Review

http://www.jcpjournal.org
pISSN 2288-3649 · eISSN 2288-3657
https://doi.org/10.15430/JCP.2022.27.4.199

JCP

A Genomic Approach to Identify the Different between Acute and Chronic UVB Exposures in the Causation of Inflammation and Cancer

JunPyo Han, Yujin Jang, Dong Yeop Shin, Jun Lee, Young Rok Seo*

Department of Life Science, Institute of Environmental Medicine for Green Chemistry, Dongguk University Biomedi Campus, Goyang, Korea

As a principal component of solar radiation, ultraviolet B (UVB) exposure can be harmful depending on the duration and intensity because the human body can easily be exposed to it. Many studies have demonstrated that UVB causes a series of inflammatory and other skin disorders. UVB has been classified as the Group 1 carcinogen by the International Agency for Research on Cancer. Diverse studies have focused on UVB exposure but the complex perspective of acute and chronic UVB exposure is still lacking. This review presents the differences between acute and chronic exposure to UVB and summarizes public information in terms of toxicogenomic characteristics. We also demonstrated the differences between adverse effects of acute and chronic UVB exposure on the skin system. From the published literatures, we compared the biological pathways predict of the adverse effects caused by each UVB exposure type. Furthermore, our review not only clarifies the differences in each UVB exposure network but also suggests major hub genes related to cellular mechanisms and diseases that are thought to be affected by acute and chronic UVB exposure.

Key Words Ultraviolet radiation, Carcinogens, Skin diseases, Toxicogenetics

INTRODUCTION

Ultraviolet radiation (UVR) can be the most dangerous part of sunlight; it can cause many diseases including cancer and inflammation [1,2]. UVR can have highly accessible special features for humans under occupational exposure or daily exposure [1]. The International Agency for Research on Cancer classified solar UVR as the Group 1 carcinogen [3]. Most people are continuously exposed to UVR in their lives [4,5]. Therefore, UVR exposure is a considerable and inseparable factor in human life and health care [6].

The UVR spectrum in the solar light comprises about 5% of UVB (280–315 nm) and 95% of UVA (315–400 nm), including very low amount of UVC (100–280 nm) [7]. Even though UVA has a larger portion than UVB, UVB has more powerful potency in the aspect of action spectroscopy because of its unique short wavelength [8]. As an alternative to exposure to solar light, the devices for disinfection or other purposes using UVR become popular [9] and can also be a risk factor. Though UVB has some positive effects and contributes to vitamin D synthesis, its danger and adverse effects are considered one of the health issues.

The skin is the first barrier of our bodies that protects against a multitude of external pathogens and environmental insults including UVB [10,11]. For this reason, most studies investigating UVB exposure have mainly focused on the skin systems [12]. Some studies also demonstrated the biological association between UVB-damaged skin and other organs. UVB cannot deeply penetrate the skin because of the presence of barriers such as epidermal melanin [13]. Therefore, understanding the biological pathways and defense mechanisms in the skin can help discover the significant factors contributing to the prevention and treatment of disorders caused by UVB exposure.

This review focuses on the differences between acute and chronic exposure to UVB in terms of the toxicogenomic and biological pathways. The text-mining and analyzing software based on scientific literature were performed to summarize

Received December 27, 2022, Accepted December 29, 2022
Correspondence to Young Rok Seo, E-mail: seoyr@dongguk.edu, https://orcid.org/0000-0002-4093-4073

and visualize the relationship in each biological pathway network associated with the skin exposed to acute or chronic UVB exposure. The different features of each network presented unique adverse effects of acute and chronic UVB exposure, separately, and the corresponding biological pathways with the comparative details.

ABRIDGED DEFINITION OF UVB EXPOSURE PERIOD

Before and after the World Health Organization (WHO) warned about UVB exposure to humans, studies have explored UVB exposure in various ways [1,14,15]. UVB exposure is divided into several exposure types, namely, acute, sub-acute, and chronic exposure. According to the United States Environmental Protection Agency terminology, acute exposure is described as one-time exposure or exposure to any toxicant within 24 hours. Chronic exposure means an adverse effect in which continuous or intermittent exposure to low doses of radiation over a long period of time. A delay between exposure and any potential health effect often occurs. There are intermittent statuses between acute and chronic exposures. However, the standard of UVB exposure types is ambiguous to compare certain differences between acute and chronic UVB exposure [16].

According to the UV index (UVI) provided by the WHO, UVI 7 refers to a high-risk exposure level [1,17]. When converted to the Minimal Erythema Dose (MED) used to measure UVR levels in studies, UVI 7 is approximately 1 MED condition in 30 minutes of exposure in the case of people who have untanned skin [18,19]. Chronic UVB exposure continuously occurs in not only occupational places but also daily life. In the case of acute exposure, UVI can exceed the level 10, following accepted damage by UV in summertime.

Previous studies provided evidence supporting the importance of simultaneously considering acute and chronic exposure types in investigating their adverse effects [20,21]. Defining and simplifying each exposure type can be helpful to human health care from the biological perspective. Diverse studies have also explored acute and chronic exposure to determine their effects and pathways [22,23]. However, since acute and chronic UVB exposure can affect human health care, simultaneous analysis of both types of exposure can be a reasonable and effective method to precisely assess the consequences of solar exposure. To compare the adverse effects of UVB exposure, we limited the exposure types to acute and chronic UVB exposure because both cases easily occur in occupational and daily life situations.

ADVERSE PATHOGENIC EFFECTS OF UVB EXPOSURE

Pathogenic mechanisms underlying UVB-induced the skin damage involve not only photocarcinogenesis effects but also other skin disorders including inflammation [24,25]. In vivo and in vitro studies have revealed diverse mechanisms [26,27]. However, few studies have been performed to analyze acute and chronic exposure together and compare between their effects even though both effects and exposure types are occurring simultaneously.

Young [28] summarized the acute effects of UVB in the skin and eyes. The main adverse effects of UVB exposure on the skin physiology are represented by inflammation, physical damage, and DNA break. In addition, association between cellular responses to UVB and pathogenesis of diseases has been analyzed by using in the Comparative Toxicogenomics Database [29]. Relationships comorbid with inflammation were found to have seven types, and those related to cancer have two types in the database. These traits represent the types of inflammation that most likely causes a more dominant effect of acute UVB exposure than other adverse effects.

The dose of daily UVB exposure is different from that of acute UVB exposure [26]. Therefore, when studies establish a daily UVB exposure condition, low-dose chronic UVB exposure is mainly considered. Even though the exposure dose is low, emerging skin diseases caused by chronic UVB exposure have some similarities to acute exposure. Omer et al. [30] demonstrated that the chronic low-dose UVB exposure is related to acute and chronic inflammation mediated through cytokine and immune pathways. However, Grivennikov et al. [31] described the effects of inflammation and immune response on cancer. Comprehensively, chronic inflammation caused by chronic low-dose UVB exposure can promote photocarcinogenesis. In the carcinogenic aspect of DNA damage, several studies have proven that UVB can break down DNA via several pathways even at a low dose. The remaining and continuous DNA damages by UVB exposure finally cause carcinogenesis in the skin [32,33]. Therefore, chronic UVB exposure is considered a highly carcinogenic factor associated with inflammation and DNA damage.

In this review, we utilized a biological network-based approach to compare the similarities and differences between the adverse effects of acute and chronic UVB exposure by using transcriptomic data derived from scientific literatures. Through the predicted biological networks, we reviewed the toxicogenomic pathways related to acute and chronic UVB exposure on the skin. Because two types of UVB exposure represent different interpretation networks such comparative studies can provide conducive information and predictions of their adverse effects, including photocarcinogenesis.

ACUTE AND CHRONIC UVB EXPOSURE-DEPENDENT EXPRESSION ANALYSIS

The expression data of acute and chronic UVB exposure have been described. However, relevant interactions among biomolecules and the biological networks involving genomic

dataset based on scientific literatures have not been clearly defined. This approach allows elucidating the conception of delineating numerous cellular processes and diseases to UVB exposure related genes.

We applied data sets of UVB exposure from the experimental conditions of the two GEO datasets: GSE45493 as acute UVB exposure and GSE56754 as chronic UVB exposure [34,35]. We deployed five control groups and five of 1 MED UVB-exposed groups under acute UVB exposure, and seven control groups and seven of 0.5 MED UVB-exposed groups under chronic UVB exposure after same 24 hours for reaction period in GEO2R. GEO2R is facilitated to compare the groups of samples to identify differentially expressed genes (DEGs) under different experimental conditions [36].

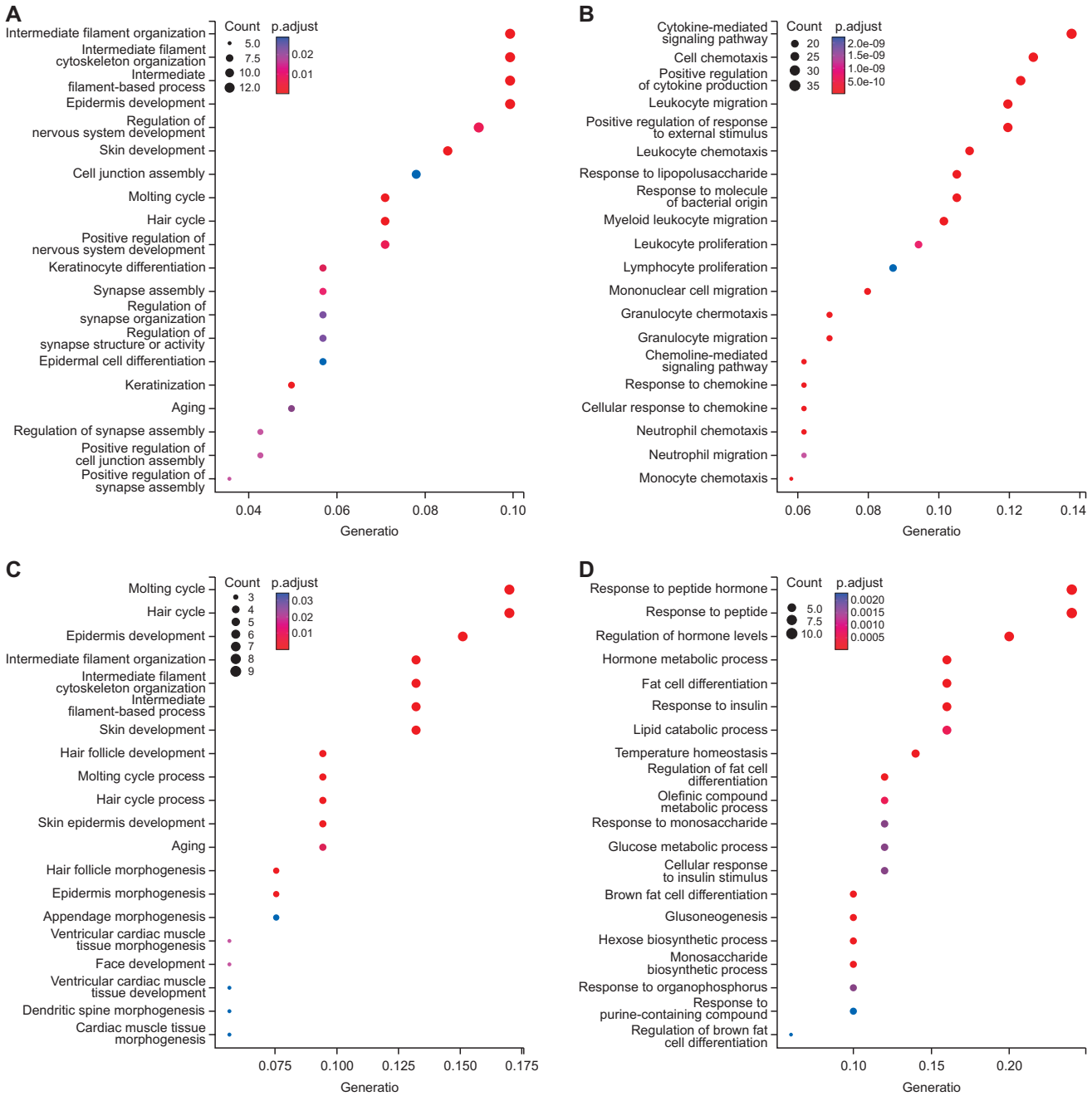

Figure 1. Summarized cell processes from the DEGs. This Summarization was performed using R software (version 4.2.1). (A) Summarized cell processes of acute UVB exposure-related upregulated genes and (B) downregulated genes were used to understand which processes were affected. Similar to the pattern in acute UVB exposure, (C) Summarized cell processes of the chronic UVB exposure-related upregulated genes and (D) downregulated genes. These analyses represent the GO terms related to the DEGs. UVB, ultraviolet B; GO, Gene Oncology; DEGs, differentially expressed genes.

A volcano plot was drawn to represent the up-regulated and down-regulated genes under acute UVB exposure and chronic UVB exposure to determine the probabilistic significance [37]. Uniform manifold approximation and projection computed that the UVB exposure samples were distinct from the control samples generally for selection [38]. Heatmap research analysis was enforced to illustrate the differences between expression data of DEGs under acute and chronic UVB exposure. The DEGs were identified for the two UVB exposure groups and compared with each corresponding control group.

A total of 500 genes were expressed under acute UVB exposure (390 downregulated genes and 190 upregulated genes), while 134 genes were expressed under chronic UVB exposure (62 downregulated genes and 70 upregulated genes). The defined genes were compared using a Venn diagram to exclude overlapping genes and to present the differences. Therefore, 465 genes associated with acute UVB exposure and 99 genes related to chronic UVB exposure were deployed to compare the biological network related to the skin.

GENE ONCOLOGY (GO) TERM ANALYSIS OF THE BIOLOGICAL PATHWAY COMPONENTS FROM THE UVB EXPOSURE NETWORKS

Pathway Studio web version 12.5.0.2 (Elsevier, Amsterdam, Netherlands) in tandem with R software version 4.2.1 (https://www.r-project.org/) was performed to identify cell processes and genes related to the skin cancer and order disorders. Literature-based software were employed to perform and visualize biological pathway networks related to UVB exposures [39,40]. Pathway Studio administers text-mining modules that contain the curated database that is used to search for the information about interactions between bio-factors.

Fifty-one and 18 genes were deployed in the acute and chronic UVB exposure networks, respectively based on the curated references. R software was applied to analyze cell processes involving DEGs. Data were clustered using the clusterProfiler package version 4.4.0 (https://bioconductor.org/packages/release/bioc/html/clusterProfiler.html), and visualized with the cowplot package in ggplot2 version 1.1.1 (https://cran.r-project.org/web/packages/cowplot/index.html) [41]. Data presenting DEGs-related cell processes were obtained to determine which DEGs respond in biological processes for UVB exposure. We subjected each exposure group's DEGs to GO term analysis with up-regulated and down-regulated groups (Fig. 1).

GO term analysis was utilized to associate each DEGs with biological pathways, cellular components, and molecular functions [42]. Intermediate filament organization, intermediate filament cytoskeleton organization, and intermediate filament-based processes were presented as upregulated GO terms in acute UVB exposure (Fig. 1A). The cytokine-mediated signaling pathway, cell chemotaxis, and positive regulation of cytokine production were presented as downregulated GO terms in acute UVB exposure (Fig. 1B). The GO term results on acute UVB exposure were inserted into Pathway Studio based on the Pathway Studio databases.

In the chronic UVB exposure, molting cycle, hair cycle, and epidermis development were presented as upregulated GO terms (Fig. 1C), and response to peptide hormone, response to peptide, and regulation of hormone levels are presented as downregulated GO terms (Fig. 1D). The GO term results on chronic UVB exposure were inserted into Pathway Studio based on the Pathway Studio databases to increase the accuracy of the data.

DISEASES RELATED TO UVB EXPOSURE-DEPENDENT DEGs

We focused on the two types of diseases, namely, inflammatory diseases and cancer that mainly affect the skin under UVB exposure. The number of symptoms under these two types of disorder can help us understand the differences between two types of UVB exposure. The relationships of 23 diseases to the corresponding DEGs by acute UVB exposure were defined. In acute UVB exposure, 'psoriasis,' 'dermatitis,' and 'atopic dermatitis' had a higher degree of related gene connection. These diseases are associated with the adverse inflammatory effects of UVB exposure. DEGs related to diseases can help demonstrate genotoxicity and biological pathways affected by UVB exposure. Interleukin-6 (IL-6), C-X-C motif chemokine ligand 10 (CXCL-10), and matrix metalloproteinase-9 (MMP-9) occupy many proportions among disease-related DEGs. Acute UVB exposure had more inflammatory diseases including 'allergic contact dermatitis,' 'dermatomyositis,' and 'contact dermatitis' than cancer-associated abnormalities.

The relationships of 15 diseases and the DEGs related to chronic UVB exposure were identified. Similar to acute UVB exposure, chronic UVB exposure was associated with 'psoriasis', 'dermatitis,' and 'atopic dermatitis' with a higher degree of related gene connection. However, several differences were observed in disease components except these three abnormalities. 'Cutaneous neoplasm,' 'epithelial cancer,' and 'intraepithelial neoplasia' known as Carcinomic disorders occupy more proportions in the chronic UVB exposure disease group [43]. In genomic aspects, prostaglandin endoperoxide synthase 2 (PTGS2) is remarkably associated with chronic UVB exposure compared with that of acute UVB exposure. Considering these relations, chronic UVB exposure could have both risks of cancerous as well as inflammatory diseases with a higher risk than acute UVB exposure.

BIOLOGICAL NETWORK INTERPRETATION OF ACUTE AND CHRONIC EXPOSURE

We presented biological networks among the DEGs, diseases and clustered cell processes based on the curated references. The biological network of acute UVB exposure in terms of the skin system had 51 diseases and 10 curated cell processes related to acute UVB exposure (Fig. 2A). The biological network associated with chronic UVB exposure had 18 related genes and 10 curated cell processes in the alteration of the skin system (Fig. 2B).

In the acute UVB exposure network, 'dermatitis,' 'psoriasis,' and 'photoaging' were the main diseases that could mainly occur as a consequence of inflammation. The case of carcinomic diseases that include 'cutaneous neoplasm,' and 'metastatic melanoma' also had several relations in biological network affected by acute UVB exposure [44]. However, the main cellular processes in the acute UVB exposure network that contained 'chemotaxis,' 'leukocyte migration,' 'neutrophil migration,' and 'cytokine-mediated signaling pathway' were related to inflammation [45,46]. Therefore, inflammation mainly occurred under acute UVB exposure.

Parallel to acute UVB exposure, chronic UVB exposure had 'psoriasis' and kinds of 'dermatitis' as the main components. However, from the perspective of cancer, significant differences in proportion and association between components were observed. Cell processes including 'adipocyte differentiation,' 'gluconeogenesis,' and 'aging' were detected in the chronic UVB exposure network. Although the cell process including 'adipocyte differentiation' and 'gluconeogenesis' are well known as causing type 2 diabetes (T2D), cancerous diseases account for a large proportion of the chronic UVB exposure network; recent studies discovered the correlation of T2D and cancer [47]. 'Aging' is the most powerful factor

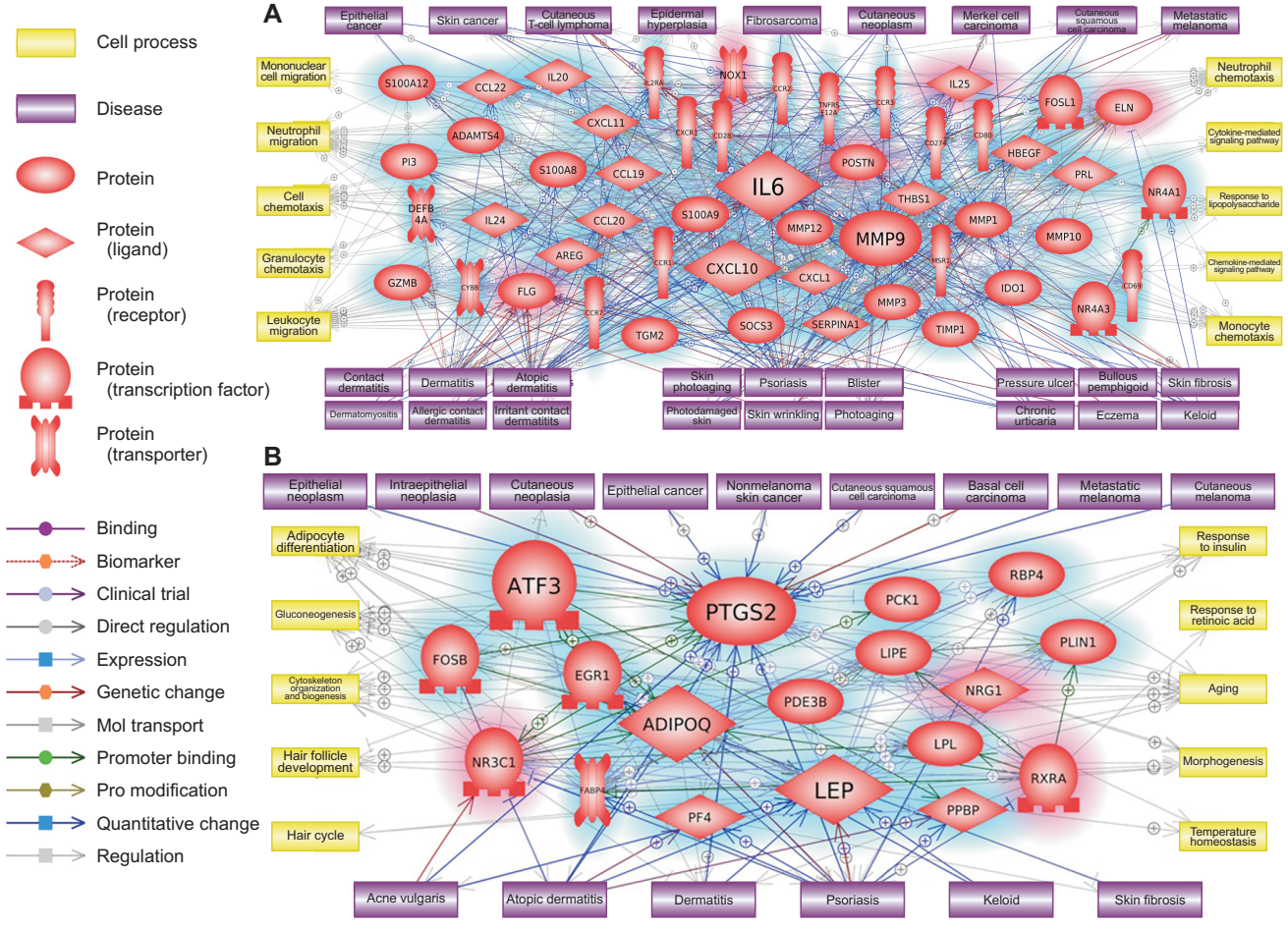

Figure 2. Potential biological signaling networks related to UVB exposure. Cell processes and diseases were selected in terms of the association with the skin. (A) The acute UVB exposure signaling pathways of differentially expressed genes, cell processes, and diseases. (B) The chronic UVB exposure signaling pathways of DEGs, cell processes, and diseases. Large entities are predicted as major genes in the network based on connectivity and betweenness centrality with other genes. UVB, ultraviolet B; IL-6, interleukin-6; MMP9, matrix metalloproteinase-9; CXCL-10, C-X-C motif chemokine ligand 10; ADIPOQ, Adiponectin, complement component 1q and collagen domain containing; LEP, leptin; PTGS2, prostaglandin-endoperoxide synthase 2; ATF3, activating transcription factor 3.

that accompanies several DNA mutation and carcinogenesis [48]. Therefore, cancer has major disease types in the chronic UVB exposure network in the skin.

POTENTIAL HUB BIOLOGICAL NETWORK ANALYSIS

UVB exposure networks should be simplified to predict the adverse effects based on the hub genes. Hub genes were selected according to our own principle of the degree and betweenness centrality among genes only to eliminate the side effects derived from other factors such as cellular processes and diseases in the networks. Cytoscape version 3.9.1 (https://cytoscape.org/) was utilized to analyze each DEG through bioinformatics [49].

The selected hub genes under acute UVB exposure are those encoding IL-6, CXCL-10, and MMP-9 (Fig. 3A). IL-6 is involved in proinflammatory and oncogenic signaling [50,51]. CXCL-10 is involved in apoptosis, cell growth, and angiogenesis [52,53]. MMP-9 plays a role in metastasis, disassembly of extracellular components, and photoaging [54,55]. We deduced the relationships between hub genes involved in not only cancer but also various skin disorders. Based on the connection with hub genes, cellular processes and diseases were also linked in the hub network of acute UVB exposure. 'Leukocyte migration,' 'cytokine-mediated signaling,' and 'neutrophil movement' were presented as inflammation and immunity that occur in the UVB-exposed skin [56,57]. The predicted diseases that occurred with inflammation and immunity were 'dermatitis,' 'blister,' and 'psoriasis' under acute UVB exposure [58] (Fig. 3A). Although inflammation mainly occurs in acute UVB exposure, cancer could also be a serious risk factor. Numerous studies have demonstrated that continuous inflammation can promote carcinogenesis [59,60]. Therefore, inflammatory diseases as well as cancer would be the main risk factors in response to acute UVB exposure.

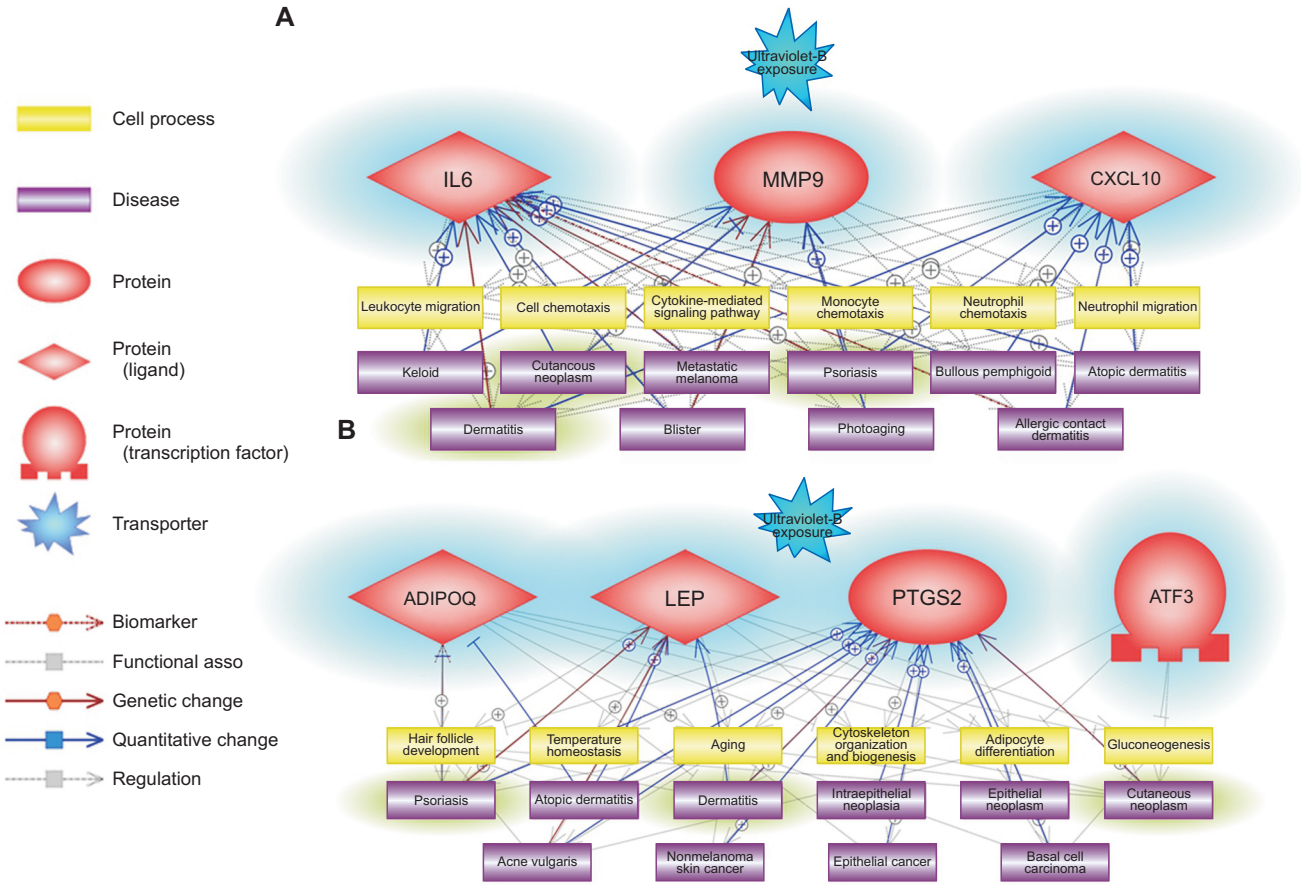

Figure 3. Potential major biological signaling networks related to UVB exposure. Cell processes and diseases were selected in terms of the association with the skin. (A) Potential biological signaling pathways of hub elements caused by acute UVB exposure. IL6, MMP9 and CXCL10 are assumed as hub genes. (B) Potential biological signaling pathways of hub elements caused by the chronic UVB exposure. ADIPOQ, LEP, PTGS2, and ATF3 are assumed as hub genes. The same diseases were highlighted in green. Networks were visualized by Pathway Studio. The schematic legend is provided on the left side. UVB, ultraviolet B; IL-6, interleukin-6; MMP9, matrix metalloproteinase-9; CXCL-10, C-X-C motif chemokine ligand 10; ADIPOQ, Adiponectin, complement component 1q and collagen domain containing; LEP, leptin; PTGS2, prostaglandin-endoperoxide synthase 2; ATF3, activating transcription factor 3.

Adiponectin, Cyclooxygenase/prostaglandin endoperoxide synthase 1 and collagen domain containing (ADIPOQ), leptin (LEP), PTGS2, and activating transcription factor 3 (ATF3) were identified by hub genes in the case of the chronic UVB exposure network (Fig. 3B). ADIPOQ presents adiponectin, which is a regulator of lipid and glucose metabolism in skin homeostasis [47,61]. LEP affects endocrine metabolism and several skin diseases such as 'psoriasis' and 'skin cancer' [62]. ATF3 is involved in oncogenesis, immunity, and T2D metabolism [63,64]. PTGS2 regulates inflammation, thrombosis, and pain. PTGS2 also participates in the development of cancer and Alzheimer's disease [65,66]. Compared to acute UVB exposure, the major cellular processes were different, whereas the diseases had similarity under chronic UVB exposure. 'Adipocyte differentiation' and 'aging' were indicated to be the main cell processes in the chronic UVB exposure network, indicating that the potential threat of cancer in circumstance of chronic UVB exposure increases faster than acute UVB exposure dose [67,68]. Even though 'dermatitis,' 'psoriasis,' and 'cutaneous neoplasm' were considerable diseases in both networks, the portion of cancerous diseases, the relationships between inflammation and cancer, and cellular processes indicate that chronic UVB exposure is a leading carcinogenic risk factor.

CONCLUSION

In this review, we compared the biological features between the acute and chronic exposure types of UVB. We analyzed and visualized the association between acute and chronic UVB exposure to understand the biological networks in both pathways from public databases. Our prediction with literature- and data-based platforms summarizes the differential genomic profiles induced by acute and chronic UVB exposure and suggests the hub genes of each network. Although further studies should be required to validate hub genes and pathways, our data presented here could help clarify relationship between two UVB exposure types and provide the evidence for a screening outline to analyze a genomic network for human health care including cancer and other disorders.

FUNDING

This study was supported by the grant from the Amorepacific Corporation R&I Center, Yongin, Republic of Korea.

CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

ORCID

JunPyo Han, https://orcid.org/0000-0001-6324-0878
Yujin Jang, https://orcid.org/0000-0002-8643-2722
Dong Yeop Shin, https://orcid.org/0000-0003-1575-3614
Jun Lee, https://orcid.org/0000-0003-3135-9748
Young Rok Seo, https://orcid.org/0000-0002-4093-4073

REFERENCES

1. World Health Organization, World Meteorological Organization, United Nations Environment Programme, International Commission on Non-Ionizing Radiation Protection. Global solar UV index: a practical guide. Geneva, World Health Organization, 2002.
2. Narayanan DL, Saladi RN, Fox JL. Ultraviolet radiation and skin cancer. Int J Dermatol 2010;49:978-86.
3. International Agency for Research on Cancer. Exposure to artificial UV radiation and skin cancer. Lyon, World Health Organization, International Agency for Research on Cancer, 2006.
4. Bodekær M, Harrison GI, Philipsen P, Petersen B, Triguero-Mas M, Schmalwieser AW, et al. Personal UVR exposure of farming families in four European countries. J Photochem Photobiol B 2015;153:267-75.
5. Peters CE, Nicol AM, Demers PA. Prevalence of exposure to solar ultraviolet radiation (UVR) on the job in Canada. Can J Public Health 2012;103:223-6.
6. Fahy K, Liu L, Rapp CM, Borchers C, Bihl JC, Chen Y, et al. UVB-generated microvesicle particles: a novel pathway by which a skin-specific stimulus could exert systemic effects. Photochem Photobiol 2017;93:937-42.
7. International Agency for Research on Cancer. Radiation. Lyon, International Agency for Research on Cancer, 2012.
8. Ikehata H, Higashi S, Nakamura S, Daigaku Y, Furusawa Y, Kamei Y, et al. Action spectrum analysis of UVR genotoxicity for skin: the border wavelengths between UVA and UVB can bring serious mutation loads to skin. J Invest Dermatol 2013;133:1850-6.
9. Kovács RJ, Kovács JZ, Szolga LA. Device for identifying the UV emission spectrum. Sensors (Basel) 2022;22:4852.
10. Chambers ES, Vukmanovic-Stejic M. Skin barrier immunity and ageing. Immunology 2020;160:116-25.
11. Barresi R, Chen E, Liao IC, Liu X, Baalbaki N, Lynch S, et al. ARTICLE: alteration to the skin barrier integrity following broad-spectrum UV exposure in an ex vivo tissue model. J Drugs Dermatol 2021;20:23s-8s.
12. Matsumura Y, Ananthaswamy HN. Toxic effects of ultraviolet radiation on the skin. Toxicol Appl Pharmacol 2004;195:298-308.
13. D'Orazio J, Jarrett S, Amaro-Ortiz A, Scott T. UV radiation and the skin. Int J Mol Sci 2013;14:12222-48.
14. Nordström M, Hardell L, Magnusson A, Hagberg H, Rask-Andersen A. Occupation and occupational exposure to UV light as risk factors for hairy cell leukaemia evaluated in a case-control study. Eur J Cancer Prev 1997;6:467-72.
15. Lopes FCPS, Sleiman MG, Sebastian K, Bogucka R, Jacobs EA, Adamson AS. UV exposure and the risk of cutaneous melanoma in skin of color: a systematic review. JAMA Dermatol

2021;157:213-9.
16. Dadvand P, Basagaña X, Barrera-Gómez J, Diffey B, Nieuwenhuijsen M. Measurement errors in the assessment of exposure to solar ultraviolet radiation and its impact on risk estimates in epidemiological studies. Photochem Photobiol Sci 2011;10:1161-8.
17. Fioletov V, Kerr JB, Fergusson A. The UV index: definition, distribution and factors affecting it. Can J Public Health 2010;101:I5-9.
18. Heckman CJ, Chandler R, Kloss JD, Benson A, Rooney D, Munshi T, et al. Minimal Erythema Dose (MED) testing. J Vis Exp 2013;(75):e50175.
19. Blumthaler M. UV monitoring for public health. Int J Environ Res Public Health 2018;15:1723.
20. Sinha RP, Häder DP. UV-induced DNA damage and repair: a review. Photochem Photobiol Sci 2002;1:225-36.
21. Mullenders LHF. Solar UV damage to cellular DNA: from mechanisms to biological effects. Photochem Photobiol Sci 2018;17:1842-52.
22. Tadokoro T, Kobayashi N, Zmudzka BZ, Ito S, Wakamatsu K, Yamaguchi Y, et al. UV-induced DNA damage and melanin content in human skin differing in racial/ethnic origin. FASEB J 2003;17:1177-9.
23. Khalil C, Shebaby W. UVB damage onset and progression 24 h post exposure in human-derived skin cells. Toxicol Rep 2017;4:441-9.
24. Coussens LM, Werb Z. Inflammation and cancer. Nature 2002;420:860-7.
25. Rass K, Reichrath J. UV damage and DNA repair in malignant melanoma and nonmelanoma skin cancer. Adv Exp Med Biol 2008;624:162-78.
26. World Health Organization. The effect of occupational exposure to solar ultraviolet radiation on malignant skin melanoma and non-melanoma skin cancer: a systematic review and meta-analysis from the WHO/ILO joint estimates of the work-related burden of disease and injury. Geneva, World Health Organization, 2021.
27. Godar DE. UV and reactive oxygen species activate human papillomaviruses causing skin cancers. Curr Probl Dermatol 2021;55:339-53.
28. Young AR. Acute effects of UVR on human eyes and skin. Prog Biophys Mol Biol 2006;92:80-5.
29. Davis AP, Wiegers TC, Johnson RJ, Sciaky D, Wiegers J, Mattingly CJ. Comparative Toxicogenomics Database (CTD): update 2023 [published online ahead of print September 28, 2022]. Nucleic Acids Res. doi: 10.1093/nar/gkac833.
30. Omer SAE, Badi RM, Garelnabi MEM, Altayeb OA, Hussein MO, Fadul EA, et al. Effects of acute and chronic exposure to natural sunlight and UVB on CD4/CD8 ratio and circulating pro-inflammatory and anti-inflammatory cytokine levels in mice. Sci Afr 2019;4:e00102.
31. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. Cell 2010;140:883-99.
32. Roos WP, Thomas AD, Kaina B. DNA damage and the balance between survival and death in cancer biology. Nat Rev Cancer 2016;16:20-33.
33. Basu AK. DNA damage, mutagenesis and cancer. Int J Mol Sci 2018;19:970.
34. Coelho SG, Valencia JC, Yin L, Smuda C, Mahns A, Kolbe L, et al. UV exposure modulates hemidesmosome plasticity, contributing to long-term pigmentation in human skin. J Pathol 2015;236:17-29.
35. Bustamante M, Hernandez-Ferrer C, Tewari A, Sarria Y, Harrison GI, Puigdecanet E, et al. Dose and time effects of solar-simulated ultraviolet radiation on the in vivo human skin transcriptome. Br J Dermatol 2020;182:1458-68.
36. Barrett T, Wilhite SE, Ledoux P, Evangelista C, Kim IF, Tomashevsky M, et al. NCBI GEO: archive for functional genomics data sets--update. Nucleic Acids Res 2013;41(Database issue):D991-5.
37. Li W. Volcano plots in analyzing differential expressions with mRNA microarrays. J Bioinform Comput Biol 2012;10:1231003.
38. Kleino I, Frolovaitė P, Suomi T, Elo LL. Computational solutions for spatial transcriptomics. Comput Struct Biotechnol J 2022;20:4870-84.
39. Nikitin A, Egorov S, Daraselia N, Mazo I. Pathway studio--the analysis and navigation of molecular networks. Bioinformatics 2003;19:2155-7.
40. Sepulveda JL. Using R and bioconductor in clinical genomics and transcriptomics. J Mol Diagn 2020;22:3-20.
41. Yu G, Wang LG, Han Y, He QY. clusterProfiler: an R package for comparing biological themes among gene clusters. OMICS 2012;16:284-7.
42. Reijnders MJMF, Waterhouse RM. Summary visualizations of gene ontology terms with GO-Figure! Front Bioinform 2021;1:638255.
43. Waldman A, Schmults C. Cutaneous squamous cell carcinoma. Hematol Oncol Clin North Am 2019;33:1-12.
44. Sample A, He YY. Mechanisms and prevention of UV-induced melanoma. Photodermatol Photoimmunol Photomed 2018;34:13-24.
45. Petri B, Sanz MJ. Neutrophil chemotaxis. Cell Tissue Res 2018;371:425-36.
46. Yoshihisa Y, Rehman MU, Nakagawa M, Matsukuma S, Makino T, Mori H, et al. Inflammatory cytokine-mediated induction of serine racemase in atopic dermatitis. J Cell Mol Med 2018;22:3133-8.
47. Siitonen N, Pulkkinen L, Lindström J, Kolehmainen M, Eriksson JG, Venojärvi M, et al. Association of ADIPOQ gene variants with body weight, type 2 diabetes and serum adiponectin concentrations: the Finnish Diabetes Prevention Study. BMC Med Genet 2011;12:5.
48. Guida S, Pellacani G, Ciardo S, Longo C. Reflectance confocal microscopy of aging skin and skin cancer. Dermatol Pract Concept 2021;11:e2021068.
49. Smoot ME, Ono K, Ruscheinski J, Wang PL, Ideker T. Cytoscape 2.8: new features for data integration and network visualization. Bioinformatics 2011;27:431-2.

50. Jiang XP, Yang DC, Elliott RL, Head JF. Down-regulation of expression of interleukin-6 and its receptor results in growth inhibition of MCF-7 breast cancer cells. Anticancer Res 2011;31:2899-906.
51. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol 2014;6: a016295.
52. Liu M, Guo S, Stiles JK. The emerging role of CXCL10 in cancer (Review). Oncol Lett 2011;2:583-9.
53. Bagheri H, Pourhanifeh MH, Derakhshan M, Mahjoubin-Tehran M, Ghasemi F, Mousavi S, et al. CXCL-10: a new candidate for melanoma therapy? Cell Oncol (Dordr) 2020;43:353-65.
54. Yabluchanskiy A, Ma Y, Iyer RP, Hall ME, Lindsey ML. Matrix metalloproteinase-9: many shades of function in cardiovascular disease. Physiology (Bethesda) 2013;28:391-403.
55. Vandooren J, Van den Steen PE, Opdenakker G. Biochemistry and molecular biology of gelatinase B or matrix metalloproteinase-9 (MMP-9): the next decade. Crit Rev Biochem Mol Biol 2013; 48:222-72.
56. Altan-Bonnet G, Mukherjee R. Cytokine-mediated communication: a quantitative appraisal of immune complexity. Nat Rev Immunol 2019;19:205-17.
57. Kameritsch P, Renkawitz J. Principles of leukocyte migration strategies. Trends Cell Biol 2020;30:818-32.
58. Awad F, Assrawi E, Louvrier C, Jumeau C, Giurgea I, Amselem S, et al. Photoaging and skin cancer: is the inflammasome the missing link? Mech Ageing Dev 2018;172:131-7.
59. Zaalberg A, Moradi Tuchayi S, Ameri AH, Ngo KH, Cunningham TJ, Eliane JP, et al. Chronic inflammation promotes skin carcinogenesis in cancer-prone discoid lupus erythematosus. J Invest Dermatol 2019;139:62-70.
60. Singh N, Baby D, Rajguru JP, Patil PB, Thakkannavar SS, Pujari VB. Inflammation and cancer. Ann Afr Med 2019;18:121-6.
61. Oh J, Lee Y, Oh SW, Li T, Shin J, Park SH, et al. The role of adiponectin in the skin. Biomol Ther (Seoul) 2022;30:221-31.
62. Dopytalska K, Baranowska-Bik A, Roszkiewicz M, Bik W, Walecka I. The role of leptin in selected skin diseases. Lipids Health Dis 2020;19:215.
63. Hellmann J, Tang Y, Zhang MJ, Hai T, Bhatnagar A, Srivastava S, et al. Atf3 negatively regulates Ptgs2/Cox2 expression during acute inflammation. Prostaglandins Other Lipid Mediat 2015;116-117:49-56.
64. Ku HC, Cheng CF. Master regulator activating transcription factor 3 (ATF3) in metabolic homeostasis and cancer. Front Endocrinol (Lausanne) 2020;11:556.
65. Chandrasekharan NV, Simmons DL. The cyclooxygenases. Genome Biol 2004;5:241.
66. Tudor DV, Bâldea I, Lupu M, Kacso T, Kutasi E, Hopârtean A, et al. COX-2 as a potential biomarker an d therapeutic target in melanoma. Cancer Biol Med 2020;17:20-31.
67. Cavinato M, Jansen-Dürr P. Molecular mechanisms of UVB-induced senescence of dermal fibroblasts and its relevance for photoaging of the human skin. Exp Gerontol 2017;94:78-82.
68. Chen S, He Z, Xu J. Application of adipose-derived stem cells in photoaging: basic science and literature review. Stem Cell Res Ther 2020;11:491.