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doi:10.36849/JDD.7070

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Ultraviolet B-Rays Induced Gene Alterations and DNA Repair Enzymes in Skin Tissue

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ABSTRACT

Background: Ultraviolet (UV) radiation leads to deoxyribonucleic acid (DNA) damage and changes in gene expression. Topical DNA repair enzymes in liposomes are capable of undoing this damage.
Objective: To evaluate gene expression changes induced by ultraviolent B-rays (UVB) light and assess the effect of topical DNA repair enzymes extracted from *Micrococcus luteus* (*M. luteus*) and photolyase in modifying these changes.
Methods: Non-invasive, adhesive patch collection kits were used to sample skin on the right and left post-auricular areas before and 24 hours after UVB exposure (n=48). Subjects applied topical DNA repair enzymes to the right post-auricular area daily for 2 weeks. Subjects returned 2 weeks later for repeat non-invasive skin sample collection.
Results: Eight of 18 tested genes demonstrated significant changes 24 hours following UVB exposure. DNA repair enzymes from *M. luteus* or photolyase had no significant effect on genetic expression compared with the control at 2 weeks post UV exposure.
Conclusion: UVB exposure causes acute changes in gene expression, which may play roles in photo-aging damage and skin cancer growth and regulation. While non-invasive gene expression testing can detect UV damage, additional genomic studies investigating recovery from UV damage at different time periods are needed to establish the potential of DNA repair enzymes to minimize or reverse this damage.

J Drugs Dermatol. 2023;22(5):465-470. doi:10.36849/JDD.7070

INTRODUCTION

Deoxynucleic acid (DNA) damage caused by ultraviolet (UV) light in humans has been well documented and described in the literature.[1-5] However, the ability to detect DNA damage is typically only confirmed after gross morphological evidence exists, as seen in precancerous and cancerous lesions on the skin.

The ability to treat DNA damage and restore skin to the original state before it is grossly damaged remains a clinical challenge. There are intrinsic mechanisms known to repair DNA damage in bacteria, plants, and some animals, but humans seem to have limited options for this process and are thought to rely mainly on nucleotide excision repair (NER) mechanisms.[6-8] Moreover, there is evidence that impaired DNA repair may be a susceptibility factor for sunlight-induced skin cancer in the general population.[9] The use of topical DNA repair enzymes, specifically T4 Endonuclease V (T4N5) and photolyases, have previously demonstrated the ability to assist in the removal of cyclobutane pyrimidine dimers formed after UV irradiation.[10-12] These DNA repair enzymes have also been proven to reduce skin cancer and precancerous skin lesions, namely actinic keratoses.[13,14] Wolf et al demonstrated that application of T4N5 after UV exposure nearly completely prevented the upregulation of interleukin-10 and tumor necrosis factor alpha (TNFα), cytokines that are normally upregulated in UV-induced immune suppression.[15] In addition, a cousin DNA repair enzyme derived from *Micrococcus luteus* (*M. luteus*), has shown promise in the prevention of actinic keratoses and skin cancers.[16-19]

The innovation of non-invasive, adhesive skin collection kits (DermTech, Inc., La Jolla, CA) may allow for the early detection of DNA damage in human skin cells at the molecular level after acute and/or chronic exposure to ultraviolet light. This new technology may also have the ability to monitor the recovery

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of DNA damage caused by UV light and assess the ability of topical agents to assist in this recovery process.

The primary objective of this trial is to determine the changes in gene expression among certain gene families 24 hours following exposure to ultraviolent B-rays (UVB) irradiation and subsequently 2 weeks later to evaluate the natural recovery mechanisms of skin. Secondary objectives include determining if the addition of topical DNA repair enzymes aids in the repair of UV damage at the molecular level.

MATERIALS AND METHODS

Study Participants

Between April 23, 2018, and August 20, 2018, 48 subjects between the ages of 22 and 89 years were recruited from a single site in Southern California (Table 1). Both healthy volunteers and volunteers with a history of skin cancer(s) were recruited with Fitzpatrick skin types I to IV. Patients were recruited independently and had to fulfill both inclusion and exclusion criteria prior to study enrollment.

Study Design

This was a single-center clinical study conducted by the principles of the Declaration of Helsinki and Institutional Review Board (IRB) approval. The study was split into a screening, baseline, follow-up, and final visit. Treatment was carried out with the Xtrac Velocity 400 laser manufactured by PhotoMedex, Inc at a wavelength of 308 nm (UVB) to illicit DNA damage on 2 areas of skin, each approximately 2 cm x 2 cm, on both post-auricular sides of the participant. This wavelength falls into the normal range of sun radiation. Erythema, burning, stinging, itching, and dryness were recorded on a scale of 0 to 3 at each study visit. Skin samples were collected with 8 non-invasive, adhesive patches from both post-auricular test sites on the day of the participant's first visit before laser treatment (time 0, to establish baseline before laser treatment), and from the same laser-treated skin areas (postauricular) on the next day after laser treatment (24 hours, post laser treatment). Participants were then randomized into 2 groups, one group received *M. luteus* topical DNA repair enzyme, applied twice daily for 2 weeks, to the laser treated area on the right post-auricular side only. The other group received photolyase cream, applied once daily for 2 weeks, to the laser treated area also on the right post-auricular side only. In both groups, the laser treated area from the left post-auricular side received no topical treatment throughout the 2-week study, serving as the topical treatment control.

The *M. luteus* cream consisted of approximately 0.6 g of liposomes containing DNA repair enzymes per 30 mL unit. The photolyase cream included DNA enzymes (Barnet Photosomes: Plankton Extract) at approximately 0.3 g photolyase per 30 mL unit. Erythema and associated symptoms were graded at 24 hours following UVB exposure using the clinical questionnaire. At the end of the 2-week topical treatment, skin samples were collected again from all participants from both the left (received laser treatment only) and right postauricular site (received both laser and topical treatment) for analysis of topical treatment effect on repairing damage caused by laser treatment.

Gene Expression Analyses

Total RNA collected via adhesive tape was reverse transcribed to complementary DNA (cDNA) using a qPCR™ cDNA SuperMix kit from Quanta Biosciences™. The resulting cDNA was subsequently used for target gene expression analysis with TaqMan qPCR on an ABI7900 PCR system (Life Technologies). Each qPCR reaction used 30 pg of total cDNA, in duplicate, in 20 uL volume on 384-well PCR reaction plates using pre-designed gene-specific TaqMan probe chemistries (Life Technologies). An averaged cycle threshold (Ct) value of the duplicate measurements was used in the analysis. A lower Ct value indicates more target gene products in the qPCR reaction or an increased gene expression in the skin sample. As Ct value from RT-qPCR is also affected by the input quantity of RNA to the reactions (more RNA input would lead to a lower Ct value), analysis of a housekeeping gene (human β-actin, or ACTB) is included in the test to normalize the impact of RNA input on target gene analysis. On all samples, ACTB was analyzed in qPCR in parallel with the target genes, for the calculation of ΔCt (=$Ct._{ACTB}$-$Ct._{target}$) on each target gene. As ACTB is a strongly expressed housekeeping gene, yielding a low Ct value, a smaller ΔCt value would mean a stronger expression of the target gene in test samples.

TABLE 1.

Demographics		
Subject Demographics	***M. Luteus***	**Photolyase**
Mean Age (Range) in yrs	47.13 (23-89)	48.5 (23-77)
Male/ Female	5/19	9/15
Total Sample Size	24	24*
Skin Type		
Fitzpatrick Skin Type I, II	14	8
Skin Cancer History *n* (%)	11 (45.8%)	12 (50%)

*Original number of participants enrolled in study prior to losing 2 subjects to follow up.

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TABLE 2.

Significant Gene Expression Changes at Twenty-Four Hours Following UVB Exposure			
Gene	Gene Family	Gene Expression Changes at 24 Hours After UVB Exposure	*P*-Value
CRABP2	vitamin A	downregulation	*P*<0.01
IL1RN	interleukin	upregulation	*P*<0.01
IL36G	interleukin	upregulation	*P*<0.01
MUCL1	mucin	downregulation	*P*<0.01
PDCD4	programmed cell death protein	downregulation	*P*<0.01
SPRR1A	small proline-rich protein	downregulation	*P*<0.01
CST6	cystatin	downregulation	*P*<0.01
KLK10	keratinocyte	downregulation	*P*<0.01

While ΔCt reflects the expression level of target gene in test samples, ΔΔCt, calculated from ΔCt from samples before and after treatment ($\Delta\Delta Ct = \Delta Ct._{\text{target gene after treatment}} - \Delta Ct._{\text{target gene before treatment}}$), shows how the treatment (UVB or topical DNA repair enzymes) has caused the change of target gene expression in samples following the treatment (by UVB or topical DNA repair enzymes). A negative ΔΔCt value indicates an increased gene expression (upregulation), while a positive value indicates a reduced gene expression (downregulation) caused by UVB exposure and the treatment. The fold change (FC) of gene expression was calculated as $FC=2^{-\Delta\Delta Ct}$. We used ΔΔCt to show gene expression changes relating to treatment throughout the study.

The potential effects of covariates were also considered, including analysis of the potential effect of sample collection site (left or right), sample analysis batch, test subjects' age, gender, skin type, and skin history (with or without skin cancers) on gene expression response to low dose UV exposure. It was concluded that none of these factors, including subjects' skin cancer history, affected the gene expression results.

Gene Families Investigated

Eighteen genes were examined for changes in expression from skin samples collected before UVB exposure (time 0, baseline), 24 hours after exposure, and 2 weeks after exposure with and without the addition of topical DNA repair enzymes. The genes were selected based on prior research conducted by DermTech, Inc and their well-studied association with cutaneous malignancies. The genes studied were CRABP2, IL1RN, IL22RA1, IL36B, IL36G, CDKN1A, MUCL1, PDCD4, SPRR1A, CST6, KLK10, ACTB, ADAMTSL, KIF18B, MKI67, SLAMF7, TRIP13, and UHRF1. These 18 genes were narrowed down to 9 genes belonging to 8 gene families after results in the first quarter of subjects demonstrated changes at 24 hours post UVB exposure. The 8 gene families included the vitamin A family, interleukin family, cyclin-dependent kinase inhibitor family, mucin family, small proline-rich protein, programmed cell death protein, keratinocyte family, and cystatin gene family. Some of these genes have been linked to UV exposure and inflammation but to our knowledge, none have been proven to be directly linked with acute DNA damage in the skin.

Statistical Analysis

All statistical analyses and gene expression comparisons were performed using Microsoft Excel. All 'undetermined' Ct counts from qPCR were assigned a value of 40 (the maximal thermal cycling number in a given qPCR reaction). Statistical significance for the covariant analysis was determined to be any *P*-value below 0.05 (2-tailed test).

RESULTS

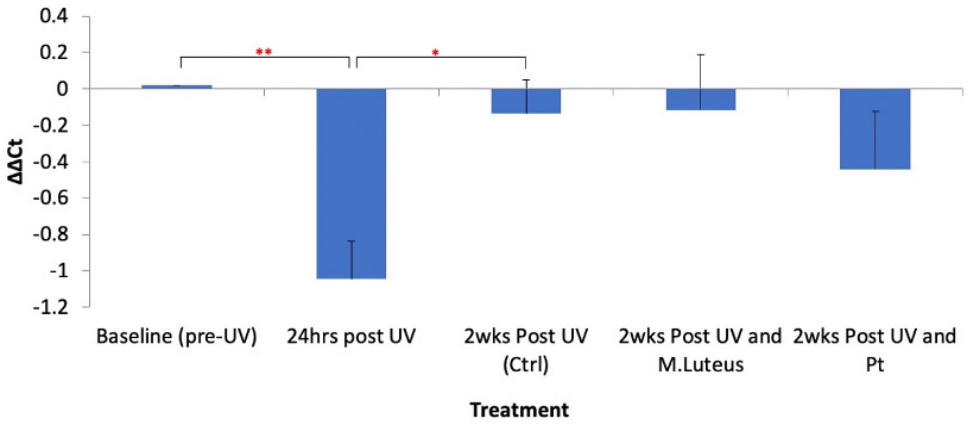
Forty-eight subjects were enrolled and 46 subjects completed the study (average age 49, with subjects ranging from 23 to 89 years of age) with 2 subjects lost to follow up (1 subject moved during the course of the study). Fifteen (33%) men and 31 (67%) women completed the study. Twenty-two (48%) subjects had a history of skin cancer (13 basal cell carcinoma, 9 squamous cell carcinoma, and 2 melanoma), and 24 (52%) subjects had no history of skin cancer. Twenty-four (52%) subjects were randomized into the *M. luteus* group and 22 (48%) into the photolyase group. Immediately after UVB exposure, clinically visible erythema was recorded in 25/48 (52%), and mild burning was reported by subjects in 3/48 (6%), mild stinging in 1/48 (2%), and mild itching in 1/48 (2%). There were no reports of dryness. Twenty-four hours after treatment, mild to moderate erythema localized to the treatment sites were visualized clinically in 33 (69%), mild burning in 15 (31%), mild stinging in 13 (27%), mild to moderate itching in 10 (21%), and mild to moderate dryness in 5 (10%), suggesting sufficient UVB exposure to illicit a local reaction. Two weeks after UVB exposure, mild symptoms persisted in 14/46 (30%) of subjects.

Eight of the 18 genes investigated demonstrated changes in gene expression at 24 hours representing 7 gene families (Table 2). Twenty-four hours after UV exposure the interleukin family was significantly upregulated (*P*<0.01) compared with

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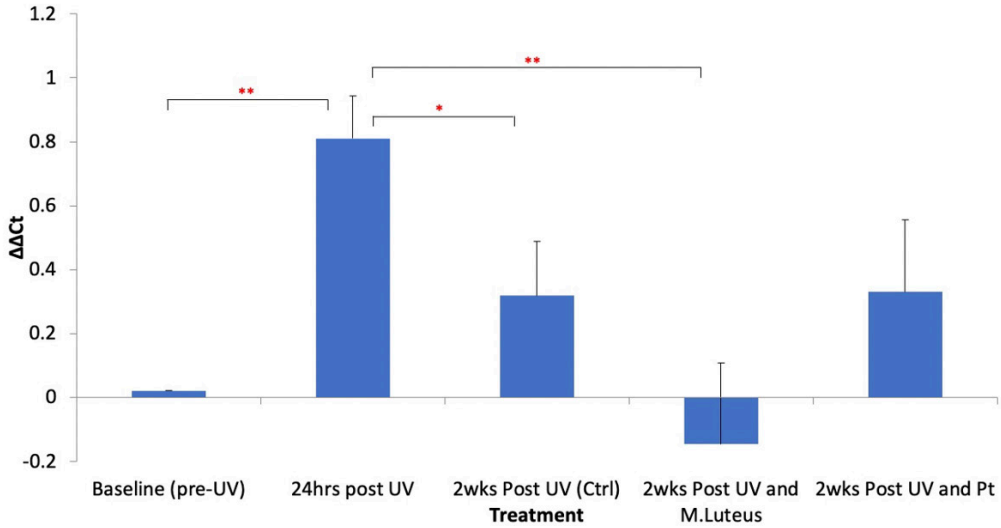
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FIGURE 1. Interleukin-1 gene expression changes. Expression of interleukin-1 family of genes 24 hours after UVB radiation.



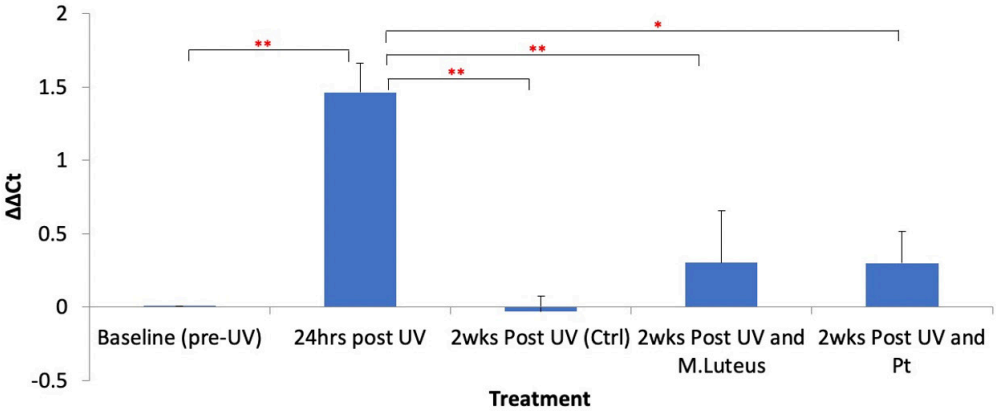
*represents *P*<0.05
**represents *P*<0.01

FIGURE 2. Small proline-rich protein gene expression changes. Expression of small proline-rich protein genes w24 hours after UVB radiation, and again from both the left- (received laser treatment only) and right-post auricular site (received both laser and topical treatment).



*represents *P*<0.05
**represents *P*<0.01
Error bar represents mean +/- SD.

FIGURE 3. Programmed cell death protein gene expression changes. Expression of programmed cell death protein genes was studied 24 hours after UVB radiation, and again from both the left- (received laser treatment only) and right-post auricular site (received both laser and topical treatment).



*represents *P*<0.05
**represents *P*<0.01
Error bar represents mean +/- SD.

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baseline (Figure 1). In contrast, vitamin A, mucin, small proline-rich protein (SPRR) (Figure 2), programmed cell death protein (PCDP) (Figure 3), cystatin, and keratinocyte families were all significantly downregulated ($P<0.01$) compared with baseline.

Across all the gene families, analyses of the 2-week arms did not find any significant differences between the control and *M. luteus* or photolyase topicals.

DISCUSSION

The present study demonstrates that skin tissues may respond rapidly to UV exposure, and significant changes in gene expression can be seen within 24 hours. Additionally, non-invasive, adhesive skin collection kits can detect changes in gene expression following exposure to UV light and monitor the recovery of these changes over time. This study also tested the effect of 2 topical DNA repair enzymes, T4N5, and photolyase, on UV induced genetic changes. However, our data did not suggest any significant relationship between topical DNA repair enzymes and expression of the genes that were studied.

Eight of the 18 genes originally demonstrated a change in gene expression 24 hours following exposure to UVB light at 300 mJ by the excimer laser. These genes included CRABP2, IL-1RN, IL-36G, MUCL1, PDCD4, SPRR1A, CST6, and KLK10. The vitamin A, mucin like protein, programmed cell death protein, small proline rich protein, cystatin, and keratinocyte gene families all exhibited a downregulation in gene expression at 24 hours while 2 members of the interleukin gene family, IL-1RN and IL-36G, exhibited an upregulation in gene expression at 24 hours after UVB exposure. This is consistent with previous findings that showed an upregulation of interleukin in keratinocytes in response to UV-induced DNA damage.[15,20,21] These results indicate that the aforementioned genes are acutely impacted by exposure to UV light and reflect inflammation and other changes caused by UVB light exposure and sun damage. Additionally, the role of these genes has been studied in the pathogenesis and prognosis of cutaneous malignancies, including mucin, cystatin in squamous cell carcinoma, and Vitamin A in melanoma.[22-26] Other genes may show a similar response to UVB light exposure that may be meaningful in the detection of UV damage.

Natural Recovery (No Treatment)

Two weeks following exposure to UVB light, 5 of the 7 genes tested, IL-1RN, IL-36G, MUCL1, PDCD4, and CST6 demonstrated profound UV-induced acute changes in gene expression compared with 24 hours post exposure. These changes exhibited a reversal towards baseline or pre-UVB exposure. Mucin-like protein, programmed cell death protein, and cystatin gene families exhibited a decrease in the acute downregulation seen at 24 hours. The interleukin family displayed a decrease in the acute upregulation of gene expression. These results indicate that human epidermal cells appear to be able to naturally recover from DNA damage caused by acute UV exposure over the course of 2 weeks, but additional repair may be needed to fully return to baseline. Future studies should assess the minimal amount of time needed to achieve full recovery. In addition, other gene families that may not fully recover from UVB exposure should be investigated to better understand UV events that lead to skin cancers. Genes that are directly related to DNA damage will also need to be found to better assess topical agents that best repair sun damaged skin and prevent skin cancer.

The Effect of Topical DNA Repair Enzymes

In this study, no significant difference in the genes examined was seen between the topical DNA repair enzyme treatment areas and the placebo areas at week 2. Future studies will focus on direct comparisons between natural DNA repair and the addition of topical DNA repair enzymes at multiple time points to truly assess the benefit of adding topical DNA repair enzymes as treatment options for subjects wanting to minimize the effects of sun damage and prevent skin cancers.

Limitations

There are a few limitations to this study. First, the study had a small sample size which may limit the generalizability and power of the results. We were not able to observe the longitudinal results of natural recovery vs topical DNA repair enzyme application because the scope of this study was limited to 2 weeks following UVB exposure. Therefore, it is possible that 2 weeks of application was not enough time to see significant gene expression changes in some of the other gene families of interest. Additionally, the DNA repair enzyme groups may have demonstrated an expedited return to baseline in certain gene families within the 2-week window that was not observed due to the gap in follow up. Finally, the genes that this study examined may not have changed with the addition of topical DNA repair enzymes because of the possibility that these genes are associated with UV light damage but not DNA repair.

CONCLUSION

In summary, this study demonstrates that certain genes are altered by UV exposure and may subsequently play a role in skin cancer growth and development. This study also supports the use of noninvasive skin collection kits in the detection of UV-induced genetic changes. While no significant difference was observed between the 2-week control and 2-week topical DNA repair enzyme groups, significant changes may be seen outside of this time frame or in genes that were not examined. Further studies should investigate the acute effect of topical DNA repair enzymes on the time to recovery after UVB induced damage as well as the longer effects of topical DNA repair enzymes with continued use.

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DISCLOSURES

James Rock and Zuxu Yao are paid employees of DermTech with equity interest. The other authors have no conflicts of interest to declare.

IRB approval status: Reviewed and approved by Aspire IRB on March 5, 2018: Protocol Number 18-1.

ACKNOWLEDGMENT

We would like to thank Burkhard Jansen for his significant contributions to this paper.

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