



Assessment of the Connection Between Blue Light and Anxiety: A System Biology Approach

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Abstract

Introduction: Blue light with therapeutic properties is the high-energy part of the visible light spectrum with various biological effects. The main aim of this study is to elucidate blue light exposure and anxiety via protein-protein interaction (PPI) network analysis.

Methods: Anxiety-related genes were extracted from the GeneCards database and assessed via gene clustering and PPI network analysis to identify the hub genes. Blue light-targeted genes in 3D skin were revealed from the Gene Expression Omnibus (GEO) database, and the significant differentially expressed genes (DEGs) were identified. The significant DEGs were searched among the hub genes. The common significant DEGs and the hub genes, together with their first neighbors, were determined and discussed.

Results: A total number of 56 significant DEGs were pointed out as the targets of blue light. Among the 10696 anxiety-related genes, 772 individuals were selected as top genes and evaluated via PPI network analysis. IL6 appeared as the common gene between the significant DEGs and the 55 hub genes of the PPI network. Twelve genes were pointed out as the first neighbors of IL6. GIFTs analysis showed that IL6, H3-5, PFN1, DEFB103A, HMGB1, and RPLP1 were genes related to anxiety and were targeted by blue light.

Conclusion: In conclusion, six targeted genes by blue light were related to anxiety. Downregulation of IL6 appeared as a factor in improving anxiety. However, the first neighbors of IL6 were not consistent with the role of IL6 in the decrement of anxiety.

Keywords: Blue light; Anxiety; Network analysis; Gene expression; Skin.



Introduction

The visible light spectrum from sunlight which reaches the earth surface includes a wavelength of 400-700 nm. Photoreceptive chromophores of visible light can absorb light. Biomolecules such as opsin, heme, and melanin are photoreceptors.¹ Blue light as the high energy part of the visible light spectrum is characterized by a range of 380-495 nm waves.² Since blue light can penetrate deeply into the skin, it has attracted the attention of experts in the field of dermatology. It is highlighted that blue light is involved in the progression of hyperpigmentation and photoaging of the skin. However, the beneficial effect of blue light on eczema, psoriasis, actinic keratosis, acne, and cutaneous malignancies has caused it to be referred to as a therapeutic tool.³ In Chen and colleagues' examination, 30 people with behavioral and psychological symptoms of dementia (which are often the associated symptoms with dementia) were exposed to blue-enriched light in comparison with

30 individuals who received the conventional light. Their findings demonstrated that blue-enriched light exposure was accompanied by beneficial effects.⁴ Raikes and colleagues' investigation showed that blue light therapy improved daytime exhaustion and sleepiness and sleep disruption in the patient with mild traumatic brain injury. An improvement in depression severity was also highlighted.⁵

Gene expression analysis as a suitable tool has been used to detect the molecular mechanism of many diseases and biological events. Hamzeloo-Moghadam et al have highlighted EGR1 as a crucial targeted gene by blue light in human keratinocytes.⁶ On the other hand, protein-protein interaction (PPI) network analysis is an appropriate method for studying the relationship between a set of genes. In this approach, the queried genes are connected with edges to form an interactome. Each member of the constructed network has its topological property. The

nodes of the network with a high degree value are known as the hub nodes. The hub gene plays a critical role in the network-related functions.^{7,8} Basar et al have published a document about the relationship between depression and stress via PPI network analysis. They have introduced the top 10 common genes including CREB1, APP, TP53, ESR1, AKT1, CTNNB1, SIRT1, HSPA4, ABL1, and AR for both depression and stress.⁹ In the present study, the gene expression profiles of 3D skin samples in the presence of blue light versus the control are downloaded from the GEO database. The anxiety-related genes are extracted from GeneCards and assessed via gene clustering and PPI network analysis. The significant DEGs of the 3D skin samples were searched in the hub genes of the anxiety-related hub genes to find the critical targeted genes by blue light that are connected to anxiety. The findings open a new window about the non-visual effects of blue light on the psychological functions of the body.

Methods

Data Collection and Pre-evaluation

Data of the GSE190106 were downloaded from the GEO database (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE190106>). The gene expression profiles of 3D skin samples, exposed to an LED blue wavelength of digital light for one hour and repeated sequentially over four days in comparison with the control samples, were extracted from GSE190106. More details of the experiment are described in Lago and colleagues' publication.¹⁰ Data were assessed using the GEO2R program. The Uniform Manifold Approximation and Projection (UMAP) plot, box plot, and Venn diagram were applied to visualize the findings. To find the effect of the blue light on anxiety, "anxiety" was searched in the GeneCards (<https://www.genecards.org/Search/Keyword?queryString=anxiety&pageSize=25000&startPage=0&sort=Gifts&sortDir=Descending>). The related genes to the anxiety were downloaded and classified in groups with the GIFTS interval of 10. The top group based on GIFTS was selected for analysis via PPI network analysis.

PPI Network Analysis

The member of the top group of anxiety-related genes was included in the "Protein query" of the STRING database via Cytoscape software.¹¹ The undirected PPI network was constructed, with a confidence score=0.9. The PPI network was analyzed via the "Network Analyzer" application of Cytoscape.¹² The hub nodes were identified based on a degree value cutoff (mean+2(standard deviation)). The related significant DEGs of blue light analysis were searched among the introduced hub nodes. The common significant DEGs and hub nodes which are related to anxiety were pointed out as the targeted genes by blue light. To find the first neighbors of the common genes, the significant DEGs were included

in a PPI network. The common DEGs and their first neighbors which are involved in anxiety were selected as the targets of blue light. Due to an increase in the number of connections between the queried DEGs, a confidence score of 0.1 was considered. To find the possible connection between the first neighbors of the common DEGs and anxiety, the GIFTS and rank of these genes were determined in GeneCards.

Results

As depicted in Figure 1, the radiated samples are separated completely from the control individual. The Four radiated samples are located on the left-right side of the UMAP plot. Each sample is compared with three neighbors (nbrs=3). The comparability of the samples is demonstrated in Figure 2. The gene expression profiles of the samples are median-centric. A total number of 56 significant DEGs among 13,141 dysregulated genes were pointed out for more analysis (see Figure 3). A total

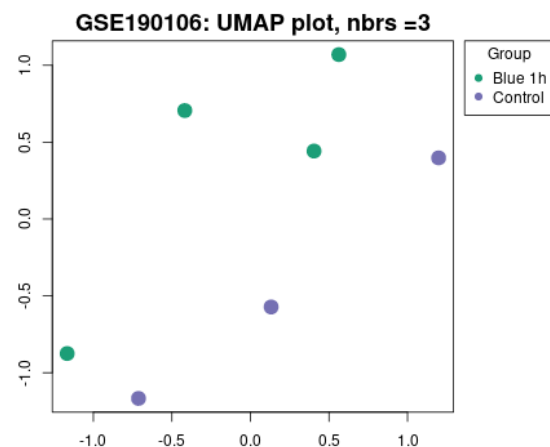


Figure 1. UMAP plot of the Gene Expression Profiles of the Exposed Samples to Blue Light Versus the Control Individuals

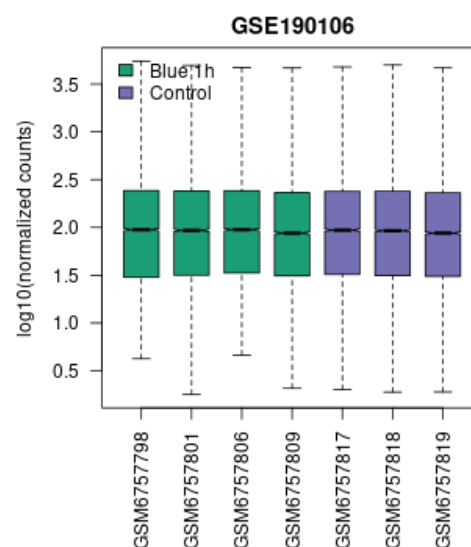
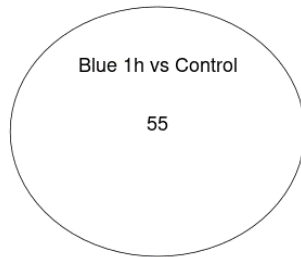


Figure 2. Box Plot of the Gene Expression Profiles of the Exposed Samples to Blue Light Versus the Control Individuals

number of 10696 genes related to anxiety were extracted from the GeneCards database. The maximum value of GIFtS was 69. Seven groups of genes based on GIFtS value with an interval of 10 were provided. The frequency of genes in the groups is shown in Figure 4.

A total number of 772 high-score genes of the top group of anxiety-related genes formed a PPI network. A degree value cutoff set at 242 was considered to determine the hub nodes. Analysis revealed that there

GSE190106: DESeq2, Padj<0.05



Total: 13141

Figure 3. Venn Diagram of the Gene Expression Profiles of the Exposed Samples to Blue Light Versus the Control Individuals. The 55 significant DEGs versus 13 141 dysregulated genes are highlighted

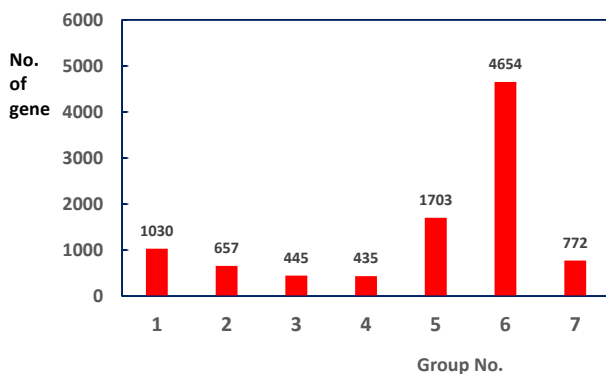


Figure 4. Grouping of 10696 Anxiety-Related Genes From the GeneCards Database Into Seven Groups Based on a GIFtS Interval of 10 (From 1-70)

were 55 hub nodes. The assessment showed that IL6 is a common gene between the significant DEGs of blue light analysis and the hub genes of anxiety. IL6 is characterized by GIFtS=64 and rank=117 in GeneCards. The PPI network of the significant DEGs is shown in Figure 5. IL6 and its first neighbors were extracted from the PPI network (see Figure 6). As depicted in Figure 6, IL6, H3-5, PFN1, NLRP10, DRAM1, MT1G, BEFB4B, DEFB103A, SPRR2B, SPRR2A, KRT15, RPLP1, and HMGB1 were considered as the targeted genes by blue light which are related to anxiety. The GIFtS and rank of the first neighbors of IL6 were identified in GeneCards. Findings indicated that NLRP10, DRAM1, SPRR2A, SPRR2B, KRT15, BEFB4B, and MT1G were not related to anxiety and were ignored for more analysis. Characters of IL6, H3-5, PFN1, DEFB103A, HMGB1, and RPLP1 as the related genes to anxiety are demonstrated in Table 1.

Discussion

IL6 is an inflammatory cytokine that plays a role in several biological processes. Various cell lineages such as hematopoietic cells, stromal cells, muscle cells, or epithelial cells produce IL6.¹³ Involvement in bone metabolism and embryonic development, hematopoiesis, immune response, and inflammation are attributed to IL6. The significant role of immune and non-immune cells, tumor necrosis factor alpha (TNF- α), IL1B, transcription nuclear factor-kappa B (NF- κ B), IL6, and signal transducer and activator of transcription 3 (STAT3) is highlighted in inflammation. The hyper-activation of NF- κ B and STAT3 leads to the activation of IL6 which triggers a positive feedback loop (the IL6 amplifier) to activate NF- κ B. The IL6 amplifier plays a crucial role in senescence, infection, stress, smoking, obesity, and injury promotion.¹⁴ Investigations demonstrated that the IL6 level is elevated in anxiety. It is reported that a vigorous increase in IL-6 is associated with stress and it can propagate IL1-mediated inflammation and anxiety.^{15,16} In our analysis, IL6 is

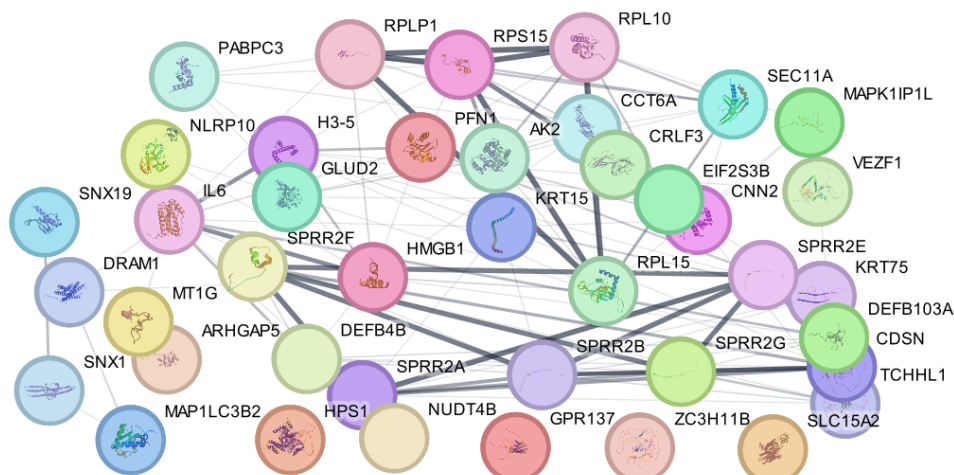


Figure 5. PPI Network of the Significant DEGs of Blue Light Analysis. The nodes are connected via undirected edges

downregulated after blue light. This effect of blue light can be considered as the psychological aspect of blue light. The possible role of blue light in the treatment of bulimia, premenstrual depression, and anxiety is demonstrated in the literature. It is emphasized that blue light is a strong synchronizing mediator for the circadian system via the suprachiasmatic nuclei of the hypothalamus. The role of blue light in cognitive performance during the day has been investigated and reported.¹⁷

As depicted in Table 1, all first neighbors of IL6 have been upregulated. HMGB1 is the first neighbor characterized by a GIFtS=439. This gene belongs to the top group of the relevant genes to anxiety. Based on the literature, the upregulation of HMGB1 expression in the medial prefrontal cortex is accompanied by the onset of anxiety.¹⁸ The upregulation of IL6 in the presence of HMGB1 in the cultured nasal epithelial cells is reported by Shimizu et al.¹⁹ PFN1 is another upregulated first neighbor of IL6. The participation of PFN1 in biological processes such as cell growth, adhesion, division, motility, and cell morphology maintenance has been investigated and reported. The expression of PFN1 is increased after the long-term administration of stresses.²⁰ PFN1 plays a role in cell protection from DNA damage via the regulation of DNA repair machinery and damage response.²¹ As depicted in Murk and colleagues' publication, PFN1 loss disturbs brain development associated with cortex and cerebellum malformation.²² The involvement of PFN1 in hypertension, development of atherosclerosis, and diabetes is highlighted by Yu et al. It is emphasized that

intermittent PFN1 encourages M2 microglial polarization and stops ischemic brain damage.²³

RPLP1 is the first neighbor of IL6 with a GIFtS=52. Exposure to chronic downfall stress induced progression anxiety and depression-like states in male mice. This condition was associated with several molecular changes in the brain. The upregulation of the RPL gene in the hypothalamus and its downregulation in the hippocampus were detected.²⁴ H3.5 histone is another gene that is tabulated in Table 1. As depicted in HUMAN PRTEIN ATLAS, the maximum value of H3-5 expression in the brain is nTPM=0.8 for the cerebral cortex. Its expression in other parts of the brain is not significant (by 0.1 nTPM) (<https://www.proteinatlas.org/ENSG00000188375-H3-5/brain>). TPM stands for "transcript per million". There is a document that the prefrontal cortex regulates anxiety in primates.²⁵ The last targeted gene by blue light which is related to anxiety is Defensin beta 103A. Defensins, including α -defensins, β -defensins, and θ -defensins, are cationic peptides with antiviral and antimicrobial properties. These peptides act as an immunomodulator and participate in many physiological processes.²⁶

Conclusion

In conclusion, gene expression analysis revealed that blue light targets at least six anxiety-related genes. It was pointed out that IL6 is a key gene in the onset and promotion of anxiety. It seems that the down-regulation of IL6 by blue light inhibits anxiety. Our evaluation demonstrated that the first neighbors of IL6, including HMGB1, PFN1, RPLP1, H3-5, and DEFB103A, are not consistent with the role of IL6 in suppressing anxiety. However, the noteworthy role of IL6 was confirmed via PPI network analysis. It can be suggested that an in vivo experiment can explore the important therapeutic role of IL6 versus anxiety.

Authors' Contribution

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Supervision: Mostafa Rezaei-Tavirani, Reza M Robati.

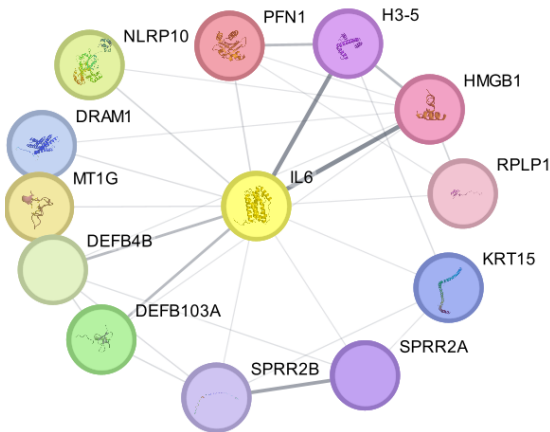


Figure 6. A Sub-network of IL6 and its First Neighbors

Table 1. GIFtS, Rank of IL6 and its First Neighbors (Anxiety-Related Genes) Found in GeneCards

No.	Gene	Description	GeneCards Rank	Gifts	Log (Fold Change)
1	IL6	Interleukine 6	117	64	-0.569
2	HMGB1	high mobility group box 1	439	62	3.042
3	PFN1	Profilin 1	1216	59	1.130
4	RPLP1	ribosomal protein lateral stalk subunit P1	5037	52	1.639
5	H3-5	H3.5 histone	7613	44	6.216
6	DEFB103A	Defensin beta 103A	8466	36	2.560

Validation: Babak Arjmand, Zahra Razzaghi.

Visualization: Mostafa Rezaei-Tavirani, Babak Arjmand.

Writing-original draft: Mostafa Rezaei-Tavirani, Babak Arjmand, Zahra Razzaghi, Reza M Robati.

Writing-review & editing: Mostafa Rezaei-Tavirani, Babak Arjmand, Zahra Razzaghi, Reza M Robati.

Competing Interests

None declared.

Ethical Approval

This project was approved by Shahid Beheshti University of Medical Sciences under IR.SBMU.LASER.REC.1403.027 ethical code.

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