Shining Light on Skin Pigmentation: The Darker and the Brighter Side of Effects of UV Radiation†

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Abstract

The term barrier function as applied to human skin often connotes the physical properties of this organ that provide protection from its surrounding environment. This term does not generally include skin pigmentation. However, skin pigmentation, which is the result of melanin produced in melanocytes residing the basal layer of the skin and exported to the keratinocytes in the upper layers, serves equally important protective function. Indeed, changes in skin pigmentation are often the most readily recognized indicators of exposure of skin to damaging agents, especially to natural and artificial radiation in the environment. Several recent studies have shed new light on a) the mechanisms of involved in selective effects of subcomponents of UV radiation on human skin pigmentation and b) the interactive influences between keratinocytes and melanocytes, acting as 'epidermal melanin unit', that manifest as changes in skin pigmentation in response to exposure to various forms of radiation. This article provides a concise review of our current understanding of the effects of the non-ionizing solar radiation, at cellular and molecular levels, on human skin pigmentation.

INTRODUCTION

Human skin interfaces between the body and external environment, acts as a barrier against physical, chemical and biological attacks from the environment. Exposure to solar radiation and sun sensitivity are associated with increased risk for skin cancers (1, 2). The incidence of skin cancer (including melanoma and non-melanoma skin cancers) has been increasing substantially in the United States (3, 4). Solar UV radiation induces genotoxic effects by damaging wide variety of bio-organic molecules including DNA, proteins and other small molecules such as folate. Biological macromolecules or small compounds present in the skin act as chromophores and absorb radiation of specific wavelength to bring about a cascade of reactions within the cell. Nucleic acid, urocainic acids, co-factors NADPH and NADH, aromatic amino acids- tryptophan and tyrosine, riboflavins, porphyrins and melanins and their precursors are all chromophores present in the skin. They absorb protons and undergo a series of structural and chemical changes (5). Melanin synthesized in the melanocytes plays an important role in protecting the skin from radiation-induced damage. Melanocytes transfer melanosomes to keratinocytes, where melanin is localized above the nucleus in the form of a cap like structure to protect the cellular DNA (6). UV radiation induces immediate pigment darkening (IPD) by chemical modification of melanin, and possibly spatial redistribution of melanosomes in keratinocytes and melanocytes (7). UV exposure also leads to delayed tanning (DT) by new synthesis of melanin over several days after UV exposure and persists for weeks (8). UV-induced pigmentation is thought to play a protective role by

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preventing DNA damage and accumulation of mutations. Given the importance of melanin and skin pigmentation in providing protection from solar radiation, the evolutionary aspects of human skin pigmentation have received much attention. Skin pigmentation is thought to have evolved as protective adaptation from the damaging effects of direct exposure of the skin to solar radiation (9). However, since melanin pigment absorbs solar radiation, which is required for synthesis of vitamin D in the skin, the primary site of production of this molecule essential for a wide range of physiological processes, loss of dark pigmentation and evolution of fair skin, in order to maximize the absorption of solar radiation for vitamin D synthesis (10) but while simultaneously increasing the susceptibility to its damaging effects, is thought to be the evolutionary price of migration of early humans to higher latitudes. This review provides an overview of the current knowledge on the biological mechanisms of the effects of solar radiation on melanocytes, melanin and human skin pigmentation.

BIOLOGY OF SKIN PIGMENTATION

Human skin color phenotype is determined by the amount and distribution of melanin and ranges from white to black with various shades in between. Fitzpatrick scale of skin phototype classification is based on the color of the skin and eye and ability of the skin to burn and tan when exposed to UV radiation. Type I-III are white skin, type I- always burns, never tans; type II- always burns, minimal tan; type III- burns minimally, tans moderately and gradually; whereas type IV- light brown skin, burns minimally and tans well; type V- brown skin, rarely burns, tans deeply and type VI- dark brown/black skin, never burns, tans deeply (11). Skin pigmentation is determined by over a 100 genes including those that encode transcription factors, enzymes, hormones, autocrine and paracrine factors and their receptors. There are several excellent and comprehensive reviews on biochemistry, cell biology and genetics of skin pigmentation (6, 12–14). Here, only a brief outline of the biology of pigmentation as it relates to its response to environmental radiation will be presented. The photoprotective function of skin resides primarily in the keratinocytes present in the outer layers of the epidermis with the melanin pigment producing melanocytes embedded within the basal layer of keratinocytes (6). The pigment melanin is synthesized in the melanocytes and helps to protect the skin from the deleterious effects of solar radiation by several mechanisms (15). Accordingly, patients with impaired production of melanin, for example as in vitiligo, or lack pigment altogether as in albinos, have higher rate of skin cancers (16, 17).

Two chemically distinct types of melanins are found in the skin; an insoluble black-brown eumelanin and an alkali soluble red-yellow pheomelanin. Eumelanin is a polymeric compound consisting of 5, 6-dihydroxyindole (DHI) and 5, 6- dihydroxyindole carboxylic acid (DHICA) monomers and is the primary melanin involved in photoprotection, with the precursors DHI and DHICA having considerable antioxidant properties (18, 19). Pheomelanin is also a polymeric compound; however it is made up of sulfur and nitrogen containing benzothiazine monomers. The biochemical mechanisms of the initial reactions by which these two types of melanins are synthesized are well understood. However, the terminal reactions that make the insoluble polymers, especially pheomelanin, are not understood and thought to occur through spontaneous reactions. This makes the microenvironment within the melanosome, where these pigments are formed critically important (20). The pathway begins with the production of DOPA and DOPA quinone from tyrosine, catalyzed by the enzyme tyrosinase (TYR), the most important and rate-limiting enzyme in pigmentation. Tyrosinase catalyzes the only step common to both eumelanin and pheomelanin synthesis. Mutations in tyrosinase cause albinism, a deficiency of production of both types of melanin, externally characterized by the complete or partial lack of skin, hair and eye pigmentation (21). Pheomelanin synthesis pathway is thought to proceed

spontaneously, controlled by the concentrations of metabolites and inherent pH controlled by the other pigmentary gene products. Synthesis of eumelanin on the other hand, is catalyzed by additional tyrosinase related enzymes TYRP1 and TYRP2 (also known as dopachrome tautomerase, DCT) (22, 23). Tyrosinase and TYRPs are membrane bound enzymes. They are synthesized and transported through the ER-Golgi secretory pathway and finally incorporated into the melanosomes (20). The relationship between total melanin content, ratio of eumelanin:pheomelanin ratio and the activity levels of the key melanogenic enzyme tyrosinase has been investigated in an exhaustive study by Ito and his coworkers (24). Classifying melanocytes isolated from individuals based on visual skin pigmentation as very light, light, fairly dark and dark, it was noted that total melanin content correlated with tyrosinase activity levels across all skin types, and while eumelanin levels correlated with visual skin pigmentation, pheomelanin levels were consistently higher in lighter skin (24). The melanocyte master controller known as micropthalmia transcription factor, MITF, controls many aspects of skin pigmentation- from development of melanocytes to their response to environmental stimuli including expression of melanogenic enzymes (25).

The mature melanosomes when fully deposited with melanin pigment are transported from the melanocyte cell body into the dendrites and transferred to the keratinocytes, where melanosomes localize to the perinuclear area (26). Mutations in cytoskeletal components that affect melanosome movement within the melanocyte result in overall pigment lightening due to the inability of the melanosomes to be transported along the dendrites and thus transferred to the keratinocytes (27). The transfer of melanosomes to keratinocytes is known to be regulated by protease-activated receptor 2 (PAR2) and its peptide activator SLIGRL (26). Although the molecular details of this process and how it is regulated are poorly understood, it generally accepted that it provides an additional site of regulation for both constitutive and facultative skin pigmentation.

ELECTROMAGNETIC RADIATION AND PIGMENTATION

Electromagnetic radiation consists of electrical, radio, microwave, infrared, visible, UV, X-rays and gamma-rays. Solar radiation that reaches the earth's surface is primarily nonionizing radiation (UVR, visible light, and infrared radiation) (Fig.1). Radio waves have the largest wavelength but lowest frequency and energy, whereas gamma rays have small wavelength but highest energy. Radio frequency energy is used for several therapeutic and cosmetic purposes (28). There are several reports of its efficacy in non-invasive skin tightening (29). Radio waves have can penetrate into deeper layers of the skin and generate heat. This thermal effect of radiofrequency radiation causes tightening of the skin in the sub-dermal layers (30). Karinen *et al.* found differences in protein expression in volunteers forearm skin exposed to radiofrequency modulated electromagnetic field (RF-EMF, mobile phone radiation) and suggested protein expression in human skin might be affected by the exposure to RF-EMF (31). The exponential increase in the usage of mobile phones, which emit radiofrequency, has prompted some studies on the effects prolonged use of mobile phones on skin and risk of melanoma (32). Infrared radiation with intermediate energy causes an increase in the vibrational energy of biomolecules and causes the production of free radicals within the skin (33). Microwave radiation is also a form of non-ionizing radiation that does not possess enough energy to cause significant harm to the skin. However, intense exposure to this type radiation can cause change in dielectric field within cells that increases friction between polar water molecules, and thus increases the ambient temperature and can lead to burns. However, only limited information is available on the effects of radio or microwave radiation on human skin pigmentation.

CHROMOPHORES IN THE SKIN

Solar radiation is absorbed by endogenous chromophores like nucleic acids, aromatic amino acids and melanin precursors present in the epidermis (5). DNA absorbs 4-fold less of UVA than UVB radiation resulting in production of DNA photo-damage and mutations. Tyrosine and tryptophan absorb UV radiation and bind to DNA and produce photodamage, and also cause damage to adjacent amino acids within proteins. Melanin absorbs UV radiation and reduces the UV-induced damage in the melanocytes and keratinocytes. Moan *et al.* proposed that the evolutionary and biological role of facultative skin pigmentation is to protect folate and its derivatives against photodegradation (34). Recently, rhodopsin, a photopigment that is present in the eye and involved in visual transduction has been reported to be present in melanocytes and contribute to UV phototransduction in these cells (35). However, the full complement of chromophores in the skin and specifically in the melanocytes and the mechanisms of cutaneous phototransduction remain to be fully understood.

UV RADIATION

Effects of UV radiation on the skin have been studied extensively due to the physiological and the pathological implications of natural and recreational exposure to solar and non-solar UV radiation sources. Solar UV spectrum spans from 100 nm to 400 nm wavelength and it is divided into UVA (320 nm-400 nm), UVB (280 nm-320nm) and UVC (100 nm-280 nm). UV radiation of wavelengths shorter than ~310 nm are absorbed by earth's ozone layer and therefore natural exposure to UVC component of the solar radiation is thought to be minimal. Approximately 90–95% of UVA and 5–10% of UVB in the solar radiation reaches human skin (36, 37). UVA can penetrate deep into dermis and 20–50% of solar UVA can reach the depth of the melanocytes, whereas only 9–15% solar UVB reaches melanocytes in the skin (6). The causative role of UV radiation in melanoma has been investigated extensively. This topic has been covered by several comprehensive reviews (37–40).

Increased production and distribution of melanin within melanocytes and the conversion of keratinocytes into a hornlike substance or stratified squamous epithelium are the morphological and physiological response to UV radiation in skin (41). Higher dose of UV radiation initiate apoptosis in keratinocytes and melanocytes. De Leeuw *et al.* irradiated melanocytes (skin type II) and keratinocytes with UV and found melanocytes less sensitive to UV radiation than keratinocytes (42). UV-induced oxidative stress increases the production of ROS and in response to the accumulating ROS, keratinocytes release factors that act on melanocytes and induce hyperpigmentation. A potential target for cosmetic skin-lightening systems would be to increase the anti-oxidants (43).

Geographical differences in bioactivity, strength, seasonal distribution of UVA and UVB have been recorded, but influence of these differences on human skin pigmentation is not well understood. For example, latitudinal bands of UVA distribution are wider than UVB and higher levels of UVA exist towards the poles. Western Europe receives highest UVA compared to UVB and whereas equatorial regions receive slightly less UVA than tropical and subtropical areas (9). In an elegant review, Jablonski and Chaplin summarized the effects of UVA and UVB on human body and selective mechanisms involved in the evolution of pigmentation. They proposed that evolutionarily two clines of human skin pigmentation were produced by natural selection based on UV radiation- one at the equator with darker skin pigmentation and the second with depigmented skin in response to lower UVB availability and its requirement for vitamin D photosynthesis. In a detailed discussion of the effects of UV on folate, which is essential for cell division, DNA repair and melanogenesis, these authors propose that photolysis of folate directly by UVA and depletion of folate by ROS may have played a role in evolution of pigmentation.

Additionally, sensitivity of tyrosinase to high levels of ROS generated in response to UVA exposure is thought to disrupt melanin production (9). In addition to evolution of skin types in response to UV, solar UV continues remain a significant factor in human skin pigmentation.

Exposure to UVA induces immediate pigment darkening (IPD) within a short time, as little as few hours, by acting on preexisting melanin. UVA can also cause persistent pigment darkening (PPD) in the skin. Both types of skin darkening by UVA are more readily observed in dark-skinned individuals than in fair-skinned persons. Recent extensive *in vivo* studies on human subjects by Hearing's laboratory, using state of the art immunohistochemical and molecular methodologies, have contributed significantly to our understanding of the mechanisms of UV induced pigment changes (44–46). Based on their study on subjects repeatedly irradiated with UV, five times a week for two weeks, Choi *et al.* reported that UVA, unlike UVB, induces minimal changes in expression of pigmentation related genes (45). In another study, where subjects were given a challenge dose of UVA following the 2-week UVA exposure, Miyamura *et al* reported that although UVA exposure resulted in DNA and cellular damage, the UVA-induced pigmentation/tanning offered no photoprotective effect upon UVA challenge (44). Thus, the UVA exposure can cause formation of singlet oxygen radicals which induce DNA-strand break, nuclear base damage and mutations (47). Garland *et al.* hypothesized that exposure to UVA could induce melanoma and demonstrated potential carcinogenic effect of UVA in cultured human melanocytes. Endogenous pigment and/or melanin-related molecules are thought to enhance UVA-induced DNA damage via photo-sensitization reactions that generate reactive oxygen species (ROS) (48). UVA generated ROS can damage mitochondria and induce apoptosis in cell culture (49). Pheomelanin and/or melanin intermediates are thought to act as photosensitizers in DNA single-strand breaks caused by UVA (50). Marrot *et al.* also demonstrated that endogenous pigments and/or melanin-related molecules enhance DNA damage, evidenced by higher DNA breakage in melanocytes than in fibroblasts and higher in cells with high melanin content (51).

Although UVA reaches the dermal layers of the skin and its effects on photoaging and keratinocyte invasiveness are well studied (52), melanocytes seem to be more susceptible to the damaging effects of UVA. For example, exposure of cultured melanocytes and keratinocytes from the same donor to UVA and UVB showed that UVA-induced oxidative lesions contributed to a larger extent to DNA damage in melanocytes than in keratinocytes (53). Cui *et al.* demonstrated that keratinocytes absorb UV radiation and activate p53 mediated propiomelanocortin (POMC) promoter, which leads to an increased expression of POMC, and POMC derived beta-endorphins and alpha-melanocyte stimulating (alpha-MSH) hormone (54). Keratinocyte- secreted alpha-MSH stimulates melanocytes and increases pigment production by binding to melanocortin 1 receptor (MC1R) receptor and activation of cAMP pathway (55). Increased alpha-MSH secretion in response to UV exposure can cause both melanocyte proliferation and increased melanogenesis (56). Scott *et al.* showed that while the alpha-MSH, the ligand for MC1R increased MC1R mRNA expression, treatment of melanocytes with the MC1R antagonist agouti protein or UV downregulated MC1R expression. These authors also investigated regulation of MC1R by paracrine and endocrine factors and suggested differential regulation of MC1R may contribute to the variation in constitutive and UV induced pigmentation in humans (57). MC1R signaling, presumably via paracrine mechanism, appears to participate in both constitutive and facultative skin pigmentation. Thus, the critical role of MC1R as key regulator of skin pigmentation has been well documented. Accordingly, allelic variants of MC1R that result in receptor molecules with varying response to binding to alpha-MSH have been shown to be associated with red hair phenotype, tanning response to solar radiation and susceptibility to melanoma and non-melanoma skin cancers (13, 58, 59).

Exposure to UVB radiation, on the other hand, causes erythema and delayed tanning (DT) and UVB is more efficient than UVA in causing these effects (60). UVB-induced DT is a result of increased melanin synthesis and skin darkening that develops days after UV exposure (34). Repetitive 2-week exposure of human skin to UVB radiation significantly increased the levels of eumelanin and pheomelanin in the skin (61). Miyamura *et al.* exposed human skin and three-dimensional reconstructed human skin equivalents to 2-week repetitive UVB radiation and then challenged with a 2 MED of UV dose and observed a significant increase in melanin content and melanocyte density in human skin and human skin equivalents (44). In another detailed study using immunohistochemistry and whole human genome microarray techniques, Choi *et al.* showed exposure of human skin to UVB radiation increased melanin content and increased expression of melanocyte-specific genes and proteins (45). Thus, UVA or UVB effects on skin pigmentation are distinct, where UVB induce skin pigmentation by increasing melanin synthesis, whereas UVA elicit visible pigmentation by oxidation or distribution of existing melanin (44, 61, 62).

UVB exposure also causes DNA damage by formation of covalent bonds between adjacent thymidine molecules (thymidine dimers), pyrimidine dimers (CPD) and other protoproducts such as cytidine and cytidine-thymidine dimers (63). Folate and its derivatives such as 5-methyltetrahydrofolate can also absorb UVB radiation; however, due to its lower penetration, unlike UVA, UVB does not cause significant photodegradation of folate and its metabolites (64). Repeated and prolonged UVB exposure is known to be potential inducer of skin cancer. Carcinogenic effects of UVB have been extensively investigated in relation to melanomagenesis and other skin cancers and reviewed elsewhere (38).

VISIBLE LIGHT

Solar radiation also consists of radiation of 400–700 nm wavelength that is visible to human eye. Visible light causes skin erythema at a much higher dose. Kollias and Baqer studied the change in pigmentation brought about by visible and near infrared region (polychromatic radiation 390–1700 nm). These authors used the lower inner arm skin of volunteers to determine the changes in skin color that occur following irradiation with this broad band light. Using remittance spectroscopic technique, they found increase in skin pigmentation without evidence of erythema- associated color change (65). Porges *et al*, on the other hand, observed pigment changes accompanied by erythema. They exposed individuals of skin types II, III and IV to visible light and observed induction of IPD, immediate erythema and persistent delayed tanning reaction. IPD and immediate erythema faded over a period of 24 hours, whereas tanning response remained for 10 days (66). Mahmoud *et al.* in their review speculated that this discrepancy could be due to use and lack of non-standardized light sources for studies on the effects visible light on human skin pigmentation (67). A recent study on induction of pigmentation in Fitzpatrick skin types IV-V by UV radiation and a better defined light source for visible light showed that IPD induction by visible region of sunlight is not significantly different from that of UV fraction. However, increase in persistent pigment darkening (PPD) is significantly lower in visible region than compared to UV fraction. These authors suggest that UV and visible light interact with the same precursors, however UV can induce 25 times more pigmentation per J cm^{-2} compared to visible light (68). These studies may be relevant in view of the increasing 'light pollution', the excessive or obtrusive artificial light that surrounds us both day and night, that is being recognized as significant human health hazard.

GROWTH FACTOR RESPONSES TO RADITAION

In addition to MSH, production and secretion of other paracrine factors in the skin that influence melanocyte biology are known to be affected by exposure to radiation (69).

Among these factors, basic FGF (bFGF) may be considered one of the most important factors. UVA and UVB stimulate bFGF secretion by both kertainocytes and melanocytes (70). Endothelin-1 (ET-1) is of considerable interest in the context of melanogenic response to UV. ET-1 binds to its cognate receptor ET B on melanocytes and appears to have a biphasic effect on melanin production-stimulatory effect at low concentration and inhibitory effect at higher concentrations. More importantly, ET-1 also modulates the survival response of melanocytes to UVB exposure. Interestingly, UVA appears to significantly downregulate ET-1 production by keratinocytes (71). Another keratinocyte-derived factor, macrophage migration inhibitory factor (MIF), which is secreted in response to UVB was recently shown to increase skin pigmentation indirectly by increasing expression of PAR-2 that enhances phagocytosis of melanosomes by keratinocytes. The indirect effect of MIF on pigmentation is supported by the observation that there was no effect on melanin production when cultured human melanocytes were treated with this factor in the absence of keratinocytes (72). MIF also stimulated secretion of stem cell factor (SCF), an important keratinocyte-derived factor involved in melanocyte survival and UVB induced pigmentation (72, 73). Hepatocyte growth factor (HGF) is known to promote cell motility and proliferation of keratinocytes and melanocytes. Dermal fibroblast is the main source of HGF in the skin and UV irradiated keratinocytes strongly induce the production of HGF. Fibroblasts secrete HGF when neighboring keratinocytes are exposed to UVR, but not when they themselves are exposed to UV, suggesting a paracrine mechanism. Mildner *et al.*, data suggest that upregulation of HGF plays an important role in skin homeostasis after UV irradiation (74). Keratinocyte growth factor (KGF) increases the melanosome transfer from melanocytes to keratinocytes and thus increases the amount of melanin transferred when exposed to UV radiation. KGF-induced melanosome transfer was more significant in keratinocytes isolated from fair-skinned individuals compared to keratinocytes isolated from dark skin, due to an increased expression of KGF receptor in fair-skinned keratinocytes (75). The Nerve growth factor (NGF) released by keratinocytes prevents UV induced apoptosis in melanocytes by upregulating Bcl2 expression and this UV induced protection is thought to be especially significant in the lower layers of the skin (76, 77). UVB irradiated keratinocytes secrete the antioxidant adult T cell leukemia-derived factor/thioredoxin (ADF/TRX) and increase the binding capacity/binding of the melanocyte stimulating hormone (MSH) and an increase in melanogenesis, a protective mechanism for keratinocytes and melanocytes (78). Keratinocytes releases nitric oxide (NO) in response to UV radiation which decreases cell growth and increases the dendricity and melanin synthesis in melanocytes by upregulating the production of tyrosinase and TYRP1 (79). ACTH and TGF-beta1increases the melanin production in melanocytes as well as the cornification in keratinocytes (41). These studies illustrate the cooperative influences within the epidermal melanin unit that consists of one melanocyte and several keratinocytes acting as a functional unit.

CONCLUSION

Natural variation in skin pigmentation, the most readily visible human trait with significant social and psychological implications, is a complex and dynamic biological feature that appears to have evolved in response to geographical migration of early humans and the varying exposure to environmental solar radiation. This intrinsic response of skin to radiation continues to be exploited by humans for therapeutic and cosmetic purposes. However, while our knowledge on the genetics, cell biology and biochemistry of skin pigmentation has expanded exponentially, our understanding of the effects of radiation on skin pigmentation remains incomplete. Availability of more well defined experimental radiation sources and state of the art non-invasive methods of assessment of pigmentary changes in vivo could further refine our classification of subcategories of radiation, specifically UVA and UVB. Such refinements will have implications for many therapeutic as well a cosmetic uses of radiation for affecting skin pigmentation.

Acknowledgments

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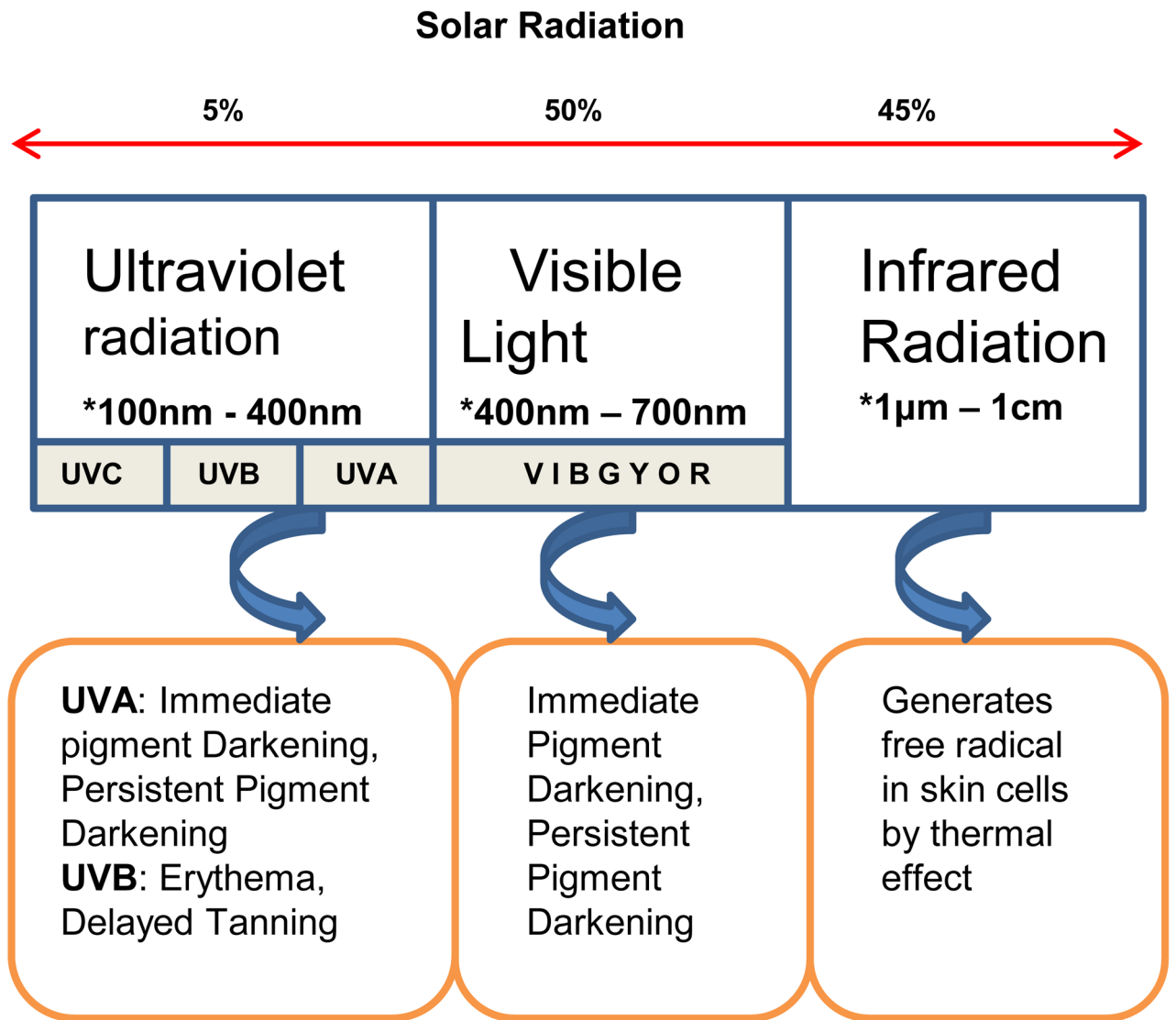
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Biographies

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Solar Radiation

5%   50%   45%

Ultraviolet radiation *100nm - 400nm	Visible Light *400nm – 700nm	Infrared Radiation *1µm – 1cm
UVC | UVB | UVA	VIBGYOR	

UVA: Immediate pigment Darkening, Persistent Pigment Darkening **UVB**: Erythema, Delayed Tanning	Immediate Pigment Darkening, Persistent Pigment Darkening	Generates free radical in skin cells by thermal effect

Approximate wavelength range

Figure 1.
Solar radiation spectrum and effects of radiation on skin pigmentation.