Vitamin D–fense: The Balancing Effects of Vitamin D Supplementation and UV Exposure on Broad Gene Expression

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Introduction

The 17th century discovery of the relationship between ultraviolet radiation (UVR) and vitamin D synthesis reshaped human understanding of the sun's remedial powers.

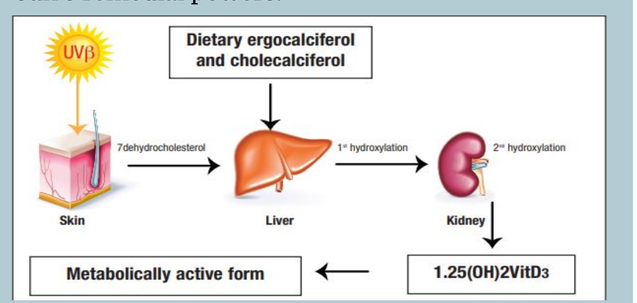


Figure 1: The vitamin D pathway

Deficiency of this "sunshine vitamin" remains common, precipitating bone illnesses such as osteoporosis and rickets. On the other hand, adequate vitamin D production can decrease the risk of chronic illnesses including cancer, autoimmune disorders, infectious diseases, and cardiovascular disease. Yet the same UVR which produces vitamin D also mutates DNA, facilitates carcinogenesis, and alters cell signaling, mitotic regulation, and cell cycle progression[1]. Thus, a paradox arises between the positive and negative effects of solar exposure. **This analysis aims to compare existing data on how solar UVR exposure and vitamin D3 supplementation simultaneously impact broad gene expression. We hypothesize that vitamin D can improve some of the hazardous impacts caused by UV exposure., particularly those relating to cancer.**

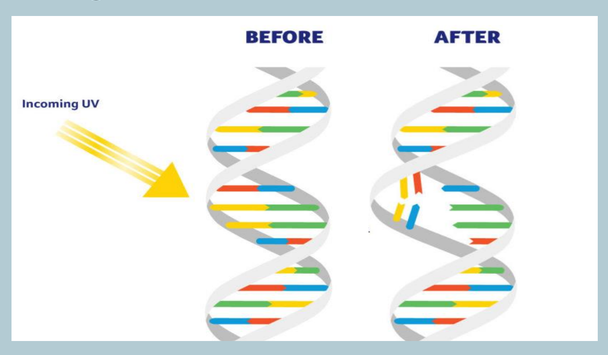


Figure 2: How UVR mutates DNA

Methodology

Broad gene expression analyses in two separate studies were compared. In the first study, 30 healthy adults were supplemented with either 600, 4000, or 10,000 IU/day of vitamin D3 for 6 months in a randomized controlled double-blind clinical trial. Broad gene expression of peripheral white blood cells was evaluated[2]. In the second study, a separate gene expression analysis was conducted for human HaCaT keratinocytes after exposure to solar-simulated UVR (ssUVR) in either a single dose or 5 repetitive doses. Comprehensive analyses of cell gene expression profiles, as well as functional annotation, were performed at 24 hours post irradiation[3].

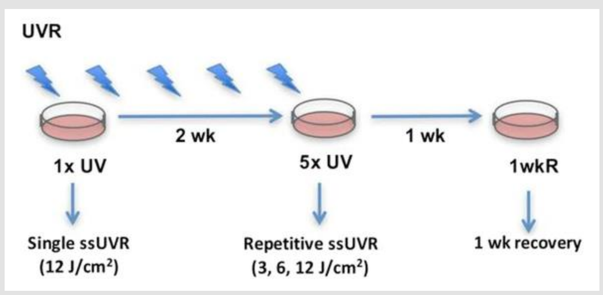


Figure 3: Experimental procedure for ssUVR-exposed keratinocytes

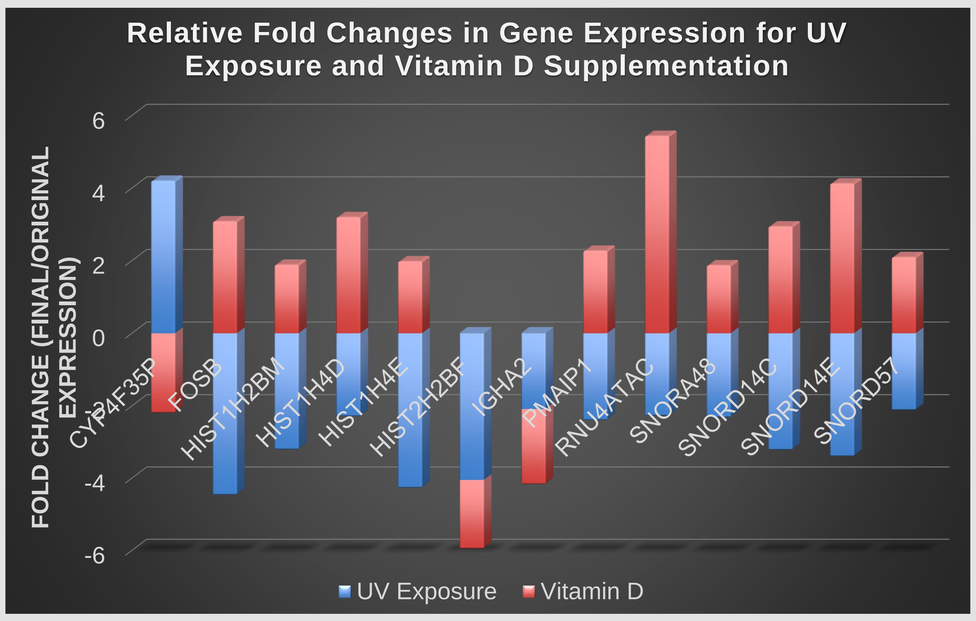
The genes found to be differentially expressed in ssUVR-exposed keratinocytes were compared with differentially expressed genes (DEGs) in the peripheral white blood cells of initially deficient or insufficient healthy adults (serum 25(OH)D concentration < 30 ng/mL) who received 6 months of 10,000 IU/day vitamin D supplementation[2,3]. Other subjects were excluded from the gene expression profiling comparison as the 10,000 IU/day regimen exhibited the greatest degree of expression in terms of genes affected. DEGs in the vitamin D dataset were filtered for |fold change| > 1.9 to be considered significantly altered, while log2-fold change was considered in the UVR dataset. Positive fold changes were considered up-regulation, and negative values down-regulation. All genes were filtered for p-value less than 0.05.

Results

A comparison of the affected genes and their regulatory changes (up/down) identified 13 total shared genes: CYP4F35P, FOSB, HIST1H2BM, HIST1H4D, HIST1H4E, HIST2HBF, IGHA2, PMAIP1, RNU4ATAC, SNORA48, SNORD14C, SNORD14E, and SNORD57. 11 genes were oppositely regulated; 2 genes were both down-regulated (Table 1).

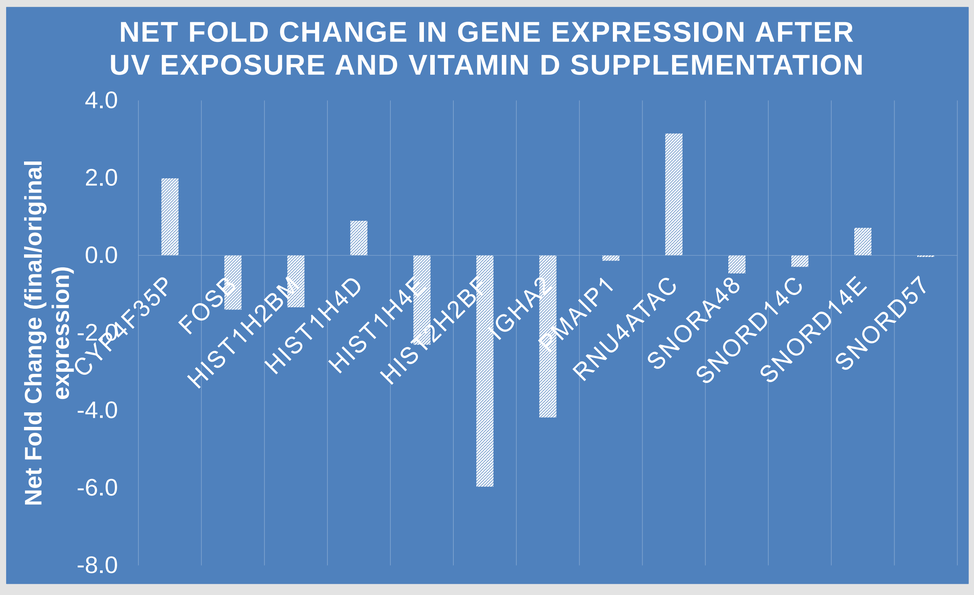
Common Genes	UV Reg	VitD Reg	Function
CYP4F35P	Up	Down	Psuedogene
FOSB	Down	Up	Encodes FosB regulatory protein that forms transcription factor complex AP-1
HIST1H2BM	Down	Up	Encodes Histone H2B type 1-M protein
HIST1H4D	Down	Up	Encodes Histone H4 protein
HIST1H4E	Down	Up	Encodes Histone H4 protein
HIST2H2BF	*Down*	*Down*	*Encodes Histone H2B type 2-F protein*
IGHA2	*Down*	*Down*	*Contributes to immunoglobulin receptor binding activity*
PMAIP1	Down	Up	Encodes Noxa protein
RNU4ATAC	Down	Up	Encodes RNA, U4atac small nuclear part of U12-dependent minor splicesosome complex
SNORA48	Down	Up	Encodes Small nucleolar RNA SNORA48
SNORD14C	Down	Up	Encodes Small nucleolar RNA SNORD14
SNORD14E	Down	Up	Encodes Small Nucleolar RNA, C/D Box 14E
SNORD57	Down	Up	Encodes Small nucleolar RNA SNORD57

Table 1: Regulatory change and function of shared genes



Graph 1: Relative fold changes per gene for UVR and vitamin D

Across the 13 genes, UV exposure resulted in an average fold change of -2.46. Vitamin D supplementation led to an average fold change of 1.7. The net fold change (calculated by UV fold change + vitamin D fold change) averaged to -0.7. The PMAIP1, SNORA48, SNORD14C, and SNORD57 genes exhibited a net absolute fold change of less than 0.5, suggesting that the up and down-regulation of these genes nearly negate each other perfectly.



Graph 2: Net fold change per gene with UVR and vitamin D

Discussion

Among the genes found to be oppositely regulated include those with cancer-related functions. The Noxa protein, encoded by the PMAIP1 gene, serves as a pro-apoptotic factor in the cell cycle and is primarily regulated by the tumor suppressor p53.

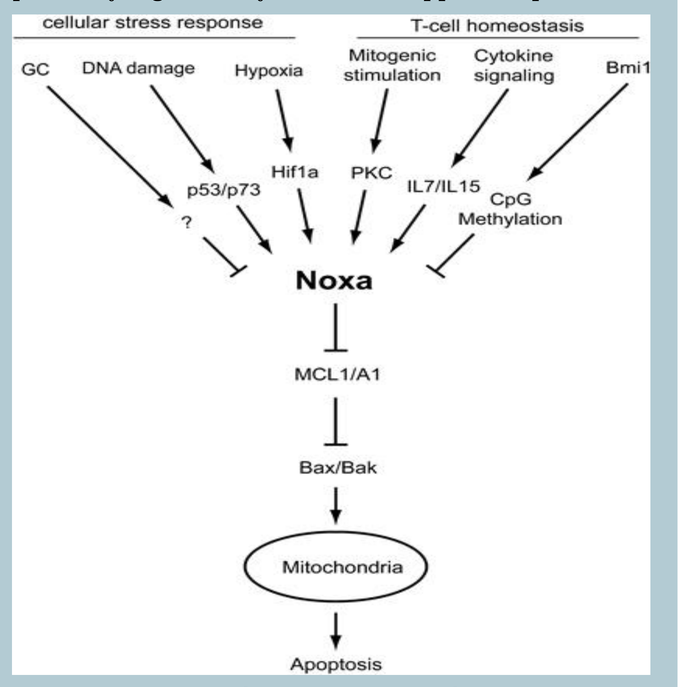


Figure 4: The Noxa apoptosis pathway

Thus, the down-regulation of the PMAIP1 gene caused by UV exposure increases vulnerability to cancerous growths. Conversely, the up-regulation of the same gene by vitamin D supplementation defends against cancerous growths.

Recent research also suggests that altered regulation of histones plays a key role in tumorigenesis. As 3 histone-regulating genes exhibited opposite changes in expression, further research should examine the role of sunlight in impacting cancer via histone expression.

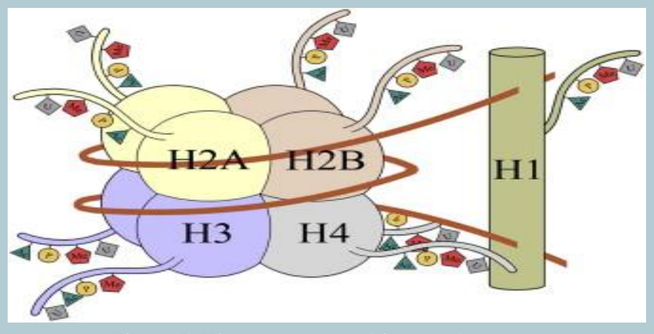
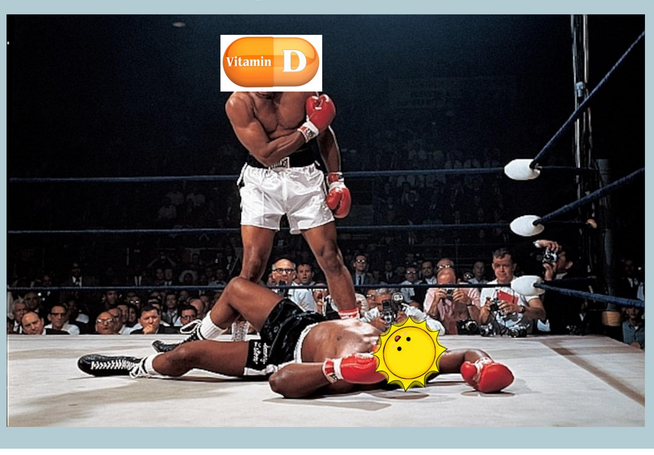


Figure 5: Histones arranged in a nucleosome

The inverse associative relationship between sunlight and vitamin D exposure in 11 genes suggests that the evolution of vitamin D served to counteract the harmful effects of sunlight, particularly in relation to skin cancer. This uncovers vitamin D as a biological defense mechanism against the mutating effects of UVR. These findings shed light on the evolution of vitamin D, demonstrate how it may be applied to treat the negative effects of sunlight, and pave the way for future research to establish a causative relationship.



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3. Marais, T. L.; Kluz, T.; Xu, D.; Zhang, X.; Gesumaria, L.; Matsui, M. S.; Costa, M.; Sun, H. Transcription Factors and Stress Response Gene Alterations in Human Keratinocytes Following Solar Simulated Ultra Violet Radiation. *Scientific Reports* **2017**, *7*(1).

Acknowledgements

Thank you to Dr. Arash Shirvani and Dr. Michael F. Holick for the invaluable guidance, knowledge, and resources they contributed toward the completion of this project. My deepest gratitude is extended to my lab partners Josh Choi and Brian Liu for their unrelenting support, camaraderie, and brotherhood throughout the extent of the RISE program. Finally, none of this would have been possible without Boston University, RISE program director Michael Raymond, and my parents – who have sacrificed without hesitation and always encouraged me to explore and question.