is deficient in generalized atrophic benign epidermolysis bullosa. *J Clin Invest* 95:1345–52

Karamatic Crew V, Burton N, Kagan A et al. (2004) CD151, the first member of the tetraspanin (TM4) superfamily detected on erythrocytes, is essential for the correct assembly. *Blood* 104:2217–23

Kopecki Z, Arkell R, Powell BC et al. (2009) Flightless I regulates hemidesmosome formation and integrin-mediated cellular adhesion and migration during wound repair. *J Invest Dermatol* 129:2031–45

Litjens SHM, de Pereda JM, Sonnenberg A (2006) Current insights into the formation and breakdown of hemidesmosomes. *Trends Cell Biol* 16:376–83

Michels C, Buchta T, Bloch W et al. (2009) Classical cadherins regulate desmosome formation. *J Invest Dermatol* 129: 2072–75

Mitra SK, Hanson DA, Schlaepfer DD (2005) Focal adhesion kinase: in command and control of cell motility. *Nat Rev Mol Cell Biol* 6:56–68

Ozawa T, Tsuruta D, Jones JCR et al. (2010)

Dynamic relationship of focal contacts and hemidesmosome protein complexes in live cells. *J Invest Dermatol* 130:1624–35

Pfendner E, Uitto J (2005) Plectin gene mutations can cause epidermolysis bullosa with pyloric atresia. *J Invest Dermatol* 124:111–5

Pulkkinen L, Rouan F, Bruckner-Tuderman L et al. (1998) Novel ITGB4 mutations in lethal and non-lethal variants of epidermolysis bullosa with pyloric atresia: missense vs. nonsense. *Am J Hum Genet* 63: 1376–87

Sterk LM, Geuijen CA, Oomen LC et al. (2000). The tetraspan molecule CD151, a novel constituent of hemidesmosomes, associates with the integrin alpha6beta4 and may regulate the spatial organization of hemidesmosomes. *J Cell Biol* 149:969–82

Vasioukhin V, Bowers E, Bauer C et al. (2001) Desmoplakin is essential in epidermal sheet formation. *Nat Cell Biol* 3:1076–85

Yin T, Green KJ (2004) Regulation of desmosome assembly and adhesion. *Stem Cell Dev Biol* 15:665–77

# The Other End of the Rainbow: Infrared and Skin

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**Although infrared radiation (IRR) is ubiquitous in the terrestrial milieu, its effects on human skin have until now been largely ignored. Recent studies suggest an important role for infrared A (IRA) radiation (760–1440 nm) in dermal inflammation, photoaging, and photocarcinogenesis. In this issue, Calles et al. identify and analyze the IRA-induced transcriptome in human dermal fibroblasts. Their work paves the way for new research directions in IRA photobiology and raises important clinical questions regarding photoprotection and IRR-based dermatotherapy.**

## Introduction

The refraction of light into its constituent colors was first described in the eleventh century by the scientist and polymath Ibn al-Haytham (Alhacen) and was fully developed in Sir Isaac Newton's description of the electromagnetic spectrum in 1671. In 1800, astronomer William Herschel published his discovery of "calorific rays" beyond the red part of the visible spectrum. He found that refraction of light through a prism separated out a set of electromagnetic rays—later known as infrared radiation (IRR)—that produced an increase in temperature on a thermometer beyond that recorded in the visible spectrum (Mahmoud et al., 2008). Although IRR has been known to science for 210 years (1 year longer than has UVR), the impact of IRR on cutaneous pathology has received far less attention than its UV and visible counterparts. With the publication of the study by Calles and co-workers (2010, this issue), this may begin to change. These investigators exposed human dermal fibroblasts to infrared A (IRA) radiation and analyzed the IRA-induced transcriptome using microarray technology. The changes observed differed in several respects from those induced by UVR, and Calles et al. identified a number of candidate genes that could contribute to photoaging and carcinogenesis.

Unna (1894) first described a photodistributed dermatosis in sailors that he called *Seemanshaut*, a localized photoaging that he attributed to prolonged sun exposure. Early in the following century, Hyde (1906) and Dubreuilh (1907) published the first evidence linking human skin cancer to sunlight. Subsequent studies in mice isolated wavelengths in the ultraviolet spectrum (280–400 nm)—in particular, within UVB (280–320 nm)—as most proficient in causing nonmelanoma skin cancer (Findlay, 1928; Freeman, 1978). As such, photoprotection strategies have focused almost exclusively on limiting exposure to UVB and, increasingly, to UVA (320–400 nm).

Nonetheless, UVR constitutes only 7% of the solar energy that reaches the skin; 39% lies in the visible light spectrum (400–760 nm). But the most considerable fraction of solar energy (54%) consists of IRR (Kochevar et al., 1999), which comprises IRA (760–1440 nm), IRB (1440–3000 nm), and IRC (3000 nm–1 mm). Of these, only IRA—30% of the IRR that reaches the human body—penetrates deeply into the skin, and 65% of that portion reaches the dermis (Schroeder et al., 2010). Thus, IRA is well positioned to exert effects at that level.

### Infrared radiation in clinical and experimental dermatology

Until recently, chronic exposure to IRR (when administered below the threshold for inducing thermal injury) was recognized as the cause of only one skin disorder, erythema ab igne,

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a reticulate hyperpigmentation classically seen on the legs of those sitting too close to hearth fires. This constellation of epidermal atrophy, pigment incontinence, collagen degeneration, and dermal elastosis has seen a revival of late with the increased popularity of laptop computers. When allowed to rest on the legs for prolonged periods of time, these devices can also produce this uncommon dermatosis. Additionally, IRR was reported as causative in one case of keratosis lichenoides chronica (Vernassiere et al., 2004). IRA is present in the light produced by some tanning beds, and it has been implicated in the potentiation of UVR-induced damage in murine dermis (Kligman, 1982). On the other hand, IR pretreatment has recently been observed to reduce UVB-induced DNA damage in murine epidermis, apparently by stimulating nucleotide excision repair (Jantschitsch et al., 2009). Moreover, IRR is employed in cosmetic dermatology for the treatment of rhytides and skin laxity because of its ability to stimulate the production of dermal type I and III collagen and elastin (Tanaka et al., 2009b), and it has found clinical or investigative therapeutic utility in such skin conditions as scleroderma (Meffert et al., 1990), acne vulgaris (Orringer et al., 2007), wounds (Horwitz et al., 1999) and burns (Ezzati et al., 2009), and (in mice) in the treatment of melanoma (Dees et al., 2002).

But therapeutic uses may come at a price (Schieke et al., 2003). As mentioned previously, IRA wavelengths are much longer than those within the UV spectrum; therefore, they can penetrate deeply into the skin, making specific chromophores and dermal fibroblasts, which are critical for structural integrity and dermal elasticity, prime targets. Indeed, IRA-induced activation of mitogen-activated protein kinase (MAPK) signaling pathways upregulates matrix metalloproteinase-1 (MMP-1) expression in dermal fibroblasts. MMP-1 has been shown to be important for photoaging as well as for UV carcinogenesis. IRA-induced MMP-1 expression is due at least in part to retrograde mitochondrial

signaling, which results in the production of free radicals in the skin (Darvin et al., 2007; Schroeder et al., 2008). In this regard, it has been proposed that the terminal enzyme of the mitochondrial respiratory chain, cytochrome c oxidase, is an infrared chromophore (Karu et al., 2008).

> IRA penetrates deeply into skin to reach chromophores that activate unique molecular targets, ultimately producing unique biologic effects.

## Characterizing IRA-induced gene regulation

The current study extends our understanding of IRA-induced gene regulation in several exciting new directions. First, by assessing the IRA-induced transcriptome in cultured human fibroblasts and employing a selection algorithm to filter out interindividual differences, Calles et al. (2010) succeeded in identifying 599 differentially regulated gene transcripts that can be stratified into four primary categories: genes related to (i) extracellular matrix (ECM) homeostasis, (ii) calcium ion homeostasis, (iii) stress signaling, and (iv) apoptosis-related signaling. In each category, the differences in gene expression between irradiated and unirradiated fibroblasts shed new light on IRA-triggered pathways.

Among the genes of the extracellular matrix, MMP-1 is upregulated, but its compensatory tissue inhibitor of MMP-1 is not, creating an imbalance in favor of ECM degradation and supporting a role for IRA in photoaging. Additionally, proteins involved in cell adhesion and migration—fibronectin 1, VCAM-1, cadherin CDH10, and two integrin genes—were found to be downregulated by IRA irradiation, suggesting that IRA might impair wound healing processes. These data must be reconciled with the in vivo experimental

data (summarized by Peplow et al., 2009) that support the salutary effects of infrared laser photobiomodulation in murine wound healing. Of course, laser irradiation, focused at specific wavelengths (typically at the shorter end of the IRA spectrum), could be expected to demonstrate differences in gene transcription from IRA lamps emitting throughout the entire IRA spectrum, and the differences in transcriptomes at different specific IRA wavelengths would be an interesting subject for further study. Dosage may also play a role, because reduced stimulation—and even inhibition—of wound healing has been noted at higher doses in two studies (reviewed in Peplow et al., 2009).

Interestingly, one gene transcript that is upregulated is collagen I (COL1A1), consistent with the murine in vivo findings of Tanaka et al. (2009a), who observed the preferential induction of softer collagen I, resulting in increased dermal resiliency, after IRA irradiation of photoaged skin.

With respect to calcium ion homeostasis, the current study identifies 18 relevant IRA-modulated genes. Included among these are key players in calcium-induced signaling that are diminished in photoaging—the Na/K ATPase and key proteins in the phosphoinositol signaling pathway. At the same time, a constellation of upregulated genes appears to reflect the intracellular changes catalyzed by mitochondrial retrograde signaling in the context of oxidative stress.

The work of Calles et al. (2010) extends our knowledge in the realm of stress signaling as well. Previous work has shown that IRA activates the MAPK pathway (Schieke et al, 2003; Shibata et al, 2009). By employing inhibitors of the three main components of this pathway, the authors report that several stress-related genes activated by IRA are dependent on the extracellular signal-related kinase-1/2, p38, and c-Jun N-terminal kinase pathways.

The antiapoptotic and proliferative STAT3, an important mediator of tumor-promoting inflammation (Yu et al., 2009), is one of the stress-related genes that is upregulated by IRA. STAT3 is an important mediator of tumor-promoting inflammation (Yu

*et al.*, 2009), and this may help explain the role of chronic IRA in skin cancer. On the other hand, the IL-12/23 p40 subunit (*IL-12B* gene) was found to be upregulated by IRA. Both IL-12 and IL-23 have been found to trigger nucleotide excision repair in keratinocytes and to stimulate apoptosis. These cytokines also have been found to be effective in preventing UVR-induced immunosuppression and inhibiting UVR-induced regulatory T cells (Majewski *et al.*, 2010; Schwarz *et al.*, 2005). Cyclobutane pyrimidine dimers and UVR-induced immunosuppression are key factors in skin cancer initiation and promotion, and the upregulation of IL-12 and IL-23 in the dermal milieu by IRA may begin to explain the reported beneficial effects of IRA on UVR damage *in vivo* (Jantschitsch *et al.,* 2009).

Finally, Calles *et al.* elucidate the complex role of IRA in apoptosis, demonstrating downregulation of proapoptotic BAX and upregulation of survival proteins FASTK and TNFRSF6B on the one hand and upregulation of proapototic BAD via reactive oxygen species (ROS) induction of the P13K/AKT pathway on the other. As the authors note, this may help to explain the differential effects on apoptosis reported by others, depending on whether IRA irradiation precedes apoptogenic UVB irradiation (in which case it is antiapoptotic) or is applied alone (in which case it is proapoptotic). Future studies are warranted to delineate the mechanics of these effects more fully.

### Future directions at bench and bedside
Calles *et al.* (2010) open the door for further research into the biological actions of IRR on the skin. This form of radiant energy penetrates deeply into the skin, reaches a distinct set of chromophores, activates a unique set of molecular targets, and, as a consequence, produces unique biologic effects on the skin. The changes in genes well known for their roles in photoaging and photocarcinogenesis by IRA radiation are relevant to investigative dermatology, and these findings will guide studies in *in vivo* models. As noted above, differential effects on gene expression at different wavelengths within the IRA spectrum should be defined, and the intracellular IRA chromophores should be identified.

Calles and co-workers' findings are relevant to both prevention and therapy. As Schroeder *et al.* (2010) have noted, sun protection strategies must be reconsidered. Current sunscreens have not been evaluated for, and are unlikely to possess, efficacy against IRA. Topical application of antioxidants has been shown to abrogate IRA-induced MMP-1 production (Schroeder *et al.,* 2008), and this may be a viable anti-IRA strategy.

Although UVR effects on keratinocytes and IRR effects on dermal fibroblasts share a number of biological end points, there are substantial differences in gene expression, and the chromophores that initiate these processes, as well as the intracellular pathways that are activated by them, are quite different. This raises the question of whether there is cause for concern about the effects of visible light, which lies between UV and IR on the electromagnetic spectrum. Chromophores within the visible spectrum are present in skin, and recent electron spin resonance spectroscopy studies have demonstrated significant ROS generation in skin by visible light (Zastrow *et al.*, 2009).

New data about the effects of IRR on skin hold the promise of a greater understanding of cutaneous diseases, such as photoaging, with the ultimate goal of more effective preventive and therapeutic strategies for the functions in which this form of radiant energy participates.

### CONFLICT OF INTEREST
The authors state no conflict of interest.

### REFERENCES
Calles C, Schneider M, Macaluso F *et al.* (2010) Infrared A radiation influences the skin fibroblast transcriptome: mechanisms and consequences. *J Invest Dermatol* 130:1524–36

Darvin ME, Gersonde I, Albrecht H *et al.* (2007) *In vivo* Raman spectroscopic analysis of the influence of IR radiation on the carotenoid antioxidant substances beta-carotene and lycopene in the human skin. Formation of free radicals. *Laser Phys Lett* 4:318–21

Dees C, Harkins J, Petersen MG *et al.* (2002) Treatment of murine cutaneous melanoma with near infrared light. *Photochem Photobiol* 75:296–301

Dubreuilh W (1907) Epitheliomatose d'origine solaire. *Ann Dermatol Syphiligr* 8:387–416

Ezzati A, Bayat M, Sodabe T *et al.* (2009) Low-level laser therapy with pulsed infrared laser accelerates third-degree burn healing process in rats. *J Rehabil Res Dev* 46:543–54

Findlay GM (1928) Ultra-violet light and skin cancer. *Lancet* 2:1070–3

Freeman RG (1978) Action spectrum for ultraviolet carcinogenesis. *Natl Cancer Inst Monogr* 50:27–9

Horwitz LR, Burke TJ, Carnegie D (1999) Augmentation of wound healing using monochromatic infrared energy. Exploration of a new technology for wound management. *Adv Wound Care* 12:35–40

Hyde JN (1906) On the influence of light in the production of cancer of the skin. *Am J Med Sci* 131:1–22

Jantschitsch C, Majewski S, Maeda A *et al.* (2009) Infrared radiation confers resistance to UV-induced apoptosis via reduction of DNA damage and upregulation of antiapoptotic proteins. *J Invest Dermatol* 129:1271–9

Karu TI (2008) Mitochondrial signaling in mammalian cells activated by red and near-IR radiation. *Photochem Photobiol* 84:1091–9

Kligman LH (1982) Intensification of ultraviolet-induced dermal damage by infrared radiation. *Arch Dermatol Res* 272:229–38

Kochevar IE, Pathak MA, Parrish JA (1999) Photophysics, photochemistry, and photobiology. In: Freedberg IM, Eisen AZ, Wolff K *et al.* (eds) *Fitzpatrick's Dermatology in General Medicine*. McGraw-Hill: New York.

Mahmoud BH, Hexsel CL, Hamzavi IJ *et al.* (2008) Effects of visible light on the skin. *Photochem Photobiol* 84:450–62

Majewski S, Jantschitsch C, Maeda A *et al.* (2010) IL-23 antagonizes UVR-induced immunosuppression through two mechanisms: reduction of UVR-induced DNA damage and inhibition of UVR-induced regulatory T cells. *J Invest Dermatol* 130:554–62

Meffert H, Buchholtz I, Brenke A (1990) Mild infrared A hyperthermia in treatment of systemic scleroderma. *Dermatol Monatsschr* 176:683–6

Orringer JS, Kang S, Maier L *et al.* (2007) A randomized, controlled, split-face clinical trial of 1320-nm Nd:YAG laser therapy in the treatment of acne vulgaris. *J Am Acad Dermatol* 56:432–8

Peplow PV, Chung T-Y, Baxter GD (2009) Laser photobiomodulation of wound healing: a review of experimental studies in mouse and rat animal models. *Photomed Laser Surg*; e-pub ahead of print 8 December 2009

Schieke SM, Schroeder P, Krutman J (2003) Cutaneous effects of infrared radiation: from

clinical observations to molecular response mechanisms. *Photodermatol Photoimmunol Photomed* 19:228–34

Schroeder P, Lademann J, Darvin ME *et al.* (2008) Infrared radiation-induced matrix metalloproteinase in human skin: implications for protection. *J Invest Dermatol* 128:2491–7

Schroeder P, Calles C, Benesova T *et al.* (2010) Photoprotection beyond ultraviolet radiation—effective sun protection has to include protection against infrared A radiation-induced skin damage. *Skin Pharmacol Physiol* 23:15–7

Schwarz A, Maeda A, Kernebeck K *et al.* (2005) Prevention of UV radiation-induced immunosuppression by IL-12 is dependent on DNA repair. *J Exp Med* 201:173–9

Shibata Y, Araki H, Oshitani T *et al.* (2009) Effects of linear polarized infrared light irradiation on the transcriptional regulation of IL-8 expression in IL-1beta-stimulated human rheumatoid synoviocytes involves phosphorylation of the NF-kappaB RelA subunit. *J Photochem Photobiol B* 94:164–70

Tanaka Y, Matsuo K, Yuzuriha S *et al.* (2009a) Differential long-term stimulation of type I versus type III collagen after infrared irradiation. *Dermatol Surg* 35:1099–104

Tanaka Y, Matsuo K, Yuzuriha S (2009b) Long-term evaluation of collagen and elastin following infrared (1100 to 1800 nm) irradiation. *J Drugs Dermatol* 8:708–12

Unna PG (1894) *Die Histopathologie der Hautkrankheiten*. Hirschwald: Berlin, Germany.

Vernassiere C, Reichert Penetrat S, Martin S *et al.* (2004) Kératose lichénoïde striée et exposition prolongée aux infrarouges. *Ann Dermatol Venereol* 131:575–7

Yu H, Pardoll D, Jove R (2009) STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer* 9:798–809

Zastrow L, Groth N, Klein F *et al.* (2009) The missing link—light-induced (280-1,600 nm) free radical formation in human skin. *Skin Pharmacol Physiol* 22:31–44