High-Dose Ultraviolet Light Exposure Reduces Scar Hypertrophy in a Rabbit Ear Model

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Background: The effects of ultraviolet light exposure on scar pigmentation are well documented. There is a commonly held belief among physicians that sun exposure may also worsen the appearance of fresh scars and result in excess collagen deposition. However, few studies have documented a relationship between ultraviolet light exposure and hypertrophic scarring. This study sought to evaluate the effect of ultraviolet light exposure on scar hypertrophy in an established rabbit model of cutaneous scarring.

Methods: Four 7-mm ulcers were created on the ventral ears of eight rabbits. Starting on postoperative day 15, half of the wounds were exposed to ultraviolet-B radiation daily for either 7 or 14 days. Ultraviolet-B–exposed ($n = 16$) and control ($n = 16$) scars were harvested on postoperative day 32 for histologic and reverse-transcriptase polymerase chain reaction analysis.

Results: Exposure to ultraviolet-B radiation for 7 or 14 days was associated with a 52 percent ($p < 0.01$) or 74 percent ($p < 0.05$) reduction in scar volume, respectively, compared with controls. In wounds subjected to ultraviolet-B radiation for 14 days, collagen type I-α2 mRNA expression was 29 percent lower than in controls ($p < 0.05$). There was no difference in the mRNA expression of transforming growth factor-β1.

Conclusions: These short-term observations demonstrate that ultraviolet-B radiation exposure reduces scar hypertrophy in this clinically relevant animal model. A reduction in collagen production or increase in collagen breakdown may account for this result. However, sunscreen should still be used as primary protection when skin is exposed to direct sunlight. (*Plast. Reconstr. Surg.* 121: 1165, 2008.)

Cutaneous scarring is a natural sequela of cutaneous injury. It is characterized on a gross level by distinct changes in skin texture, color, elasticity, vascularity, and elevation.[1] On a histologic level, there is an abundance of collagen fibers in varying states of disorganization (when compared with normal dermis), with concomitant inflammatory cells (depending on the stage of scar maturation). There is a widespread perception among patients and physicians that sun exposure, and specifically ultraviolet radiation, can worsen cutaneous scarring in fresh surgical wounds, and that for areas of scar that are entirely beneath the skin surface, such as rhinoplasty, sun exposure is detrimental for a couple of months. Many surgeons advocate avoidance of sunlight in the immediate postoperative period for scars located in cosmetically sensitive areas. However, an exhaustive review of the literature in the PubMed database from 1995 to 2005 associating scar formation and maturation with ultraviolet radiation does not yield significant experimental evidence that derangements in scar development occur with such

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stimuli. In fact, ultraviolet light (phototherapy) is widely used in dermatologic inflammatory conditions, such as vitiligo, psoriasis, scleroderma, lupus erythematosus, and atopic dermatitis, and induces collagenase in fibroblasts in vitro in a dose-dependent fashion.[2–10] Therefore, we hypothesized that the clinical practice of avoiding sun exposure on fresh surgical sites may be incorrect, and perhaps phototherapy could even benefit scars.

Our laboratory has developed a model of robust hypertrophic scarring that we have found to be a useful tool for quantifying the effects of various treatments on hypertrophic scarring. We have been successful in showing a reduction in scar formation when treating wounds with silicone or Mederma (Merz Pharmaceuticals, Greensboro, N.C.) occlusion and steroid injection.[11–16] This model is useful for testing the effects of pharmacologic and mechanical interventions on scar outcome. The model demonstrates reduced scar hypertrophy in aged rabbits, a phenomenon shared in humans.[17] Initial studies revealed histologic findings consistent with a collagen-dense dermis as seen in human scars. Our most recent data support the importance of collagen in the formation of hypertrophic scars by blocking the hydroxylation of procollagen, a requirement in the formation of mature collagen, leading to a reduction in hypertrophic scar formation.[13]

Using the rabbit model, we sought to observe the clinical and histologic effects of ultraviolet-B irradiation that have the greatest effect on skin erythema and that we felt would best mimic the potentially injurious effects of sunlight on hypertrophic scar formation. In addition, we examined the expression of collagen type I-α2, and transforming growth factor (TGF)-β1 mRNA in treated and control wounds.

MATERIALS AND METHODS

Hypertrophic Scar Model

In this study, the Animal Care and Use Committee of Northwestern University approved all procedures. The rabbit model of cutaneous hypertrophic scarring was used as previously described.[13–17] Female White New Zealand rabbits weighing 2.5 to 5 kg (3 to 6 months of age) were kept under standard conditions and fed ad libitum. Animals were anesthetized with ketamine (45 mg/kg intramuscularly) and xylazine (7 mg/kg intramuscularly) followed by a single prophylactic dose of penicillin (25,000 IU/kg intramuscularly). Before wounding, the ventral surface of each ear was shaved with clippers and hair removed with Nair (Church & Dwight, Mississauga, Ontario, Canada), followed by preparing of the skin with ethanol and povidone-iodine. Four full-thickness 7-mm wounds per ear were created down to cartilage using a 7-mm biopsy punch. A dissecting microscope was used to remove skin and perichondrium, leaving bare cartilage at the base of the wound. Postoperatively, the ventral surface of each ear was thinly coated with Mastisol adhesive (Ferndale Laboratories, Inc., Ferndale, Mich.), and each wound was covered with Tegaderm dressing (3M Health Care, St. Paul, Minn.). Wounds were inspected daily for evidence of infection or desiccation, and Tegaderm dressings were removed once reepithelialization was complete (14 days). Two experimental cohorts consisting of four animals per group were assigned randomly to have half of their wounds irradiated with ultraviolet-B light for 7 or 14 days beginning on postoperative day 15, after complete wound epithelialization. The other half of the wounds were used as untreated controls. Treated wounds exemplified typical sequelae of sunburn: erythema, rubor, and epithelial sloughing.

Ultraviolet Light Treatment

The end point for irradiation was to mimic prolonged exposure to direct sunlight. This study used an artificial handheld ultraviolet-B light source for irradiating wounds [UVP (Upland, Calif.), UVM-57 midrange ultraviolet-B irradiation, 302 nM] in a fashion similar to that previously described.[18] Before ultraviolet-B irradiation, one animal was tested to determine the minimal erythema dose by exposing designated regions of depilated ventral unwounded ear skin with elevating doses of ultraviolet light. Approximately 24 hours after exposure, sites were evaluated visually for erythema, and the site that produced a just perceptible erythema of the exposure region using the smallest dose of energy was visually determined to be the inherent minimal erythema dose.[19] Each animal was considered to have the same minimal erythema dose because all rabbits were albino. On postoperative day 15, Tegaderm dressings were removed and wounds were exposed for 5 minutes per day at a distance of 3 inches, the minimal erythema dose calculated as described above. Treated ears were inspected daily for blistering and Buprenex (0.1 to 0.5 mg/kg intramuscularly) (Reckitt Benckiser, London, England) was administered for pain relief. Opposite ears served as control wounds and were covered with an ultraviolet light–impenetrable material.

Wound Harvesting and Tissue Preparation

Wounded animals were anesthetized before wound harvest as previously described, and wounds were photographed with a digital camera. Animals were then killed with a single intracardiac dose of sodium pentobarbital (90 mg/kg) immediately before wound harvesting. Scars were excised leaving a 0.5-mm margin of surrounding unwounded tissue and bisected through the point of maximal height of hypertrophy. One-half of each wound was placed into 10% buffered zinc-formalin for 24 hours, processed, embedded in paraffin, and cut for histologic analysis. The remaining half was snap frozen in liquid nitrogen and total RNA was extracted according to protocol using the RNeasy column-based mini kit (Qiagen, Inc., Valencia, Calif.).

Scar Elevation Index

Histologic sections (4 μm) of postoperative day–32 scars were stained with hematoxylin and eosin for quantification of scar hypertrophy. Using light microscopy (Nikon, Inc., Melville, N.Y.), the degree of hypertrophy within wounds was expressed as the scar elevation index in a manner previously described by this laboratory.[13–17] Briefly, the total area of new scar contained between the nicks in the cartilage was quantified using a calibrated lens square reticule and then compared with the thickness of the dermis lying outside of the nicks. The scar elevation index represents the ratio of total wound area tissue height to the area of normal tissue below the hypertrophic scar. A scar elevation index of 1 indicates a scar that is equal in height to the surrounding tissue, whereas a scar elevation index greater than 1 indicates a raised, hypertrophic scar. The scar elevation index of each scar was measured twice by blinded observers, and then averaged.

Primer and Probe Design and Validation

Primers and probes for polymerase chain reaction were designed using Primer Express software (Applied Biosystems, Inc., Foster, Calif.) based on GenBank (National Center for Biotechnology Information, Bethesda, Md.) sequence data for TGF-β1 and type I collagen. The 5′ ends of the reporter probes were labeled with 6-carboxyfluorescein, and the 3′ ends were labeled with 6-carboxytetramethylrhodamine. Sequences for primers and their corresponding amplicon sizes are shown in Table 1. Before use, each primer set was evaluated to ensure acceptable efficiency and specific binding as previously described.[20] Commercially available primers for 18S rRNA, labeled with a Vic probe (Applied Biosystems), were used as an endogenous control.

Reverse Transcription and Real-Time Multiplex Polymerase Chain Reaction

First-strand cDNA was synthesized from 1 μg total RNA using the High Capacity cDNA Archive Kit (Applied Biosystems) using random hexamer primers according to the manufacturer's instructions. mRNA expression was measured in triplicate using real-time multiplex polymerase chain reaction on an ABI Prism 7000 Sequence Detection System (Applied Biosystems). Each polymerase chain reaction contained 1 μl of cDNA template (equivalent to 10 ng of total RNA), 900-nM target primers, and 1.25 μl of 18S primers in a final reaction volume of 25 μl. Cycling parameters were as follows: 50°C (2 minutes), 95°C (10 minutes), and 40 cycles of 95°C (15 seconds) and 60°C (1 minute). No-template controls were run to check for amplification of genomic DNA. The fluorescence curves of the polymerase chain reaction products were evaluated by assigning a cycle threshold (Ct) value using ABI Prism 7000 SDS Study software (Applied Biosystems). Relative expression of TGF-β1, collagen type I-α2, and matrix metalloproteinase-9 was measured by normalizing their cycle thresholds to those of the corresponding 18S (DCt). These normalized cycle threshold values were compared with those of unwounded skin, yielding a value (DDCt) that is expressed as a percentage difference from baseline (2^{-DDCt}).

Statistical Analysis

All wounds were created and harvested in a matched fashion. Histologic data are expressed as

Table 1. Oligonucleotide Forward and Reverse Primer and Probe Sequences Used for Real-Time Reverse-Transcriptase Polymerase Chain Reaction

Gene	Sequence	Amplicon Size (bp)
TGF-β1	Forward: 5′-TGCGGCAGCTGTACATTGAC-3′ Reverse: 5′-GGCAGAAGTTGGCGTGGTA-3′ Probe: 5′-AAGGACCTGGGCTGGAAGTGGATCC-3′	83
Collagen-Ia2	Forward: 5′-TTCTGCAGGGCTCCAATGAT-3′ Reverse: 5′- TCGACAAGAACAGTGTAAGTGAACCT-3′ Probe: 5′-TTGAACTTGTTGCCGAGGGCAACAG-3′	70

mean ± SEM. Statistical analysis was performed using a paired *t* test. Differences in mRNA expression levels were evaluated for significance using one-way analysis of variance with Tukey's post hoc testing where appropriate. A value of $p < 0.05$ was considered significant.

RESULTS

Gross Wound Appearance

For the purpose of this study, when examining wounds grossly, we focused on color and morphology of the actual scar itself, with less emphasis on surrounding tissue. On postwounding day 7, the wounds began to fill with a fresh bed of granulation tissue rich with new vascular supply, and the edges of the wounds were slightly raised circumferentially. Reepithelialization was complete by day 14 after wounding, with slightly contracted and raised tissue, resembling early scar formation. After 1 week of irradiation, tissue surrounding scars exhibited typical sequelae of sunburn (i.e., hyperemia and epithelial sloughing), but no blistering was noted. The second cohort of animals, irradiated for 2 weeks, demonstrated scars that had become increasingly hyperemic, with minimal blistering to surrounding tissue. Control scars showed no evidence of crossover ultraviolet-B radiation exposure, indicating successful shielding from ultraviolet-B radiation. Treated ears in both groups were noticeably warm to touch compared with untreated ears. By postwounding day 32, wounds had taken the appearance of mature scars. Before wound harvesting on postoperative day 32, digital photographs were taken as depicted in Figures 1 and 2.

Histology

Full-thickness ear wounds are used to assess the formation of hypertrophic scars. They require an extensive coordination of many cell types, creating an inflammatory response with robust collagen deposition. Hematoxylin and eosin staining of wounds was performed at day 32 after wounding in both cohorts of animals (Fig. 2). All wounds demonstrated features of scar tissue with an extracellular matrix exhibiting disorganized collagen fibers, rich with fibroblasts, and a well-organized vasculature. The volume of tissue represented as the scar elevation index described below appeared reduced under microscopic examination in wounds irradiated for 1 and 2 weeks of ultraviolet-B light. This was confirmed when calculating the scar elevation index.

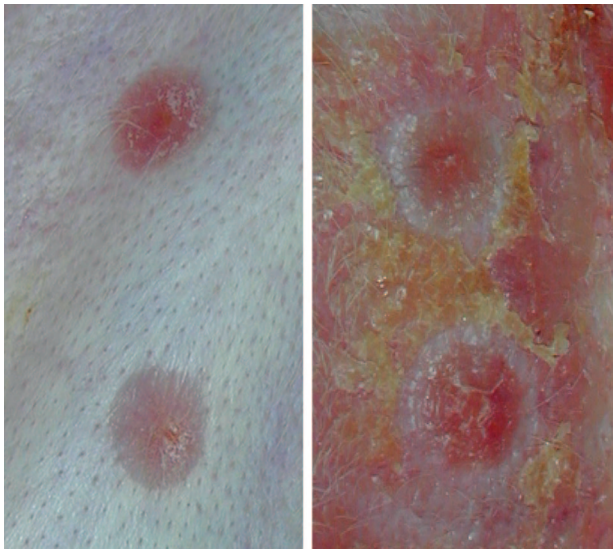

Fig. 1. Typical gross appearance of treated and control wounds. (*Left*) Control wounds at postwounding day 28. There is no evidence of ultraviolet light exposure, and the wounds are noticeably hypertrophic. (*Right*) Ultraviolet light–treated wounds at postwounding day 28 after being irradiated with ultraviolet light for 14 days. Wounds exhibit typical sequelae of sunburn, hyperemia and desquamating skin.

Determination of Scar Elevation Index

Histomorphometric quantification of scar prominence was performed at postoperative day 32. An adequate margin of normal tissue was harvested on each side of the scar, serving as an internal control when measuring scar elevation parameters. By day 32, all wounds showed adequate clinical scar maturation, and histologic evidence of scarring was present. The mean scar elevation index for scars irradiated with 7 days of ultraviolet-B light was 1.3 ($n = 11$) compared with 1.6 ($n = 13$) in control scars ($p < 0.01$). The mean scar elevation index for scars irradiated with 14 days of ultraviolet-B light was 1.2 ($n = 12$) compared with 1.7 ($n = 11$) in control scars ($p < 0.05$). This represents dose-dependent decreases in scarring of 52 and 74 percent, respectively.

Collagen Type I-α2 and TGF-β1 mRNA Levels after Ultraviolet Treatment (14 Days)

Collagen type I-α2 mRNA was associated with a 29 percent reduction in scars irradiated for 14 days ($n = 10$, $p < 0.05$) compared with controls ($n = 11$) (Fig. 3, *above*). TGF-β1 mRNA expression was unchanged between irradiated and control scars (Fig. 3, *below*).

DISCUSSION

This study sought to test the commonly accepted hypothesis that ultraviolet light—specifi-

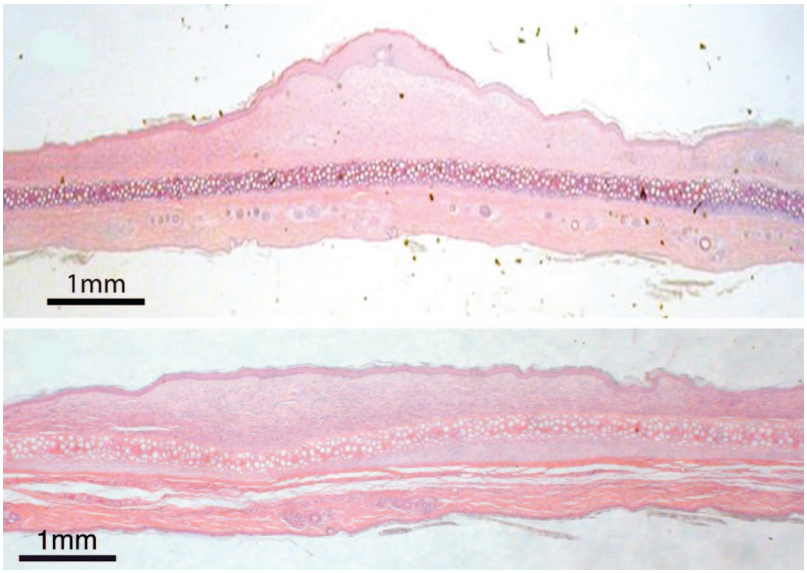

Fig. 2. Cross-sections shown are typical effects of ultraviolet treatment on scars compared with control wounds. (*Above*) Cross-section of wound stained with hematoxylin and eosin on postwounding day 32. This wound was irradiated with ultraviolet light for 14 days. (*Below*) Cross-section of wound stained with hematoxylin and eosin on postwounding day 32. This wound was not irradiated with ultraviolet light.

cally, ultraviolet-B light exposure—worsens cutaneous scarring. Little research has explored the effects of ultraviolet light exposure on acute wounds. The use of therapeutic ultraviolet light treatment has been limited by concerns surrounding hyperpigmentation and carcinogenesis. It is important to note that although scar appearance may be a function of multiple parameters such as pigmentation and scar shape and volume and texture, we sought to specifically focus on scar formation as assessed by histologic analysis of thickness and collagen deposition. Thus, in this study, pigmentation changes of scar were not assessed and would be the focus of future projects involving nonalbino animals. Using an established animal model of hypertrophic scarring, we have shown that ultraviolet-B light exposure for 7 or 14 days in fact reduces scar hypertrophy in the early short-term observation of these hypertrophic scars. This reduction in scarring was accompanied by a decrease in the transcription of collagen type I, the primary protein component of scars.

This model creates injury through the epidermal and dermal layers to the level of the underlying cartilage. The cartilage prevents wound contraction from occurring, which significantly prolongs healing compared with many traditional animal models. The time necessary to achieve epithelial coverage in a 7-mm wound leads to a predictable raised scar that is similar to human hypertrophic scarring in appearance and behavior. The scars produced with this model are apparent at 1 month and last at least 9 months. The TGF-β family of growth factors plays a pivotal role in orchestrating normal wound repair and scar formation.[21] However, excessive TGF-β activity has been implicated in the cause of a wide variety of fibrotic disorders, including hypertrophic scars.[22] As in humans, these scars are reduced by topical silicone application and steroid injection and are less robust in aged animals.[13,14,17,23,24]

Accurately modeling daily sun exposure in an animal model is difficult. Sunlight is divided into a spectrum of electromagnetic radiation having different wavelengths. Ultraviolet radiation comprises ultraviolet-A (320 to 400 nm), ultraviolet-B (280 to 320 nm), and ultraviolet-C (200 to 280 nm) radiation. Ultraviolet-C radiation is blocked from reaching the earth's surface by the ozone layer. Ultraviolet-A and ultraviolet-B radiation both produce inflammation of the skin and melanogenesis (tanning) at the epidermal and dermal layers.[25] Ultraviolet-A predominately affects the dermis, inducing wrinkling and aging, and is weakly carcinogenic; whereas ultraviolet-B affects the epidermis, leading to erythema, burning, and eventually skin cancer.[26,27] We chose to irradiate wounds with an ultraviolet-B light source because of its superior abil-

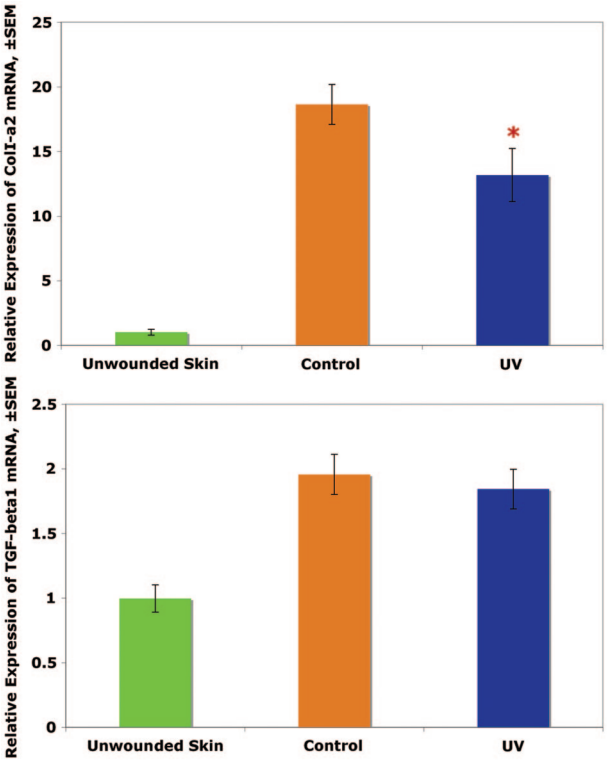

Fig. 3. (*Above*) Expression of collagen in wounds irradiated for 14 days. mRNA expression was decreased by 29 percent in ultraviolet light–irradiated wounds ($n = 10$) (*$p < 0.05$) when compared with untreated controls ($n = 11$). (*Below*) Expression of TGF-β1 in wounds treated for 14 days. mRNA expression of TGF-β1 showed no difference between wounds treated for 14 days compared with untreated controls. Results shown are expressed as mean ± SEM.

ity to cause sunburn in exposed skin and its ability to penetrate the epidermal and dermal layers.[27]

Moreover, human exposure to it is intermittent and cumulative. To avoid making a type II error, we used an artificially high dose of ultraviolet-B radiation to test the hypothesis that it worsens scarring. The dose we used led to predictable clinical changes characterized by erythema, warmth, and tenderness, which mimics sunburn. Although it is not likely that humans would endure the same magnitude of exposure in such a short time, the end result, sunburn, manifests clinically in an analogous fashion.

The effects of ultraviolet radiation in sunlight on human skin are well known. Acutely, ultraviolet light causes erythema, increased melanogenesis, and local immunosuppression by means of the release of cytokines such as tumor necrosis factor-α and interleukin-10. Ultraviolet light exposure also leads to a net decrease in the amount of Langerhans cells, the main antigen-presenting cells in skin, thus adding to its immunosuppressive effect.[19,28] Chronic ultraviolet light exposure damages dermal collagen and is carcinogenic. Histologically, ultraviolet irradiation leads to thickening of the epidermal and dermal layers and dermal or perivascular edema.[27]

The mechanisms whereby hypertrophic scars form remain enigmatic, and many treatments have relied on anecdotal evidence rather than prospective studies using control groups.[29,30] There are several potential mechanisms that might explain our observations. Inflammation, an important initiator of wound healing, may worsen scar hypertrophy when it is especially strong. An increase in immunocompetent cells, such as mast cells, leads to the release of cytokines that promote hypertrophic scarring.[1,31] Ultraviolet light has been shown to exert an immunosuppressive effect in the skin by altering cytokine profiles, inducing apoptosis, and attenuating the function of antigen-presenting cells, which may lead to a net decrease in collagen sythesis.[10,32] Additional research confirms that ultraviolet light exposure of human skin and cultured fibroblasts leads to decreased procollagen synthesis by means of a TGF-β/Smad pathway.[33–35] Indeed, phototherapy is a useful modality for treatment of the cutaneous manifestations of several autoimmune diseases.[2–7] Exposure of human dermal keratinocytes and fibroblasts to ultraviolet light in vitro and in vivo was associated with increased production of collagenases and matrix metalloproteinases, which degrade components of the extracellular matrix.[8,9,36–39] Given these established effects, it is plausible that a combination of decreased collagen production and increased degradation might account for our findings. Recently, a single case study has illustrated the ability of long-wave ultraviolet radiation to induce cosmetic flattening of hypertrophic scar tissue by altering collagen and elastic fiber orientation.[40] Given that hypertrophic scarring might arise from a prolonged inflammatory response in wounds, information gathered from this experiment may suggest new targets for intervention to combat hypertrophic scaring by inhibiting the degree of the immune response in early wounds or induction of metalloproteinases.

Although ultraviolet light exposure has long been known to induce pigmentary changes in scars, the precise contribution of ultraviolet radiation on cosmetic scar outcome is still unclear. In part, this issue is attributable to the lack of research that may lead to meaningful insights into the pathogenesis of ultraviolet irradiation on cosmetic scarring. In this study, we were unable to substantiate the common notion that sun exposure worsens scar hypertrophy. Indeed, the reduc-

tion in scarring that we observed in ultraviolet-B light–treated wounds suggests the opposite.

The effect of sunlight on the *appearance* of scars is not a simple calculus of ultraviolet light exposure to the wound or incision alone. These scars are healing in the context of the surrounding skin. Sunlight and concomitant ultraviolet light exposure may have differential effects on scar and the skin immediately adjacent; for instance, it may be that the pigmentary and color changes on a fresh wound vis-à-vis untouched skin result in enhanced visual contrast of the scar (which will thereby make the scar more visible). The caveat here is that this study examines the scar in isolation from its surrounding context and does not purport to investigate such important variables of appearance as color and pigment. In other words, the relationship between sunlight and scar appearance—especially in relation to the effect of sun on surrounding tissue—may be a little more complex than the specific relationship between ultraviolet light and scar. However, further molecular analysis of the action of ultraviolet light on cutaneous scarring may yield insights into the mechanisms of pathologic scarring and inform future therapies. The favorable outcome in our model of reduced hypertrophic scarring with ultraviolet-B irradiation may warrant further research in this direction.

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