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Sun Exposure: What Molecular Photodermatology Tells Us About Its Good and Bad Sides

Jean Krutmann[1], Akimichi Morita[2] and Jin Ho Chung[3]

The health consequences of sun exposure have concerned mankind for more than 100 years. Recent molecular studies in photodermatology have greatly advanced our understanding of this important topic. We will illustrate this progress by focusing on the following selected topics: (i) the nature of the DNA damage–independent part of the UVB response of human skin and the role of the arylhydrocarbon receptor in cutaneous biology, (ii) the contribution of wavelengths beyond the UV spectrum to solar radiation–induced skin damage, (iii) the emerging evidence that subcutaneous fat is a target tissue for sunlight, and (iv) the most recent insight into the mode of action of phototherapy.

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INTRODUCTION

It is without question that exposure to solar radiation causes significant damage to human health (Kochevar *et al.*, 2008). Historically, the link between sun exposure and skin cancer has been suggested already in 1894 (Unna, 1894) and causally proven in the 1920s (Findlay, 1928; Blum, 1959). Similarly, the cause–effect relationship between chronic sun exposure and extrinsic skin aging has been suggested more than a 100 years ago by Unna in Germany and Dubreiulh in France when they attributed ''farmers'' and ''sailors'' skin to excessive sun exposure (Kligman, 2006). In addition, sun exposure may cause, trigger, and aggravate a number of specific diseases including photodermatoses such as polymorphic light eruption or solar urticaria, autoimmune diseases such as lupus erythematodes, as well as phototoxic or photoallergic reactions (Lim and Soter, 1993). On the other hand, sun exposure of human skin is required for sufficient vitamin D synthesis and thus benefits human health (Holick, 2004). Sunlight or selective parts of it have been used with ever growing success in the treatment of some of the most frequent skin disorders including psoriasis and atopic dermatitis (Krutmann and Morita, 2007).

Within the past 2 decades, photodermatological research has made enormous progress in deciphering the molecular mechanisms that form the basis for the good and the bad sides of sun exposure. In this review, we will illustrate this development by focusing on a selected number of topics that we feel are highly representative for a process in which insight into basic molecular mechanisms of solar radiation–induced modulation of cutaneous functions has had consequences not only at a scientific, but also, in particular, at a clinical level. The topics we haven chosen to discuss include (i) the nature of the DNA damage–independent part of the UVB stress response in human keratinocytes, (ii) the contribution of wavelengths beyond the UV spectrum to solar radiation–induced skin damage, (iii) the emerging evidence that in addition to the epidermis and dermis subcutaneous fat is a target tissue for sunlight, and (iv) the mode of action of phototherapy. We will discuss these examples in the context of their historical background in order to illustrate how the most recent discoveries related to these topics have impacted on clinical practice by improving photoprotection or phototherapy. It goes without saying that our selection is subjective in nature and by no means intended to be complete.

LIGHTENING UP THE UVB RESPONSE

Within the past 2 decades, strong efforts have been made to elucidate the molecular basis of the UVB stress response in mammalian cells in general and human skin cells in particular (Herrlich *et al.*, 1992; Devary *et al.*, 1993; Rosette and Karin, 1996). As DNA is the major chromophore for UVB radiation, it has originally been thought that the UVB stress response is initiated in a cell's nucleus as a consequence of UVB radiation–induced DNA damage (Bender *et al.*, 1997). In support of this concept, it has been shown that UVB stress responses (i) were enhanced in cells deficient in nucleotide excision repair (Stein *et al.*, 1989) and (ii) diminished if irradiated cells were treated with exogenously added DNA repair enzymes (Kulms *et al.*, 1999; Stege *et al.*, 2000; Dong *et al.*, 2008). This concept, however, was challenged when Karin and co-workers (Rosette and Karin, 1996) demonstrated the occurrence of the UVB stress response in cells that had been enucleated prior to irradiation (Devary *et al.*, 1993). Although this experiment, which originally was suggested by Patrick Bäuerle from Munich, did not completely exclude a

[1]*IUF—Leibniz Research Institute for Environmental Medicine, Düsseldorf, Germany;* [2]*Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan and* [3]*Department of Dermatology, Seoul National University College of Medicine and Institute of Dermatological Science, Seoul National University, Seoul, Korea*

Correspondence: Jean Krutmann, IUF—Leibniz Research Institute for Environmental Medicine, Auf'm Hennekamp 50, Düsseldorf D-40225, Germany. E-mail: krutmann@rz.uni-duesseldorf.de

Abbreviations: AhR, arylhydrocarbon receptor; HSP, heat-shock protein; IR, infrared; MMP-1, matrix metalloproteinase 1; Th17, T helper 17; Treg, regulatory T cell

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role for DNA as a chromophore (which might have been present in mitochondria; see below), it clearly indicated that at least a major part of the UVB stress response can be initiated outside of the cell's nucleus. Subsequent work led by Herrlich *et al.*'s laboratory in Germany and Karin's group (Rosette and Karin, 1996) in San Diego established that this UVB response was indeed independent of DNA damage and identified changes at the level of the cell membrane, i.e., in particular, clustering and subsequent internalization of cell membrane–bound growth factor receptors as very early, initiating events (Sachsenmaier *et al.*, 1994; Rosette and Karin, 1996). For many years, however, the nature of the responsible chromophore and its localization within the cells remained enigmatic. In fact, it was not before 2007 when Fritsche *et al.* (2007) answered this question by showing that the arylhydrocarbon receptor (AhR) is an integral part of the UVB stress response in human skin cells, and that its activation in UVB-irradiated human epidermal keratinocytes caused the DNA damage–independent part of the UVB response such as EGFR activation and internalization (Fritsche *et al.*, 2007). The AhR is a member of the basic helix–loop–helix protein family and functionally serves as a transcription factor, which in its inactive state is part of an intracytoplasmic complex containing the AhR, a c-src kinase and heat-shock protein (hsp)90 (Kahl *et al.*, 1980; Knutson and Poland, 1980). This very well-studied transcription factor was first used by toxicologists, where it became well known as the so-called ''dioxin receptor'', as 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced toxicity was found to be mediated through AhR activation (Fernandez-Salguero *et al.*, 1995; Schmidt *et al.*, 1996). More recently, however, the availability of AhR knockout and transgenic animals has given insight into the physiological functions of the AhR, and, as a consequence, this molecule is currently experiencing its second springtime (reviewed in Haarmann-Stemmann *et al.*, 2009; Abel and Haarmann-Stemmann, 2010). At present, we know that the AhR is critically involved in some of the hottest areas of cell and immune biology including tumor development (Shimizu *et al.*, 2000; Yang *et al.*, 2005; Kawajiri *et al.*, 2009; Tan *et al.*, 2010), tissue development (Abbott *et al.*, 1999; Chesire *et al.*, 2004; Labvis *et al.*, 2005; Shin *et al.*, 2007), the development of regulatory T cells (Tregs; Quintana *et al.*, 2008; Veldhoven *et al.*, 2008; Zhang *et al.*, 2010), and cutaneous biology. The latter field of research was in fact pioneered by the observation of Fritsche *et al.* (2007) that the AhR is activated in human epidermal keratinocytes upon exposure to UVB (but not to UVA) radiation (Fritsche *et al.*, 2007). The chromophore for UVB-induced AhR activation is the free amino acid tryptophan, which is present in the cytoplasm of cells and which—upon irradiation—forms a number of photoproducts serving as physiological AhR ligands (Wei *et al.*, 1998; Fritsche *et al.*, 2007). Among these tryptophan photoproducts, formylindolo-*3,2b*-carbazole obtains the strongest affinity to the AhR and is also the best one studied. In context of the UVB stress response, Fritsche *et al.* (2007) showed that exposure of human epidermal keratinocytes to physiologically relevant doses of UVB radiation leads to the intracellular formation of formylindolo-*3,2b*-carbazole and the subsequent activation of the AhR signaling pathway, which consists of two different limbs (Figure 1; Enan and Matsumura, 1996; Köhle *et al.*, 1999; Park and Matsumura, 2006; Fritsche *et al.*, 2007). Accordingly, after formylindolo-*3,2b*-carbazole binding to the AhR and the subsequent dissociation of the AhR/c-src/hsp90 complex, the AhR translocates from the cytoplasm to the nucleus where it binds to its partner molecule, AhR nuclear translocator, and subsequently activates xenobiotic response elements in the promoter region of genes, such as cytochrome P450 1A1 or 1B1. The second limb of this signaling pathway, however, involves the cell membrane and is mediated by the c-src kinase, which translocates from the cytoplasm to the cytoplasmic membrane where it phosphorylates growth factor receptors including the EGFR. Subsequent EGFR internalization and mitogen-activated protein Kinase activation then transduce the signal from the plasma membrane to the nucleus where it is responsible for increased transcription of genes including cyclooxygenase-2. This discovery lightens up the UVB stress response by demonstrating that its DNA damage–independent part is initiated in the cytoplasm of cells and mediated via the AhR signaling

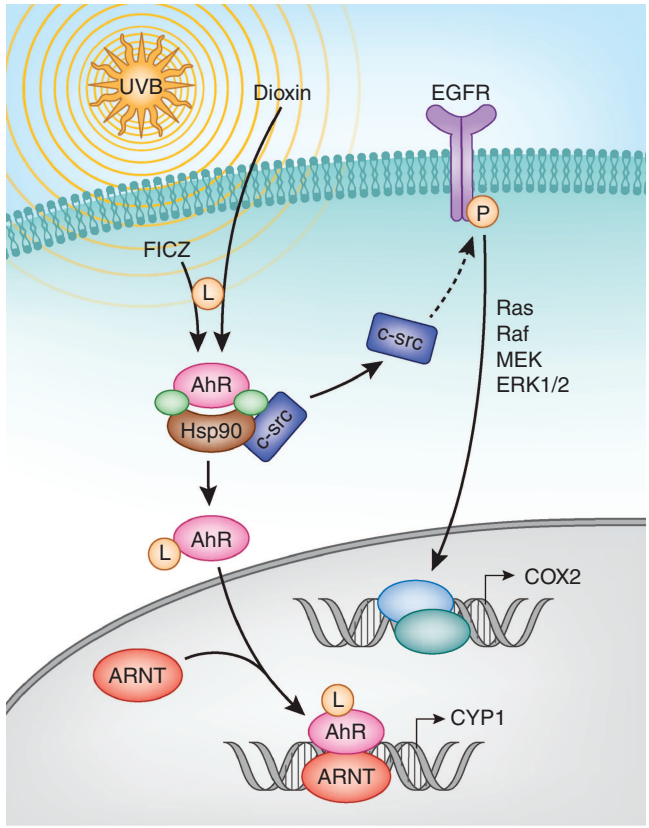

Figure 1. The arylhydrocarbon receptor in human keratinocytes mediates the DNA damage–independent part of the UVB stress response. AhR, arylhydrocarbon receptor; ARNT, AhR nuclear translocator; COX2, cyclooxygenase-2; CYP1, cytochrome P450 1; ERK, extracellular signal–regulated kinase; FICZ, formylindolo-*3,2b*-carbazole; Hsp90, heat-shock protein 90; MEK, mitogen-activated protein/extracellular signal–regulated kinase.

pathway. It has been suggested that UVB radiation–induced activation of the AhR signaling pathway is of great clinical relevance. Accordingly, cyclooxygenase-2 (Fritsche *et al.*, 2007) and matrix metalloproteinase (MMP)-1 (Tigges *et al.*, 2011) are among the genes that are being activated via the AhR signaling pathway in UVB-irradiated keratinocytes, indicating that AhR activation may have a role in photocarcinogenesis and photoaging. Along the same lines, it was recently discovered that the AhR is a negative regulator of nucleotide excision repair in human epidermal keratinocytes (Haarmann-Stemmann *et al.*, 2011). Prevention of UVB-induced AhR activation may thus represent a new strategy to reduce UVB radiation–induced skin damage. In this regard, a topical AhR antagonist was developed and launched for use in sunscreen products very recently (EP:1008593). It is important to note that UVBR-induced AhR activation does not exclusively occur in keratinocytes. For example, melanocytes are of particular importance because (i) they express functionally active AhRs and (ii) stimulation of melanocyte AhR with the UV photoproduct formylindolo-*3,2b*-carbazole triggers melanocyte proliferation and/or melanin synthesis and thus skin pigmentation, indicating the possibility that UVB radiation–induced AhR activation is part of the natural tanning response (Luecke *et al.*, 2010; Jux *et al.*, 2011).In addition, as Langerhans cells express the AhR (Jux *et al.*, 2009) and as the AhR is involved in the development of regulatory (Quintana *et al.*, 2008; Veldhoven *et al.*, 2008) and skin gamma/delta T cells (Kadow *et al.*, 2011), UVB radiation–induced AhR activation may even affect the skin immune system (Esser *et al.*, 2009).

It should be noted that the original caveat concerning the Karin study (Devary *et al.*, 1993), i.e., a possible role of mtDNA as a chromophore for UVR, has found to be true, although absorption of UVR by mtDNA does not seem to contribute to acute stress responses in human skin cells (which is in contrast to other wavelengths: see below). Accordingly, compelling evidence has been provided that mtDNA serves as a chromophore for both UVB and UVA radiation, and that UVR-induced damage to mtDNA may occur in epidermal keratinocytes and dermal fibroblasts (reviewed in Krutmann and Schroeder, 2009). In proliferating tissues such as the epidermis, however, negative selection mechanisms do not allow for the accumulation of cells with damaged mtDNA molecules. This is in marked contrast to postreplicative tissues such as the dermis, where chronic exposure to solar radiation causes an increase in the amount of mtDNA molecules showing point mutations and large-scale deletions (Berneburg *et al.*, 1997, 1999; Birch-Machin *et al.*, 1998; Koch *et al.*, 2001). The presence of the latter type of damage is of pathophysiological relevance for human skin as it is causally related to photoaging. Accordingly, the accumulation of large-scale deletions of mtDNA in human dermal fibroblasts alters mitochondrial functions (Berneburg *et al.*, 2005) and induces retrograde signaling responses, which at the organ level cause many hallmarks of photoaged dermis and epidermis such as a rarefication of collagen fibers and epidermal atrophy (Majora *et al.*, 2009, 2011; Krutmann and Schroeder, 2009). At least with regard to photoaging, there is thus an important qualitative difference between UVR-induced DNA damage responses initiated in mitochondria versus the cell's nucleus: whereas mtDNA damage tends to accumulate and trigger chronic mechanisms driving the aging process, nuclear DNA damage can result in immediate stress responses, which additionally accelerate skin aging.

BEYOND THE RAINBOW: SKIN DAMAGE BY INFRARED RADIATION

Traditionally, photodermatology has mainly, if not exclusively, been concerned with the effects UVB (290–320 nm) and UVA (320–400 nm) radiation exert on human skin (Kochevar *et al.*, 2008). This is somewhat surprising if one takes into account that at least 50% of the total energy that is being emitted by the sun and that reaches human skin is in the infrared (IR) range (i.e., wavelengths reaching from 770 nm up to 1 mm). In addition, within the IR range, IRA (770–1,400 nm) rays, which represent one-third of the total solar energy, are very well capable of penetrating human skin and directly affecting cells located in the epidermis, dermis, and subcutis (reviewed in Schieke *et al.*, 2003). This is in contrast to IRB (1,400–3,000 nm) and IRC (3,000 nm–1 mm) radiation, which is completely absorbed at the epidermis (IRC) or only marginally affects the dermis (IRB). Radiation of these wavelengths is primarily responsible for increased skin temperature, and thus is experienced as pleasantly warm to burning hot.

A role for IR radiation in actinic skin damage was already suggested by Kligman (1982) when she reported that exposure of guinea-pig skin to irradiation from lamps, which in addition to UVR emit significant amounts of IR, cause more actinic damage than exposure to UVR alone. At this time, no irradiation devices were available to allow UV-free IR radiation exposure, and it was therefore not before 2002 that IR and, in particular, IRA radiation effects on human skin were studied in a systematic manner (Schieke *et al.*, 2002). There is now increasing evidence that IRA radiation, similar to UVB or UVA radiation, can cause skin damage (reviewed in Schroeder *et al.*, 2010), and, e.g., significantly contributes to photoaging of human skin. Accordingly, exposure of human skin fibroblasts *in vitro* (Schieke *et al.*, 2002) and human skin *in vivo* (Schroeder *et al.*, 2008) to physiologically relevant doses of IRA causes an increase in MMP-1 without a concomitant upregulation of tissue inhibitor of metalloproteinase-1 expression. Along the same lines, IRA exposure also reduces type 1 collagen expression, possibly by reducing the production of procollagen-1–stimulating transforming growth factor-β1, -2, and -3 expression in human skin (Kim *et al.*, 2006b). Collectively, these independent studies indicate that IRA causes the rarefication of collagen fibers in human skin and thereby photoaging. Indeed, repetitive IRA irradiation produces significant wrinkle formation in hairless mice (Kim *et al.*, 2005). It has therefore been proposed that efficient sun protection should include protection against IRA (Schroeder *et al.*, 2010).

On a first glance, IRA radiation–induced photoaging of human and murine skin is reminiscent of photoaging induced by UVB or UVA radiation (Schieke *et al.*, 2003). Accordingly,

all three types of radiation can elicit intracellular stress responses that lead to increased MMP-1 expression in human skin fibroblasts. It is important to realize, however, that the underlying mechanisms responsible for UVB-, UVA-, and IRA-induced MMP-1 expression markedly differ. This is not surprising because the three different wavelengths are expected to use different chromophores. As previously discussed, the major chromophores for UVB appear to be nuclear DNA and cytoplasmic-free tryptophan, whereas the UVA stress response is initiated at the level of cell membrane lipid rafts (reviewed in Grether-Beck and Krutmann, 2009). In marked contrast, IRA radiation is strongest absorbed intramitochondrially, where copper atoms present in complex IV of the respiratory chain might serve as the major chomophore (Karu, 2008). In fact, the earliest biological event following IRA irradiation of human skin fibroblasts, which has been described thus far, is an increase in intramitochondrial production of reactive oxygen species (Schroeder *et al.*, 2007; Darwin *et al.*, 2010). Such reactive oxygen species initiate a signaling response that leaves the mitochondria, alters intracytoplasmic calcium levels, activates mitogen-activated protein kinases, and ultimately reaches the nucleus where it causes increased transcriptional expression of MMP-1 (Krutmann and Schroeder, 2009; Figure 2). The discovery of this IRA-induced retrograde mitochondrial signaling response is of direct clinical importance because it indicates that mitochondrially targeted antioxidants may be used to protect human skin against IRA radiation–induced damage. Indeed, antioxidants with a mitochondrial leader sequence are highly effective in preventing IRA-induced signaling in cultured human skin fibroblasts, and topical application of a mixture of selected antioxidants to human skin *in vivo* prior to irradiation partially diminished the IRA-induced MMP-1 response (Schroeder *et al.*, 2008).

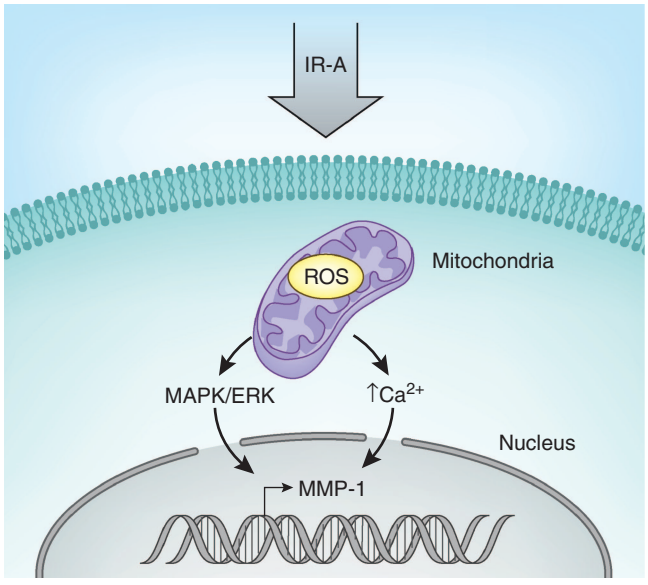

Figure 2. Infrared (IR) A radiation–induced retrograde signaling in human skin fibroblasts. ERK, extracellular signal–regulated kinase; MAPK, mitogen-activated protein kinase; MMP-1, matrix metalloproteinase; ROS, reactive oxygen species.

On the basis of these observations, sunscreen as well as daily-care products claiming IRA protection have been launched by different brands in Europe since 2006.

It should be noted that MMP-1 by far is not the only gene that is being transcriptionally regulated by IRA radiation. Systematic analyses of the IRA-induced transcriptome changes in primary human skin fibroblasts revealed that approximately 600 genes are IRA responsive, and that the vast majority of these genes are regulated via intramitochondrial reactive oxygen species signaling responses (Calles *et al.*, 2010). This finding also indicates that biological effects associated with IRA radiation exposure of human skin extend beyond collagen degradation. For example, IRA radiation induces angiogenesis in human skin (Chung and Eun, 2007) by a mechanism that might involve the increased expression of vascular endothelial growth factor and suppression of its functional antagonist thrombospondin-1 (Kim *et al.*, 2006a). In addition, IRA radiation was recently reported to increase the number of mast cells in human skin *in vivo* (Kim *et al.*, 2009). Both effects are characteristic of photoaging, and thus these observations further emphasize the relevance of IRA radiation for extrinsic skin aging (Krutmann and Gilchrest, 2006). A question of obvious importance relates to the carcinogenic potential of IRA radiation. Until now, very few studies have been conducted to address this critical issue, and a definitive answer cannot be given at this stage of research. However, IRA exposure if provided prior to UVB radiation may prevent UVB-induced apoptosis in human keratinocytes (Jantschitsch *et al.*, 2009), and this biological effect may contribute to the development of skin cancer.In addition, in a very recent photocarcinogenesis study, IRA irradiation preceding UVB irradiation did not cause earlier or more tumor growth, but was associated with significantly accelerated, more aggressive tumor growth and a higher number of more malignant skin tumors (Jantschitsch *et al.*, 2011). These *in-vivo* data are supported by functional clustering of IRA-responsive genes, which came under groups involved in extracellular matrix homeostasis, apoptosis, cell growth, and stress responses (Calles *et al.*, 2010). These gene functions are not highly indicative, but nevertheless in a broader sense related to photocarcinogenesis.

As most of the studies discussed above used artificial irradiation devices, which do not mimic natural sunlight but emit preferentially or even selectively IRA radiation, it has been argued that the findings described above are of limited relevance for natural IRA irradiation during sun exposure (Piazena and Kelleher, 2010). In this regard, it is important to note that the IRA doses used in those studies were carefully selected to be of physiological relevance (Schieke *et al.*, 2003). Moreover, this question has recently been readdressed in a very elegant study by Cho *et al.* (2008), in which the effects of natural sunlight, sunlight minus UVR, or the heat component within the natural sunlight only were directly compared with each other. Therefore, human buttock skin was exposed to sunlight with/without an UV filter (to block UVR below 400 nm) or a black cloth (which absorbs IR and generates heat). UV-filtered sunlight significantly increased MMP-1 expression in exposed skin, indicating that IRA

radiation contributes to natural sunlight–induced skin responses. Interestingly, increased MMP-1 expression was also observed in skin areas that were covered with a black cloth. This points to the possibility that heat exposure might exert biological effects on human skin, as well and that heat-inducing IRB and IRC rays should perhaps not be regarded as biologically inert. The possible role of heat in photoaging of human skin is currently controversial even among the authors of this review paper, as Krutmann *et al.* (unpublished data) found that exposure of human skin to artificial IRB/IRC radiation did not induce MMP-1 expression in human skin (Krutmann *et al*, unpublished data), whereas on the other side heat is well known to cause erythema *ab igne* (Hurwitz and Tisserand, 1987), IRA-induced biological effects may or may not be linked to heat formation (Jantschitsch *et al.*, 2009; Piazena and Kelleher, 2010), and evidence was provided for a process termed thermal aging (Cho *et al.*, 2009). Thereby, heat exposure might trigger biological responses in human skin, which may be mediated via the transient receptor potential ion channel-1, and thus contributes to skin aging (Li *et al.*, 2007; Lee *et al.*, 2008, 2009a, b). It should be noted that the nature of these responses is completely different from the IRA response described above, which occurs independent of heat-shock responses (Schieke *et al.*, 2002) via a clearly defined retrograde mitochondrial signaling response (Schroeder *et al.*, 2007; Krutmann and Schroeder, 2009).

Even more controversial has been the question whether similar to UVB, UVA and IRA, also rays in the visible range may cause skin damage. This is in fact an ongoing area of research and it is too early for a definitive answer, which currently must be restricted to the following two conclusions: (i) there is growing evidence that visible light can affect the production of reactive oxygen species in human skin cells *in vitro* and in human skin *in vivo* (Darwin *et al.*, 2010), but (ii) the biological relevance of these effects is not known, or, in other words, there is no solid proof that visible light damages human skin.

As mentioned above, some of these wavelengths such as the IRA deeply penetrate human skin and reach significant dose levels below the dermis. It is therefore conceivable to speculate that, similar to the epidermis and dermis, the subcutis may be a target for solar radiation. Although this has not yet been addressed for IRA radiation, a very recent study has provided compelling evidence that this speculation might in fact be true for wavelengths within the UV range. Accordingly, Kim *et al.* (2011) reported that the amount of free fatty acids and triglycerides in the subcutaneous fat of sun-exposed skin is significantly less than that in sun-protected skin of the same individual. Similarly, the expression of a number of important lipogenic enzymes was also significantly decreased in photoaged human skin. This was not simply by coincidence because UV irradiation (2 MED) of human buttock skin dramatically decreased the levels of free fatty acids and triglycerides in the underlying subcutaneous fat. These studies indicate that loss of subcutaneous fat, which is most prominent in humans in UV-exposed skin areas such as the face, is caused or at least aggravated by exposure to solar radiation (Kim *et al.*, 2011). This conclusion is supported by the observation of Majora *et al.* (2010) that mice with a deficient Cockayne Syndrome B protein, similar to Cockayne Syndrome B patients, show spontaneous loss of subcutaneous fat (Kamenish *et al.*, 2010), which can be markedly accelerated and enhanced if these animals are chronically exposed to UVR. As UVR does not reach the subcutis, it was speculated that paracrine mechanisms are involved in UVR-induced loss of subcutaneous fat (Kim *et al.*, 2011; Figure 3). The fact that keratinocyte/fibroblast-derived, UV-inducible soluble mediators such as IL-6, IL-8, PIGF, and monocyte chemotactic protein-3 are capable of modulating the metabolic activity of subcutaneous fat supports this explanation (Kim *et al.*, 2011). We believe that these findings, which identify the subcutis as a target for solar radiation, are of great clinical relevance because they may not only be cosmetically undesirable (e.g., the loss of facial volume as a hallmark of photoaging), but—more importantly—pose medical problems as well. Maintenance of good health among other factors requires a balance between the amount of subcutaneous fat on one side, which improves insulin sensitivity and lowers the risk of related diseases, and visceral fat on the other side, which is associated with an increase in the metabolic syndrome (Tran *et al.*, 2008). Unfortunately,

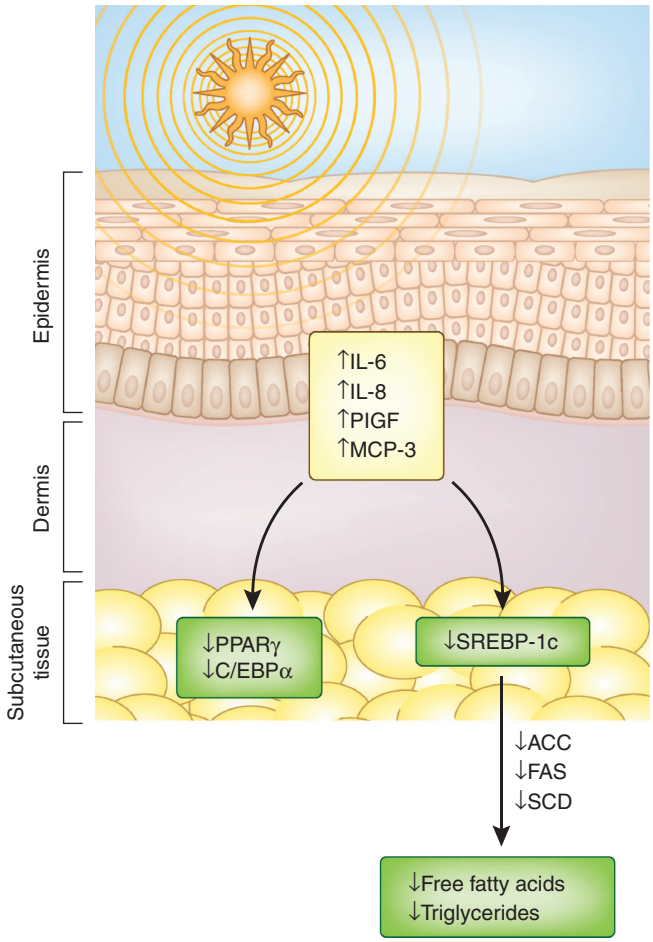

Figure 3. The subcutis is a target tissue for solar radiation. MCP-3, monocyte chemotactic protein-3; PPARγ, peroxisome proliferator–activated receptor-γ.

aging is associated with a progressive inability of the human body to maintain an adequate subcutaneous adipose tissue mass and at the same time keep the amount of intra-abdominal fat steady. By destroying subcutaneous fat, solar radiation may thus reduce the ability of subcutaneous adipocytes to function as lipid storage sites and to adequately take up circulating free fatty acids, which ultimately may contribute to the development of serious health problems such as dyslipidemia, insulin resistance, and metabolic syndrome.

THE GOOD SIDE OF SUN EXPOSURE: HOW PHOTOTHERAPY WORKS

Besides its well documented role in vitamin D synthesis (Holick, 2004), exposure to natural sunlight is known to benefit humans with a variety of different diseases. More than 100 years ago, the use of solar radiation for the treatment of patients with lupus vulgaris was proposed by Nils Finsen, who has been the first and only dermatologist to ever win the Nobel Prize for Medicine. Since that time, heliotherapy, i.e., the therapeutic use of natural sunlight, had its place in the treatment of dermatological patients. Recent studies now indicate that natural sunlight has potent immunemodulatory effects, and that in psoriasis patients sun exposure significantly reduces CD4+ and CD8+ T cells in the epidermis and dermis of lesional skin, whereas FOXP3+ Tregs are increased (Søyland *et al.*, 2011). In the peripheral blood of these patients, heliotherapy decreases the number of cutaneous lymphocyte–associated antigen (CLA)+ (=skin homing) T cells and reduces the capacity of peripheral blood mononuclear cells to produce proinflammatory cytokines. These observations indicate that (i) heliotherapy has a mechanistic substrate, i.e., the anti-inflammatory capacity of natural sunlight, and (ii) that natural sunlight contains wavelengths that are beneficial for patients with inflammatory skin diseases. In daily practice, this conclusion has been verified by the increasingly successful use of selected spectra in modern phototherapy. The introduction of narrowband UVB (311–313 nm) and UVA-1 (340–400 nm) phototherapy dramatically improved the efficacy and safety of dermatological phototherapy and opened up a number of important new indications such as connective tissue diseases (reviewed in Krutmann and Morita, 2007; Krutmann *et al.*, 2009). More recently, the principal mode of action for these modalities was identified and found to involve two major mechanisms: (i) the triggering of apoptosis in skin-infiltrating, proinflammatory cells and (ii) the induction of immunoregulatory mechanisms mediated by Treg cells (Figure 4). Accordingly, narrowband UVB and UVA-1 phototherapy are highly effective in inducing apoptosis in skin-infiltrating T cells in psoriasis (Ozawa *et al.*, 1999) or atopic dermatitis (Morita *et al.*, 1997); they cause depletion of T cells from lesional skin and thereby clearance of skin lesions. This anti-inflammatoty effect, however, fails to explain the relatively long remission period of approximately 4–6 months in psoriatic patients undergoing phototherapy. It was therefore of great interest to learn that phototherapy also induces the generation of Treg cells (Shintani *et al.*, 2008; Saito *et al.*, 2009). Such Tregs have a key role in peripheral tolerance (Shevach, 2002), and

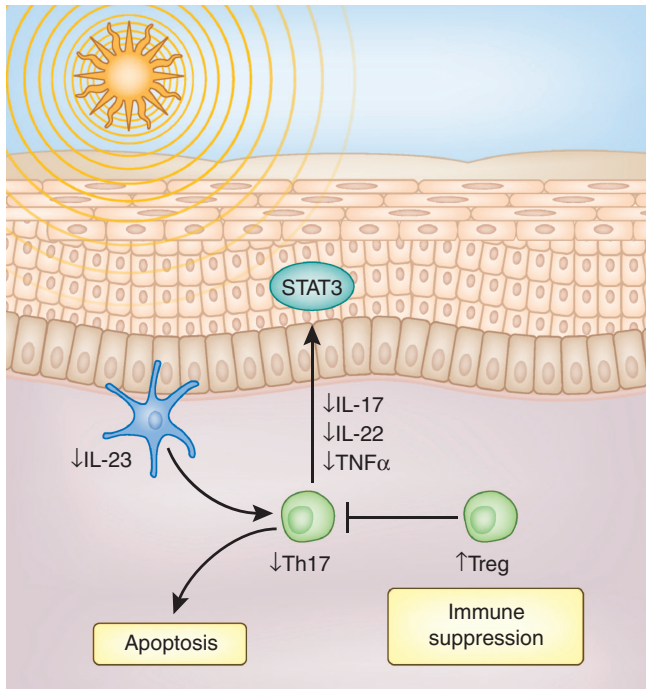

Figure 4. The mode of action of phototherapy. STAT3, signal transducer and activator of transcription-3; Th17, T helper type 17; TNFα, tumor necrosis factor-α; Treg, regulatory T cell.

their appearance under phototherapy would thus support the concept that psoriasis is an autoimmune disease. It is worth noting that in psoriasis, a functional defect in Treg suppressor activity was described earlier (Sugiyama *et al.*, 2005) and that an imbalance between Treg cells on one side and T helper type 17 (Th17) cells on the other side is thought to contribute to the pathogenesis of this disease (Johnson-Huang *et al.*, 2010). Th17 cells produce the cytokines IL-17, IL-22, and tumor necrosis factor-α. In a study with 14 patients with moderate to severe psoriasis undergoing phototherapy, narrowband UVB irradiation suppressed the IL-23/IL-17 pathways, including IL-12/23p40, IL-23p19, IL-17, and IL-22 in phototherapy-responsive plaques, but not in unresponsive skin lesions (Johnson-Huang *et al.*, 2010). In another study, gene expression profiling using epidermal RNA from lesional and nonlesional skin showed that narrowband UVB phototherapy downregulated the Th17 pathway (Rácz *et al.*, 2011). Very recent evidence also suggests that circulating Th17 cells are reduced in psoriasis patients undergoing narrowband UVB phototherapy, and that this is associated with a significant decrease in increased serum levels of IL-17 and IL-22a and a corresponding reduction in the Psoriasis Area and Severity Index (Lo *et al.*, 2010; Furuhashi *et al.*, 2011a, b). Taken together, these studies indicate that phototherapy causes a decrease in Th17 and an increase in Tregs, and thereby helps to overcome the Th17/Treg imbalance in these patients. The induction of these immunomodulatory effects is most likely not specific for narrowband UVB phototherapy, as the generation of Treg cells also occurs in psoriasis patients undergoing bath-psoralen plus UVA (Saito *et al.*, 2009) or excimer light (308 nm) therapy as well

(Furuhashi *et al.*, 2011a, b). In view of these most recent findings, phototherapy may thus be regarded as a combination of a highly effective anti-inflammatory drug (inducing apoptosis) with a potent, topically applied immune modulator, with the enormous advantage of well-known safety and an unbelievably low-cost profile (especially when compared with modern immunomodulatory drugs).

CONFLICT OF INTEREST

The authors state no conflict of interest.

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