Abstract

The negative health consequences of acute ultraviolet (UV) exposure are evident, with reports of 30,000 emergency room visits annually to treat the effects of sunburn in the United States alone. The acute effects of sunburn include erythema, edema, severe pain, and chronic overexposure to UV radiation, leading to skin cancer. Whereas the pain associated with the acute effects of sunburn may be relieved by current interventions, existing post-sunburn treatments are not capable of reversing the cumulative and long-term pathological effects of UV exposure, an unmet clinical need. Here we show that activation of the vascular endothelial growth factor (VEGF) pathway is a direct and immediate consequence of acute UV exposure, and activation of VEGF signaling is necessary for initiating the acute pathological effects of sunburn. In UV-exposed human subjects, VEGF signaling is activated within hours. Topical delivery of VEGF pathway inhibitors, targeted against the ligand VEGF-A (gold nanoparticles conjugated with anti-VEGF antibodies) and small-molecule antagonists of VEGF receptor signaling, prevent the development of erythema and edema in UV-exposed mice. These findings collectively suggest targeting VEGF signaling may reduce the subsequent inflammation and pathology associated with UV-induced skin damage, revealing a new postexposure therapeutic window to potentially inhibit the known detrimental effects of UV on human skin. It is essential to emphasize that these preclinical studies must not be construed as suggesting in any way the use of VEGF inhibitors as a sunburn treatment in humans because warranted future clinical studies and appropriate agency approval are essential in that regard.

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recent sunburn, they were using a form of sun protection, including sunscreen on the face, neck, and chest (38.8% of participants), sunscreen on the body (19.9%), wearing sunglasses (34.2%), wearing a baseball cap or visor (15.7%), staying in the shade (15.4%), wearing a wide-brimmed hat (12.3%), wearing clothes to the ankles (6.6%), or wearing a long-sleeved shirt (4.3%).9 Participants in this US-based survey reported that sunburns most frequently occurred while swimming or spending time in water (32.5%), working outdoors at home (26.2%), traveling or vacationing (20.7%), and performing nonswimming physical activity (14.2%).9 Although the risk of sunburns can be minimized by using various forms of sun protection, this study’s findings highlight the challenges associated with sunburn prevention, such as the need to reapply sunscreen during outdoor aquatic activities or the relatively low usage of pants and long-sleeved shirts for sun protection. Indeed, nearly 80% of participants recollected using at least one form of sun protection during the occurrence of their most recent sunburn.9 Current sunburn treatments, such as nonsteroidal anti-inflammatory medications, aloe vera gels, and systemic and topical corticosteroids, may provide immediate pain relief but do not reverse the cumulative and chronic pathological effects of UV exposure.10 Thus, viable postexposure sunburn treatments represent an unmet clinical need.

In addition to DNA damage,11 UV exposure causes immunomodulation through multiple molecular mechanisms in innate and adaptive immune systems. Acute inflammation is a well-established hallmark of the human body’s response to sunburn.12 However, the immediate pathological effects of sunburn (ie, pain, itching, swelling, redness, and skin that feels hot to the touch) can occur hours before the acute inflammatory response. Angiogenesis, the process of new blood vessel formation from pre-existing vessels, has been implicated in the initial skin response to UV exposure.13,14 Angiogenesis is characterized by the migration and proliferation of vascular endothelial cells and increased microvascular permeability. Vascular endothelial growth factor (VEGF) was initially discovered as “vascular permeability factor” (VPF), a tumor-secreted factor that strongly promotes vascular permeability,15 and subsequently identified as VEGF, an endothelial mitogen essential for the development of blood vessels.16 Vascular endothelial growth factor is upregulated following UV exposure in mice, and increased VEGF causes sensitization to UV and increased severity of sunburn, including greater vascularity and edema.13,14 However, the importance of VEGF activation in response to acute UV-induced skin damage remains underappreciated.

The VEGF family of proteins includes VEGF-A, VEGF-B, VEGF-C, VEGF-D, placenta growth factor, parapoxvirus VEGF-E, and snake venom VEGF-F. Vascular endothelial growth factor ligands bind with high affinity to the receptor tyrosine kinases, VEGFR-1, VEGFR-2, and VEGFR-3, which exhibit differences in their mode of activation, signal transduction, and downstream functional consequences.17 Receptor tyrosine kinase VEGFR-2 is the primary receptor in blood endothelium and signals to mediate endothelial cell permeability, proliferation, survival, and migration.18,19 Given that VEGF-A is the primary isoform involved in regulating angiogenesis via its interaction with VEGFR-2, VEGF-A will be referred to as “VEGF” henceforth as the focus of this overview. VEGF also binds to coreceptors, such as neuropilin-1, -2, and heparan sulfate proteoglycans,20-25 to form complexes consisting of receptors, coreceptors, and non-VEGF binding adaptors, such as integrins and ephrin B2.26 VEGF binding to a VEGFR results in receptor dimerization, stimulation of tyrosine kinase activity, and autophosphorylation of intracellular tyrosine residues.27 These VEGFR phosphotyrosines serve as docking sites for adaptor molecules that initiate various signaling pathways to regulate angiogenesis (Figure 1).17

We hypothesize that activation of the VEGF pathway is a direct and immediate consequence of acute UV exposure and is essential for initiating the pathological effects
VEGF can:

- Activate T-cells.
- ↑ IL-6 and TNFα in PBMCs.
- Push T-cells toward Th1 phenotype

**VEGF-producing cell**

UVB radiation

**VEGF-transcription & translation**

**VEGF**

**Paracrine**

**VEGF**

**Lymphangiogenesis**

**Endothelial cell**

**Vasculogenesis**

**Phosphatidylinositol (3,4,5)-trisphosphate**

**Diacylglycerol**

**Calcium**

**ER**

**Ca2+**

**Prostaglandin I2**

**Cell survival**

**Migration**

**Permeability**

**Proliferation**

**Angiogenesis**

**FIGURE 1.** Ultraviolet B (UVB) radiation activates vascular endothelial growth factor-A (VEGF-A)/VEGFR-2 signaling in endothelial cells and lymphocytes to regulate cellular functions. Ultraviolet B radiation causes increased production of VEGF-A, which binds to VEGFR-2 expressed on the surface of endothelial cells and immune cells. VEGF-A, a member of a family of proteins including VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, and placenta growth factor (PIGF), binds VEGFR-2 and various coreceptors to activate downstream signal transduction pathways that regulate survival, migration, and permeability in endothelial cells. In lymphocytes, VEGF/VEGFR-2 interactions stimulate T-cell activation and a shift towards a type 1 T helper (Th1) phenotype along with upregulation of interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-alpha) in peripheral blood mononuclear cells (PBMCs). VEGF-A also interacts with VEGFR-1 and VEGFR-3 to promote vasculogenesis and lymphangiogenesis, respectively.
of sun exposure in the epidermis. Supporting evidence suggests that UV induces VEGF and VEGFR-2 upregulation and that upregulation of VEGF sensitizes the skin to UV and increased sunburn severity. Therefore, we reason that VEGF signaling inhibition may prevent or reduce the pathological consequences of UV-induced skin damage, including the development of erythema and edema associated with acute sunburn. Acute ultraviolet B (UVB)–induced edema, erythema, and increased vascularity can be substantially reduced by disrupting VEGF signaling via systemic or topical anti-VEGF antibody administration.

Antibody-mediated suppression of VEGF signaling can be enhanced by gold nanoparticles (GNPs), which possess intrinsic antiangiogenic properties due to selective inhibitory interactions with heparin-binding growth factors, such as VEGF and bFGF.28 Nanoparticles represent an emerging type of broadly applicable nanotechnology, defined as nanometer-scale materials (0.1-100 nm) composed of a basic unit approximately equivalent to the size of 10 to 100 atoms arranged closely together.29,30 As early as 1857, Faraday reported the light-scattering potential of GNP, characterized by the change of red color and colloidal properties of nanomaterials.31 More recently, metal nanoparticles have been used for various medical applications, including drug and gene delivery, radiation therapy, diagnostics, and radiology.32 In particular, GNPs boost strong biocompatibility, very high surface area amenable to loading large amounts of conjugates, straightforward characterization, and easy surface modification to enable attachment of drugs, peptides, and antibodies.28,32,33 Here, we use GNPs conjugated to anti-VEGF antibodies to enhance VEGF signaling inhibition and amplify the associated reduction of angiogenesis. We have previously shown potential therapeutic applications of this approach by enhancing anti-VEGF antibody-mediated apoptosis of B-chronic lymphocytic leukemia cells by treating them with GNPs attached to anti-VEGF antibodies, which exhibited increased cellular cytotoxicity relative to antibody or GNPs administered alone separately.34

Here, we tested the hypothesis that activation of the VEGF pathway is a direct and immediate consequence of acute UV exposure and is essential for initiating the pathological effects of sun exposure in the epidermis. We propose that VEGF induction causes edema and the related immediate impact on the skin while working concomitantly with reactive oxygen species to induce inflammation. Specifically, we show that VEGF signaling is activated within hours of solar-simulated light exposure in human subjects. Using a mouse post-UV exposure model, we show that topical delivery of VEGF pathway inhibitors, targeted against the ligand VEGF-A (GNPs conjugated with anti-VEGF antibodies) and small-molecule antagonists of VEGF receptor signaling can dramatically prevent the subsequent development of erythema and edema associated with acute sunburn. Together, these results show a novel and clinically relevant method of skin injury treatment following UV exposure, highlighting the understudied role of the VEGF/VPF pathway in both acute and chronic sun damage.

METHODS

Mice
Six- to 8-week-old female SKH1-Elite hairless mice were purchased (Stain Code: 477, Charles River). All mice were housed in a temperature-controlled room with alternating 12-hour light/dark cycles, allowed 1 week to acclimate to their surroundings, and fed a standard diet. All animal work was conducted in accordance with the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health, and all animal protocols were approved by the Institutional Animal Care and Use Committee at Mayo Clinic and the University of Minnesota.

UV Irradiation Studies
Six- to 8-week-old female SKH1-Elite hairless mice were exposed to graded doses of a single UVB irradiation using fluorescent
lamps. The height of the lamps was adjusted to deliver 0.82 mW/cm² at the dorsal skin surface. The minimal erythema dose (MED) was determined by irradiation of eight 1-cm² areas on the skin on the front of mice with seven graded doses of UVB irradiation ranging from 0.056 J/cm² to 0.4 J/cm² as well as sham irradiation. Erythema formation was evaluated after 48 hours by two independent observers. To determine the systemic effect of VEGF inhibition on acute UVB skin injury, mice were treated with 50 μg VEGF-neutralizing antibody 2C3 by intraperitoneal injection 24 hours before exposure 0.144 J/cm² of UVB radiation to the ears. The extent of ear edema was determined by measuring ear thickness as previously described. Samples of dorsal skin and ears were snap-frozen in liquid nitrogen or fixed in formaldehyde. To evaluate topical treatment effectiveness on acute UVB exposure, ears of 6- to 8-week-old female C57BL/6 (n = 5 per group) were exposed to one dose of 0.144 J/cm² UVB radiation. Topical treatments (25 μg/mice mixed in 1 mL of Vanicream) or control vehicle (Vanicream) were applied 2 hours postradiation. The extent of ear edema was determined by measuring the change in ear thickness 48 hours postradiation. Samples of ears were snap-frozen in liquid nitrogen or fixed in formaldehyde. All mice were administered carprofen via their drinking water 48 hours before UV exposure to reduce pain from the UV-induced skin damage.

Preparation of GNP Antibody Cream
Vanicream (Pharmaceutical Specialties, Inc, Rochester, MN) was mixed with an equal GNP-antibody conjugate volume. The typical dose of GNP-antibody administered topically to each mouse was 25 μg unless indicated otherwise. VEGF-neutralizing antibodies used were 2C3 (Peregrine Pharmaceuticals, Tustin, CA) and bevacizumab (Avastin, Genentech, Washington, DC).

Gold Nanoparticle Antibody Conjugation
Naked GNP were synthesized by adding 500 mL of an aqueous solution containing 43 mg of sodium borohydride (Sigma Aldrich, St Louis, MO) to 1000 mL of 0.1 mM HAuCl₄ (Sigma Aldrich) solution under constant stirring, overnight at room temperature. The desired antibody (800 μg of 2C3, Avastin, or immunoglobulin G) was suspended in 1 mL of molecular biology grade water and added dropwise to 200 mL of naked GNP solution under constant stirring at ambient temperature for 2 hours. The mixture was centrifuged at 22,000 rpm in a Beckman Coulter ultracentrifuge at 4°C for 65 minutes twice to separate the GNP antibody conjugate from naked antibody. The supernatant was removed, and the conjugated GNP antibody pellet was suspended in molecular biology grade water to the desired concentration.

Quantitative Polymerase Chain Reaction Analysis
Purified RNA was isolated from mouse skin using the RNeasy Plus Mini Kit (Qiagen, Hilden, Germany) after pulverizing the frozen skin tissue and homogenization with the QIAshredder system (Qiagen). Quantitative polymerase chain reaction (PCR) was performed using the QuantiTech SYBR Green RT-PCR kit (Qiagen) per the manufacturer’s instructions. Briefly, RNA (50 ng) was added to 30-μL reactions with QuantiTech SYBR Green RT master mix, QuantiTech RT mix, and 0.5 pmol/μL of each of the oligonucleotide primers.

Total RNA was isolated from frozen mouse skin tissues using the RNeasy Plus kit (Qiagen) according to the manufacturer’s instructions. Mice skin tissues chopped with a sterile scalpel were lysed and homogenized with the QIAshredder system (Qiagen). Isolated RNA (30 ng) was subjected to quantitative real-time PCR analysis using iTaq Universal SYBR Green One-Step Kit (Bio-Rad, Hercules, CA) in the 7500 Real-Time PCR System (Applied Biosystems, Waltham, MA). The comparative threshold cycle method (ΔΔCt) was used to quantify relative amounts of murine VEGF-A transcripts. Mouse glyceraldehyde 3-phosphate dehydrogenase gene acts as an endogenous reference control. Primer sequences (forward and reverse, respectively) used for quantitative
real-time PCR were as follows: VEGFA: 5'-CAGGCTGCTGTAACGATGAA-3' and 5'-TCACCGCCTTGCTTGTACG-3'; glyceraldehyde 3-phosphate dehydrogenase: 5'-AACTTTGGCATTGTGGAAGG-3' and 5'-ACACATTGGGGTAGGAACA-3'.

Immunohistochemistry Staining
Human skin tissue specimens were collected from each of four human subjects at 5 minutes, 1 hour, 5 hours, and 24 hours post-exposure to 2.5 MED solar-simulated UV light at the University of Arizona in accordance with Institutional Review Board approval and informed written consent of all study participants.35 Formalin-fixed, paraffin-embedded, serially sectioned specimens mounted on glass slides were a generous gift from Dr Clara Curiel-Lewandrowski at the University of Arizona. Slides were immunostained using antibodies that recognize total VEGFR-2 (#2479, Cell Signaling Technology, Danvers, MA) and phosphorylation of VEGFR-2 at Y1175 (#2478, Cell Signaling Technology) as previously described.36 Pathological review and analysis of the immunostaining were performed by a board-certified pathologist (DMS) at the University of Minnesota, and histological findings have been reported in Figure 2 and the Supplemental Table (available online at http://www.mayoclinicproceedings.org).

Tissue was harvested from the ears of mice exposed to a single 1.0 MED UVB exposure of 0.144 J/cm², preceded by intraperitoneal injection with 50 μg VEGF-neutralizing antibody 2C3 or negative control phosphate-buffered saline (PBS) 24 hours before UVB exposure. Formalin-fixed, paraffin-embedded, serially sectioned specimens mounted on glass slides were immunostained using a polyclonal CD31 antibody (sc-1506, Santa Cruz Biotechnology, Dallas, TX). Following analysis of the immunostaining, representative histological images have been reported in the Supplemental Figure (available online at http://www.mayoclinicproceedings.org).

Statistical Analysis
Statistical comparisons were performed with one-way analysis of variance using GraphPad Prism 8 software. Differences between groups were considered significant when values of P<0.05. Dunnett multiple comparison tests were performed in all applicable experiments after one-way analysis of variance to make comparisons between groups.

FIGURE 2. Ultraviolet (UV) exposure activates vascular endothelial growth factor (VEGF) signaling in human subjects. Skin tissue specimens collected from human subjects (n=4) at 5 minutes, 1 hour, 5 hours, and 24 hours post-exposure to 2.5 minimal erythema dose (MED) solar-simulated UV light were immunostained using antibodies that detect total VEGFR-2 protein (left column) and VEGFR-2 phosphorylated at its Y1175 residue (p-VEGFR-2; right column). Representative images are shown. Scale bar indicates 20 μM.
Data are expressed as mean ± SEM and representative of at least two independent experiments.

RESULTS

We assessed whether activation of the VEGF pathway is a direct and immediate consequence of acute UV exposure in human subjects exposed to solar simulated UV light. We performed immunostaining for total VEGFR-2 protein and phosphorylation of VEGFR-2 at Y1175 (pVEGFR-2) using skin tissue specimens obtained from four human subjects exposed to a 2.5 MED of solar-simulated UV light (Figure 2). We observed virtually undetectable pVEGFR-2

![Graph A: VEGFA expression](image1)

![Graph B: Change in ear thickness](image2)

![Graph C: Change in ear thickness](image3)

![Graph D: Topical inhibition of VEGF](image4)

![Graph E: Relative VEGFA expression](image5)

**FIGURE 3.** Topical inhibition of vascular endothelial growth factor (VEGF) signaling reduces ultraviolet (UV)-induced skin damage in mice. A, Quantitative polymerase chain reaction (qPCR) was used to measure induction of VEGF transcript in mouse skin at 48 hours postexposure to various indicated doses of ultraviolet B (UVB) radiation (n=3 mice). B and C, Ears of mice (two separate experiments, n=4 mice per group) were exposed to a single 1.0 minimal erythema dose (MED) UVB exposure of 0.144 J/cm² after treatment with 50 µg VEGF-neutralizing antibody 2C3 or negative control phosphate-buffered saline (PBS) by intraperitoneal injection 24 hours prior. B, Representative images are shown. C, Extent of ear edema was determined by measuring ear thickness 48 hours postradiation. D, Ears of mice (n=5 mice per group) were exposed once to 1.0 MED of UVB radiation at 0.144 J/cm². Indicated topical treatments (25 µg per mouse; 12.5 µg per ear) or control vehicle (Vanicream) were applied 2 hours postradiation. Extent of ear edema was determined by measuring the change in ear thickness 48 hours postradiation. E and F, Topical administration of gold nanoparticle (GNP)—VEGF antibody (25 µg per mouse; 12.5 µg per ear) or small molecule inhibitor of VEGF signaling, sorafenib (25 µg per mouse; 12.5 µg per ear), reduces edema (two separate experiments, n=5 mice per group). All treatments were applied 2 hours following 1.0 MED UVB exposure of 0.144 J/cm² UVB. Ear thickness was measured 2 days after UVB exposure. F, Quantitative PCR was used to measure induction of VEGF transcript in mouse ear skin following UV exposure and treatment in a subset of mice.
immunostaining at 0, 5, and 60 minutes following UV exposure. At 5 hours post-UV exposure, mild to moderate pVEGFR-2 was observed within the stratum basale of the epidermis. By 24 hours post-UV exposure, similar pVEGFR-2 was also detectable but at a lesser frequency (Figure 2, Supplemental Table). Strong total VEGFR-2 staining was present within the dermis of human skin at all time points, whereas greater epidermal total VEGFR-2 expression positively correlated with increased duration of solar-simulated UV exposure (Figure 2, Supplemental Table). Together, these results suggest VEGF signaling is activated within 5 hours of UV exposure in humans.

Exposure to UVB irradiation induces skin alterations such as erythema, dilation of dermal blood vessels, vascular hyperpermeability, and epidermal hyperplasia, which comprises acute photodamage. To determine the MED required to induce these pathological features of acute skin damage, various UVB doses were applied to flank skin of immunocompetent, hairless SKH1 mice. Erythema was observed in mice by 48 hours, following exposure to 0.144 J/cm² or greater UVB. We performed quantitative PCR to determine VEGF expression level using mRNA derived from mice 48 hours after exposure to various doses of UVB. We observed dose-dependent increases in the skin starting at 0.144 J/cm² UVB (Figure 3A).

To determine whether VEGF induction is necessary for acute photodamage development, we treated mice with an intraperitoneal injection of 50 µg VEGF antibody 2C3 and exposed their ears to 1.0 MED. Along with erythema and increased vascularity, UVB-exposed, untreated mice showed signs of edema as evidenced by increased ear thickness. Intraperitoneal administration of 2C3 decreases blood vessel dilation (Figure 3B), reduces edema as shown by 50% decrease in ear thickness (Figure 3C), and reduces angiogenesis as shown by decreased CD31-positive endothelial cells in UVB-exposed mouse ears (Supplemental Figure). These findings suggest that VEGF is induced early and necessary for the development of acute photodamage.

We investigated the efficacy of topical administration of GNP-conjugated VEGF antibody in preventing acute photodamage after UVB exposure. As we intended this as a treatment instead of prophylactic measures, we applied the topical treatment 2 hours after exposing healthy mice ears to UVB. We showed that topical GNP conjugated to two different VEGF antibodies (2C3 or Avastin) is superior in reducing edema compared with topical VEGF antibody or GNP alone (Figure 3D). Topical administration of sorafenib, a small-molecule VEGFR-2 tyrosine kinase inhibitor, similarly reduced mouse ear thickness caused by UVB exposure (Figure 3E). Quantitative PCR of skin tissue RNA confirmed that topical administration of sorafenib or GNP conjugated VEGF antibody reduced VEGF transcript levels in UVB exposed mice (Figure 3F). These results suggest topical inhibition of VEGF signaling after UVB exposure effectively prevents the development of acute photodamage. To our knowledge, this is the first study demonstrating that acute UVB-induced skin injury can be prevented following exposure.

**DISCUSSION**

Solar UV radiation is subdivided into three categories: ultraviolet A (UVA), UVB, and ultraviolet C (UVC). Most UVB rays penetrate the epidermis or upper region of the dermis. Ultraviolet B light is 1000 to 10,000 times more carcinogenic than UVA radiation measured by DNA damage and erythema. Our studies focus on the molecular initiation of UVB-induced skin damage and its associated pathology and suggest that topical inhibition of VEGF/VPF signaling reduces photodamage in vivo, which occurs well before activating the innate immune response.

We propose that early activation of VEGF signaling is a direct and immediate response to acute UVB exposure that leads to edema and related pathological effects on the skin. We demonstrate through immunostaining that VEGFR-2 activation via phosphorylation
of the Y1175 residue in the epidermis of human subjects exposed to solar-simulated UV rays peaks at 5 hours postexposure. Reverse-phase protein arrays using similar human specimens suggested that VEGFR-2 Y996 was increased at 1 hour and 5 hours post-UV exposure. Although the functional consequences of VEGFR-2 Y996 are unknown, this residue serves as a docking site for SH2, SH3, or PTB domain-containing proteins to convey downstream signaling. VEGFR-2 Y1175 phosphorylation stimulates the PLCg-ERK1/2 cascade, regulates Ca2+ signaling, and cell survival and proliferation. Human keratinocytes and epidermis express VEGF receptors and coreceptors, and autocrine VEGF/VEGFR-2 signaling is activated in response to moderate UVB irradiation. VEGF is produced through distinct mechanisms by UVB and reactive oxygen species, as UVB has been shown to activate VEGF in the presence of antioxidants. UVB and inflammatory mediator prostaglandin E2 directly upregulate VEGF in human dermal fibroblasts and indirectly elevate VEGF in human epidermal keratinocytes. Potentiation of the VEGF/VEGFR-2-mediated angiogenic response induced by UVB in VEGF transgenic mice stimulated UV-induced cutaneous skin damage yet did not contribute to wound healing and repair mechanisms.

We show that VEGF-A is induced immediately following acute UVB exposure in mice. The acute UVB-induced edema, erythema, and increased vascularity can be substantially reduced by disrupting VEGF signaling via systemic or topical anti-VEGF antibody administration. Gold nanoparticles possess intrinsic antiangiogenic properties due to selective inhibitory interactions with heparin-binding growth factors, such as VEGF and basic fibroblast growth factor. Indeed, topical application of GNP conjugated to VEGF antibody synergistically reduces acute UVB-induced edema in mice. This is supported by studies demonstrating that UVB irradiation induces an angiogenic switch mediated by upregulation of VEGF and that elevation of VEGF increases photosensitivity. This effect is mediated through activation of VEGFR-2 as topical administration of sorafenib produces similar improvement. VEGF/VEGFR-2 transduces signals through JAK/STAT proteins, and inhibition of JAK2/STAT3-dependent autophagy with Sanshool exhibited a photoprotective effect in human dermal fibroblasts and hairless mice exposed to UVB irradiation.

CONCLUSION
Our findings suggest VEGF/VPF signaling is an immediate-early activator of UV-induced skin injury and plays an integral role in the associated pathology, which occurs well before the innate immune response. Thus, targeting VEGF/VEGFR-2 signaling reduces the subsequent inflammation and pathology associated with UV-induced skin damage. It is essential to emphasize that these preclinical studies must not be construed as suggesting in any way the use of VEGF inhibitors as a sunburn treatment in humans because warranted future clinical studies and appropriate agency approval are essential in that regard.

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SUPPLEMENTAL ONLINE MATERIAL
Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.
Abbreviations and Acronyms: GNP, gold nanoparticle; MED, minimal erythema dose; UV, ultraviolet radiation; UVB, ultraviolet B; VEGF, vascular endothelial growth factor; VPF, vascular permeability factor

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