



## Review Article

# Beyond UV radiation: A skin under challenge

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### Synopsis

Since ancient times, human beings have been trying to protect their skin against the adverse effects of the sun. From the first mineral sunscreens used by Egyptians, to the current more sophisticated ultraviolet (UVA/UVB) organic sunscreens, progress has been made in terms of sun protection and deeper knowledge of skin physiology has been acquired in the process. The solar spectrum is composed of radiations of various wavelengths having specific, as well as overlapping effects on skin. UVB is mainly responsible for sunburn and DNA dimer formation that can lead to mutation. UVA generates oxidative reactions affecting DNA, proteins and lipids, and is also immunosuppressive. Recently, visible light and infrared radiation (IR) have been associated with oxidative damage and IR has been additionally linked to adverse heat effects on skin. Numerous other extrinsic factors, related to environment and lifestyle, also affect the appearance of skin, precipitating ageing. New molecular mechanisms linking sun and environmental factors to skin ageing have been identified: IR affects mitochondrial integrity and specific heat receptors also mediate some of its effects, tryptophan is a chromophore for UVB, and the aryl hydrocarbon receptor (AhR) is activated by light and xenobiotics to alter skin physiology. Integrating all these new elements is changing the way we think about skin extrinsic ageing. Is UVA/UVB sunscreen protection still enough for our skin?

### Résumé

Depuis les temps anciens, les êtres humains ont essayé de protéger leur peau contre les effets néfastes du soleil. Depuis les écrans minéraux d'abord utilisés par les Égyptiens, aux filtres solaires organiques sophistiqués actuels (UVA/UVB), des progrès ont été réalisés en termes de protection contre le soleil, et une connaissance approfondie de la physiologie cutanée a été acquise durant ce temps. Le spectre solaire est composé de radiations de longueurs d'onde différentes possédant des effets spécifiques, ainsi que des effets redondants sur la peau. Les UVB sont les principaux responsables des coups de soleil et de la formation de dimères d'ADN qui peuvent conduire à une mutation. Les UVA génèrent des réactions d'oxydation qui affectent l'ADN, des protéines, et les lipides, et agissent également comme immunosuppresseur. Récemment, les ra-

yonnements de la lumière visible et de l'infrarouge (IR) ont été associés à des dommages oxydatifs, et l'IR a été en outre lié à des effets indésirables de la chaleur sur la peau. De nombreux autres facteurs extrinsèques liés à l'environnement et au mode de vie affectent aussi l'aspect de la peau, accélérant le vieillissement. De nouveaux mécanismes moléculaires reliant le soleil et les facteurs environnementaux au vieillissement de la peau ont été identifiés: l'IR affecte l'intégrité mitochondriale; des récepteurs thermiques spécifiques servent également de médiateur de certains de ses effets; le tryptophane est un chromophore UVB; le récepteur d'hydrocarbures aryles (AhR) est activé par la lumière et par les xénobiotiques ce qui modifie la physiologie de la peau. L'intégration de tous ces nouveaux éléments change la façon dont nous concevons le vieillissement extrinsèque de la peau. La protection solaire UVA/UVB, est-elle encore suffisante pour notre peau?

### Introduction

Our attitude towards the sun has evolved with time and increasing knowledge of its effects on skin (Table 1). Until quite recently, people were seeking protection from the sun mainly to avoid the pain of sunburn or simply because darker skin was associated with lower social rank. Physical sunscreen, consisting of inorganic clays and mineral powders were already used by Egyptians for that purpose, whereas ancient Greeks applied a protective mixture of oil and sand to their skin.

At the beginning of the 20<sup>th</sup> Century, a link between sun exposure and the development of cancer was first established by Norman Paul from Sydney, Australia. A few years later two Germans, Karl Eilham Hausser and Wilhelm Vahle, proposed that light within the ultraviolet-B zone (UVB) (280–315 nm) was responsible for sunburn. At the time, it was concluded that UVB-induced sunburn was solely responsible for the development of sun-induced skin cancer and consequently exposure to wavelengths other than UVB was considered safe. That triggered research for new organic sunscreens aimed at blocking UVB effects on skin. One of the first formulations to be commercialized, under the name of 'Ambre Solaire', was invented by Eugene Schueller, the founder of L'Oréal. The name reflected Schueller's thinking that it was possible to tan without burning. That led to the 'Dark Ages' of tanning habits when things, such as a 'healthy tan' were pushed forward, products were labelled as 'suntan lotions' and people were 'working' on their tan by lying down immobile for hours under the sun.

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**Table 1** Landmarks in photoprotection

Date	Landmark	Ref.
1500BC	Egyptians used inorganic clays and mineral powders to protect their skin; they considered lighter skin as being more attractive than darker skin.	
400BC	In ancient Greece, athletes covered their body with a protective mixture of oil and sand when training under the sun for the Olympic Games.	
1801	Johann Wilhelm Ritter (Germany) discovered the existence of ultraviolet rays (UV).	[1]
1820	Sir Everad Home (England) was first to propose that melanin acts as a sunscreen and is protective to skin, a concept that is now being challenged.	[2]
1878	Otto Veiel (Austria) discovered that tannins may work as sun protectors. However, their persistent staining of skin precluded their commercial development for that application.	
1918	Norman Paul (Australia) linked sun exposure to skin cancer.	
1922	Karl Eilham Hausser and Wilhelm Vahle (Germany) first reported a causal link between UV light (280–315 nm) and sunburn.	
1936	Eugene Schueller (France, the founder of l'Oréal), is credited of inventing the first sunscreen.	
1938	Franz Greiter (Swiss) created the <i>Gletscher Crème</i> (Glacier cream) after suffering from sunburn while climbing the Alps.	
1940	Benjamin Green (USA) developed a petroleum-base red jelly, commonly named Red-Vet-Pet (red veterinary petroleum), that was used by soldiers during World War II to protect their skin from sunburn. It was greasy and unpleasant to wear so did not survive the war.	
1944	The same Benjamin Green (USA) refined his formulation that became the famous Coppertone suntan cream.	
1962	Franz Greiter (Swiss) introduced the concept of sun protection factor (SPF) by developing a method to measure the effectiveness of a sunscreen to suppress sunburn.	
1969	Albert Kligman (USA) published first evidence that sun exposure causes structural damage to the skin that can be differentiated from the intrinsic ageing process.	[3]
1977	Isaac Willis (USA) was the first to describe distinctive ultrastructural changes in skin following UVA exposure.	[4]
1979	The first UV tanning salons open in the US.	
1980	Coppertone commercialized the first UVA/UVB sunscreen.	
1982	Lorraine Kligman (USA) first supported a role for Infrared (IR) radiation (760–4 000 nm) in premature skin ageing.	[5]
1986	Albert Kligman (USA) developed the concept of photoageing.	[6]
1990's	Several studies unveiled the molecular basis of photodamage response.	
2006	First evidence, highlighted by Rachel Haywood (UK,) that visible light (400–700 nm) also contributes to skin damage via induction of radical production.	[7]
2007	A report from the World Health Organization (WHO) linked indoor tanning to melanoma.	
2010	Research from Andrea Vierkötter and Jean Krutmann redefined the causes of extrinsic ageing to include environmental factors other than light.	[8]

In the 60's, Franz Greiter, from Switzerland, introduced the concept of sun protection factor (SPF) by developing a method to measure the effectiveness of a sunscreen to suppress UV-induced sunburn (mainly caused by UVB rays). According to this concept, a sunscreen with an SPF 15 allows one to get exposed to 15 times more UV radiation than would normally be possible without getting sunburn. However, in the late 60's, it became apparent that sustained UV exposure was affecting skin in many ways, not only through sunburn and cancer. UVB was shown to cause skin structural damage that was enhancing the effect of age. Moreover, in the 70's, UVA radiation, so far considered as safe, was also linked to premature skin ageing. The double jeopardy of skin ageing and cancer slowly began to affect the behaviour of consumers. In the 80's, the labelling of sun products switched consequently from 'suntan lotion' to 'sunscreen' and companies started offering UVB/UVA protection.

By the turn of the 21st century, it was already clear that skin ageing was the result of both intrinsic and extrinsic factors, intrinsic being equivalent to chronological ageing and extrinsic referring to environment (including UVB/UVA) and lifestyle effects. However, there is growing evidence that our definition of extrinsic factors should be broadened to include additional wavelengths, i.e. infrared (IR) and visible light (Fig. 1). Our skin is definitely under challenge... beyond UV exposure.

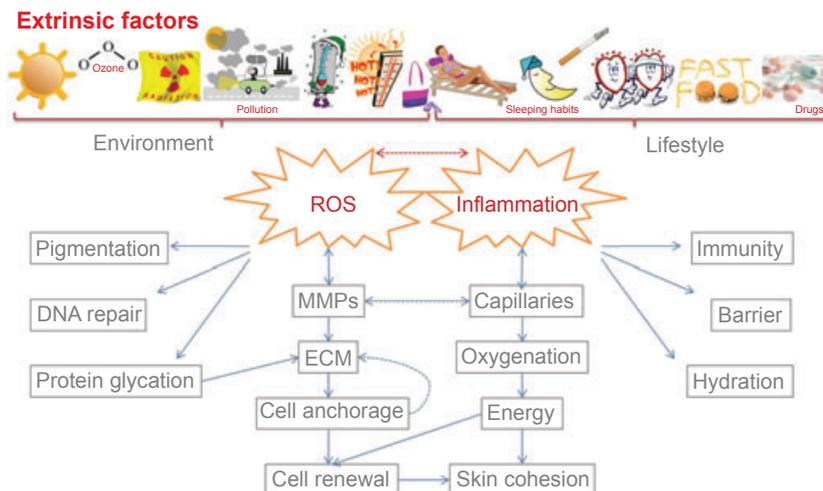
#### Effect of UV radiation on skin

What we call light is in fact a bundle of electromagnetic radiation, of which only a limited portion is detectable by the human eye.

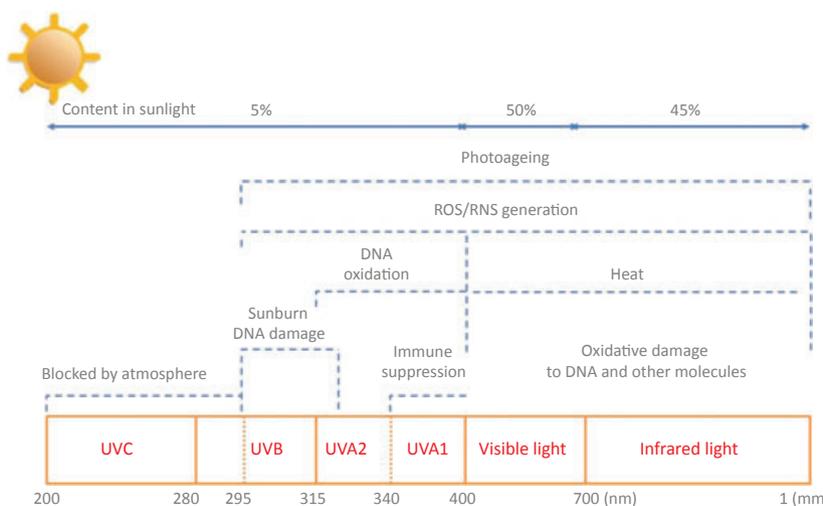
One way to look at light is to consider it as a wave that propagates through space. Each wave has some amplitude that translates into brightness and a wavelength that defines its colour. The full optical spectrum of sunlight encompasses UV, visible and IR, with wavelength ranging altogether from 200 nm to 1 mm. The solar spectrum has been shown to affect skin in ways that may vary according to wavelength (Fig. 2) [11]. Short wavelength radiations, in the UV range, have higher energy and are thus potentially more damaging.

#### UVC

UV rays may account for only 5% of the total solar spectrum, but they have a huge impact on skin. UV light can be further divided into UVC, UVB and UVA. High-energy UVC (200–280 nm) radiation is normally easily filtered by atmospheric ozone and this is very fortunate for us; UVC is so powerful that it is able to kill unicellular organisms on exposure. Depletion of the stratospheric ozone layer, as a source of increased UV exposure, has been a matter of concern since the 70s. At the time, a series of publications showed that certain inert gases, such as chlorofluorocarbons (CFCs), released in the atmosphere by human activities could affect the ozone layer. This culminated in 1985 with the report of a growing hole in the ozone layer over Antarctica [12]. In reaction, the Montreal Protocol was adopted in 1987 leading to a global ban on CFC production. Ozone kept declining until 1995, but has been slowly recovering since then. This is good news for the future; however, there is another threat to the ozone layer on the horizon, in the form of greenhouse gases and climate change [13].



**Figure 1** Extrinsic factors in skin ageing. Numerous extrinsic factors, linked to environment and lifestyle, affect the appearance of skin ageing. Sun exposure is a major trigger of skin damage. UVB, UVA, and infrared (IR) rays are known to cause skin damage and even visible light has become suspicious. Other environmental factors include ozone, ionizing radiation, industrial pollution, exhaust and extremes of temperature (either cold or hot). Lifestyle also has a major impact on skin ageing. Under this label, we find sun bed tanning, sleeping habits, smoking, exercise, nutrition and medication. Extrinsic factors have a strong impact on reactive oxygen species (ROS) production, inflammation reactions, pigmentation, DNA repair, matrix metalloproteinases (MMPs) activity, extracellular matrix (ECM) composition, skin immunity and barrier function [9]. Additional mechanisms involved in skin ageing [10] may also be altered.



**Figure 2** The solar radiation spectrum and its effects on skin. The solar spectrum is composed of various wavelength radiations having specific as well as overlapping and synergistic effects on skin. UVB is responsible for most sunburn, although short wavelength UVA may also trigger erythema to a lesser extent. Both UVB and UVA alter the immune response either alone or together but, given that UVA is 20 times more abundant in sunlight, the latter is generally considered to be the main culprit in solar-induced immunosuppression. Visible light mainly affects skin through the generation of oxidative damage, whereas IR induces heat damage and also alters mitochondrial integrity in skin cells, resulting in ROS generation. All solar wavelengths contribute altogether to skin ageing and wrinkling. UV = ultraviolet radiation; ROS = reactive oxygen species; RNS = reactive nitrogen species. Adapted from Svobodová and Vostálová, 2010 [11].

**UVB**

UVB rays (280–315 nm) are partially filtered by the ozone layer. UVB radiation is biologically active. It penetrates the superficial layers of skin, down to the basal layer of the epidermis, where it generates harmful reactive oxygen and nitrogen species (ROS and RNS), creating inflammation and sunburn and precipitating skin ageing. ROS are generated in the course of energy release after

light is absorbed by chromophores, such as melanin, in the skin. The high-energy photons of UVB can also be absorbed directly by cell DNA bases to cause mutagenic lesions falling within two classes: cyclobutane pyrimidine dimers formation (CPDs) and 6–4 photoproducts (6–4 PPs). CPDs and 6–4 PPs are both mainly repaired through a process known as nucleotide excision repair (NER). NER failure or exceeding of its repair capacity results in the

accumulation of mutations in skin cells and is an important step in UV-associated skin cancer development [14]. Delayed tanning is a defence reaction of skin to UVB exposure involving new melanin synthesis and is aimed mainly at reducing sunburn; unfortunately, its protective effect against UV-induced cancer seems at best limited [15].

#### UVA

Less energetic than UVB, but present in larger amounts, UVA radiation (315–400 nm) penetrates deeper in the skin, reaching the dermis. Besides melanin, riboflavin-containing FAD and FMN are important endogenous skin chromophores that absorb UVA energy [16]. Despite being more penetrating, UVA causes less obvious damage than UVB and, until recently, was considered to be rather inoffensive. An immediate, but short-lived tanning develops following exposure to large doses of UVA. The belief that UVA was harmless, combined with its tanning potential prompted its use in tanning salons. However, we now know that UVA generates ROS and RNS that alter proteins, lipids and DNA. Oxidative damage contributes significantly to premature skin ageing and wrinkle formation, and also indirectly increases the risk of cancers through the formation of oxidized DNA bases (mainly 8-oxo-7,8-dihydroguanine) [14, 17, 18]. Furthermore, UVA in the range of 360–380 nm is immunosuppressive, a fact that may further support the development of skin cancers [19, 20]. Importantly, UVA-induced immediate pigmentation mainly occurs through photo-oxidation of existing melanin rather than synthesis of new pigments and confers little photoprotective advantage [15]. As sun beds deliver mostly UVA radiation, the resulting tan is only minimally protective for future sun exposure.

#### New developments: A closer look at light

##### Visible light

Of even lesser energy, visible light (400–700 nm) accounts for approximately 50% of the total solar spectrum [11]. It penetrates deeply into biological tissues and about 20% reaches the hypodermis [11]. We enjoy visible light; it allows us to see the world, helps plants to grow providing us with food and oxygen, is useful in treating certain skin conditions, and certainly seems inoffensive. But is it really? Very few studies have addressed the question so far, but their results revealed that visible light affects skin physiology in many ways and this is already changing the way we are looking at light.

For instance, similar to what is seen with UVA, irradiation of skin with visible light was reported to generate ROS following photon-induced activation of endogenous photosensitizers [21, 22]. To quantify the relative contribution of UVB, UVA and visible light to ROS generation, *ex vivo* skin explants were exposed to natural midday sunlight in the presence of a set of filters. Results estimated the generation of ROS at 4% for UVB, 46% for UVA and 50% for visible light [21]. Visible light skin chromophores include haemoglobin, melanin, bilirubin, riboflavin and porphyrins [23]. At doses equivalent to 15–90 min of sunlight exposure, visible light also induces inflammatory cytokines (IL-1, IL-6, IL-8, GM-CSF) and increases the expression of matrix degrading enzymes (MMP-1 and MMP-9) in human epidermal equivalents, whereas free radical production was confirmed *in vivo* using chemiluminescence and skin biopsies [22, 24]. Visible light additionally appears to affect DNA through the formation of oxidized DNA bases as seen with UVA [25, 26], but not through dimer formation [22]. Finally, visible

light induces pigment darkening in subjects with darker skin (Fitzpatrick type IV–V) [27] and is suspected of being an aggravating factor in melasma [28].

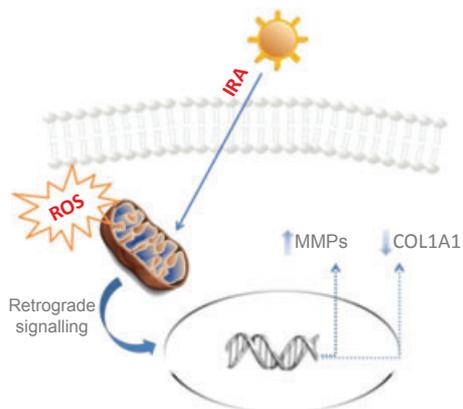
So the question rises, is visible light friend or foe? The answer most probably lies somewhere in between. Importantly, although visible light constitutes a substantial part of the solar spectrum, the strength of its physiological effects should be placed into context with that of UV radiation. For instance, UV was reported to be 25 times more efficient at inducing pigmentation in people with darker skin, compared to visible light [29]. Moreover, although visible light can affect DNA structure, a study performed on Chinese hamster cells suggested that it contributes to less than 10% of total DNA damage caused by solar exposure [26]. Finally, even though visible light has measurable effects on signalling pathways known to precipitate skin ageing, its significance in the process of photo-ageing still needs to be clarified.

##### Infrared radiation

IR has the lowest energy. However, its contribution to the solar spectrum reaching human skin is around 45%. IR comprises IRA (700–1400 nm), IRB (1400–3000 nm) and IRC (3000 nm–1 mm). IRB and IRC do not penetrate the skin very deeply, but IRA does. IRA represents about 30% of IR radiation, of which 65% reaches the dermis and 10% the hypodermis [11]. As is the case with UV and visible light, IRA generates ROS within the skin. The relative contribution of IRA to free radicals generation, in Berlin summer midday sunlight, has been estimated to be around one-fourth of that of UV [21]. IRA also induces unbalanced gene expression of MMP and decreases collagen gene expression *in vitro* and *in vivo*, favours angiogenesis, is involved in photoageing, may promote carcinogenesis and, additionally, affects mitochondrial integrity [21, 24, 30–32]. However, unlike UV and visible light, IR is poorly absorbed by usual skin chromophores, such as melanin, and is too weak to directly affect DNA. So how are all these effects occurring?

The skin response to IR type A (IRA) radiation has been proposed recently to involve mitochondria with cytochrome C oxidase (CcO) as a potential chromophore [31, 33]. Interaction of IRA with CcO could lead to disruption of the mitochondrial electron transport chain, resulting in inadequate energy production and increased generation of ROS. Such mitochondrial dysfunctions are known to trigger retrograde mitochondrial signalling from mitochondria to the cell nucleus, commanding expression of specific nuclear genes [34]. In fibroblasts, gene regulatory effects are observed at IRA dosage of 54–360 J/cm<sup>2</sup> and ROS production can be detected even at IRA intensity levels as low as 30 J/cm<sup>2</sup> [35]; considering that a dosage of 300–800 J/cm<sup>2</sup> can easily be reached under the sun, in a summer day in central Europe, these experimental dosages can be considered as physiologically relevant [36].

Retrograde mitochondrial signalling is a survival pathway of communication that operates through ERK1/2 activation and elevation of free Ca<sup>2+</sup> in the cytosol of cells. In skin, the pathway culminates in the modulation of genes involved in photoageing, including MMP-1 and type I procollagen (COL1A1) (Fig. 3) [31–33]. The combination of stimulated collagen degradation and reduced collagen renewal generated by increased MMP and lesser COL1A1 expression, respectively, is recognized to significantly contribute to the formation of wrinkles in photoageing [37]. However, when tested *in vivo*, the magnitude of IRA-induced MMP-1 upregulation in skin showed considerable interindividual variability and up to 20% of the volunteers had no response at all [38]. The reason

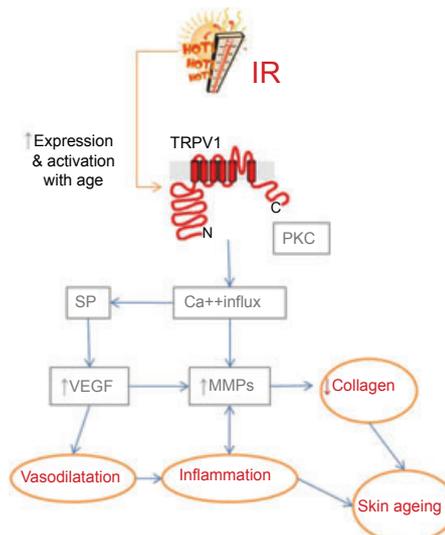


**Figure 3** Infrared A-induced retrograde signalling Infrared type A (IRA) radiation leads to a burst of mitochondrial reactive oxygen species (ROS), which in turn initiates retrograde signalling, from mitochondria to nucleus, where it alters expression of genes involved in skin ageing, such as matrix metalloproteinase-1 (MMP-1) and procollagen alpha-1 (COL1A1) [31–33]. The combination of stimulated collagen degradation and reduced collagen renewal generated by increased MMP and lesser COL1A1 expression, respectively, contributes to the formation of wrinkles in photoageing.

for such discrepancies remains unclear, but does not appear to be related to skin type [38]. However, as IRA-induced ROS production (at the basis of retrograde signalling) has been linked to skin temperature [21], one possible explanation may come from differences in IRA-induced changes in this parameter among the participants.

Indeed, part of the answer of skin to IR radiation may lie in the fact that IR light has the particularity of interacting with molecules within tissues, generating molecular vibrations that produce heat [11]. This is the cause of the warmth sensation that we feel when exposing ourselves to sunlight. IRB and IRC are mainly responsible for the generation of heat in skin. Keratinocytes, fibroblasts and melanocytes express various thermo-sensitive receptors at their membrane, including the transient receptor potential vanilloid 1 (TRPV1), which was recently proposed to be activated by IR radiation, in addition to temperature  $>43$  °C, low pH and capsaicin [39]. TRPV1 is a cell membrane channel that opens upon stimulation, allowing a flux of calcium ions to cross the membrane and rush into cell.

In skin, prolonged heat activation is associated with inflammation, elastosis and dermal collagen breakdown *in vitro* and *in vivo* [40, 41]. Chronic IR exposure has similar effects that may be mediated, at least partly, through the generation of heat [42]. The proposed mechanism involves heat-induced and protein kinase C (PKC)-potentiated activation of TRPV1 at the membrane of skin cells, allowing calcium ions inside (Fig. 4). In fibroblasts, TRPV1 activation induces MMP-1 expression, at the mRNA and protein levels, resulting in increase in collagen degradation and premature skin ageing [30, 41]. In cutaneous sensory neuronal cells, TRPV1 activation stimulates the release of neuropeptides, such as substance P (SP), which increases vasodilatation and vascular permeability in skin, through the promotion of VEGF secretion by mast cells [43]. Synergistic activation of TRPV1 on both skin cells may result in inflammation and precipitate skin ageing even further. Interestingly, TRPV1 expression is increased in old skin suggesting a link with pruritus, a common complaint in elderly people [41, 44].



**Figure 4** Activation of the TRPV1 ion channel by IR and heat in skin in keratinocytes, transient receptor potential vanilloid 1 (TRPV1) activation by infrared radiation (IR) and heat promotes calcium influx and induces matrix metalloproteinase-1 (MMP-1) expression, resulting in collagen degradation [40, 41]. On skin sensory nerve fibres, TRPV1 activation stimulates the release of substance P (SP), which mediates vasodilatation and vascular permeability, through the promotion of vascular endothelial growth factor (VEGF) secretion by mast cell [43]. Synergistic activation of TRPV1 on both skin cells favours inflammation and precipitates skin ageing. Expression of TRPV1 is increased in aged skin [44].

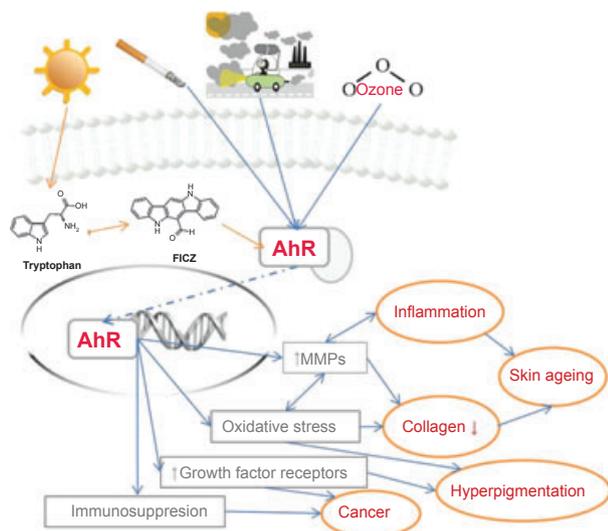
Thus, IR exposure appears to have non-negligible effects on skin physiology that are mediated through various molecular mechanisms. However, we still do not know which one is most important and to what extent these mechanisms, globally and individually, contribute to skin changes with ageing. As is the case for visible light, the biological relevance of IR effects in relation to UV needs to be clarified.

#### Additional extrinsic factors

As discussed in the introduction, the damaging effects of sun exposure on skin have been recognized for quite some time. However, more recently, the contribution of environmental xenobiotics has started to emerge (Fig. 1). Urban life exposes our skin to increased challenge resulting from air pollution, exhaust, ozone and various types of radiation. Industrialization has also changed our lifestyle and new habits have developed that challenge the skin, including smoking, usage of tanning beds, intake of unhealthy food and beverages, sedentary lifestyle and insufficient sleep.

#### Environmental factors

Pollutants, exhaust, smog-derived ozone and cigarette smoke exposure have been associated with precipitated skin ageing and increased cancer risks [8, 45, 46]. These factors share a common mechanism involving the aryl hydrocarbon receptor (AhR). The AhR is a ligand-activated transcription factor found in various skin cells, including keratinocytes, fibroblasts, melanocytes and Langerhans cells [47]. Non-activated AhR is trapped in a cytosolic multiprotein complex. Upon ligand binding, although, the complex



**Figure 5** Activation of AhR by UVB and xenobiotic factors in skin. Activation of the aryl hydrocarbon receptor (AhR) by light and xenobiotics results in its translocation to the cell nucleus, where it regulates the expression of a number of genes involved in melanogenesis, skin inflammation, immunosuppression, skin ageing, and carcinogenesis [47].

dissociates and AhR translocates to the nucleus where it stimulates the expression of genes containing the xenobiotic responsive element (XRE) (Fig. 5). Some of these genes control the expression of proteins involved in oxidative stress reactions, inflammation, immunosuppression, pigmentation, premature ageing, and cancer in skin [47].

Incidentally, UVB was recently shown to interact with AhR in a reaction involving the formation of a tryptophan-derived photoproduct (FICZ) [47, 48]. In other words, the free amino acid tryptophan in skin cell cytoplasm can act as a chromophore to absorb UVB energy and the resulting photoproduct activates AhR signaling (Fig. 5). Importantly, AhR contributes to UVB-induced skin tanning and inflammation in skin [49, 50].

#### Lifestyle factors

Epidemiological studies have evidenced the influence of lifestyle factors on skin ageing and skin health. For instance, twin studies have associated smoking with increased wrinkles, tissue laxity and pigmentary changes in humans. One study estimated that, 10 years of smoking difference in twins corresponds roughly to a 2½ years older appearance [51]. Moreover, eating unhealthy food is associated with all kind of skin problems, ranging from acne to signs of skin ageing. On the opposite, a healthy diet rich in antioxidants may delay chronological ageing effects and twins who avoid excessive alcohol intake have a younger perceived age [51, 52]. Having proper rest is also important. The number of sleeping hours needed may vary among people, but having regular sleeping habits tends to be associated with healthier and younger looking skin. Exercising is also beneficial for skin; it brings tonus and stimulates blood circulation helping to evacuate metabolic wastes and bringing oxygen to skin tissues. Medicine intake may present additional risks for the skin, as some medicinal drugs can increase the photosensitivity of skin and therefore decrease the time it takes to

burn. Finally, one of the worst habits is probably sun bed tanning, which is pretty damaging to skin. The intensity of UVA radiation emitted by a powerful tanning bed is 10–15 times higher than what we normally get under midday summer sun [11]. Exposure to artificial UV is an important risk factor for melanoma, especially among younger people [53].

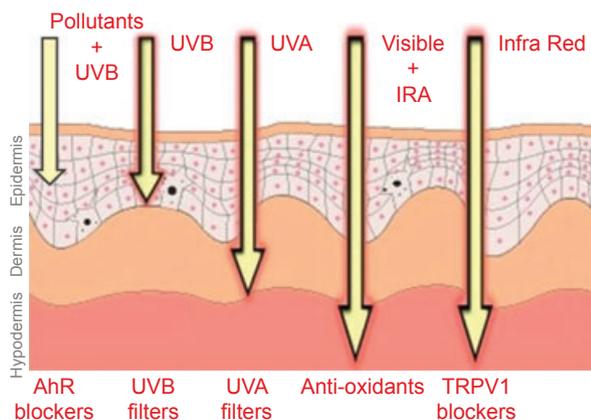
The incidence of melanoma, a most serious form of skin cancer involving melanocytes, is on the rise all over the world. It is currently increasing at the alarming rate of 4–5% per year in industrialized countries [54]. According to the Canadian Dermatology Association, melanoma is now the seventh most frequent cancer in Canada, affecting one man in 74 and one woman in 90. In comparison, the lifetime risk of melanoma for Americans in the 1930's was one in 1,500. Most alarming is the fact that melanoma is reaching epidemic proportions within the 15–29 age group, for which it represents the third most common cancer and constitutes 11% of all new cancer cases annually. Recent large epidemiological studies in Minnesota, Australia, Norway, and Sweden have, without any doubt, linked artificial UV tanning and melanoma [53]. The reason why the young generation appears more vulnerable is not totally clear at the moment. However, it has been suggested that early age at first use of a sun bed is rather a marker for cumulative sun bed exposure than an indication of increased susceptibility for younger people [55].

#### Conclusion

Our relationship with sun is still, the less to say, ambivalent. We enjoy its warming effect on the body and soul, but fear its harmful burning power and the long-term skin damage that can result from sun exposure. The need for better skin protection from sunlight has pushed scientists to constantly develop and improve sunscreen products. Until recently, sun protection was essentially addressing the effects of UV radiation on skin. However, new experimental data have raised concerns about the potential damaging effects of IR and even visible light on skin. Moreover, it has become evident that other environmental and lifestyle factors are contributing to extrinsic skin ageing and pigmentation disorders. UVB-UVA sunscreen may not be sufficient anymore.

In support of this, in human subjects, application of a UVA/UVB sunscreen was unable to inhibit free radicals generated from visible light, whereas addition of a combination of anti-oxidants to the formulation significantly reduced their number by 54% [22]. Moreover, the use of various conventional broad-spectrum sunscreens on skin equivalents conferred only partial protection from solar-stimulated ROS production. In the latter experiment, even a cream with SPF 50 and high UVA protection was only efficient at 53% against solar-stimulated ROS and was not protective at all against visible light induced ROS [56]. Similarly, skin protection from ROS induced under IR exposure could not be achieved with a conventional UVA/UVB sunscreen, but addition of a blend of anti-oxidants resulted in the neutralization of up to 56% of the ROS generated [57]. To what extent these free radicals, left unchecked by UVA/UVB filters under sun exposure, affect skin physiology still has to be fully evaluated and put into perspective with other UV effects. Nevertheless, given the deep dermal penetration of visible light and IRA photons, they are likely to have non-negligible repercussions.

These findings suggest that we should be seeking for a more comprehensive protection approach that would cover all mechanisms involved beyond UV radiation. A similar global and integral approach has been described previously for other skin concerns,



**Figure 6** Ideal integral dermo-protection against extrinsic ageing. Pollutants and radiations of different wavelengths are affecting the skin in different ways. To fully protect the skin, all mechanisms involved in these adverse effects should be covered simultaneously. AhR blockers may address pollution and part of the UVB effects on skin; proper filters may block UVB and UVA effects in the epidermis and the dermis respectively; anti-oxidants may counter ROS originating from visible and IRA in the epidermis and the dermis; and TRPV1 modulators may prevent the effects of IR-induced heat on skin.

including skin ageing and skin pigmentation [10, 58]. As illustrated in Fig. 6, based on a new understanding of the physiology of extrinsic skin ageing, an integral dermo-protection approach should ideally include an AhR blocker to counteract some adverse effects of environmental factors, an array of anti-oxidants to neutralize pro-oxidative influence of visible light and IRA radiation, a modulator of TRPV1 to protect from IR-induced thermal ageing, in addition to the regular UVB and UVA filters. However, additional work

is needed to delineate the relative burden of the various extrinsic factors in skin ageing.

The recommendation for such integral skin protection, especially if used year-round, may raise concerns about a possible interference with cutaneous vitamin D synthesis leading to low circulating vitamin D levels in some people. Vitamin D, which is not really a vitamin, but a true hormone, is essential for bone health. Its deficiency has been associated recently with a surprising number of health conditions, from autoimmune diseases, to cardiovascular problems, metabolic syndrome, infections, and cancer [59]. Sun exposure is a non-negligible source of vitamin D. Exposing the skin to UV radiation initiates vitamin D synthesis starting with 7-dehydrocholesterol. The molecule is located in the membranes of skin cells where it absorbs UVB photons and converts into previtamin D. The latter then thermally isomerises into vitamin D over a period of 12–24 h.

So the question arises: does sunscreen use prevent or reduce vitamin D production? In theory, it could, as sunscreen protects from UVB absorption in the wavelength needed for vitamin D synthesis. However, normal sunscreen usage has never been so far associated with vitamin D insufficiency, as, very little incidental sun exposure is sufficient to maintain proper vitamin D levels. For Caucasians, living in the northern hemisphere, unprotected sun exposure of arms and legs for 5–15 min, three times a week during spring, summer and fall is sufficient to get all the vitamin D needed [52]. However, levels of vitamin D have been shown to fall, sometimes even below sufficiency, for Caucasians living North during winter months; for these people, vitamin D supplementation may be advisable during the cold season to achieve a healthy range above 30 ng/ml [60].

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