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The Other End of the Rainbow: Infrared and Skin

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Summary

Although infrared radiation is ubiquitous in the terrestrial milieu, the effects of infrared radiation on human skin have traditionally been ignored. Recent studies suggest an important role for infrared A 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 IR-based dermatotherapy.

Introduction

The refraction of light into its constituent colors was first described in the 11th 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, which later became 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 infrared radiation has been known to science for 210 years, one year longer than ultraviolet radiation (UVR), the impact of infrared radiation on cutaneous pathology has received far less attention than its ultraviolet 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 IRA radiation and using microarray technology have analyzed the IRA-induced transcriptome. The changes observed differed in several respects from UV and identified a number of candidate genes that could contribute to photoaging and skin cancer.

Unna in 1894 first described a photodistributed dermatosis in sailors that he called "Seemanshaut," localized photoaging which 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), and in particular within the UVB (280–320 nm) as the most proficient at causing nonmelanoma skin cancers (Findlay, 1928; Freeman, 1978) among those wavelengths that reach the terrestrial surface (290–4,000 nm). As such, photoprotection strategies have focused almost exclusively on limiting exposure to wavelengths within the UVB and, increasingly, the UVA (320–400 nm).

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Conflict of Interest
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Nonetheless, ultraviolet radiation 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 infrared radiation (Kochevar *et al.*, 1999). IR radiation is divided into IRA (760–1440 nm), IRB (1440–3000 nm) and IRC (3000 nm-1 mm). Of these, only the IRA fraction – 30% of the IR radiation 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 on the dermis.

Infrared radiation in clinical and experimental dermatology

Until recently, chronic exposure to infrared radiation (when administered below the threshold for inducing thermal injury) was recognized as the cause of only one skin disorder, erythema ab igne, 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 had a revival of late with the increased popularity of laptop computers. Laptop computers, allowed to rest on the legs for prolonged periods of time, can also produce this uncommon dermatosis. Additionally, IR was reported as causative in one case of keratosis lichenoides chronica (Vernassiere *et al.*, 2004). IRA is present in some tanning beds and has been implicated in the potentiation of UV-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, IR is also 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 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 this indulgence comes at a price (Schieke, et al, 2003). As was mentioned, IRA wavelengths are much longer than those within the UV spectrum and therefore penetrate more deeply into the skin. This makes additional chromophores and dermal fibroblasts, which are critical for structural integrity of the skin and dermal elasticity, prime targets of this form of radiant energy. 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 at 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).

Identifying IRA-induced gene regulation

The current study extends this knowledge in several exciting new directions. First, by assessing the IRA- induced transcriptome in cultured human fibroblasts, and employing a selection algorithm to filter out inter-individual differences, Calles *et al.* succeeded in identifying 599 differentially regulated gene transcripts which can be stratified into four primary groups: genes related to (a) extracellular matrix (ECM) homeostasis; (b) calcium ion homeostasis; (c) stress signaling; and (d) apoptosis-related signaling. In each category, the differences in gene expression between irradiated and unirradiated fibroblasts shed new light upon IRA-triggered pathways.

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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, 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 down-regulated by IRA irradiation, suggesting that IRA might impair wound healing processes. This data needs to be reconciled with the *in vivo* experimental data (summarized by Peplow *et al*.,2009) that supports 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. Also, dosage may play a role, as reduced stimulation, and even inhibition, of wound healing, has been noted at higher doses in two studies (Peplow *et al.*, 2009).

Interestingly, one gene transcript that is upregulated is collagen I (COL1A1). These findings are consistent with the in vivo findings of Tanaka, *et al.* (2009a) in mice 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 genes is upregulated that appear to reflect the intracellular changes catalyzed by mitochondrial retrograde signaling in the context of oxidative stress.

The study 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). Employing inhibitors of the three main components of this pathway, the authors have found that several stress related genes activated by IRA are dependent on the ERK 1/2, p38 and JNK pathways.

The anti-apoptotic and proliferative STAT3, an important mediator of tumor-promoting inflammation (Yu H *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 H *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 two cytokines have additionally been found to have efficacy 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 help to begin to explain the reported beneficial effects of IRA on UVR damage in vivo (Jantschitsch *et al.*, 2009).

Finally, the current study provides further information regarding 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 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 upon whether IRA irradiation precedes apoptogenic UVB irradiation (in which case it is antiapoptotic) or

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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

This report opens the door for further research into the biological actions of IR on the skin. This form of radiant energy penetrates more deeply into the skin, has a distinct set of chromophores, activates a unique set of molecular targets, and, as a consequence, produces biologic effects on the skin that are different from other forms of radiant energy. The changes in genes well-known for their roles in photoaging and photocarcinogenesis by IRA radiation is of obvious relevance to investigative dermatology, and these findings will be of immense help in guiding studies in in vivo models. As noted above, differential effects upon gene expression at different wavelengths within the IRA spectrum should be defined, and the intracellular IRA chromophores will need to be identified.

The clinical relevance of these findings touches upon aspects of both prevention and therapy. As Schroeder *et al.* (2010) have noted, sun protection strategies need to 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 endpoints, 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 interesting question as to whether there is cause for concern about visible light, which lies between UV and IR on the electromagnetic spectrum. Chromophores within the visible spectrum are present in the skin and recent electron spin resonance spectroscopy studies have demonstrated significant ROS generation in skin by visible light (Zastrow *et al.*, 2009).

The generation of new knowledge about the effects of IR on the skin holds the promise of greater understanding of cutaneous diseases, such as photoaging, with the ultimate goal of more effective preventative and therapeutic strategies in which this form of radiant energy participates.

References

Darvin ME, Gersonde I, Albrecht H, Zastrow L, Sterry W, Lademann J. *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 Physics Letters 2007;4:318–21.

Dees C, Harkins J, Petersen MG, Fisher WG, Wachter EA. Treatment of murine cutaneous melanoma with near infrared light. Photochem Photobiol 2002;75:296–301. [PubMed: 11950096]

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

Ezzati A, Bayat M, Sodabe T, Mohsenifar Z. Low-level laser therapy with pulsed infrared laser accelerates third-degree burn healing process in rats. J Rehabil Res Dev 2009;46:543–54. [PubMed: 19882488]

Findlay GM. Ultra-violet light and skin cancer. Lancet 1928;2:1070–1073.

Freeman RG. Action spectrum for ultraviolet carcinogenesis. Natl Cancer Inst Monogr 1978;50:27–9. [PubMed: 753977]

Horwitz LR, Burke TJ, Carnegie D. Augmentation of wound healing using monochromatic infrared energy. Exploration of a new technology for wound management. Adv Wound Care 1999;12:35–40. [PubMed: 10326355]

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

Jantschitsch C, Majewski S, Maeda A, Schwarz T, Schwarz A. Infrared radiation confers resistance to UV-induced apoptosis via reduction of DNA damage and upregulation of antiapoptotic proteins. J Invest Dermatol 2009;129:1271–9. [PubMed: 19037232]

Karu TI. Mitochondrial signaling in mammalian cells activated by red and near-IR radiation. Photochem Photobiol 2008;84:1091–9. [PubMed: 18651871]

Kligman LH. Intensification of ultraviolet-induced dermal damage by infrared radiation. Arch Dermatol Res 1982;272:229–38. [PubMed: 7165330]

Kochevar, IE.; Pathak, MA.; Parrish, JA. Photophysics, photochemistry, and photobiology. In: Freedberg, IM.; Eisen, AZ.; Wolff, K.; Austen, KF.; Goldsmith, LA.; Katz, SI., et al., editors. Fitzpatrick's Dermatology in General Medicine. McGraw-Hill; New York: 1999.

Mahmoud BH, Hexsel CL, Hamzavi IJ, Lim HW. Effects of visible light on the skin. Photochem Photobiol 2008;84:450–462. [PubMed: 18248499]

Majewski S, Jantschitsch C, Maeda A, Schwarz T, Schwarz A. 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 2010;130:554–62. [PubMed: 19727119]

Meffert H, Buchholtz I, Brenke A. Mild infrared A hyperthermia in treatment of systemic scleroderma. Dermatol Monatsschr 1990;176:683–6. [PubMed: 2083608]

Orringer JS, Kang S, Maier L, Johnson TM, Sachs DL, Karimipour DJ, et al. A randomized, controlled, split-face clinical trial of 1320-nm Nd:YAG laser therapy in the treatment of acne vulgaris. J Am Acad Dermatol 2007;56:432–8. [PubMed: 17239987]

Lim CP, Phan TT, Lim IJ, Cao X. Stat3 contributes to keloid pathogenesis via promoting collagen production, cell proliferation and migration. Oncogene 2006;25:5416–25. [PubMed: 16619044]

Peplow PV, Chung T-Y, Baxter GD. Laser photobiomodulation of wound healing: a review of experimental studies in mouse and rat animal models. Photomed Laser Surg. 2009 advance online publication, 8 December, 2009. 10.1089/pho.2008.2446

Ren ZP, Ponten F, Nister M, Ponten J. Two distinct p53 immunohistochemical patterns in human squamous-cell skin cancer, precursors and normal epidermis. Int J Cancer 1996;69:174–9. [PubMed: 8682583]

Schieke SM, Schroeder P, Krutman J. Cutaneous effects of infrared radiation: from clinical observations to molecular response mechanisms. Photodermatol Photoimmunol Photomed 2003;19:228–234. [PubMed: 14535893]

Schroeder P, Lademann J, Darvin ME, Stege H, Marks C, Bruhnke S, et al. Infrared radiation-induced matrix metalloproteinase in human skin: implications for protection. J Invest Dermatol 2008;128:2491–7. [PubMed: 18449210]

Schroeder P, Calles C, Benesova T, Macaluso F, Krutmann J. Photoprotection beyond ultraviolet radiation – effective sun protection has to include protection against infrared A radiation-induced skin damage. Skin Pharmacol Physiol 2010;23:15–7. [PubMed: 20090404]

Schwarz A, Maeda A, Kernebeck K, et al. Prevention of UV radiation-induced immunosuppression by IL-12 is dependent on DNA repair. J Exp Med 2005;201:173–9. [PubMed: 15657287]

Shibata Y, Araki H, Oshitani T, et al. 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 2009;94:164–170. [PubMed: 19135383]

Tanaka Y, Matsuo K, Yuzuriha S, Shinohara H. Differential long-term stimulation of type I versus type III collagen after infrared irradiation. Dermatol Surg 2009;35:1099–1104. [PubMed: 19438688]

Tanaka Y, Matsuo K, Yuzuriha S. Long-term evaluation of collagen and elastin following infrared (1100 to 1800 nm) irradiation. J Drugs Dermatol 2009;8:708–12. [PubMed: 19663107]

Unna, PG. Die Histopathologie der Hautkrankheiten. A. Hirschwald; Berlin: 1894.

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Vernassiere C, Reichert Penetrat S, Martin S, Barbaud A, Schmutz JL. Kératose lichénoïde striée et exposition prolongée aux infrarouges. Ann Dermatol Venereol 2004;131:575–7. [PubMed: 15318141]

Yu J, Pardoll D, Jove R. STATs in cancer inflammation and immunity: a leading role for STAT3. Nat Rev Cancer 2009;9:798–809. [PubMed: 19851315]

Yu XJ, Li CY, Dai HY, Cai DX, Wang KY, Xu YH, et al. Expression and localization of the activated mitogen-activated protein kinase in lesional psoriatic skin. Exp Mol Pathol 2007;83:413–8. [PubMed: 17599830]

Zastrow L, Groth N, Klein F, Kockott D, Lademann J, Renneberg R, et al. The missing link—light-induced (280–1,600 nm free radical formation in human skin. Skin Pharmacol Physiol 2009;22:31–44. [PubMed: 19122479]