Review Article

Photoaging of the skin

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Solar radiation at the surface of the earth includes ultraviolet radiation (UV : 290-400nm), visible light (400-760nm) and infrared radiation (760nm-1mm) (*Fig 1*).

Extrinsic skin aging is superimposed on intrinsic skin aging process and is due primarily to UVR (solar ultraviolet radiation) and partly by other factors, such as infrared light, smoking and air pollutants. UVR has been divided into ultraviolet B (UVB: 290-320nm) which principally generates pyrimidine dimer type DNA damage through direct absorption and ultraviolet A (UVA: 320-400nm), which indirectly produces base oxidation via UV-induced ROS. Recently, UVA radiation at high dose is reported to produce cyclobutane pyrimidine dimers.

Intrinsic aging of the skin, on the other hand, is characterized by the decline of biological function, a decrease in adaptation to

stress, and structural damage due to reactive oxygen species (ROS) from cellular metabolism.

Recent advances in understanding mechanisms of aging and photoaging have enhanced our ability to develop strategies to prevent, slow, and rejuvenate the altered structure and function of photoaged skin.

In this review, we discuss the mechanisms of photoaging of the skin with relevance to acute and chronic skin reactions to solar UVB, UVA and infrared radiation, and summarize briefly the clinical approaches for prevention and the treatment of photoaging with topical and systemic use of anti-aging materials. Finally, a range of therapeutic modalities available to reverse or retard the visible signs of photoaged skin will be discussed briefly.

Fig. 1. Solar light reaching on the surface of the earth

There are three lights with different waveband, infrared light (IR) having waveband between 760nm and 1mm, visible light (VL) from 400nm to 760nm, and ultraviolet light (UV) from 290nm to 400nm. IR, VL and UV occupy 42 %, 52 % and 6 % of the solar light on the earth, respectively. UV light is divided into two types according to waveband, UVA having waveband between 320nm and 400nm and UVB from 290nm to 320nm. Sunburn, acute skin reaction is caused predominantly by UVB which occupies only 5~6 % of total UV light. UVA radiation, however, penetrates deeply into the dermis, around 20 % of the surface of the skin.

1. Solar ultraviolet light and its acute effects on human skin

The acute effects of UVR on human skin have been well characterized. Upregulation of TNF- α is a key early response to ultraviolet B (UVB) by keratinocytes (KCs), and represents an important component of the inflammatory cascade in skin. UVB irradiation induces TNF- α expression in both KCs and dermal fibroblasts, with TNF- α mRNA induction seen as early as 1.5 h after UVB.¹⁾ The immediate reaction also includes epidermal keratinocyte release of pro-inflammatory cytokines such as interleukin-1 (IL-1) and interleukin-6 (IL-6)^{2,3)}. This release is believed to be due to DNA lesions characteristic to UVR, cyclobutane pyrimidine dimers (CPDs) and 6-4 photoproducts⁴⁻⁶⁾. UVB radiation induces not only IL-1 and IL-6, and TNF- α , but IL-10 and IL-12, UVA radiation, however, induces only IL-10, mainly produced by dermal CD11b + macrophages and neutrophils that infiltrate epidermis after intense UV. IL-10 is shown to be responsible for suppressing T cell-mediated immune response and can induce immune tolerance to neoantigens, whereas IL-12 can reverse UV-induced immune suppression, and break immune tolerance⁷⁻⁹⁾. Interestingly, Reeve and Tyrrell reported that UVA induces heme oxygenase which upregulates IL-12 and counteracts UVB-induced immunosuppression¹⁰⁾.

UVB and UVA exposure also depletes cellular antioxidants and results in the production of reactive oxygen species such as hydrogen peroxide, superoxide anion, singlet oxygen, hydroxyl radicals and nitric oxide (NO)^{11,12)}. Free radical-induced peroxidation of membrane lipids play a role in producing proinflammatory prostaglandins via activated phospholipase A2,¹³⁾.

Nuclear factor kappa B (NF κ B) and activator protein-1 (AP-1) are transcription factors regulated by cellular redox states, and involved in regulation of gene expression¹⁴⁾. These two transcription factors are responsible for the regulation of a wide range

of extracellular signaling molecules involved in inflammation, cell proliferation, apoptosis, tumorigenesis, and tissue repair^{15,16)}. Because these transcription factors seem to be very important in the UVR-induced degenerative processes associated with aging and photoaging¹⁷⁻¹⁹⁾ such as induction of the matrix metalloproteinases, they are frequent targets of anti-aging preventive therapies.

DNA photolesions and DNA fragments resulting from repair are responsible for acute cutaneous responses to UV radiation, including erythema (sunburn), pigmentation (suntan, melanogenesis), and immune suppression²⁰⁻²⁵⁾. In order to maintain genomic integrity most DNA lesions are repaired efficiently by nucleotide excision repair mechanisms constitutively expressed in all live cells in the body.^{26,27)} However, there are several DNA products that are highly characteristic of specific UVR wavelengths.

Ultraviolet C (UVC : 200-290nm) radiation is efficiently absorbed by cellular and mitochondrial DNA and produces pyrimidine dimers, such as cyclobutane pyrimidine dimers (CPD) and (6-4) photoproducts [(6-4PP) (*Fig 2*)]. UVC radiation, however, does not reach the surface of the earth, since virtually all is absorbed by stratospheric ozone. UVC radiation emitted from artificial light sources can cause DNA damage (CPD and 6-4PP) in cells to the level of spinous layers, but it does not penetrate to the basal layer²⁸⁾. One concern that has developed over the last few decades is the decreasing thickness of the ozone layer over the southern hemisphere, declining by 10 to 40 percent during the winter and spring months. As a rule a 10% reduction in the ozone layer causes about a 20% increase in UVB-radiation and a 40% increase in skin cancers. Thus relatively minor changes in the ozone layer may have a marked impact on health²⁹⁾.

UVB is only partially blocked by ozone layer and comprises approximately 1 to 10% of the UVR reaching the earth³⁰⁾ UVB is absorbed by nuclear and mitochondrial DNA but does not penetrate very efficiently past the stratum corneum. The UVB that does reach the living layers of the epidermis and dermis, however,

Fig. 2. DNA damage caused by solar radiation

Cyclobutane pyrimidine dimers (CPD) and 6-4 photoproducts (6-4PP) are main DNA damages caused directly by solar UVB light. UVA radiation is known to produce CPD and 6-4PP at around 1000 times higher dose than UVB. These DNA damages are repaired efficiently after cessation of UV light. Nearly 100 % of 6-4PPs are repaired at the first 6 h, and CPDs are repaired about 50 % at 24 h. Cytosine-cytosine dimer (C=C dimer) is shown to be the most frequently miss-repaired, leading to a mutation of gene related to skin cancer formation.

yields CPD and 6-4PP that have been observed after realistic exposures in human subjects³¹⁾ Further, UVB radiation has 3/11/2009 been shown to produce 8-hydroxy-deoxyguanosine (8-OHdG), the most common ROS-induced DNA damage, and one that is highly mutagenic if left unrepaired^{32,33)}.

The UVA dose required to produce CPD in cultured cells is reported to be about 5J/cm² and therefore produces CPD and 6-4PP about 1/1,000 less effectively than UVB, but UVA can penetrate significantly farther into the living epidermis and dermis. In fact, the UVA-induced mutations of greatest concern occur in the basal layer of the epidermis where they may transform stem cells.³⁴⁾

UVA exposure most characteristically results in ROS and base oxidation of DNA, including 8-OHdG (**Fig 3**) and thymine glycol. Thus, the primary difference in damage between UVB and UVA radiation is that UVB yields primarily CPD (TT, CC, CT and TC) and (6-4)PP with some 8-OHdG, and UVA was reported to yield primarily oxidative (DNA) damage in the form of 8-OHdG with minor amounts of CPD (most commonly TT dimers), but the yields of CPDs by UVA radiation was reported to be ~3 fold higher than that of 8-OHdG upon UVB exposure.^{35,36)} Visible and infra-red radiations have not been shown to produce CPD, 6-4PP or 8-OHdG.

UVB radiation can induce erythema in skin at a single dose at or above 20-40mJ/cm². The minimal dose of UVB radiation required to produce visible erythema with sharp margin 24h after radiation is defined as the minimal erythema dose (MED)³⁷⁾. 20 minutes exposure to the sun around noon on a sunny mid-summer day is approximately equal to one MED for Japanese skin type I (Fitzpatrick's skin phototype II ~ III)³⁸⁾. UVA radiation can also produce erythema, but requires a dose about 1,000 times higher than UVB.

Suntan (an increase in pigmentation and skin color caused by sun exposure) is attributable primarily to UVB radiation and usually develops by the 3rd day, limited to the area exposed to UVR. UVB-induced pigmentation results from stimulation of

both epidermal keratinocytes (KC) and melanocytes (MC). KC exposed to UVB produce and release neuropeptides (α -MSH : α -melanocytes stimulating hormone, ACTH : adrenocorticotrophic hormone)^{39,40)} and cytokines (ET-1 : endothelin-1, SCF : stem cell factor, ADF : adult T-cell leukemia cell derived factor) which stimulate MC in a paracrine manner to increase their melanin synthesis and transfer of melanosomes to KC⁴¹⁻⁴⁴⁾.

UVA induces immediate tanning and persistent pigment darkening through oxidation of pre-existing melanin or melanogenic precursors, while UVB induces tanning, which takes a few days or longer to observe and requires activation of melanocytes. Immediate pigment darkening and persistent pigment darkening induced by UVA radiation may occur through epidermal melanin photooxidation which polymerizes the colorless melanogenic precursors 5,6-dihydroxy indole carboxylic acid (DHICA) and 6-hydroxy-5-methoxy indole carboxylic acid (6HSMICA)⁴⁵⁾ to irreversible brownish black pigments. This UVA-induced basal and suprabasal pigmentation takes place outside of melanocytes and does not involve enzymatic melanin synthesis.

In tanning, new melanin in melanosomes is transferred from MC to the neighboring KC^{46,47)}, possibly by phagocytic function of KC. The melanosomes concentrate in KC above the nucleus in a formation known as the as the nuclear cap. This protective structure blocks UVB and UVA radiation to a level 1/3-1/5 lower than that of pre-irradiated skin^{48,49)}. An abundance of evidence connects DNA photolesion repair to UVR-induced erythema. One example is that xeroderma pigmentosum patients (XP) with low nucleotide excision repair (NER) capacity exhibit severe sunburn reactions after a few minutes of sun exposure⁵⁰⁻⁵²⁾. XP group A patients with less than 5% of normal NER levels develop erythema reactions at 1/5 MED of healthy subjects⁵²⁾. Cockayne's syndrome patients (CS) who have a DNA repair defect in transcription coupled repair (TCR) also show hypersensitivity to UVR in their erythema reaction⁵³⁾. The increase of UV dose induces more marked erythema and increase of CPD⁵⁴⁾, and protection of human

Fig. 3. Chemical structure of oxidized guanine, 8-hydroxy-deoxyguanosine (8-OHdG)

8-OHdG is produced by UVA and UVB radiation in the nucleus of the cells immediately after irradiation by reactive oxygen species and electron transfer. Miss-repair of 8-OHdG is reported to cause mutation, leading to UV-induced skin cancer in mice.

skin by sunscreen reduces both erythema and CPD formation in vivo. Further, Ley suggested a role of CPD in sunburn, using animal (*Monodelphis domestica*)⁵⁵. In addition, we showed higher yield of DNA damage in Japanese photo-skintype I who burn easily and tan slightly⁵¹.

Thymidine dinucleotides (pTT) and the telomere 3-prime overhang sequence (T-oligos) are shown to increase melanogenesis by increased melanogenic proteins leading to 3- to 5-fold UV protection multiple with distinct nuclear capping in many keratinocytes in vivo⁵⁶⁻⁵⁸. Studies using oligonucleotides are also shown to be effective in inducing protective responses in human skin, such as increase of DNA repair capacity and prolonging cell cycle arrest⁵⁹. pTTs are reported to be effective as much as 33% of the TTGAAA sequence in stimulating these UV-induced SOS-like protective responses.

Sunburn is an erythema reaction, and has been shown to be induced by increased prostaglandin E₂ (PGE₂) and nitric oxide (NO) in circulating blood produced by UV irradiation on skin (Fig 4)^{60,61}.

UV stimulates epidermal keratinocytes to upregulate mRNA of cyclooxygenase 2 (COX-2)⁶² and inducible nitric oxide synthase (iNOS), which produce PGE₂ and NO, respectively. These two chemical mediators are known to increase melanogenesis of melanocytes in vitro cultured system. In XPA cells, COX-2 mRNA level and PGE₂ are shown to increase after a low dose of UVB irradiation in vitro⁶³.

These results strongly suggest that UV radiation-induced DNA damage enhances the expression of COX-2 and iNOS mRNA, and increased PGE₂ and NO produce sunburn and suntan, although the detailed mechanisms of the stimulation of mRNA level of COX-2 and NO by DNA photolesions still remains to be elucidated. Further, direct stimulation of membrane components of epidermal keratinocytes by UV radiation is also a possible mechanism to enhance the expression of mRNA levels of COX-2 and iNOS.

2. Role of DNA repair

DNA damage in human skin is mostly caused by environmental UVR. Photolesions are known to play a role in the induction of cell death including apoptosis, mutation, and tumorigenesis, in addition to photoaging. To avoid cancer, the entire genome must be accurately transmitted through repetitive cell divisions, as the skin is one of the organs continuously self-renewing. DNA repair mechanisms, particularly nucleotide excision repair (NER) and base excision repair (BER) are present to maintain genomic integrity⁶⁴, but beyond a certain level of DNA damage, mistakes slip past. Among CPDs, thymine-cytosine (C-T) and cytosine-cytosine (C-C) are known to be the most mutagenic, possibly due to the rule of "A"⁶⁵ which takes place at photolesions remained in the strand under DNA synthesis. These misleading DNA damages which increase mutation frequency are indeed found at higher rate in p53 gene of UV-induced skin pre-cancer and cancer cells, such as basal cell carcinoma and squamous cell carcinoma⁶⁶⁻⁶⁸. 6-4PPs are repaired more efficiently than CPDs, usually within 6 hs after UV exposure of the cells, whereas, only a half of CPDs are repaired within 24 hs.

NER effectively eradicates CPD and (6-4)PP produced in epidermal keratinocytes (KC), Langerhans cells and melanocytes and dermal fibroblasts.

Among these cells, KCs have been shown to repair CPD most efficiently than MCs and fibroblasts (Fig 5). Nearly 30 factors are involved in NER⁶⁹. There are two repair systems in NER, global genome repair (GER) and transcription coupled repair (TCR). Photolesions in DNA strands actively transcribed by DNA polymerase II are repaired more rapidly than those in the non-transcribed strand of active genes, and those in global genome^{70,71}. CSA and CSB proteins, and XPC-hHR23B-centrin2 play a recognition step of DNA damage in TCR and GGR, respectively⁷². Further, DNA damage binding proteins (DDB 1 and 2) take part

Fig. 4. Sunburn induction by solar UVB radiation, by DNA damage remained and signal transduction via cellular membrane. DNA damages produced by UVB and remained, particularly at transcribing strands are responsible for the production of prostaglandins and nitric oxides which increase vascular circulation, leading to sunburn and suntan. UVB also stimulates cell membrane and increase the production of these chemical mediators.

Fig. 5. A rule of “A”

Among cyclobutane pyrimidine dimers, C-T and C-C are shown to be the most mutagenic damages, since a rule of “A” does play a role in repair process to make a mis-pairing on the opposite strand. In DNA synthesis of the strand free from DNA damage, a guanine base is incorporated into the opposite site of cytosine (C) on the opposite strand. Adenine (A), however, is wrongly incorporated at around 50% rate into the opposite site of cytosine at DNA damage of C-T and C-C. This mis-uptake of adenine instead of guanine is called as “A rule of A”. Keratinocytes in epidermis are most frequently exposed to solar UV and are known to frequently develop to basal and squamous cell carcinoma, particularly in white skin populations. Since skin cells of children divide more frequently than adults and elderly, there is more chance for “A rule of A” takes place in epidermal cells, leading to a mutation in the important genes relevant to skin cancer and solar lentigines.

Fig. 6. DNA repair of different epidermal and dermal cells

Keratinocytes are reported to repair CPD most efficiently than other cells, MCs and fibroblasts at the low dose of UV irradiation, when measured by ELISA technique using monoclonal antibody against CPD.

in this recognition. Transcription factor II H (TFIIH, XPB, XPD, TTDA), XPG protein, XPA protein and recognition protein (RPA) are also involved in this recognition step of both TCR and GGR^{73,74}.

After recognition of the damaged lesion, endonucleases XPF-ERCC1 and XPG make incisions at the 5' and 3' sites of the lesion, respectively, resulting in the excision of a photodamaged site, leaving a gap of ~30 DNA nucleotides. The gap is filled by DNA polymerase δ/ϵ , PCNA (proliferating cell nuclear antigen) and RFC (replication factor C), and finally sealed by DNA ligase I.

Oxidized bases, such as 8-OHdG, are repaired by the BER system. The oxidized base is excised by DNA glycosylase and remaining AP site is excised by AP endonuclease. The remaining gap lesion is synthesized by DNA polymerase β , XRCC1 and DNA ligase III (Fig 6)⁷⁴.

3. Photoaging of the skin caused by chronic sun exposure

3-(1) Characteristics of photoaged skin

Photoaged skin is characterized by coarse wrinkles, loss of elasticity, pigmented spots, dryness, verrucous papules, and telangiectasia. The age at onset and expression of these photoaged characteristics appear to differ between racial phenotypes or pigmentary groups⁷⁵. It is commonly held that lighter skinned people tend to manifest photoaging by wrinkles, whereas Asian ethnicities exhibit pigmented spots (solar lentigines) rather than wrinkles. The severity of photoaging in any case depends on cumulative sun exposure, and is usually most determined by occupation and life-style⁷⁶. Histopathologically, aged skin undergoes progressive disorientation of dermal collagen and elastic fiber bundles^{77,78}. In photoaged skin, there can be a significant increase in space between fiber bundles, thinning of fibers and increased disorganization of fiber proteins.

Intrinsic and photoaged skin shows an age-dependent reduction of cutaneous microvasculature, leading to decreased skin temperature and decreased nutritional supply which possibly may cause thinning of nail plates and skin⁷⁹. It is reported that there are age-dependent decreases in the cutaneous vascularity of both sun-exposed facial and sun-protected buttock skin, but the alteration is more prominent in photoaged skin⁸⁰ (Fig 7). In intrinsically aged skin, there is no significant difference in the vascular density, although there is a decrease in vessel size between aged and young skin⁸¹. However, the papillary dermis of photoaged facial skin of elder donors showed apparent decreases in vessel size, vascular number, compared with that of younger skin.

Acutely, UV exposure stimulates angiogenesis through vascular endothelial growth factor (VEGF) upregulation via MEK-ERK activation and thrombospondin-1 (TSP-1) downregulation via P13K-Akt activation in human epidermis, although with chronic

exposure blood vessels may be decreased in UV-damaged skin⁸².

Among non-fibrous components in dermis and epidermis, hyaluronan (HA) plays an essential role in supporting tissue architecture, and is also involved in cell migration and differentiation during inflammation⁸³. Further, HA is known as one of the important factors to protect skin from dryness by its capacity to bind water. An age-dependent decrease in hyaluronan content has been reported⁸⁴. In addition, the rate of UVB-induced HA synthesis 24 h after UVB irradiation is also decreased in aged human skin compared to young skin.⁸⁵

HA metabolism in human skin is rapidly and differentially regulated by acute UVB irradiation. HA content in epidermis and dermis decreases 3h after a single UVB exposure due to increased degradation and decreased synthesis of HA. In epidermis, new HA increases by 24 h after UV irradiation, but remains lower in the dermis. In dermis, HA degradation products increase for 24 h-post irradiation, suggesting that balance between HA synthesis and degradation determines HA recovery in tissue after UV irradiation⁸⁶.

3-(2) Mechanisms of solar lentigine development

Solar lentigines, small brown pigmented spots sharply demarcated in sun-exposed skin, may be induced by mutations of KC and MC genes which play a role in pigment formation and transfer. Stem cell factor (SCF) mutations in KC have been suggested to be responsible for the development of solar lentigine, although details of the mechanism has not yet been elucidated. Other KC and MC genes which control melanin formation in MC may also be responsible for pigment spot formation. It seems reasonable to suggest that gene mutations would be responsible for the induction of lentigos, since XP patients who have abnormally low ability to repair DNA damage have numerous pigmented spots as early as a few-months of age, limited to the sun-exposed face, after minor exposures to sunlight⁵². Through its ability to induce mutations in cutaneous cells, UVB radiation is thought to be the extrinsic factor most responsible for pigment spot development.

Fig. 7. Nucleotide excision repair (NER) mechanisms of CPD

There are two distinctively different repair system in NER, global genome repair (GGR) and transcription coupled repair (TCR). UV-induced CPD and 6-4PP in DNA strand which are actively transcribed by DNA polymerase II are repaired more rapidly than those in the non-transcribing strand of active genes and those in global genome.

3-(3) Mechanisms of wrinkle formation

Transcription factor AP-1 is a critical mediator of acute photodamage that is involved in both overexpression of matrix metalloproteinases (MMPs) and reduction of type I procollagen. Increased MMP activity would be expected, over time, to degrade dermal connective tissue. In human skin UVR-induced ROS activate signaling kinases in epidermal KCs and dermal fibroblasts. AP-1 (activation protein-1) is activated through MAPK signaling pathway, and controls the transcription of matrix metalloproteinases MMPs⁸⁷⁾. Another transcription factor NF- κ B is also activated by UV radiation, and stimulates the transcription of inflammatory cytokines which attract neutrophils which express neutrophil collagenase-2 (MMP-8).

MMPs up-regulation occurs after a low dose UV exposure, less than one minimal erythema dose⁸⁸⁾. Therefore, daily exposures to a low dose solar UV radiation below sunburn are thought to be sufficient to induce MMPs up-regulation and to degrade skin collagen and elastic fiber, leading to wrinkle formation.

Keratinocytes exposed to UVB radiation produce and secrete cytokines IL-1 α , IL-6, and TNF α , which stimulate epidermal KC and dermal fibroblasts, in autocrine and paracrine manners, respectively, and upregulate the levels of mRNA and MMPs 1, 2 (gelatinase A), 9 (gelatinase B) and 12 which degrade dermal collagen and elastic fibers, leading to the development of wrinkle formation (Fig 8)⁸⁹⁻⁹¹⁾.

Human skin constitutively expresses three distinct collagenases, 1 and 2, and 3, also referred to as matrix metalloproteinases (MMP) -1, -8 and -13 respectively. UVB radiation induces MMP-1, -3, and -9 in normal human epidermis. UVA radiation also induces mRNA expression MMP-1, -2, and -3 in fibroblasts⁹²⁾. MMP-1 and MMP-8 cleave fibrillar collagen type I and III in the dermis, then which are further degraded by MMP-2 and -9. Elastic fibers and collagen type V and VII are also cleaved by other MMPs, such as MMP-12 derived from macrophages⁹³⁾, and serine protease derived from inflammatory infiltrating cells, and skin fibroblast elastase. UVB radiation may contribute to wrinkle formation by inducing fibroblast elastase via cytokines released by

UVB-exposed keratinocyte or directly by UV radiation⁹⁴⁾.

Collagen synthesis is also stimulated by UVB and UVA radiation, but degradation exceeds the production of collagen and elastic fibers, resulting in the reduction of dermal fiber components. UVR upregulates the mRNA level of MMPs via reactive oxygen species, suggesting that anti-oxidants might have a protective effect on UVR-induced wrinkle formation (Fig 9)⁹⁵⁾. Alteration of basement membrane is also reported to play a role in wrinkle formation⁹⁶⁾. Type VII collagen is reduced in photoaged skin at the dermo-epidermal junction, although a role of for this in wrinkle formation has not yet been fully elucidated. At present, wrinkles are understood to result from several related factors, including the decrease of collagen and elastin fibers in dermis⁹⁷⁾, the degradation of basement membrane at the dermal-epidermal junction, and an decrease in the three dimensional organization of the extracellular matrix.

The histopathological changes seen in intrinsically aged skin are characterized by the general atrophy of the extracellular matrix with decreased elastin and disintegration of elastin fibers. Photoaged skin is characterized by a loss of mature collagen, and basophilic degeneration of connective tissue, evidenced by denatured elastin fiber and collagen fibers. Elafin, a molecule found in actinically damaged skin, has been shown to be induced by UVA in fibroblasts *in vitro*. It inhibits the binding of, elastase to elastin by forming an elafin-elastin complex which is increased in photoaged upper to middle dermal connective tissue⁹⁸⁾. The complex prevents elastic fibers from elastolytic degradation, leading to the accumulation of elastic fibers, and thus, elafin is now understood to be a molecule integral to actinic elastosis. Accompanying the changes in collagen and elastin, there is an increase in the deposition of glycosaminoglycans.

In summary, solar UV radiation has been implicated in wrinkle formation through its exacerbation of the decline in tensile strength and elasticity and its ability to cause the degradation of the supporting structural components of the dermal extracellular matrix. Infrared radiation is another factor in sun exposure that is now believed to play a role in the development of solar elastosis and premature skin aging^{99,100)}. Experimentally, heat increases

Fig. 8. Cutaneous vascularity in young and elderly
Photoaged skin shows smaller number of vessels than that of young skin, but there is no decrease of vessel number in photo-protected aged skin.

Fig. 9. Mechanisms of UVB-induced wrinkle formation

Keratinocytes exposed to UVB radiation produces and secretes cytokines, such as IL-1 α , IL-6 and TNF α which stimulate keratinocytes and dermal fibroblasts to produce matrix metalloproteinases (MMPs), leading to destruction of collagen and elastic fibers, and formation of wrinkles in sun-exposed skin.

collagenase and stromelysin mRNA in dermal fibroblasts¹⁰¹. The expression of MMP-1 and MMP3 mRNA and protein levels is increased by heat in a dose-dependent manner, possibly mediated by the activation of ERK and JNK¹⁰². Further, heat increases the expression of IL-6 mRNA in cultured dermal fibroblasts, which upregulates the expression of MMP-1 and MMP-3, leading to the degradation of extracellular matrix proteins and induction of wrinkles. A major regulator of collagen types I, II and III synthesis, TGF- β 3, has been shown to be downregulated by heat treatment in cultured fibroblasts and also in human skin *in vivo*¹⁰³. The dose used experimentally to induce altered expression of MMPs was extremely high compared to the dose we are exposed to the sunlight in usual life. Therefore, it remained to be elucidated in the future how much chronic solar infrared radiation may contribute to the enhanced photoaging of the skin.

3-(4) DNA repair in human skin declines with age

Wei *et al.*¹⁰⁴ showed that young people with skin cancers in sun-exposed area have a lower post-UV NER ability compared to age-matched healthy subjects. Further, using a host cell reactivation assay of the UV-irradiated plasmid, decrease of the post-UV DNA repair ability in cells derived from aged Caucasian donors compared to that of young donors was demonstrated. Moriwaki *et al.*¹⁰⁵ confirmed an increased mutation frequency with aging, using a UV-irradiated shuttle vector plasmid. Goukassian *et al.*¹⁰⁶ demonstrated that there was a significant decrease in the repair rates of both CPD and 6-4PP in dermal fibroblasts correlated with increasing age. These results indicate that age-related increases of skin cancer and lentigos may be caused by an accumulation of mutated genes due to lower NER with aging.

4. Preventions and treatment of photoaging

Chronically sun-exposed skin is characterized by pigmented spots (lentigos), deep wrinkles (so-called leathery skin) and verrucous papules, superimposed on chronologically degenerated skin. This structural and functional change is termed photoaging. There are essentially three strategies to prevent photoaging: (1) prevention of UV penetration into skin, (2) inhibition of inflammation by anti-oxidants and anti-inflammatory molecules, (3) medically based rejuvenation treatments of photoaged skin.

4-(1) Prevention of UV penetration by sunscreens

The primary approach to preventing photoaging is by sun avoidance and by the proper use of sunscreen, appropriate clothing, and hats. Adopting a healthy attitude about sun exposure can prevent the unwelcome signs of aging such as wrinkles and lentigos as well as non-melanoma skin cancer. When out-of-doors, this would imply that shade seeking behavior would prevail. Proper daily use of protective materials against solar ultraviolet radiation (UVR) should prevent both acute and chronic damage of the skin.

Sunscreen use is generally accepted to reduce the level of DNA damage and protect sun-exposed skin from erythema, suggesting a protective role against UVR-induced photoaging and skin carcinogenesis¹⁰⁷⁻¹⁰⁹. Our epidemiological study of the effect of annual UVR on skin pigmented freckles in women, conducted in the northern and southern Japan, Akita prefecture and Kagoshima prefecture, respectively showed that the number of small pigmented spots at age 40 of women living in Kagoshima (exposed to a higher UVR flux) was almost equal to those of women at around 60 years old at Akita, indicating that chronic UVR efficiently promotes pigmented lesions¹¹⁰. In another epidemiological study on skin cancer incidence in Japan, subjects who live in Okinawa, where annual ambient UVR is about 2 times higher than subjects who live in Kasai-city, Hyogo prefecture had a 4-5 times higher incidence of precancerous actinic keratosis¹¹¹ (Table 1).

Table 1 Incidence of skin pre-cancer in Kasai city and ie-son in Japan

Place	year	No. of subjects	No. of patients ^a	Incidence ^b	OR	95% CI
Kasai-city	1993-2002	2406.3	8.5	118.9	1.00	-----
Ie-son	1994	1118	14	734.4	6.17	5.09-7.49
	1995	1014	15	637	5.35	4.40-6.50
	1996	1035	20	625.5	5.25	4.22-6.39
	1997	996	20	612.1	5.14	4.22-6.25
	1998	1199	20	675.2	5.67	4.67-6.89
	1999	1313	17	578.9	4.86	3.99-5.92
	2000	1262	10	410.4	3.44	2.86-4.22
	2001	1213	8	341.6	2.86	2.32-3.52
	2002	614	6	347.6	2.91	2.36-3.58
	1994-2002	1079.6	14.4	551.4	4.63	3.80-5.64

a ; Number of actinic keratosis patients diagnosed in each year

b ; No. of patients corrected at age and sex based on the Japanese population in 1990

Further, it is shown that the yearly exposure dose of school children not using any specific photoprotection in USA and Japan is roughly 150 MEDs to 300 MEDs¹¹². Exposure to UVA is of particular concern because the UVA energy reaching the earth's surface 90-99% of the total, UVA passes through glass, and only decreases by 50% in winter. Further, UVA radiation causes DNA damage, such as CPD and 8-OHdG and induces photoaging as mentioned earlier.

There are two types of sunscreens, chemicals which absorb UV photons and physical agents which reflect or scatter UV light. Sunscreens have long been known to protect against UV-induced erythema, as reflected by SPF values. In the 1980's and early 1990's sunscreen was expected to protect skin from UV-induced carcinogenesis¹¹³⁻¹¹⁵. In the past few years, however, the importance of broad-spectrum protection covering both UVB and UVA radiation has been recognized¹¹⁶⁻¹¹⁹. Taken together, it is recommended to use daily broadspectrum sunscreen that blocks both UVB and UVA radiation^{120,121}. At present, a safe level of daily UVR exposure to the public has not been established, however, it can recommended that the public reduce their life-time UVR exposure to a level as low as possible.

Many commercial sunscreens on the market are formulated to be broad-spectrum, and new technology has increased their photostability.

Modern sunscreens such as Parsol 1789 and Mexoryl SX and XL cover at least part of the UVA spectrum, and together with efficient UVB absorbers and reflective micro-sized titanium dioxide are highly effective broad-spectrum filters, often used to protect patients with UVA sensitivity¹²².

Consumers can be advised to adjust their sunscreen to the environmental and activity related conditions: a broad-spectrum sunscreen with SPF 50 and PA +++ for outdoor activities on sunny days in summer, and a sunscreen with SPF 10-20, PA ++ for daily, incidental exposure.

Currently, there is controversy over the link between low serum levels of vitamin D and the risk of cancers originated in several organs^{123,124}. Suberythral doses of UVB (several minutes to a quarter of hour exposure at noon in summer) produce vitamin D₃ (Vit D₃) for daily calcium and bone metabolism¹²⁵. However, repeated suberythral UVR exposures on human skin have been shown to induce significant DNA damage in epidermal cells and even sunburn erythema after consecutive exposures¹⁰⁷. At this time, the American Academy of Dermatology recommends that the sun protection measures outlined above be followed and that vitamin D levels be maintained by dietary and supplemental vitamin D.

4-(2) Prevention of UV-induced ROS and inflammation

Enzymes which convert ROS to harmless water and molecular oxygen protect skin from ROS-induced damages. The levels of these major endogenous anti-oxidant enzymes, superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase are shown to decrease after a single and repeated exposure to UVB radiation in mice and pig^{127,128} and also in aged and photoaged skin of human¹²⁸. The level of catalase in epidermis is much higher than in the dermis, and decreases after a single UVB and UVA exposure, recovering 3-4 weeks after exposure.

Topical and oral administration of biologically relevant antioxidants, such as vitamin E, vitamin C, coenzyme Q, polyphenols and carotenoids have minimal evidence that they provide photoprotection and reduce acute photodamage in human skin¹²⁹⁻¹³⁴. Recently, we found that CoQ10 suppresses UV-induced MMP1 production of fibroblasts by inhibiting the production of cytokines in KC. We speculate that anti-oxidative activity of CoQ10 may inhibit the production of inflammatory cytokines in UV irradiated KCs¹³⁵. Several polyphenolic antioxidants of plant, such as green tea, grape seed, pomegranate and others, have been shown to be effective *in vitro* for prevention of cellular photodamage, and green tea extract has been shown to reduce photoaging and skin cancer¹³⁶⁻¹⁴². Resveratrol derived from grape skin is a novel agent for anti-aging and anti-photoaging treatment of the skin, possibly through its antioxidant properties and through regulation of energy metabolism in mitochondria and epidermal cell differentiation^{143,144}.

Topical retinoids have been demonstrated to inhibit UV-induced inflammation mediated by AP-1 and NFκB transcription factors^{145,146}. All-trans-retinoic acid (ATRA) prevents UV-induced accumulation of c-Jun protein, resulting the suppression of AP-1 binding to MMPs gene. Further, ATRA is shown to stimulate the breakdown of jun protein through ubiquitin-proteasome degradation.

In conclusion, we recommend the use of sunscreen from childhood to prevent acute severe sunburn and to reduce the level of accumulated DNA damage caused by daily repeated exposures, and to both retard the onset of visible photoaging, and reduce the risk for melanoma and non-melanoma skin cancer.

4-(3) Treatment and rejuvenation of photoaged skin

Retinoids are one of the most commonly used topical agents to reverse the signs of photoaging. Topical use of ATRA for several months proved to reduce wrinkle numbers, length and depth by increasing fiber components in dermis and make epidermis thick^{147,148}. A new retinoic acid agonist, N-retinoyl-D-glucosamine has been shown to be effective on photoaged skin without the irritation commonly seen in ATRA treatment¹⁴⁹. Further ATRA and its derivatives are shown to reduce melanin pigment such as mottled hyperpigmentation, freckles and solar lentigines by topical use possibly by increased turnover rate of epidermis¹⁵⁰. To treat acute inflammation, topical immune suppressant, tacrolimus, non-steroidal anti inflammatory drugs (NSAIDs) and corticosteroid hormone are extremely effective.

Recent advances in non-ablative laser and light therapy of pigmented skin and wrinkles have made it possible possible to treat photo-damaged skin effectively and safely.

Noninvasive cosmetic procedures are now popular worldwide, since they are effective, and relatively painless and safe compared to deep chemical peels more common decades ago^{151,152}. Chemical peeling by salicylic acid in polyethylene glycol can be used to

treat photodamaged skin and has been shown to suppress skin tumor development in irradiated hairless mice ¹⁵³).

Pigmented lesions are commonly treated by laser, IPL (intense pulsed light), superficial chemical peel and topical application of whitening agents, cosmetics and drugs. Further, a highly effective drug delivery system, electroporation, is also available for whitening and wrinkle care. In many cases, patients are treated by combined use of these modalities, depending on the disease and skin conditions.

Chemical peels are effective for both superficial wrinkle amelioration and for whitening of pigmented spots. Glycolic acid (GA) and salicylic acid (macrogoles) are popular in Japan. Dainichi *et al* showed that chemical peeling by macrogoles suppresses p53 expression and normalizes keratinocyte differentiation, leading to the reduction of UV-induced skin cancer development in mice ¹⁵³. These acid formulations essentially dissolve the upper layer of skin, whereas trichloroacetic acid (TCA) can be used for lower dermal layer (medium depth peel).

Laser resurfacing is a technique used where the molecular bonds of the skin cells are dissolved by a laser. It is used for the treatment of wrinkles, solar lentigenes, sun damage, scars, actinic keratosis and telangiectasias or “spider veins”. Laser treatment is based on the theory that selective removal of skin tissue triggers a wound-healing response, remodeling of collagen fibers, dermal matrix, and rebuilds epidermal components. For discoloration, Q-switch ruby laser is commonly used, particularly is useful for the treatment of melanin pigment located in dermis. IPL is also very effective to reduce and often erase epidermal pigment in solar lentigenes and freckles by killing keratinocytes containing melanin ¹⁵⁴. Complete resurfacing was first done with a CO₂ laser. More commonly now, laser resurfacing is done with a fractional laser. The term fractional pertains to the method in which the laser light is transferred. Tiny pinpoint of laser light are used to deliver the laser to the surface of the skin in only a fraction of the area. Several hundred or thousands of pinpoint may be used per square inch, leaving healthy skin in between the ablated areas. This is intended to allow more rapid healing and less risk.

Radiofrequency devices delivers energy by waves in the range of radio signals and aims to destroy the upper and some of the lower skin layers, leading to contraction and tightening of the skin. This has been associated with a high degree of pain and inflammation.

Topically applied botanical extracts and synthetic molecules have been in widespread use for centuries in the case of the former and more recently in the case of the latter to rejuvenate photoaged skin. **Table 2** lists some of the most commonly used chemicals (cosmetics and drugs) for skin rejuvenation (**Table 2**).

Table 2 *Whitening and anti-wrinkle agents, and their mechanisms*

1	Arbutin	Inhibition of tyrosinase activity (competitive inhibitor) Inhibition of dendrite formation and extension in UV-stimulated melanocytes Inhibition of O2- and ON- production
2	Kogic acid	Inhibition of tyrosinase activity (Chelation of Cu++) Inhibition of melanin polymer
3	Vitamin C derivatives	Inhibition of tyrosinase activity Reduction of dopaquinone to dopa Reduction of oxidized black melanin
4	Kanzo extracts	Inhibition of tyrosinase activity
5	Retinoids	Inhibition of tyrosinase activity Enhancement of KC turn over
6	Kamitsure extract	Blocking of endothelin 1 receptor
7	Linoleic acid	Increased degradation of tyrosinase Enhancement of KC turn over
8	Ellagic acid	Inhibition of tyrosinase activity (Chelation of copper)
9	Rucinol	Inhibition of tyrosinase activity Inhibition of TRP1 activity
10	a- hydroic acid	Inhibition of mRNA expression of tyrosinase Increased KC turn over
11	Hydroquinone	Inhibition of tyrosinase activity(competitive inhibitor) Toxicity to melanocyte Degradation of melanosome
12	Vitamin E	Inhibition of tyrosinase activity Inhibition of DHICA polymerization
13	Tranexamic acid	Inhibition of melanocyte proliferation
14	Cysteine	Increased pheomelanin production Inhibition of mRNA expression of tyrosinase Inhibition of POMC mRNA expression induced by UVB
15	Glutathione	Suppression of tyrosinase maturation by release inhibition from ER
16	Retinoic acid	Increase of pro-collage production Inhibition of metalloproteinases production
17	Vitamin C	Stimulate procollagen hydroxylation Suppression of metalloproteinases activity Increase of intracellular lipid production in epidermis
18	Emilin(tetrapeptides)	Stimulate the production of pro-collagen, elastic fiber and hyaluronan
19	Astaxanthin	Inhibition of UV-induced metalloproteinase-1 production

References

- 1) Bashir MM, Sharma MR, Werth VP. TNF-alpha production in the skin Arch Dermatol Res 301:87-91, 2009
- 2) Chung JH, Youn SH, Koh WS, Eun HC, Cho KH, Park KC, Youn JI : Ultraviolet B irradiation-enhanced interleukin (IL)-6 production and mRNA expression are mediated by IL-1 alpha in cultured human keratinocytes. J Invest Dermatol 106 : 715-720, 1996
- 3) Kondo S, Sauder DN, Kono T, Galley KA, McKenzie RC : Differential modulation of interleukin-1 alpha (IL-1 alpha) and interleukin-1 beta (IL-1 beta) in human epidermal keratinocytes by UVB. Exp Dermatol 3 : 29-39, 1994
- 4) Setlow RB, Carrier WL : Pyrimidine dimers in ultraviolet-irradiated DNA's. J Mol Biol 17 : 237-254, 1966
- 5) Mitchell DL, Nairn RS : The biology of the (6-4) photoproduct. Photochem Photobiol 49 : 805-819, 1989
- 6) Mitchell DL : The relative cytotoxicity of (6-4) photoproducts and cyclobutane dimers in mammalian cells. Photochem Photobiol 48 : 51-57, 1988
- 7) Boonstra A, van Oudenaren A, Barendregt B, An L, Leenen PJ, Savelkoul HF : UVB irradiation modulates systemic immune responses by affecting cytokine production of antigen-presenting cells. Int Immunol 12 : 1531-1538, 2000
- 8) Ando O, Suemoto Y, Kurimoto M, Horikawa T, Ichihashi M : Deficient Th1-type immune responses via impaired CD28 signaling in ultraviolet B-induced systemic immunosuppression and the restorative effect of IL-12. J Dermatol Sci 24 : 190-202, 2000
- 9) Ullrich SE : Mechanism involved in the systemic suppression of antigen-presenting cell function by UV irradiation. Keratinocyte-derived IL-10 modulates antigen-presenting cell function of splenic adherent cells. J Immunol 152 : 3410-3416, 1994
- 10) Reeve VE, Tyrrell RM : Heme oxygenase induction mediates the photoimmunoprotective activity of UVA radiation in the mouse. Proc Natl Acad Sci USA 96 : 9317-9321, 1999
- 11) Podda M, Traber MG, Weber C, Yan LJ, Packer L : UV-irradiation depletes antioxidants and causes oxidative damage in a model of human skin. Free Radic Biol Med 24 : 55-65, 1998
- 12) Kuchel JM, Barnetson RS, Halliday GM : Nitric oxide appears to be a mediator of solar-simulated ultraviolet radiation-induced immunosuppression in humans. J Invest Dermatol 121 : 587-593, 2003
- 13) Wilgus TA, Koki AT, Zweifel BS, Kusewitt DF, Rubal PA, Oberyszyn TM : Inhibition of cutaneous ultraviolet light B-mediated inflammation and tumor formation with topical celecoxib treatment. Mol Carcinog 38 : 49-58, 2003
- 14) Abeyama K, Eng W, Jester JV, Vink AA, Edelbaum D, Cockerell CJ, Bergstresser PR, Takashima A : A role for NF-kappaB-dependent gene transactivation in sunburn. J Clin Invest 105 : 1751-1759, 2000
- 15) Saliou C, Kitazawa M, McLaughlin L, Yang JP, Lodge JK, Tetsuka T, Iwasaki K, Cillard J, Okamoto T, Packer L : Antioxidants modulate acute solar ultraviolet radiation-induced NF-kappa-B activation in a human keratinocyte cell line. Free Radic Biol Med 26 : 174-183, 1999
- 16) Takao J, Yudate T, Das A, Shikano S, Bonkobara M, Ariizumi K, Cruz PD : Expression of NF-kappaB in epidermis and the relationship between NF-kappaB activation and inhibition of keratinocyte growth. Br J Dermatol 148 : 680-688, 2003
- 17) Adler AS, Sinha S, Kawahara TL, Zhang JY, Segal E, Chang HY : Motif module map reveals enforcement of aging by continual NF-kappaB activity. Genes Dev 21 : 3244-3257, 2007
- 18) Tebbe B, Schwarz C, Ruderisch HS, Treudler R, Orfanos CE : L-ascorbic acid increases NFkappaB binding activity in UVA-irradiated HaCaT keratinocytes. J Invest Dermatol 117 : 154-156, 2001
- 19) Tanaka K, Hasegawa J, Asamitsu K, Okamoto T : Magnolia ovovata extract and its active component magnolol prevent skin photoaging via inhibition of nuclear factor kappaB. Eur J Pharmacol 565 : 212-219, 2007
- 20) Parrish JA, Jaenicke KF, Anderson RR : Erythema and melanogenesis action spectra of normal human skin. Photochem Photobiol 36 : 187-191, 1982
- 21) Young AR, Chadwick CA, Harrison GI, Nikaido O, Ramsden J, Potten CS : The similarity of action spectra for thymine dimers in human epidermis and erythema suggests that DNA is the chromophore for erythema. J Invest Dermatol 111 : 982-988, 1998
- 22) Ichihashi M, Ueda M, Budiyo A, Bito T, Oka M, Fukunaga M, Tsuru K, Horikawa T : UV-induced skin damage. Toxicology 189 : 21-39, 2003
- 23) Eller MS, Ostrom K, Gilchrist BA : DNA damage enhances melanogenesis. Proc Natl Acad Sci USA 93 : 1087-1092, 1996
- 24) Kadekaro AL, Kavanagh R, Kanto H, Terzieva S, Hauser J, Kobayashi N, Schwemmer S, Cornelius J, Babcock G, Shertzer HG, Scott G, Abdel-Malek ZA : alpha-Melanocortin and endothelin-1 activate antiapoptotic pathways and reduce DNA damage in human melanocytes. Cancer Res 65 : 4292-4299, 2005
- 25) Nishigori C, Yarosh DB, Ullrich SE, Vink AA, Bucana CD, Roza L, Kripke ML : Evidence that DNA damage triggers interleukin 10 cytokine production in UV-irradiated murine keratinocytes. Proc Natl Acad Sci USA 93 : 10354-10359, 1996
- 26) de Laat WL, Jaspers NG, Hoeijmakers JH : Molecular mechanism of nucleotide excision repair. Genes Dev 13 : 768-785, 1999
- 27) Hoeijmakers JH : Genome maintenance mechanisms for preventing cancer. Nature 411 : 366-374, 2001
- 28) Potten CS, Chadwick CA, Cohen AJ, Nikaido O, Matsunaga T, Schipper NW, Young AR : DNA damage in UV-irradiated human skin in vivo: automated direct measurement by image analysis (thymine dimers) compared with indirect measurement (unscheduled DNA synthesis) and protection by 5-methoxypsoralen. Int J Radiat Biol 63 : 313-324, 1993
- 29) Oikarinen A, Raitio A. Melanoma and other skin cancers in circular areas. Int J Circumpolar Health. 59:52-55, 2000
- 30) Matsui MS, Deleo VA. Long wave ultraviolet radiation and promotion of skin cancer. Cancer Cells. 3:8-12, 1993
- 31) Katiyar SK, Matsui MS, Mukhtar H. Kinetics of UV light-induced cyclobutane pyrimidine dimers in human skin in vivo: an immunohistochemical analysis of both epidermis and dermis. Photochem Photobiol 72:788-793, 2000
- 32) Ahmed NU, Ueda M, Nikaido O, Osawa T, Ichihashi M : High levels of 8-hydroxy-2'-deoxyguanosine appear in normal human epidermis after a single dose of ultraviolet radiation. Br J Dermatol 140 : 226-231, 1999
- 33) Kunisada M, Sakumi K, Tominaga Y, Budiyo A, Ueda M, Ichihashi M, Nakabeppu Y, Nishigori C : 8-Oxoguanine formation induced by chronic UVB exposure makes Ogg1 knockout mice susceptible to skin carcinogenesis. Cancer Res 65 : 6006-6010, 2005
- 34) Javeri A, Huang XX, Bernerd F, Mason RS, Halliday GM : Human 8-oxoguanine-DNA glycosylase 1 protein and gene are expressed more abundantly in the superficial than basal layer of human epidermis. DNA Repair (Amst) 7 : 1542-1550, 2008
- 35) Rochette PJ, Therrien JP, Drouin R, Perdiz D, Bastien N, Drobetsky EA, Sage E : UVA-induced cyclobutane pyrimidine dimers form predominantly at thymine-thymine dipyrimidines and correlate with the mutation spectrum in rodent cells. Nucleic Acids Res 31 : 2786-2794, 2003
- 36) Kappes UP, Luo D, Potter M, Schulmeister K, Rünger TM : Short- and long-wave UV light (UVB and UVA) induce similar mutations in human skin cells. J Invest Dermatol 126 : 667-675, 2006
- 37) Youn JI, Oh JK, Kim BK, Suh DH, Chung JH, Oh SJ, Kim JJ, Kang SH : Relationship between skin phototype and MED in Korean, brown skin. Photodermatol Photoimmunol Photomed 13 : 208-211, 1997
- 38) Kawada A : UVB-induced erythema, delayed tanning, and UVA-induced immediate tanning in Japanese skin. Photodermatol 3 : 327-333, 1986
- 39) Lerner AB, McGuire JS : Effect of alpha- and betamelanocyte stimulating hormones on the skin colour of man. Nature 189 : 176-179, 1961
- 40) Chakraborty A, Pawelek J : MSH receptors in immortalized human epidermal keratinocytes: a potential mechanism for coordinate regulation of the epidermal-melanin unit. J Cell Physiol 157 : 344-350, 1993
- 41) Roméro-Graillet C, Aberdam E, Clément M, Ortonne JP, Ballotti R : Nitric oxide produced by ultraviolet-irradiated keratinocytes stimulates melanogenesis. J Clin Invest 99 : 635-642, 1997
- 42) Funasaka Y, Ichihashi M : The effect of ultraviolet B induced adult T cell leukemia-derived factor/thioredoxin (ADF/TRX) on survival and growth of human melanocytes. Pigment Cell Res 10 : 68-73, 1997

- 43) Imokawa G, Kobayashi T, Miyagishi M : Intracellular signaling mechanisms leading to synergistic effects of endothelin-1 and stem cell factor on proliferation of cultured human melanocytes. Cross-talk via trans-activation of the tyrosine kinase c-kit receptor. *J Biol Chem* 275 : 33321-33328, 2000
- 44) Imokawa G, Kobayashi T, Miyagishi M, Higashi K, Yada Y : The role of endothelin-1 in epidermal hyperpigmentation and signaling mechanisms of mitogenesis and melanogenesis. *Pigment Cell Res* 10 : 218-228, 1997
- 45) Maeda K, Hatao M : Involvement of photooxidation of melanogenic precursors in prolonged pigmentation induced by ultraviolet A. *J Invest Dermatol* 122 : 503-509, 2004
- 46) Seiberg M : Keratinocyte-melanocyte interactions during melanosome transfer. *Pigment Cell Res* 14 : 236-242, 2001
- 47) Aberdam E, Auberger P, Ortonne JP, Ballotti R : Neprilysin, a novel target for ultraviolet B regulation of melanogenesis via melanocortins. *J Invest Dermatol* 115 : 381-387, 2000
- 48) Young AR, Sheehan JM : UV-induced pigmentation in human skin. In *Sun Protection in Man*. PV Giacomoni ed. Amsterdam : Elsevier. pp357-375, 2001
- 49) Miyamura Y, Coelho SG, Wolber R, Miller SA, Wakamatsu K, Zmudzka BZ, Ito S, Smuda C, Passeron T, Choi W, Batzer J, Yamaguchi Y, Beer JZ, Hearing VJ : Regulation of human skin pigmentation and responses to ultraviolet radiation. *Pigment Cell Res* 20 : 2-13, 2007
- 50) Ramsay CA, Giannelli F : The erythral action spectrum and deoxyribonucleic acid repair synthesis in xeroderma pigmentosum. *Br J Dermatol* 92 : 49-56, 1975
- 51) Ueda M, Matsunaga T, Bito T, Nikaido O, Ichihashi M : Higher cyclobutane pyrimidine dimer and (6-4) photoproduct yields in epidermis of normal humans with increased sensitivity to ultraviolet B radiation. *Photodermatol Photoimmunol Photomed* 12 : 22-26, 1996
- 52) Ichihashi M, Fujiwara Y : Clinical and photobiological characteristics of Japanese xeroderma pigmentosum variant. *Br J Dermatol* 105 : 1-12, 1981
- 53) Nussipikel T : Nucleotide excision repair and neurological diseases. *DNA Repair (Amst)* 7 : 1155-1167, 2008
- 54) Young AR, Sheehan JM, Chadwick CA, Potten CS. Protection by ultraviolet A and B sunscreens against in situ dipyrimidine photolesions in human epidermis is comparable to protection against sunburn. *J Invest Dermatol* 115:37-41, 2000
- 55) Ley RD. Photoreactivation of UV-induced pyrimidine dimers and erythema in *Monodelphis domestica*. *Proc Natl Acad Sci. USA* 82:2409-2411, 1985
- 56) Arad S, Konnikov N, Goukassian DA, Gilchrist BA : T-oligos augment UV-induced protective responses in human skin. *FASEB J* 20 : 1895-1897, 2006
- 57) Eller MS, Maeda T, Magnoni C, Atwal D, Gilchrist BA : Enhancement of DNA repair in human skin cells by thymidine dinucleotides: evidence for a p53-mediated mammalian SOS response. *Proc Natl Acad Sci USA* 94 : 12627-12632, 1997
- 58) Hadshiew IM, Eller MS, Gasparro FP, Gilchrist BA : Stimulation of melanogenesis by DNA oligonucleotides: effect of size, sequence and 5' phosphorylation. *J Dermatol Sci* 25 : 127-138, 2001
- 59) Pedoux R, Al-irani N, Marteau C, Pellicier F, Branche R, Ozturk M, Franchi J, Doré JF : Thymidine dinucleotides induce S phase cell cycle arrest in addition to increased melanogenesis in human melanocytes. *J Invest Dermatol* 111 : 472-477, 1998
- 60) Snyder DS : Effect of topical indomethacin on UVR-induced redness and prostaglandin E levels in sunburned guinea pig skin. *Prostaglandins* 11 : 631-643, 1976
- 61) Rundhaug JE, Fischer SM : Cyclo-oxygenase-2 plays a critical role in UV-induced skin carcinogenesis. *Photochem Photobiol* 84 : 322-329, 2008
- 62) Rhodes LE, Belgi G, Parslew R, McLoughlin L, Clough GF, Friedmann PS : Ultraviolet-B-induced erythema is mediated by nitric oxide and prostaglandin E2 in combination. *J Invest Dermatol* 117 : 880-885, 2001
- 63) Kuwamoto K, Miyauchi-Hashimoto H, Tanaka K, Eguchi N, Inui T, Urade Y, Horio T : Possible involvement of enhanced prostaglandin E2 production in the photosensitivity in xeroderma pigmentosum group A model mice. *J Invest Dermatol* 114 : 241-246, 2000
- 64) Friedberg EC : How nucleotide excision repair protects against cancer. *Nat Rev Cancer* 1 : 22-33, 2001
- 65) Taylor JS : New structural and mechanistic insight into the A-rule and the instructional and non-instructional behavior of DNA photoproducts and other lesions. *Mutat Res* 510 : 55-70, 2002
- 66) Ziegler A, Jonason AS, Leffell DJ, Simon JA, Sharma HW, Kimmelman J, Remington L, Jacks T, Brash DE : Sunburn and p53 in the onset of skin cancer. *Nature* 372 : 773-776, 1994
- 67) Brash DE, Ziegler A, Jonason AS, Simon JA, Kunala S, Leffell DJ : Sunlight and sunburn in human skin cancer: p53, apoptosis, and tumor promotion. *J Invest Dermatol Symp Proc* 1 : 136-142, 1996
- 68) Nataraj AJ, Trent JC 2nd, Ananthaswamy HN : p53 gene mutations and photocarcinogenesis. *Photochem Photobiol* 62 : 218-230, 1995
- 69) Wood RD : DNA repair in eukaryotes. *Annu Rev Biochem* 65 : 135-167, 1996
- 70) Jans J, Schul W, Sert YG, Rijkssen Y, Rebel H, Eker AP, Nakajima S, van Steeg H, de Gruijl FR, Yasui A, Hoeijmakers JH, van der Horst GT : Powerful skin cancer protection by a CPD-photolyase transgene. *Curr Biol* 15 : 105-115, 2005
- 71) Bohr VA, Smith CA, Okumoto DS, Hanawalt PC : DNA repair in an active gene: removal of pyrimidine dimers from the DHFR gene of CHO cells is much more efficient than in the genome overall. *Cell* 40 : 359-369, 1985
- 72) Licht CL, Stevnsner T, Bohr VA : Cockayne syndrome group B cellular and biochemical functions. *Am J Hum Genet* 73 : 1217-1239, 2003
- 73) Svejstrup JQ : Transcription repair coupling factor: a very pushy enzyme. *Mol Cell* 9 : 1151-1152, 2002
- 74) Moriawaki S, Takahashi Y : Photoaging and DNA repair. *J Dermatol Sci* 50 : 169-176, 2008
- 75) Monestier S, Gaudy C, Gouvernet J, Richard MA, Grob JJ : Multiple senile lentigos of the face, a skin ageing pattern resulting from a life excess of intermittent sun exposure in dark-skinned caucasians: a case-control study. *Br J Dermatol* 154 : 438-444, 2006
- 76) Akiba S, Shinkura R, Miyamoto K, Hillebrand G, Yamaguchi N, Ichihashi M : Influence of chronic UV exposure and lifestyle on facial skin photo-aging--results from a pilot study. *J Epidemiol* 9(Suppl) : S136-S142, 1999
- 77) Mera SL, Lovell CR, Jones RR, Davies JD : Elastic fibres in normal and sun-damaged skin: an immunohistochemical study. *Br J Dermatol* 117 : 21-27, 1987
- 78) Warren R, Gartstein V, Kligman AM, Montagna W, Allendorf RA, Ridder GM : Age, sunlight, and facial skin: a histologic and quantitative study. *J Am Acad Dermatol* 25 : 751-760, 1991
- 79) Kelly RI, Pearse R, Bull RH, Leveque JL, de Rigal J, Mortimer PS : The effects of aging on the cutaneous microvasculature. *J Am Acad Dermatol* 33 : 749-756, 1995
- 80) Chung JH, Yano K, Lee MK, Youn CS, Seo JY, Kim KH, Cho KH, Eun HC, Detmar M : Differential effects of photoaging vs intrinsic aging on the vascularization of human skin. *Arch Dermatol* 138 : 1437-1442, 2002
- 81) Chung JH, Eun HC : Angiogenesis in skin aging and photoaging. *J Dermatol* 34 : 593-600, 2007
- 82) Yano K, Kadoya K, Kajiya K, Hong YK, Detmar M : Ultraviolet B irradiation of human skin induces an angiogenic switch that is mediated by upregulation of vascular endothelial growth factor and by downregulation of thrombospondin-1. *Br J Dermatol* 152 : 115-121, 2005
- 83) Toole BP, Wight TN, Tammi MI : Hyaluronan-cell interactions in cancer and vascular disease. *J Biol Chem* 277 : 4593-4596, 2002
- 84) Südel KM, Venzke K, Mielke H, Breitenbach U, Mundt C, Jaspers S, Koop U, Sauermann K, Knussman-Hartig E, Moll I, Gercken G, Young AR, Stäb F, Wenck H, Gallinat S : Novel aspects of intrinsic and extrinsic aging of human skin: beneficial effects of soy extract. *Photochem Photobiol* 81 : 581-587, 2005
- 85) Gherstik I, Lotti T, Camanile G, Grappone C, Dini G. Hyaluronic acid in cutaneous intrinsic aging. *Int J Dermatol* 33:119-122, 1996
- 86) Averbek M, Gebhardt CA, Voigt S, Beilharz S, Anderegg U, Termeer CC, Sleeman JP, Simon JC : Differential regulation of hyaluronan metabolism in the epidermal and dermal compartments of human skin by UVB irradiation. *J Invest Dermatol* 127 : 687-697, 2007

- 87) Fisher GJ, Wang ZQ, Datta SC, Varani J, Kang S, Voorhees JJ : Pathophysiology of premature skin aging induced by ultraviolet light. *N Engl J Med* : 337 : 1419-1428, 1997
- 88) Kang S, Fisher GJ, Voorhees JJ : Photoaging: pathogenesis, prevention, and treatment. *Clin Geriatr Med* 17 : 643-659, 2001
- 89) Inomata S, Matsunaga Y, Amano S, Takada K, Kobayashi K, Tsunenaga M, Nishiyama T, Kohno Y, Fukuda M : Possible involvement of gelatinases in basement membrane damage and wrinkle formation in chronically ultraviolet B-exposed hairless mouse. *J Invest Dermatol* 120 : 128-134, 2003
- 90) Fisher GJ, Kang S, Varani J, Bata-Csorgo Z, Wan Y, Datta S, Voorhees JJ : Mechanisms of photoaging and chronological skin aging. *Arch Dermatol* 138 : 1462-1470, 2002
- 91) Kondo S : The roles of cytokines in photoaging. *J Dermatol Sci* 23 Suppl : S30-S36, 2000
- 92) Herrmann G, Wlaschek M, Lange TS, Prenzel K, Goerz G, Scharffetter-Kochanek K : UVA irradiation stimulates the synthesis of various matrix-metalloproteinases (MMPs) in cultured human fibroblasts. *Exp Dermatol* 2 : 92-97, 1993
- 93) Chung JH, Seo JY, Lee MK, Eun HC, Lee JH, Kang S, Fisher GJ, Voorhees JJ : Ultraviolet modulation of human macrophage metalloelastase in human skin in vivo. *J Invest Dermatol* 119 : 507-512, 2002
- 94) Woodley DT, Kalebec T, Banes AJ, Link W, Prunieras M, Liotta L : Adult human keratinocytes migrating over nonviable dermal collagen produce collagenolytic enzymes that degrade type I and type IV collagen. *J Invest Dermatol* 86 : 418-423, 1986
- 95) Rabe JH, Mamelak AJ, McElgunn PJ, Morison WL, Sauder DN : Photoaging: mechanisms and repair. *J Am Acad Dermatol* 55 : 1-19, 2006
- 96) Amano S, Ogura Y, Akutsu N, Matsunaga Y, Kadoya K, Adachi E, Nishiyama T : Protective effect of matrix metalloproteinase inhibitors against epidermal basement membrane damage: skin equivalents partially mimic photoageing process. *Br J Dermatol* 153 : 37-46, 2005
- 97) Varani J, Schuger L, Dame MK, Leonard C, Fligel SE, Kang S, Fisher GJ, Voorhees JJ : Reduced fibroblast interaction with intact collagen as a mechanism for depressed collagen synthesis in photodamaged skin. *J Invest Dermatol* 122 : 1471-1479, 2004
- 98) Muto J, Kuroda K, Wachi H, Hirose S, Tajima S : Accumulation of elafin in actinic elastosis of sun-damaged skin: elafin binds to elastin and prevents elastolytic degradation. *J Invest Dermatol* 127 : 1358-1366, 2007
- 99) Kligman LH : Intensification of ultraviolet-induced dermal damage by infrared radiation. *Arch Dermatol Res* 272 : 229-238, 1982
- 100) Kim HH, Lee MJ, Lee SR, Kim KH, Cho KH, Eun HC, Chung JH : Augmentation of UV-induced skin wrinkling by infrared irradiation in hairless mice. *Mech Ageing Dev* 126 : 1170-1177, 2005
- 101) Seo JY, Chung JH : Thermal aging: A new concept of skin aging. *J Dermatol Sci Suppl* 2 : S13-S22, 2006
- 102) Park CH, Lee MJ, Ahn J, Kim S, Kim HH, Kim KH, Eun HC, Chung JH : Heat shock-induced matrix metalloproteinase (MMP)-1 and MMP-3 are mediated through ERK and JNK activation and via an autocrine interleukin-6 loop. *J Invest Dermatol* 123 : 1012-1019, 2004
- 103) Kim MS, Kim YK, Cho KH, Chung JH : Regulation of type I procollagen and MMP-1 expression after single or repeated exposure to infrared radiation in human skin. *Mech Ageing Dev* 127 : 875-882, 2006
- 104) Wei Q, Matanoski GM, Farmer ER, Hedayati MA, Grossman L : DNA repair and aging in basal cell carcinoma: a molecular epidemiology study. *Proc Natl Acad Sci USA* 90 : 1614-1618, 1993
- 105) Moriwaki S, Ray S, Tarone RE, Kraemer KH, Grossman L : The effect of donor age on the processing of UV-damaged DNA by cultured human cells: reduced DNA repair capacity and increase in DNA mutability. *Mutat Res* 364 : 117-123, 1996
- 106) Goukassian DA, Bagheri S, el-Keeb L, Eller MS, Gilchrist BA : DNA oligonucleotide treatment corrects the age-associated decline in DNA repair capacity. *FASEB J* 16 : 754-756, 2002
- 107) Young AR, Orchard GE, Harrison GI, Klock JL : The detrimental effects of daily sub-erythral exposure on human skin in vivo can be prevented by a daily-care broad-spectrum sunscreen. *J Invest Dermatol* 127 : 975-978, 2007
- 108) Sheehan JM, Cragg N, Chadwick CA, Potten CS, Young AR : Repeated ultraviolet exposure affords the same protection against DNA photodamage and erythema in human skin types II and IV but is associated with faster DNA repair in skin type IV. *J Invest Dermatol* 118 : 825-829, 2002
- 109) Gasparro FP : Sunscreens, skin photobiology, and skin cancer: the need for UVA protection and evaluation of efficacy. *Environ Health Perspect* 108 Suppl : S71-S78, 2000
- 110) Hillebrand GG, Miyamoto K, Schnell B, Ichihashi M, Shinkura R, Akiba S : Quantitative evaluation of skin condition in an epidemiological survey of females living in northern versus southern Japan. *J Dermatol Sci* 27 Suppl : S42-S52, 2001
- 111) Araki K, Nagano T, Ueda M, Washio F, Watanabe S, Yamaguchi N, Ichihashi M : Incidence of skin cancers and precancerous lesions in Japanese--risk factors and prevention. *J Epidemiol* 9(Suppl) : S14-S21, 1999
- 112) Ono M, Munakata N, Watanabe S : UV exposure. *Photochem Photobiol* 81 : 437-445, 2005
- 113) Pathak MA : Sunscreens: topical and systemic approaches for protection of human skin against harmful effects of solar radiation. *J Am Acad Dermatol* 7 : 285-312, 1982
- 114) Johnson EY, Lookingbill DP : Sunscreen use and sun exposure. Trends in a white population. *Arch Dermatol* 120 : 727-731, 1984
- 115) Kligman LH, Akin FJ, Kligman AM : Sunscreens prevent ultraviolet photocarcinogenesis. *J Am Acad Dermatol* 3 : 30-35, 1980
- 116) Moyal DD, Fourtanier AM : Broad-spectrum sunscreens provide better protection from solar ultraviolet-simulated radiation and natural sunlight-induced immunosuppression in human beings. *J Am Acad Dermatol* 58 : 58 Suppl : S149-S154, 2008
- 117) Liardet S, Scaletta C, Panizzon R, Hohlfield P, Laurent-Applegate L : Protection against pyrimidine dimers, p53, and 8-hydroxy-2'-deoxyguanosine expression in ultraviolet-irradiated human skin by sunscreens: difference between UVB + UVA and UVB alone sunscreens. *J Invest Dermatol* 117 : 1437-1441, 2001.
- 118) Poon TS, Barnetson RS, Halliday GM : Prevention of immunosuppression by sunscreens in humans is unrelated to protection from erythema and dependent on protection from ultraviolet A in the face of constant ultraviolet B protection. *J Invest Dermatol* 121 : 184-190, 2003
- 119) Young AR, Sheehan JM, Chadwick CA, Potten CS : Protection by ultraviolet A and B sunscreens against in situ dipyrimidine photolesions in human epidermis is comparable to protection against sunburn. *J Invest Dermatol* 115 : 37-41, 2000
- 120) Liardet S, Scaletta C, Panizzon R, Hohlfield P, Laurent-Applegate L : Protection against pyrimidine dimers, p53, and 8-hydroxy-2'-deoxyguanosine expression in ultraviolet-irradiated human skin by sunscreens: difference between UVB + UVA and UVB alone sunscreens. *J Invest Dermatol* 117 : 1437-1441, 2001
- 121) Gallagher RP, Rivers JK, Lee TK, Bajdik CD, McLean DI, Coldman AJ : Broad-spectrum sunscreen use and the development of new nevi in white children: A randomized controlled trial. *JAMA* 283 : 2955-2960, 2000
- 122) Fourtanier A, Moyal D, Seite S : Sunscreens containing the broad-spectrum UVA absorber, Mexoryl[®] SX, prevent the cutaneous detrimental effects of exposure: a review of clinical study results. *Photodermatol Photoimmunol Photomed* 24:164-174, 2008
- 123) Berwick M, Kesler D : Ultraviolet radiation exposure, vitamin D, and cancer. *Photochem Photobiol* 81 : 1261-1266, 2005
- 124) Wolpowitz D, Gilchrist BA. The vitamin D questions: how much do you need and how should you get it ? *J Am Acad Dermatol* 54:301-317, 2006
- 125) Holick MF. Vitamin D deficiency. *N Eng J Med* 357:266-281, 2007
- 126) Shindo Y, Witt E, Packer L : Antioxidant defense mechanisms in murine epidermis and dermis and their responses to ultraviolet light. *J Invest Dermatol* 100 : 260-265, 1993
- 127) Hashimoto Y, Ohkuma N, Iizuka H : Reduced superoxide dismutase activity in UVB-induced hyperproliferative pig epidermis. *Arch Dermatol Res* 283 : 317-320, 1991
- 128) Rhie G, Shin MH, Seo JY, Choi WW, Cho KH, Kim KH, Park KC, Eun HC, Chung JH : Aging- and photoaging-dependent changes of

- enzymic and nonenzymic antioxidants in the epidermis and dermis of human skin in vivo. *J Invest Dermatol* 117 : 1212-1217, 2001
- 129) Nusgens BV, Humbert P, Rougier A, Colige AC, Haftek M, Lambert CA, Richard A, Creidi P, Lapière CM : Topically applied vitamin C enhances the mRNA level of collagens I and III, their processing enzymes and tissue inhibitor of matrix metalloproteinase 1 in the human dermis. *J Invest Dermatol* 116 : 853-859, 2001
 - 130) Yoshida E, Watanabe T, Takata J, Yamazaki A, Karube Y, Kobayashi S : Topical application of a novel, hydrophilic gamma-tocopherol derivative reduces photo-inflammation in mice skin. *J Invest Dermatol* 126 : 1633-40, 2006
 - 131) Humbert PG, Haftek M, Creidi P, Lapière C, Nusgens B, Richard A, Schmitt D, Rougier A, Zahouani H : Topical ascorbic acid on photoaged skin. Clinical, topographical and ultrastructural evaluation: double-blind study vs. placebo. *Exp Dermatol* 12 : 237-244, 2003
 - 132) Murad H, Tabibian MP : The effect of an oral supplement containing glucosamine, amino acids, minerals, and antioxidants on cutaneous aging: a preliminary study. *J Dermatolog Treat* 12 : 47-51, 2001
 - 133) Eberlein-König B, Placzek M, Przybilla B : Protective effect against sunburn of combined systemic ascorbic acid (vitamin C) and d-alpha-tocopherol (vitamin E). *J Am Acad Dermatol* 38 : 45-48, 1998
 - 134) Fuchs J, Kern H : Modulation of UV-light-induced skin inflammation by D-alpha-tocopherol and L-ascorbic acid: a clinical study using solar simulated radiation. *Free Radic Biol Med* 25 : 1006-1012, 1998
 - 135) Inui M, Ooe M, Fujii K, Matsunaka H, Yoshida M, Ichihashi M. Mechanisms of inhibitory effects of CoQ10 on UV-induced wrinkle formation in vitro and in vivo. *BioFactors* 32:237-243, 2008
 - 136) Katiyar SK, Korman NJ, Mukhtar H, Agarwal R : Protective effects of silymarin against photocarcinogenesis in a mouse skin model. *J Natl Cancer Inst* 89 : 556-566, 1997
 - 137) Saliou C, Kitazawa M, McLaughlin L, Yang JP, Lodge JK, Tetsuka T, Iwasaki K, Cillard J, Okamoto T, Packer L : Antioxidants modulate acute solar ultraviolet radiation-induced NF-kappa-B activation in a human keratinocyte cell line. *Free Radic Biol Med* 26 : 174-183, 1999
 - 138) Elmetts CA, Singh D, Tubesing K, Matsui M, Katiyar S, Mukhtar H : Cutaneous photoprotection from ultraviolet injury by green tea polyphenols. *J Am Acad Dermatol* 44 : 425-432, 2001
 - 139) Zhao JF, Zhang YJ, Jin XH, Athar M, Santella RM, Bickers DR, Wang ZY : Green tea protects against psoralen plus ultraviolet A-induced photochemical damage to skin. *J Invest Dermatol* 113 : 1070-1075, 1999
 - 140) Mukhtar H, Katiyar SK, Agarwal R. Green tea and skin: anticarcinogenic effects. *J Invest Dermatol* 102:3-7, 1997
 - 141) Afaq F, Adhami VM, Ahmad N, Mukhtar H. Inhibition of ultraviolet B-mediated activation of nuclear kappa B in normal human epidermal keratinocytes by green tea constituent (-)-epigallocatechin-3-gallate. *Oncogene* 22:1035-1044, 2003
 - 142) Hsu S. Green tea and the skin. *J Am Acad Dermatol* 52:1049-1059, 2005
 - 143) Baur JA, Sinclair DA : Therapeutic potential of resveratrol: the in vivo evidence. *Nat Rev Drug Discov* 5 : 493-506, 2006
 - 144) Lagouge M, Argmann C, Gerhart-Hines Z, Meziane H, Lerin C, Daussin F, Messadeq N, Milne J, Lambert P, Elliott P, Geny B, Laakso M, Puigserver P, Auwerx J : Resveratrol improves mitochondrial function and protects against metabolic disease by activating SIRT1 and PGC-1alpha. *Cell* 127 : 1109-1122, 2006
 - 145) Fisher GJ, Voorhees JJ : Molecular mechanisms of photoaging and its prevention by retinoic acid: ultraviolet irradiation induces MAP kinase signal transduction cascades that induce Ap-1-regulated matrix metalloproteinases that degrade human skin in vivo. *J Invest Dermatol Symp Proc* 3 : 61-68, 1998
 - 146) Fisher GJ, Datta S, Wang Z, Li XY, Quan T, Chung JH, Kang S, Voorhees JJ : c-Jun-dependent inhibition of cutaneous procollagen transcription following ultraviolet irradiation is reversed by all-trans retinoic acid. *J Clin Invest* 106 : 663-670, 2000
 - 147) Kligman AM, Grove GL, Hirose R, Leyden JJ : Topical tretinoin for photoaged skin. *J Am Acad Dermatol* 15 : 836-859, 1986
 - 148) Weiss JS, Ellis CN, Headington JT, Tincoff T, Hamilton TA, Voorhees JJ : Topical tretinoin improves photoaged skin. A double-blind vehicle-controlled study. *JAMA* 259 : 527-532, 1988
 - 149) Kambayashi H, Otake Y, Takada K, Funasaka Y, Ichihashi M, Kato S : N-retinoyl-D-glucosamine, a new retinoic acid agonist, mediates topical retinoid efficacy with no irritation on photoaged skin. *Br J Dermatol* 153 Suppl : S30-S36, 2005
 - 150) Ortonne JP : Retinoid therapy of pigmentary disorders. *Dermatol Ther* 19 : 280-288, 2006
 - 151) Glogau RG, Matarasso SL : Chemical peels. Trichloroacetic acid and phenol. *Dermatol Clin* 13 : 263-276, 1995
 - 152) Dinner MI, Artz JS : Chemical peel--what's in the formula? *Plast Reconstr Surg* 94 : 406-407, 1994
 - 153) Dainichi T, Amano S, Matsunaga Y, Iriyama S, Hirao T, Hariya T, Hibino T, Katagiri C, Takahashi M, Ueda S, Furue M : Chemical peeling by SA-PEG remodels photo-damaged skin: suppressing p53 expression and normalizing keratinocyte differentiation. *J Invest Dermatol* 126 : 416-421, 2006
 - 154) Negishi K, Kushikata N, Takeuchi K, Tezuka Y, Wakamatsu S. Photorejuvenation by intense pulsed light with objective measurement of skin color in Japanese patients. *Dermatol Surg* 32 : 1380-1387, 2006