 isolated genes, 3 paired units, two triples, and a main connected component was constructed. The main connected component included 69 nodes which were connected with 121 edges. Nodes of the main connected component were laid out by degree value (see Figure 3). Since the degree value of the nodes were different, the 69 elements of the main connected component were discriminated by degree value (see Figure 4). As it is shown in Figure 4, 49 nodes are characterized by a degree

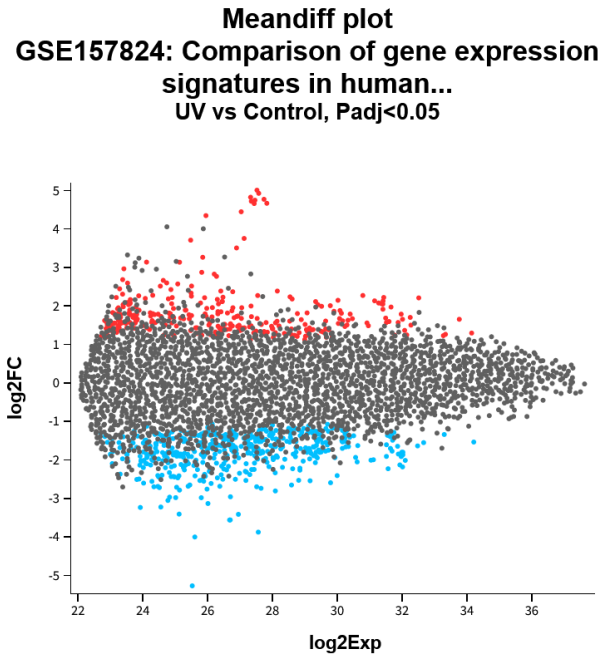

Figure 1. Meandiff Plot of Gene Expression Changes of the UV-Irradiated Human Primary Melanocyte Cells Versus Control Cells.

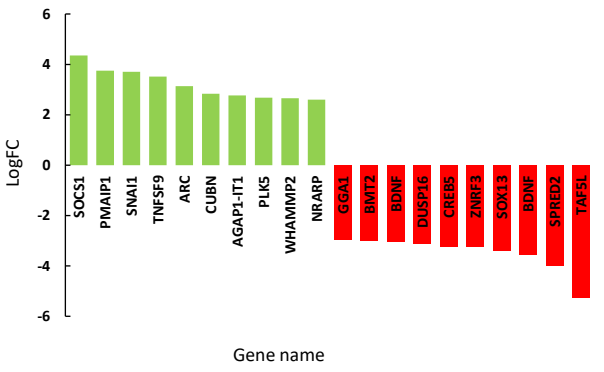

Figure 2. Expression Changes of 10 Top Up- and Down-regulated Genes for the UV-Irradiated Human Primary Melanocyte Cells Versus Control Cells.

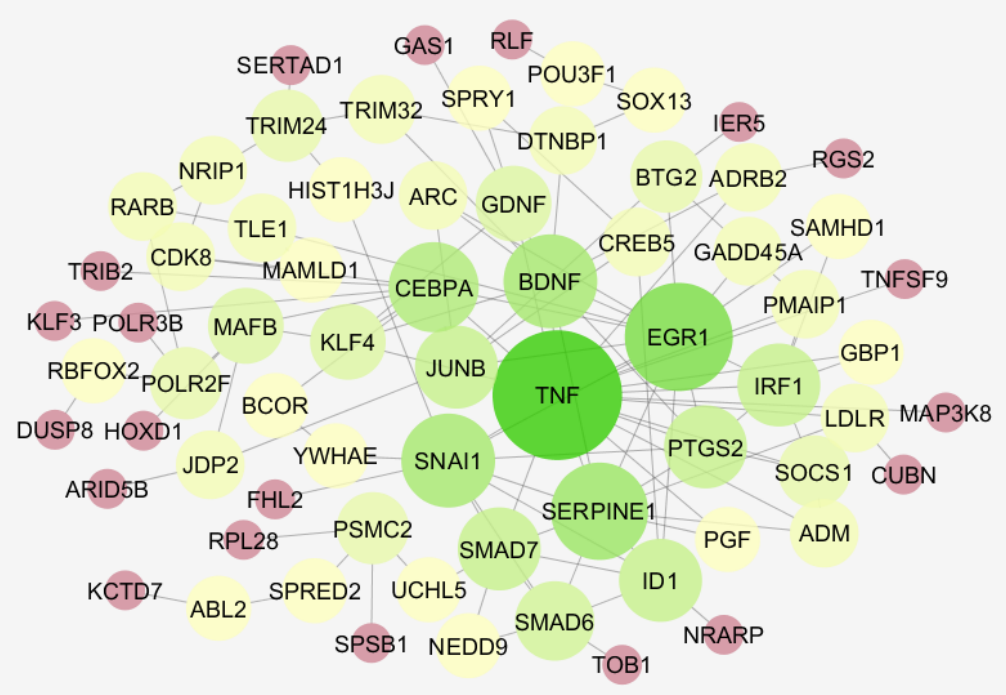

Figure 3. Main Connected Component of the PPI Network of the UV-Irradiated Human Primary Melanocyte Cells Versus Control Cells. The DEGs are laid out based on degree value. Bigger size and red to green refer to increases in degree value.

value of 1-3 and represent a discriminated pattern relative to the other 20 nodes. These 20 top nodes (based on degree value) were pointed as hub genes.

The top dysregulated genes and the hub nodes were assessed by action map (see Figure 5). There were 3 common genes between the hubs and the top dysregulated individuals including brain-derived neurotrophic factor (BDNF), SNAI1, and SOCS1. Among the 37 queried DEGs, 36 individuals were recognized by the CluePedia application of Cytoscape. Among the 36 queried genes, 16 SEGs were connected with inhibition, activation, and expression relationships.

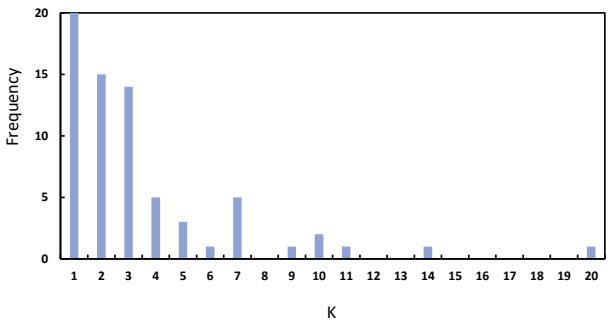

Figure 4. Main Connected Component of the PPI Network of the UV-Irradiated Human Primary Melanocyte Cells Versus Control Cells. The DEGs are laid out based on degree value. Bigger size and red to green refer to increases in degree value.

Discussion

Due to the sun's UV radiation, the assessment of gene expression change after UV radiation is an attractive subject for scientists. Kupper et al investigated the role of UV radiation in the expression change of the interleukin 1 gene in cultured human keratinocytes.[15] Today, the application of high throughput methods to explore gene set expression changes is a common trend. Koch-Paiz et al. published data about using functional genomics to analyze human cell response to UV radiation.[16] In the present study, the gene expression profiles of the human cells were investigated via network analysis. As it is shown in Figure 1, many genes were dysregulated after UV radiation. Based on data from Figure 1, there were many significant DEGs which discriminate the treated cells from control individuals.

SOCS1, PMAIP1, SNAI1, TNFSF9, ARC, CUBN, AGAP1-IT1, PLK5, WHAMMP2, and NRARP were the

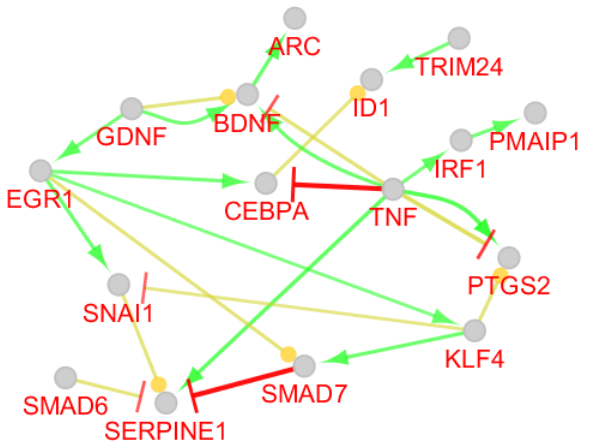

Figure 5. Action MAP of the Top Dysregulated Genes and the Hub Nodes. Green, red, and yellow refer to activation, inhibition, and expression actions.

top up-regulated genes which are presented in Figure 2, while GGA1, BMT2, BDNF, DUSP16, CREB5, ZNRF3, SOX13, BDNF, SPRED2, and TAF5L were the top down-regulated individuals. The expression of SOCS1 (the top up-regulated gene) and TAF5L (the top down-regulated gene) changed about 20 fold and 40 fold respectively. Gene expression change is an important tool to analyze the molecular function of a disease.[17] It seems that the role of the 20 introduced up- and down-regulated genes in response to UV radiation is a significant event. However, more assessments such as network analysis can be used to screen the introduced up- and down-regulated genes.

Previous investigations have shown that the hub genes control prominent processes in diseases.[18] As it is shown in Figures 3 and 4, there are several hub genes (including TNF, EGR1, SERPINE1, BDNF, SNAI1, CEBPA, ID1, IRF1, JUNB, PTGS2, SMAD7, SMAD6, GDNF, KLF4, MAFB, BTG2, POLR2F, PSMC2, SOCS1, and TRIM24) which control the constructed network. The top 5 hub genes, including TNF, EGR1, SERPINE1, BDNF, and SNAI1, are characterized by 20-, 14-, 11-, 10-, and 10-degree values respectively.

Due to the importance of two parameters of fold change and degree value, the common genes between the hubs and the top dysregulated genes are the powerful genes which are targeted by UV radiation. BDNF, SNAI1, and SOCS1 appeared as the common genes between the hubs and the top dysregulated genes.

Mapping the gene regulatory network which studied the targeted genes is applied widely in system biology.[19] Regulatory relationships between the hubs and the top dysregulated genes are presented in Figure 5. BDNF and SNAI1 among the common three genes participated in this map. BDNF is activated by GDNF and TNF while GDNF and TNF up-regulate and down-regulate BDNF respectively. The activation of ARC by BDNF is illustrated in Figure 5. EGR1as an activator activates SNAI1 and KLF4 The up-regulation of SERPINE1 by SNAI1 is presented in Figure 5. The complex regulatory relationship between the elements of the action map is formed.

BDNF as a part of neurotrophins might play a critical role in "developmental programming"; this is the concept that refers to fetal life as the origin of adult disease due to nutritional and hormonal status during pregnancy. The experimental and epidemiological findings support this concept, so the mentioned events may interfere with metabolism control.[20] The down-regulation of BDNF is reported for several diseases.[21,22] Son et al have shown that the level of BDNF decreases significantly in irradiated samples with 10Gy radiation.[23] The mentioned findings are consistent with the results of our investigation.

There are pieces of evidence that snail family transcriptional repressor 1 (SNAI1) plays a crucial role in tumor invasion.[24] The role of SNAI1 in glioma progression and promotion of gastric cancer metastasis has been reported by researchers.[25,26] The discussed roles of SNAI1 correspond to the findings of our assessment.

Conclusion

It can be concluded that BDNF and SNAI1 are the two critical targeted genes by UV radiation. Considerable down-regulation of BDNF and up-regulation of SNAI1 are accompanied by gross alteration in cell functions. Since these two dysregulated genes are involved in complex regulatory relationships with the other crucial genes, it can be expressed that BDNF and SNAI1 may control a large number of genes which are dysregulated after radiation. Experimental investigations to validate the findings are suggested.

Conflict of Interests

The authors declare that they have no conflict of interest.

Ethical Considerations

This project was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (ethical code: IR.SBMU.RETECH.REC1401.484).

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