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Mini Review

The role of near infrared radiation in photoaging of the skin

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ABSTRACT

Infrared (IR) radiation is non-ionizing, electromagnetic radiation with wavelengths between 760 nm and 1 mm, which is further divided into IRA, IRB and IRC. IR accounts for more than half of the solar energy that reaches the human skin. While IRB and IRC do not penetrate deeply into the skin, more than 65% of IRA reaches the dermis. Human skin is increasingly exposed to IRA-radiation; most relevant sources are (i) natural solar radiation consisting of over 30% IRA, (ii) artificial IRA sources used for therapeutic or wellness purposes and (iii) artificial UV sources contaminated with IRA. As part of natural sunlight, IRA significantly contributes to extrinsic skin aging.
This article reviews the cutaneous effects of IRA-radiation, the underlying molecular mechanisms and the available protective strategies.

1. Physical properties of infrared A, natural and artificial sources

Solar radiation reaching the earth surface includes the wavelengths from 290 to 4000 nm and is divided into three major bands: ultraviolet (UV) radiation (λ = 290–400 nm), visible light (λ = 400–760 nm) and infrared (IR) radiation (λ = 760 nm–1 mm). Infrared radiation is further divided into IRA (near IR, λ = 760–1440 nm), IRB (mid IR, λ = 1440–3000 nm) and IRC (far IR, λ = 3000 nm–1 mm). The main source of IR radiation is the sun, but artificial IR sources are constantly gaining importance. They are used for therapeutic (e.g. in rheumatoid arthritis and in photodynamic therapy) as well as for lifestyle purposes (e.g. for fat reduction), and beside the many beneficial effects, the questions of detrimental effects, especially due to unsupervised non-medical use poses a problem.

While the photon energy of IR is lower than that of UV, the total amount of energy transferred by the sun consists of ≈54% IR while UV only accounts for 7%. The largest part of solar IR radiation is IRA (≈30% of total solar energy), which deeply penetrates into human skin while IRB and IRC only affect the upper skin layers (Kochevar et al., 2008).

The actual solar IRA dose reaching the skin is influenced by the same factors as the UV dose, i.e. ozone layer, position of the sun, latitude, altitude, cloud cover and surface reflections.

2. Photoaging

The term photoaging refers to changes in the skin that superimpose the alterations of chronological aging. Clinically, photoaging is associated with the formation of coarse wrinkles, uneven skin pigmentation, loss of skin elasticity and a disturbance of skin barrier functions (Yaar, 2006). These changes are present due to chronic solar radiation exposure. Among the wavelength bands that reach the earth's surface the best investigated in terms of photoaging are UVA (λ = 320–400 nm) and UVB (λ = 280–320 nm), but recent results emphasis the role of infrared A (IRA, 760–1440 nm) in photoaging of the skin (Kim et al., 2005, 2006b; Schieke et al., 2002; Schroeder et al., 2008), which has first been described more than 25 years ago (Kligman, 1982). UVA, UVB and IRA all penetrate into the skin, with UVB being mainly absorbed in the epidermis, while UVA reaches epidermis and dermis (Yaar, 2006). IRA penetrates deeply into the skin and reaches even the subcutis, approximately half of the IRA is absorbed in the dermis (Schroeder et al., 2006).

Although IRA has been shown to have effects on cells of the fast regenerating epidermis as well, this review focuses on the dermal compartment of the skin, as changes in the dermis are longer lasting (Krutmann and Gilchrest, 2006). Changes in the cells and the extracellular matrix of the dermis contribute significantly to photoaging; collagen degradation and accumulation of abnormal elastic fibres are hallmarks of photoaged skin. These alterations are due to changes in expression of several genes, in particular matrix metalloproteinases (MMPs), which are induced by IRA (Schieke et al., 2002), UVA (Tyrrell, 1996) and UVB (Brenneisen et al., 2002). Under physiological conditions, MMPs are part of a coordinated network and are precisely regulated by their

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endogenous inhibitors, the tissue inhibitors of MMPs (TIMPs). Unbalanced activity of MMPs due to extrinsic noxae is a major pathophysiological factor in skin aging and several diseases such as rheumatic diseases, hepatic cirrhosis, tumor invasion and metastasis (Westermarck and Kahari, 1999).

The expression of MMPs is governed by the cellular signal transduction machinery of kinases and phosphatases (Schieke et al., 2003). Increased levels of reactive oxygen species (ROS) due to UVA (Wlaschek et al., 1995), UVB (Brenneisen et al., 2002) or IRA (Schroeder et al., 2007) have been shown to initiate the signaling events involved. However, the primary radiation-induced reactions triggered by UVA, UVB and IRA differ substantially.

3. Biological effects of infrared A radiation on the skin

More than 25 years ago, Kligman observed that IR irradiation enhances UV induced actinic skin damage, and that IR alone caused actinic skin damage similar to that found in UV exposed skin (Kligman, 1982) in albino guinea pigs. Similarly, in 2005 IRA alone was shown to lead to wrinkle formation in hairless mice and to intensify the detrimental effect of UV radiation (Kim et al., 2005).

Concerning the molecular mechanisms involved, it was shown that IRA treatment of human skin fibroblasts leads to an increased expression of matrixmetalloproteinase-1 (MMP-1) without an concomitant increase in expression of the respective inhibitor TIMP-1 (Schieke et al., 2002). In hairless mice Kim et al. showed increased levels of MMP-3 and MMP-13 (Kim et al., 2005). Mitochondrial ROS were shown to be the initiating event and to induce increased transcription and translation of the MMP-1 gene via activation of the MAPKinases ERK1/2 (see Fig. 1) (Schieke et al., 2002; Schroeder et al., 2007).

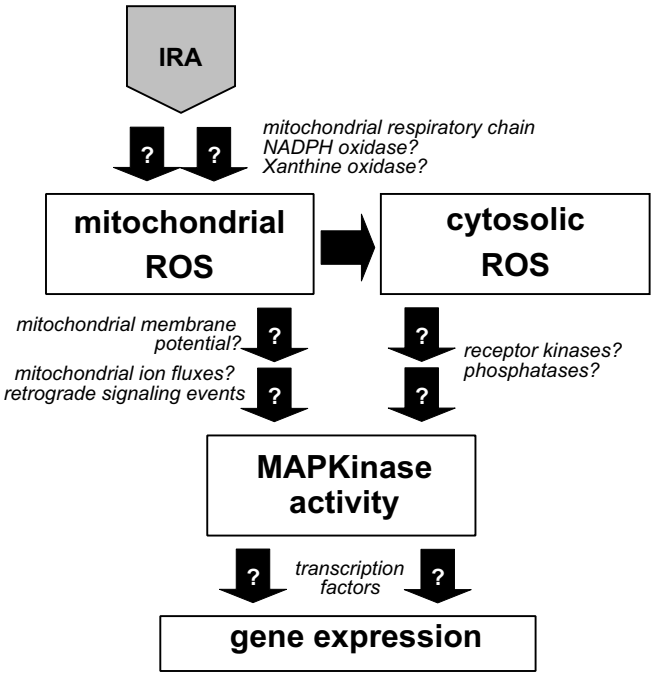

Fig. 1. IRA induces the formation of mitochondrial reactive oxygen species leads to changes in gene expression. It has been demonstrated, that IRA irradiation leads to an increased level of mitochondrial ROS which in turn leads to increased cytosolic ROS levels. Besides the mitochondrial respiratory chain, NADPH oxidase and Xanthine oxidase are discussed to play a role in the increased ROS production. Via thus far unknown mechanisms, which might involve disturbance of mitochondrial functions, mitochondrially induced ion fluxes, other retrograde signaling events (e.g. via mTOR, Ca^{2+}-dependent kinases), altered activity of upstream kinases and/or altered phosphatase activity, the activity of MAPKinases is increased. At least the MAPKinases p38 and ERK1/2 are involved in this signaling cascade. These kinases alter the expression of genes like MMP-1 and MMP-9 via modification of transcription factors. Involvement of AP-1 and other known targets of the MAPKinases activated by IRA are likely, but remain to be investigated.

An influence of IRA on the mitochondria was suggested by the finding, that IRA is absorbed by components of the mitochondrial respiratory chain (Karu, 1999). This might cause a disruption of the mitochondrial electron flow, which is known to result in turn in an increased production of mitochondrial ROS. Such a disruption of the mitochondrial function could trigger retrograde signaling processes which regulate nuclear gene expression (Butow and Avadhani, 2004). Triggering of such a mitochondria to nucleus response would clearly distinguish the IRA response from other noxae including UVA and UVB. Indeed, the mitochondrial ROS generation induced by IRA is highly specific compared to the UVs: UVA and UVB induced increased expression of MMP-1 are not affected by the use of antioxidants which specifically target the mitochondria (MitoQ) or by manipulation of function or mass of mitochondrial respiratory chain components, while the IRA response is substantially altered by these strategies (Schroeder et al., 2007). Recent advances in understanding the UVA response support this, because plasma membrane electron transport systems instead of the mitochondrial respiratory chain have been identified to be crucially involved in UVA induced ROS formation (Schauen et al., 2007). Although Schieke et al. demonstrated a difference in induction of MMP-1 between IRA irradiation and a mild heat shock (42 °C) treatment in human dermal fibroblasts (Schieke et al., 2002), Shin et al. recently reported that exposure of HaCat cells to 44 °C leads to increased MMP-1 and MMP-9 expression (Shin et al., 2008). They further reported that beside an involvement of the mitochondrial respiratory chain NADPH oxidase and Xanthine oxidase mediate this heat shock induced effect.

The involvement of the MAPKinases ERK1/2 is a common feature of MMP-1 induction by UVA, UVB and IRA. In general, three distinct MAPK pathways have been characterized: the extracellular signal regulated kinase 1/2 (ERK1/2) pathway (Raf-MEK1/2-ERK1/2), and the c-Jun N-terminal kinase (MEKK1/3-MKK4/7-JNK1/2/3) and p38 (MEKK-MKK3/6-p38 a–d) pathways; the latter two also termed stress-activated protein kinases (SAPKs). The ERK1/2 pathway is inducible by mitogen such as growth factors, whereas the SAPK pathways are predominantly induced by inflammatory cytokines as well as environmental stress such as UV, heat and osmotic shock. All three pathways have been described to react to changes in the redox-status of the cells, such as increased ROS production. Activated MAPKs translocate to the nucleus, where they phosphorylate and activate transcription factors such as c-Jun, c-Fos, ATF-2 and ternary complex factors (TCF) leading to the formation and activation of homo- or heterodimeric forms of the transcription factor AP-1 (Chang and Karin, 2001; Hazzalin and Mahadevan, 2002; Kyriakis and Avruch, 2001). The promoter region of MMP-1 carries multiple AP-1-binding sites (Angel et al., 1987; Gutman and Wasylyk, 1990). For IRA, it was demonstrated that ERK1/2 and p38 are activated in dermal fibroblasts, and that inhibition of ERK1/2 activation subdues the IRA-induced increase of MMP-1 while inhibition of p38 had no influence on IRA-induced MMP-1 expression (Schieke et al., 2002).

In addition to its effect on MMP-1, several other cellular and physiological responses to IRA-radiation are known. Kim et al. reported, that infrared exposure is involved in neoangiogenesis in human skin, because IRA induces an angiogenic switch by altering the balance between the angiogenic inducer VEGF and the angiogenic inhibitor TSP-2 (Kim et al., 2006a). Interestingly, increased neoangiogenesis is a prominent feature of photoaged human skin (Yaar, 2006). Others found that IRA irradiation led to a decrease in epidermal proliferation, Langerhans cell density and contact hypersensitivity reaction in mice (Danno and Sugie, 1996) and a subsequent study by the same group indicates, that IRA influences