Effects of Infrared Radiation and Heat on Human Skin Aging *in vivo*

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Sunlight damages human skin, resulting in a wrinkled appearance. Since natural sunlight is polychromatic, its ultimate effects on the human skin are the result of not only the action of each wavelength separately, but also interactions among the many wavelengths, including UV, visible light, and infrared (IR). In direct sunlight, the temperature of human skin rises to about 40°C following the conversion of absorbed IR into heat. So far, our knowledge of the effects of IR radiation or heat on skin aging is limited. Recent work demonstrates that IR and heat exposure each induces cutaneous angiogenesis and inflammatory cellular infiltration, disrupts the dermal extracellular matrix by inducing matrix metalloproteinases, and alters dermal structural proteins, thereby adding to premature skin aging. This review provides a summary of current research on the effects of IR radiation and heat on aging in human skin *in vivo*.

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INTRODUCTION

Infrared (IR) radiation consists of wavelengths from 760 nm to 1 mm, and it is subdivided into three regions of increasing wavelength, IR-A (760–1400 nm), IR-B (1400–3000 nm), and IR-C (3000 nm–1 mm). Given that almost half of the solar energy reaching the earth's surface is in the IR range, solar IR is expected to have significant biological effects on human skin.

Heat is a form of energy that may be transmitted by IR radiation, which results in raised skin temperature. Human skin is exposed daily to natural sunlight. We found that the temperature of human skin can increase to more than 40°C under direct IR irradiation (Lee *et al.*, 2006) due to the conversion of IR into heat. There is clinical evidence indicating that chronic heat exposure of human skin may cause alterations. The skin disease called erythema ab igne is known to be caused by chronic heat exposure. It is characterized clinically by reticular pigmentation of the skin and histologically by the presence of solar elastosis in the dermis similar to what is seen in photoaged skin. Furthermore, severe skin aging may develop occasionally on bakers' arms, because of exposure to hot ovens, and on the faces of glass blowers.

However, the effects of IR radiation and heat on cutaneous aging are still largely unknown. This review provides an overview of the current knowledge of contributions of IR radiation and heat exposure to aging in human skin.

EFFECTS OF IR RADIATION ON AGING IN HUMAN SKIN *IN VIVO*

It has been reported that IR-A can penetrate epidermal and dermal layers and reach subcutaneous tissues without increasing the skin temperature significantly, whereas IR-B and IR-C are absorbed mostly in the epidermal layers and increase skin temperature significantly (Schieke *et al.*, 2003). The few studies conducted on IR collectively have concluded that IR radiation produces heat upon exposure. Considering the general principle that all biochemical processes are affected by temperature, the effects of IR on human skin can no longer be ignored.

Effects of IR on the expression of collagen and MMPs in human skin *in vivo*

Alterations and deficiencies of collagen, the major structural component of the skin, have been suggested to be a cause of the skin wrinkling observed in both photoaged and naturally aged skin (Fisher *et al.*, 1997; Varani *et al.*, 2000). Because collagen fibrils are responsible for the strength and resilience of skin, their disarrangement during photoaging causes the skin to appear aged. Excessive matrix degradation by UV-induced matrix metalloproteinases (MMPs) secreted by various cells, including keratinocytes, fibroblasts, and inflammatory cells, contributes substantially to the connective tissue damage that occurs during photoaging (Fisher *et al.*, 1996; Chung *et al.*, 2001, 2002). Although human skin is frequently exposed to IR radiation, little is known about the

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Abbreviations: IR, infrared; MMP, matrix metalloproteinase; ROS, reactive oxygen species; TRPV, transient receptor potential vanilloid

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biological effects of IR on collagen metabolism. We reported the effects of acute and chronic IR exposure on type I procollagen expression (Kim *et al.*, 2006b). To investigate the effects of IR irradiation, we exposed human buttock skin to near-IR radiation. Previously, we had proposed the minimal heating dose as a standard unit to measure IR energy incident on human skin (Lee *et al.*, 2006). When we irradiated volunteers' skin with IR, skin temperature rose to a certain point and then plateaued. We defined this radiation dose where the skin temperature plateaued as the minimal heating dose. Three minimal heating doses were irradiated on human buttock skin once or three times a week for 4 weeks. It was found that although single IR irradiation increased type I procollagen expression, multiple irradiations reduced its expression (Kim *et al.*, 2006b). Single IR irradiation increased the expression of TGF-β1, -β2, and -β3 in human skin *in vivo*, whereas repeated IR irradiation reduced the expression of these TGF-βs. It is well known that TGF-β potently stimulates the proliferation of fibroblasts in the dermis and induces the synthesis and secretion of procollagen (Massague, 1998). Therefore, alterations in TGF-β may have influenced type I procollagen expression in IR-exposed human skin.

It was reported that a single treatment of human dermal fibroblasts with IR-A-induced MMP-1 (Schieke *et al.*, 2002). However, we demonstrated that MMP-1 was not induced by single IR irradiation in human skin *in vivo* (Kim *et al.*, 2006b). In contrast to the effects of a single IR irradiation, multiple IR irradiations significantly increased MMP-1 expression. Therefore, repeated IR exposure might induce premature skin aging (photoaging) in human skin *in vivo*.

To determine whether IR can induce wrinkles *in vivo*, mice were irradiated with IR five times a week for 15 weeks ($30\,J\,day^{-1}$) (Kim *et al.*, 2005). We observed that IR can cause skin wrinkling and augment UV-induced wrinkle formation through induction of MMPs (Kim *et al.*, 2005).

IR exposure turns on an angiogenic switch in human skin *in vivo*

Photoaging is the process whereby skin is prematurely aged by repeated exposure to solar UV radiation, and skin angiogenesis plays a critical role in this process (Yano *et al.*, 2002). Acute UV exposure of human skin is known to induce angiogenesis, that is, to form new blood vessels, in human skin. These new vessels are immature and leaky, resulting in cutaneous inflammation by extravasation of inflammatory cells and by the inflammatory mediators produced by these cells. These events may contribute to further degradation of extracellular matrix proteins, providing an adverse, less permissive environment for the maintenance of normal vessel structure and function, leading to progressive loss of cutaneous vessels in photoaged skin (Chung and Eun, 2007). As is the case with UVB, exposure of human skin to near-IR induces dermal angiogenesis and alters the balance between epidermal angiogenic factor (that is, VEGF) and endogenous angiogenic inhibitor (that is, TSP-2) (Kim *et al.*, 2006a).

Acute exposure of human skin to IR radiation increases mast cell number and tryptase expression in human skin *in vivo*

Mast cells are present in tissues throughout the body but are most prevalent at sites that are exposed to the environment, such as skin, airways, and gastrointestinal tract (Metcalfe *et al.*, 1997). Two types of mature human mast cells have been described, based on differences in their neutral protease composition (Irani *et al.*, 1986). MC_T cells contain tryptase alone, whereas MC_{TC} cells contain tryptase, chymase, and cathepsin G. UV radiation is considered an extrinsic factor that can alter the prevalence of mast cells (Grimbaldeston *et al.*, 2003). Several studies have demonstrated that sun-exposed human skin has more mast cells than sun-protected skin (Bhawan *et al.*, 1992; Bosset *et al.*, 2003). Recently, we also found that the number of mast cells in sun-exposed facial skin is always significantly higher than that in sun-protected buttock skin within the same individual (Kim *et al.*, 2009). On the other hand, the effect of IR on dermal mast cell prevalence remains unclear at present. We demonstrated that human skin mast cells are activated and recruited by IR as well as by UV. After IR irradiation of the buttock skin of young subjects, the number of MC_{TC} was significantly increased at 24 h post-IR, while the number of MC_T was not affected significantly. Tryptase expression was also clearly upregulated by IR treatment in human skin *in vivo* (Kim *et al.*, 2009).

EFFECTS OF HEAT ON AGING PROCESSES IN HUMAN SKIN *IN VIVO*

Effects of heat on the expression of MMP-12 in human skin *in vivo*

We demonstrated that heat shock induced the expression of MMP-1 and MMP-3, but not MMP-2, at the mRNA and protein levels in a dose-dependent manner in cultured normal human skin fibroblasts through activation of ERK and JNK and an autocrine IL-6 loop (Park *et al.*, 2004). This increased expression of MMPs by heat leads to degradation of extracellular matrix proteins such as collagen and elastic fibers. Heat is also known to induce MMP-12, which is capable of destroying the pre-existing elastic fiber network, thereby contributing to the accumulation of elastotic material in photoaged skin (Chen *et al.*, 2005). Therefore, heat, like UV, is a major environmental stimulus that probably plays an important role in the development of solar elastosis and premature skin aging.

Effects of heat on the expressions of tropoelastin and fibrillin-1 in human skin *in vivo*

It has been reported that chronic IR exposure can cause pronounced elastosis in mouse skin, changes that mimic the damage caused by UV (Kligman, 1982). It is known that repeated and prolonged exposure to heat insufficient to produce a burn causes erythema ab igne, which is characterized histologically by the basophilic degeneration of connective tissue and the alteration of elastic fibers, which resembles elastotic changes in photoaged skin (Hurwitz and Tisserand, 1987).

Heat was found to increase tropoelastin mRNA and protein expression in the epidermis and in the dermis (Chen *et al*., 2005). Fibrillin-1 mRNA and protein expression were increased by heat in the epidermis but were diminished in the dermis (Chen *et al*., 2005). Therefore, the abnormal production of tropoelastin and fibrillin by heat, like UV, in human skin and their degradation by various MMPs, such as MMP-12, may add to the accumulation of elastotic material in photoaged skin (Chen *et al*., 2005).

Heat induces angiogenesis in human skin *in vivo*

IR radiation accounts for approximately 40% of the solar radiation energy reaching the earth's surface, subsequently generating heat and increasing skin temperature. We demonstrated that heat increases angiogenesis in human skin *in vivo*. The ratio of VEGF to TSP-1 and 2 is increased after heat treatment, leading to increased angiogenesis (Kim *et al*., 2006a). Therefore, heat, in addition to UV, is an important physical stimulus for angiogenesis.

Effects of heat on cytokine expression in human skin

Heat can induce various cytokines in human skin. To investigate the effects of heat treatment on TGF-β expression, human buttock skin was heated for 90 minutes at 43°C. The expression of TGF-β1 and -β2 were increased at 24 hours, whereas that of TGF-β3 was decreased 24 hours after heat treatment (Seo and Chung, 2006). Heat treatment also increased the expression of IL-6 and IL-12 mRNA significantly in cultured dermal fibroblasts (Seo and Chung, 2006). Heat induces various cytokines, and these cytokines in turn regulate the extracellular matrix protein metabolism in human skin.

Effects of heat on ROS production

The transcriptional upregulation of MMPs can be mediated by the increased production of reactive oxygen species (ROS). UV irradiation induces the formation of ROS in cutaneous tissue (Kitazawa *et al*., 1997; Scharffetter-Kochanek *et al*., 1997). ROS can be generated by many different organelles in response to various stimuli. Various enzyme systems including cyclooxygenase, nitric oxide synthase (NOS), xanthine oxidase, ribonucleotide reductase, mitochondrial electron transport systems, and NADPH oxidase are involved in ROS production (Curtin *et al*., 2002). Like UV, heat shock generates H_2O_2 and $O_2^{\bullet -}$ (Hall *et al*., 1994; Zhang *et al*., 2003). Heat shock-driven generation of ROS substantially affects the signaling pathways leading to MMP-1 and MMP-9 induction. Heat shock generates H_2O_2 and $O_2^{\bullet -}$ through NADPH oxidase, xanthine oxidase, and the mitochondrial electron transport system in HaCaT cells (Shin *et al*., 2008). Heat shock-induced $O_2^{\bullet -}$ is responsible for MMP-9 expression, whereas H_2O_2 is involved in the induction of both MMP-1 and -9 (Shin *et al*., 2008).

It has been demonstrated that topical application of antioxidants, genistein or *N*-acetylcystein, can interrupt the UV-signaling cascade that leads to photoaging (Kang *et al*., 2003). These investigators demonstrated that UV increases H_2O_2 in human skin *in vivo* and that both antioxidants blocked UV-induced signaling. As heat is known to cause ROS generation, we investigated the role of ROS in heat-induced tropoelastin and fibrillin-1 expression (Chen *et al*., 2005). We found that pretreatment with *N*-acetylcystein or genistein for 24 h prior to heat treatment inhibited the heat-induced expression of tropoelastin in the epidermis, but not of fibrillin-1 (Chen *et al*., 2005). These results indicate that heat-induced ROS may play a critical role in heat-induced tropoelastin expression, but not in heat-induced fibrillin-1 expression.

Heat induces oxidative DNA damage in human skin *in vivo*

UV radiation is absorbed directly by DNA and leads to the formation of pyrimidine dimers, of which more than 75% are thymine dimers (Patrick, 1977). UV radiation produces ROS. DNA is also susceptible to oxidative damage, and 8-oxo-dG is a useful biomarker of oxidative damage in DNA (Pelle *et al*., 2003). As heat shock in human skin can produce ROS, we investigated the effects of heat shock on DNA damage in human skin *in vivo*. Interestingly, heat shock at 43°C for 90 minutes, like UV irradiation, increased the 8-oxo-dG in the epidermis and dermis of human skin *in vivo* maximally at 24 hours post-heat (Figure 1a). However, heat shock, unlike UV, did not produce thymidine dimer formation (Figure 1b). Therefore, heat-induced ROS induce cumulative DNA damage through oxidative damage.

The effects of IR and heat in the natural sunlight on human skin

In addition to UV radiation, IR plus visible light and the heat energy generated by sunlight exposure induce MMP-1 expression after exposing human skin to natural sunlight (Cho *et al*., 2008). IR plus visible light also increase MMP-9 expression and decrease type I procollagen synthesis after exposure to natural sunlight (Cho *et al*., 2008). Only UV radiation within natural sunlight results in neutrophil infiltration in human skin at least at 24 hours after exposure, whereas IR radiation and heat, in addition to UV, can recruit macrophages.

TRPV1 in the keratinocytes as a heat sensor

Transient receptor potential vanilloid (TRPV) ion channels are a large family of nonselective cation channels that are expressed in human keratinocytes, and they are known to be activated by capsaicin, noxious heat, and low pH (Szallasi and Blumberg, 1999). TRPV1 itself is known to be a heat sensor. TRPV1 can be activated by noxious heat with a threshold of about 43°C (Hayes *et al*., 2000). However, the function of TRPV1 in cutaneous physiology and pathology has not been elucidated. Recently, we found that activation of TRPV1 by heat shock mediates the heat shock-induced MMP-1 expression in HaCaT cells (Li *et al*., 2007; Lee *et al*., 2008). TRPV1 plays an important role in heat shock-induced MMP-1 expression, and a calcium-dependent PKCα signaling is required for heat shock-induced MMP-1 expression in human keratinocytes (Li *et al*., 2007; Lee *et al*., 2008). Therefore, the TRPV-1 inhibitory compound would be a good candidate to prevent heat-induced skin aging.

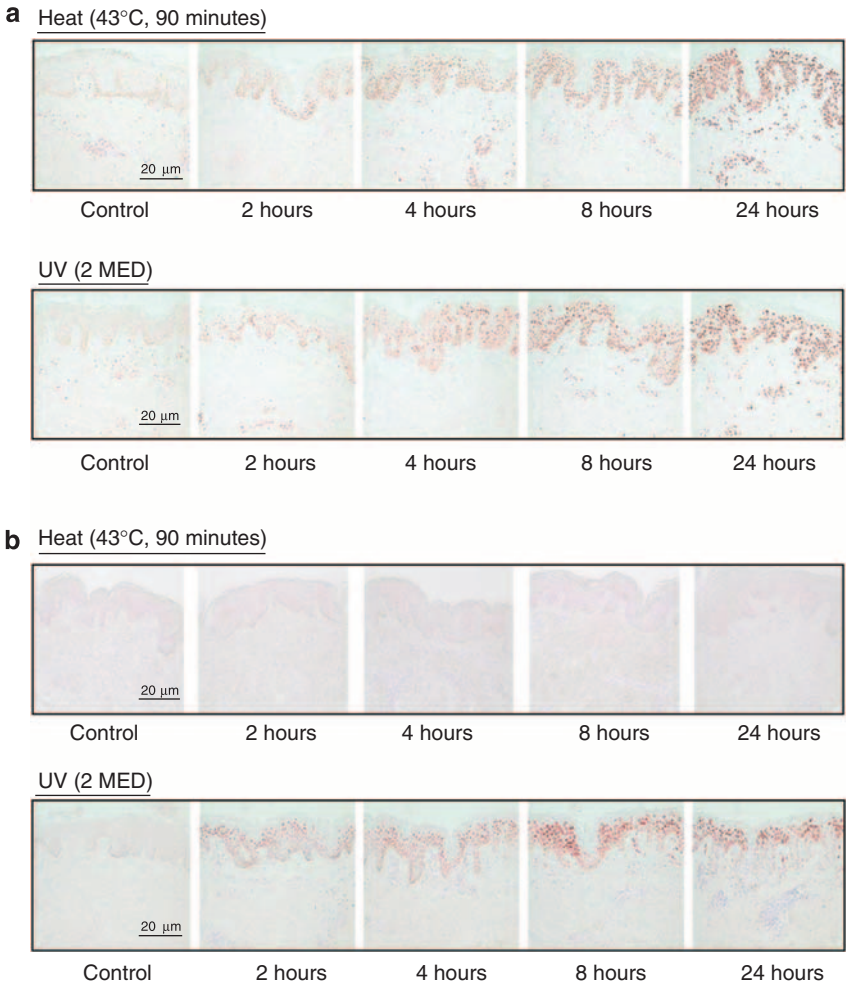

Figure 1. **The effects of heat shock and UV on DNA damage in human skin *in vivo*.** Human buttock skin was treated with heat shock at 43°C for 90 minutes or 2 MED of UV, and then obtained at indicated time points. The skin specimens were stained immunohistochemically using (**a**) anti- 8-hydroxy-2′-deoxyguanosine (Oxis International Inc., Foster City, CA) and (**b**) anti-thymidine dimer antibodies (Kamiya Co., Seattle, WA), respectively ($n = 5$). Bar = 20 μm.

CONCLUSION

Recent evidence indicates that IR and heat may induce premature skin aging, just like UV radiation: (1) IR exposure of human skin stimulates the expression of MMP-1 and decreases type I procollagen expression *in vivo*. Acute IR irradiation also increases new, leaky vessel formation and induces inflammatory cellular infiltration. (2) Heat energy, which increases skin temperature, also increases MMP-1, -3, and -12, and modulates elastin and fibrillin synthesis, resulting in the development of solar elastosis. Acute heat shock in human skin stimulates new vessel formation, recruits inflammatory cells, and causes oxidative DNA damage. Based on these observations, it can be concluded that IR and heat are important physical stimuli that may cause aging in human skin. Therefore, in addition to sunscreen to block the effects of UV, novel strategies to block IR- and heat-induced skin aging need to be developed to prevent skin aging more completely. TRPV-1 may be a good target for preventing heat-induced skin aging (thermal skin aging) in human skin *in vivo*.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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