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Activation of CDKN2A and Up-regulation of PETN Are Key Features of Sunscreen Usage Versus Light Irradiation

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Abstract

Introduction: Sunscreen plays an unexpected role in protecting the skin against the harmful effects of sunlight. Skin protection against UV rays is highlighted as the main property of sunscreen. The present study investigated the core part of the molecular mechanism of skin protection by sunscreen.

Methods: Gene expression changes of the irradiated human skin with sunlight in the presence of sunscreen were mined from the Gene Expression Omnibus (GEO) database and analyzed to find the significantly differentially expressed genes (DEGs). The central DEGs were identified via the protein-protein interaction (PPI) network and searched in skin cancer-related genes in the GeneCards database to find the critical dysregulated genes. The gene expression change of the critical genes was investigated in the Cancer Genome Atlas (TCGA) database.

Results: A total of 377 DEGs were determined as the targeted genes. HSPA4, PTEN, CDC42, ERBB2, APP, CDKN2A, PRKACA, PECAM1, and SMAD3 were identified as the critical dysregulated genes. ERBB2, SMAD3, and PRKACA were pointed out as the skin cancer-related genes.

Conclusion: In conclusion, the up-regulation of PETN and the activation of CDKN2A were highlighted as the major induced molecular events by sunscreen, which play a role in skin protection.

Keywords: Sunlight; Sunscreen; Gene expression; Skin; Cancer.

Introduction

Sunlight includes infrared radiation (IR) (700 nm to 1 mm), visible light (400 to 700 nm), and ultraviolet (UV) (100-400 nm). On the basis of biological effects, ultraviolet radiation is classified as UV-C (200-290 nm), UV-B (290-320 nm), and UV-A (320-40 0nm).[1] Vitamin D synthesis via sunshine is a well-known biological effect of sunlight. In this process, 7-dehydrocholesterol in the skin under the effect of UV-B converts to pre-vitamin D3, which isomerizes to vitamin D3.[2] The presence of serotonin in human cutaneous tissue refers to the function of the machinery of the serotonergic system in the skin. Investigations have shown the presence of serotonin transporters in human keratinocytes. In an experiment, serum serotonin levels were higher in individuals who received light via the skin relative to the controls. Results confirmed a "cutaneous pathway" for the elevation of serotonin levels.[3] The adverse effects of

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sunlight, such as inducing the malignant conversion of skin cells and overpowering the human immune system's ability to competently sense and attack malignant cells, are highlighted in the literature.[4] To protect the skin against the harmful effects of sunlight, the appeal for sunscreen has increased significantly. Sunscreen products contain active ingredients as UV-filters which protect the skin from UV rays.[5] Investigations have demonstrated that high-energy visible light, including blue light, has injurious effects such as DNA damage, photoaging, erythema, and pigmentary changes, and it triggers oxidation reactions in human skin cells. Since sunscreens are formulated against UV radiation, investigations to introduce the developed sunscreen versus solar radiation have attracted the attention of researchers and companies.[6] Gene expression analysis is a suitable method for studying the molecular events associated with skin function. Oxidative stress, different signaling pathways, and extracellular matrix changes in response to light and UV exposure in the human skin are studied via gene expression analysis.[7,8] The association between bioinformatics and gene expression analysis has caused experts to detect the core of molecular mechanisms of biological events. Skin response to the erbium: yttrium-aluminum garnet laser and NB-UVB showed that RPSA, GAPDH, TPT1, DCTN2, HSPB1, PDIA3, SMC3, ARF3, EIF5B, SMARCB1, and LAPTM5 appeared as critical genes. Cancer promotion and prevention, inflammation, apoptosis, cell proliferation, and cell cycle were highlighted as the affected processes.[9,10] In the present study, gene expression analysis via bioinformatics tools was administered to find the response of the human skin against sunlight in the presence of sunscreen. Data were mined from related databases and evaluated via network analysis and calculation methods.

Methods

Data Collection and Pre-evaluation

Six gene expression profiles of human focal skin areas exposed to 100 J/m^2 of solar-simulated radiation in the presence of sunscreen of sun protection factor (SPF) 15 (GSM549036-41 from GSE22083) in comparison with six profiles of the control individuals (the samples without the prior application of sunscreen and radiation exposure) (GSM549060-5 from GSE22083) were mined from the GEO database. Data were assessed via GEO2R software to find the significant differentially expressed genes (DEGs). The significant DEGs were identified based on p-adjusted < 0.05 and (fold change) > 1.5. Data were cleaned by removing the repeated ones and the uncharacterized individuals. The separation of samples was evaluated via the Uniform Manifold Approximation and Projection (UMAP) plot.

Protein-Protein Interaction Network Analysis

The significant DEGs were included in a protein-protein interaction (PPI) network via the "Protein query" of the STRING database using Cytoscape software v.3.10.1. To reduce the number of isolated DEGs, a confidence score = 0.2 was applied. The network was analyzed by the "Network Analyzer" application of Cytoscape software to explore the central nodes. A degree cutoff = (mean + 2(standard deviation) was calculated to find the hubs. The top 5% of nodes based on betweenness centrality were selected as bottlenecks. The common hubs and bottlenecks were selected as the hub-bottleneck genes. The queried DEGs were assessed via the directed PPI network using the CluePedia plugin of Cytoscape software to screen the genes. The network was created by activation, inhibition, and expression actions. To avoid complexity, other actions like binding, reaction, and catalysis were not considered to form the directed network.

GeneCards Assessment

"Skin cancer" was searched in the GeneCards database, and 4,575 genes were mined. The genes were grouped based on the GeneCards Inferred Functionality Score (GIFts) value using the Sturgess equation (1 + 3.3log(N)); N is the number of data. The top-ranked group of genes was selected as the skin cancer-related genes. The critical central genes were searched among the skin cancer-related genes.

The Cancer Genome Atlas (TCGA) Database Analysis

The expression change of the key genes in skin cancer was mined from The Cancer Genome Atlas (TCGA) database.

Results

A total of 2699 significant DEGs among 19 516 dysregulated individuals were mined. After cleaning, 377 DEGs were pointed out for further analysis. UMAP plot visualization demonstrated that there were differences between the sun-protected samples and the controls (see Figure 1). Among 377 queried DEGs, 365 individuals were recognized by the "Protein query" of the STRING database. The undirected PPI network, including a main connected component of 365 nodes and 2422 edges, plus an isolated one, was constructed by Cytoscape software. A "Confidence score" = 0.2 was applied to maximize connections between the interacted genes. A degree of 40 was calculated as a cutoff value to determine the hub nodes. PTEN, HSPA4, ERBB2, CDC42, H4C6, CDKN2A, APP, SMAD3, PRKACA, APOE, PECAM1, LYN, PTPN11, and FYN were introduced as the hub genes. Eighteen genes including HSPA4, PTEN, H4C6, CDC42, ERBB2, APP, CDKN2A, PRKACA, PECAM1, SMAD3, APOE, OBSL1, POLR2C, JUP, PSMG1, BCLAF1, KMT2A, and FZR1 were identified as the bottleneck nodes. HSPA4, PTEN, H4C6, CDC42, ERBB2, APP, CDKN2A, PRKACA, PECAM1, SMAD3, and APOE were highlighted as hub-bottleneck

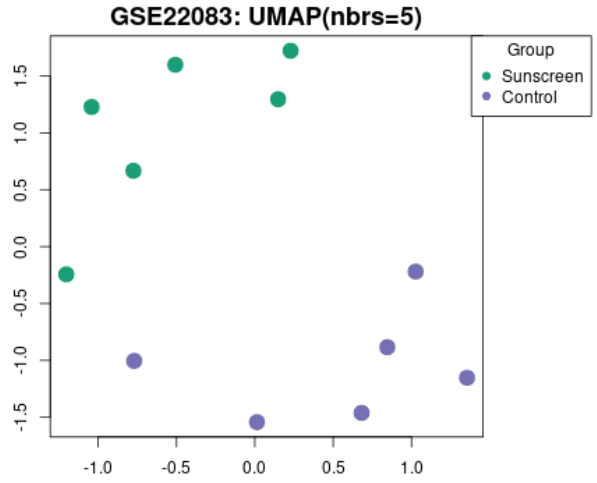

Figure 1. The UMAP plot of the gene expression profile analysis of the sun-protected samples which were irradiated by 100J/m² of solar-simulated radiation versus the controls (without radiation and sun protection)

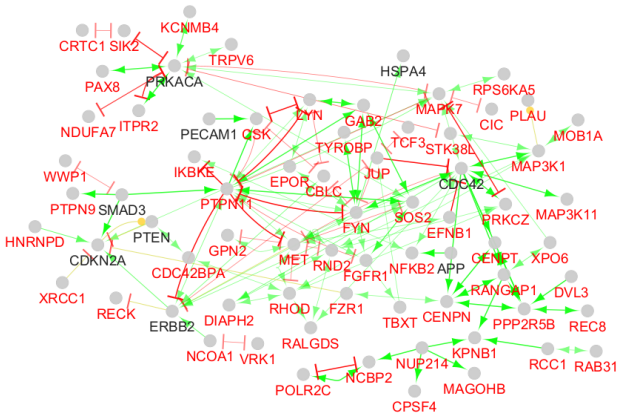

Figure 2. The Main Connected Component of the Action Map of the Queried DEGs. The hub-bottleneck nodes are labeled in black. Green, red, and yellow refer to activation, inhibition, and expression, respectively

DEGs. The queried DEGs were included in a directed interactome. The 375 queried DEGs were organized as 298 isolated individuals, six paired genes, and a main connected component of 71 nodes and 129 edges. The main connected component is presented in Figure 2. As depicted in Figure 2, APOE and H4C6 are not included in the main connected component. Both APOE and H4C6 were ignored for further analysis. As shown in Figure 3, nine critical hub-bottlenecks are included in a complex of 14 genes. It means that at least five nodes are required to form a sub-network, including the critical DEGs. A closed relationship between the critical genes refers to their significant role in the network.

The genes from the GeneCards database were classified into 14 groups based on GIFtS values with an interval = 5. As shown in Figure 4, the top-ranked group includes 82 genes. The critical hub-bottlenecks were searched in the skin cancer-related genes from the GeneCards database (see Table 1). The analysis revealed that EBBR2, smad3, and PRKACA were included in the top-ranked group of skin cancer-related genes. The rank of these genes based on the GIFtS value was below 82 (see Table 1). The expression changes of EBBR2, smad3, and PRKACA in skin cancer have been investigated in the TCGA database (see Figure 5).

Discussion

It is estimated that the universal sunscreen marketplace will reach $24.4 billion by 2029. This noteworthy value of the sunscreen market refers to the knowledge about the harmful effects of sunlight. The sunscreen industry is a growing business via developing and discovering new photoprotective ingredients.[11] It is expected that sunscreen usage maintains human the skin as normal or with minimal changes. This belief implies minor gene expression changes in the skin after exposure to sunlight in the presence of sunscreen. As mentioned in the result section, the expression of 377 genes was changed at least 1.5-fold in the skin after sunlight exposure in the presence of sunscreen. The beneficial effects of a broad-spectrum sunscreen to protect the skin from sunlight have been investigated. It is reported that sunscreen pre-application retracted or meaningfully reduced the injurious effects of UV-A radiation, such as dysregulation of catalase, matrix metalloproteinase-1, heme oxygenase-1, glutathione peroxidase, and superoxide dismutase-2 genes in the skin.[12] In this study, the up-regulation of PRKACA and SMAD3 and the down-regulation of ERBB2, as the vital skin cancer-related genes, were pointed out as the effect of sunlight exposure on the human skin in the presence of sunscreen.

Erb-B2 receptor tyrosine kinase 2 (ERBB2) is a down-regulated gene with potent relevance to skin cancer (see Table 1). Investigations indicate that the up-regulation of ERBB2 in mice is accompanied by impulsive tumor progression. It is suggested that ERBB2 inhibition is a possible method for suppressing tumor progression. The activation of ERBB2 by UV-B radiation is associated with skin tumorigenesis.[13] As depicted in Figure 5, ERBB2 is up-regulated in skin cutaneous melanoma (however, gene expression value is measured for one normal sample). It is reported that ERBB1/2/3 may be suitable early prognostic markers or efficient drug targets in cutaneous melanoma.[14] The downregulation of ERBB2 relative to the control in the presence of sunscreen cannot be attributed to the shielding effect of sunscreen. Two possible explanations for the down-regulation of ERBB2 are as follows: The infiltrated part of sunlight or the chemical properties of the ingredients of sunscreen cause ERBB2 downregulation.

The second high-impact dysregulated gene is small mothers against decapentaplegic homolog 3 (SMAD3). This gene is overexpressed in the presence of sunscreen under the effect of sunlight exposure. Skin fibrosis is a characteristic of systemic sclerosis and the TGF-β1/Smad3 pathway is pointed out as a significant part

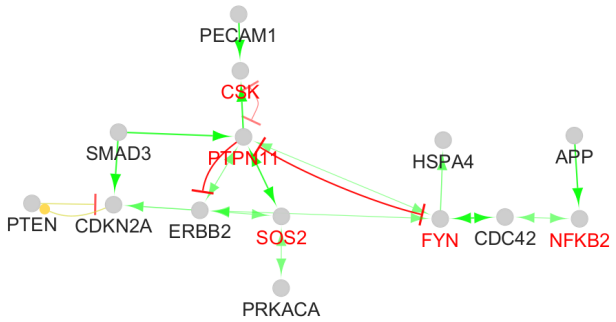

Figure 3. A sub-network of Figure 2, including the hub-bottlenecks and the minimum number of neighbors which are required for the connection between them

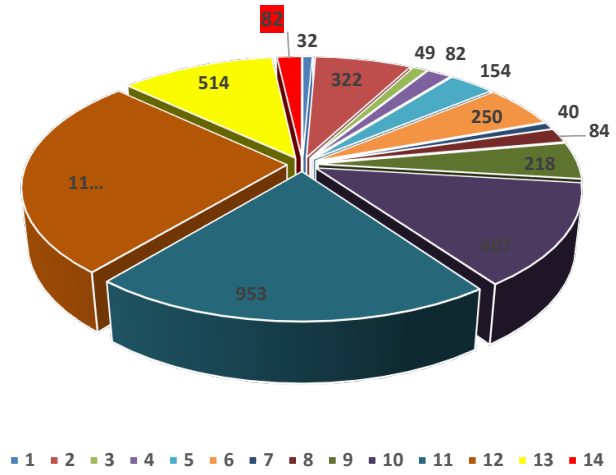

Figure 4. Fourteen groups of Skin Cancer-Related Genes From the GeneCards Database Based on GIFtS Value With An Interval = 5. The label of the top group, including 82 genes, is highlighted in red. As depicted at the bottom of the diagram, the groups are arranged clockwise based on the increment of GIFts from a group of 32 members to the top group of 82 individuals

of fibrosis. An investigation demonstrated that the inhibition of the TGF-β1/Smad3 pathway can suppress fibrosis.[15] The dysregulation of the TGF-β1/Smad3 pathway in atopic dermatitis (a skin with an obstinate and recurrent inflammatory condition) is reported in the literature. An investigation showed that both protein expression and phosphorylation of SMAD3 decreased in the skin of patients. This gene expression alteration was accompanied by a 2.5-fold upregulation of TGF-β1 mRNA expression in the lesional atopic dermatitis skin.[16] The downregulation of SMAD3 in cutaneous melanoma is presented in Figure 5. The upregulation of SMAD3 under the effect of sunscreen confirms its positive role in skin protection.

The last critical affected gene is the protein kinase A catalytic subunit (PRKACA). This gene is upregulated in the presence of sunscreen. An examination demonstrated that decreased invasion ability and tumor cell proliferation, together with impaired cell migration in skin cutaneous melanoma, are accompanied by the downregulation of PRKACA.[17] However, there is evidence about the

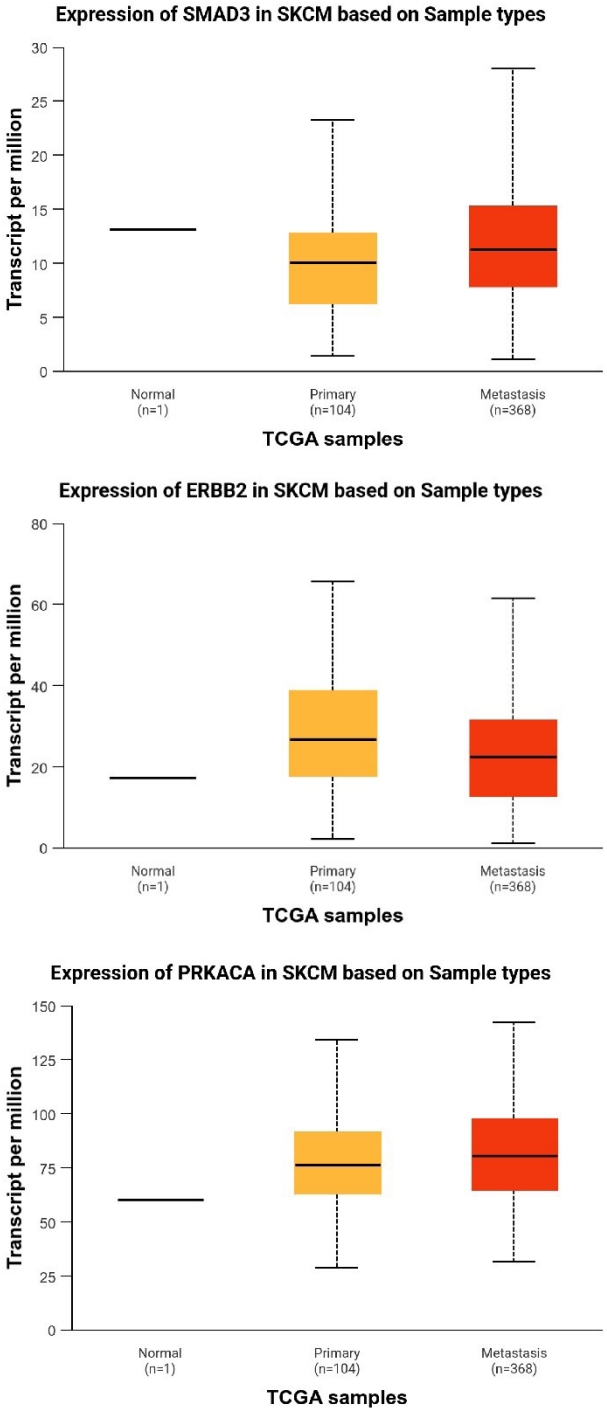

Figure 5. Gene Expression Value of Skin Cutaneous Melanoma From the TCGA Database. Medians of data are comparable

beneficial effects of organic and inorganic sunscreen on skin care, allergic reactions, and skin irritation, which are attributed to systemic absorption of chemical sunscreen.[18] As depicted in Figure 3, cyclin-dependent kinase inhibitor 2A (CDKN2A) plays a critical role as a linker between ERBB2 and SMAD3. An investigation has demonstrated that the inactivation of this tumor suppressor gene is associated with melanoma progression.[19] CDKN2A is upregulated in the presence of sunscreen. The activation

Table 1. Nine Critical Hub-Bottlenecks and Their Characteristics in GeneCards

No.	Gene	Degree	Betweenness	Rank among the skin cancer-related genes in GeneCards database	GIFtS value	Regulation
1	PTEN	97	0.083	3905	26	
2	HSPA4	93	0.095	1603	56	
3	ERBB2	80	0.063	4	68	Down
4	CDC42	79	0.072	234	63	
5	CDKN2A	75	0.052	115	64	
6	APP	64	0.056	271	63	
7	SMAD3	57	0.025	26	67	Up
8	PRKACA	52	0.038	72	66	Up
9	PECAM1	50	0.026	2025	54	

Note: Genes are ranked based on degree value.

of CDKN2A is a therapeutic strategy for controlling melanoma.[19] As illustrated in Figure 3, both SMAD3 and ERBB2 activate CDKN2A. It is reported that the inactivation of phosphatase and tensin homolog (PTEN) (as a tumor suppressor) plays a significant role in melanoma development.[20] The up-regulation of PTEN by CDKN2A and the negative feedback control of CDKN2 by PTEN are highlighted in Figure 3. The expression of PTEN increases more than 2-fold in the presence of sunscreen.

Conclusion

In conclusion, nine critical genes in the human skin were identified as the responsible genes which are affected by sunscreen. The activation of CDKN2A and the up-regulation of PETN, the two tumor suppressor genes in the human skin after the usage of sunscreen, are key features of skin protection against sunlight exposure by sunscreen. This effect can be attributed to the chemical part of sunscreen. The results can be considered for clinical trial investigations to show functional changes in the treated samples. The finding clears the effect of sunscreen on the human skin and provides new windows to develop advanced products related to skin care.

Authors' Contribution

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Project administration: Vahid Mansouri, Babak Arjmand, Farideh Razi.
Resources: Babak Arjmand.
Software: Zahra Razzaghi, Mostafa Rezaei-Tavirani.
Supervision: Mostafa Rezaei-Tavirani, Reza M Robati.
Validation: Reza M Robati, Fatemeh Bandarian.
Visualization: Zahra Razzaghi.
Writing–original draft: Mostafa Rezaei-Tavirani, Mitra Rezaei, Farideh Razi.
Writing–review & editing: Mostafa Rezaei-Tavirani, Vahid Mansouri, Hamideh Moravvej Farshi.

Ethical Approval

This project was approved by IR.SBMU.LASER.REC.1403.029 ethical code.

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