

Role of Micronutrients in Skin Health and Function

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Abstract

Skin is the first line of defense for protecting our bodies against external perturbations, including ultraviolet (UV) irradiation, mechanical/chemical stress, and bacterial infection. Nutrition is one of many factors required for the maintenance of overall skin health. An impaired nutritional status alters the structural integrity and biological function of skin, resulting in an abnormal skin barrier. In particular, the importance of micronutrients (such as certain vitamins and minerals) for skin health has been highlighted in cell culture, animal, and clinical studies. These micronutrients are employed not only as active compounds in therapeutic agents for treating certain skin diseases, but also as ingredients in cosmetic products. Here, the author describes the barrier function of the skin and the general nutritional requirements for skin health. The goal of this review is to discuss the potential roles and current knowledge of selected micronutrients in skin health and function.

Key Words: Skin disease, Skin function, Micronutrient, Therapeutic agent, Cosmetic ingredient

INTRODUCTION

The skin is composed of two primary layers, epidermis and dermis (Fig. 1), and each layer exhibits unique structural and physiological functions (Bouwstra *et al.*, 2006; Thangapazham *et al.*, 2014). Because the epidermis directly faces the external environment, including factors such as UV irradiation, pathogens, and toxic insults, it primarily functions as a barrier (Elias and Feingold, 2006). The dermis that is located below the epidermis contains nerves, blood vessels, connective tissues, hair follicle, and fibroblasts which are required for not only the maintenance of the structural foundation of the skin, but also for provision of important biological functions (Bouwstra *et al.*, 2006; Thangapazham *et al.*, 2014).

Nutritional status, dependent on both macro and micronutrients, is vital for skin health (Boelsma *et al.*, 2003; Lakdawala *et al.*, 2013). Proper nutritional intake complements endogenous factors in regulating skin barrier function (Boelsma *et al.*, 2003; Lakdawala *et al.*, 2013). Notable examples of nutrients are calcium and vitamin C, which are responsible for the differentiation of keratinocytes, a major cell type in epidermis (Bikle *et al.*, 2001; Uchida *et al.*, 2001). A decrease in nutritional status can alter the structural and biological function of skin, resulting in skin abnormalities, including dry skin (Boelsma *et al.*, 2003; Cosgrove *et al.*, 2007; Lakdawala *et al.*, 2013).

et al., 2003; Cosgrove *et al.*, 2007; Lakdawala *et al.*, 2013).

In this review paper, the author will describe briefly various functions of the epidermal barrier with a focus on the role of selected micronutrients in maintaining skin integrity.

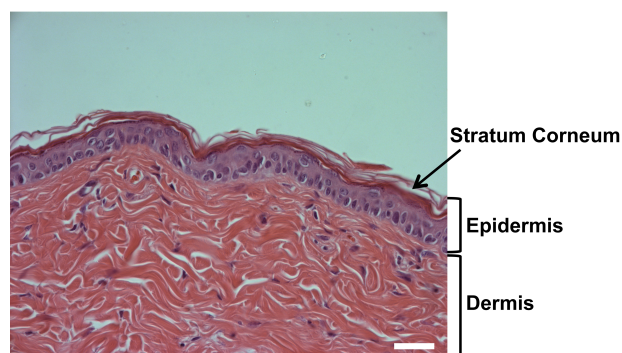


Fig. 1. Structure of mammalian skin. Intact skin of mouse was subjected to hematoxylin and eosin (H&E)-staining. The skin consists of two primary layers, epidermis and dermis. The outermost layer of epidermis is the stratum corneum. Scale bar, 20 μ m.

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Table 1. Cutaneous barrier functions

Barrier	Roles	Effectors
Permeability	Prevents excess water loss, harmful chemicals, allergens, and microbial pathogens; Maintains body temperature	Components of skin structure
Antimicrobial	Protects against multiple pathogens, e.g. Gram-positive and Gram-negative bacteria, fungi, and some viruses	Acidic pH (<5.5); Sphingoid bases; Innate immune elements, including antimicrobial peptides
Antioxidant	Protects skin from oxidative stress	α - γ -tocopherol Vitamin C and E Certain flavonoids
UV	Protects skin from UV light-mediated DNA damage, and oxidative stress	Urocanic acid Structure components, including sphingolipids

SKIN BARRIER FUNCTION

Skin deploys multiple barrier functions; *i.e.*, permeability- (Elias and Friend, 1975), antimicrobial- (Elias, 2007), antioxidant- (Thiele *et al.*, 2001), and UV-barrier (Thiele *et al.*, 2001) (Table 1), to protect our bodies from external perturbants. The permeability barrier prevents loss of excess water from nucleated layers of epidermis and penetration of harmful chemicals, allergens, and pathogens into the epidermis (Elias and Friend, 1975). Of the multiple factors that contribute to the maintenance/improvement of the permeability barrier, a well-known cutaneous lipid, ceramide, serves as a key constituent in epidermal membrane (Uchida and Hamanaka, 2006). Since maintenance of skin pH below 5.5 is vital for suppressing virulent microbial pathogen growth, including *Staphylococcus aureus*, skin acidification is essential in enhancing the antimicrobial barrier (Elias, 2007). In addition to acidification, antimicrobial barrier function can be improved by the action of antimicrobial peptides, which are expressed in epidermal keratinocytes to kill invaded microbial pathogens (Park *et al.*, 2011; Park *et al.*, 2013b). A number of antioxidant chemicals, including vitamin C, are present in the skin (Thiele *et al.*, 2001). These antioxidants maintain skin homeostasis; *i.e.*, protection of proteins/lipids from oxidation (Tyrrell and Keyse, 1990; Thiele *et al.*, 2001). The influence of UV irradiation depends upon the structure of cellular components. Urocanic acid, which is generated from histidine in skin, is a potent, endogenous UV absorbent (Barresi *et al.*, 2011). In addition, exogenous nutrients, such as α -tocopherol, β -carotene, lycopene, and lutein, could contribute to forming the UV barrier *via* enzymatic and non-enzymatic mechanisms (Thiele, 2001; Eichler *et al.*, 2002; Larsson *et al.*, 2006; Evans and Johnson, 2010).

GENERAL NUTRITION REQUIREMENTS FOR SKIN HEALTH

Glucose is the primary source of energy for most mammalian cells, including keratinocytes (Spravchikov *et al.*, 2001). It provides the carbohydrate backbone for glycosylation of proteins/lipids that comprise the extracellular environment of the skin, suggesting that altered levels of glucose in skin may cause structural changes and abnormal barrier functions (Halprin and Ohkawara, 1966; Van Hattem *et al.*, 2008). High glu-

cose concentration has been reported to increase proliferation in MCF-7 breast cancer cells (Yamamoto *et al.*, 1999), renal cortical fibroblasts (Han *et al.*, 1999), and SV40 transformed human corneal epithelium (McDermott *et al.*, 1998). However, high glucose also has been shown to inhibit proliferation in epidermal keratinocytes (Spravchikov *et al.*, 2001) and dermal fibroblasts (Hehenberger *et al.*, 1998) (Table 2), suggesting that a role for glucose in regulation of cellular proliferation appears to be cell/tissue specific. In studies conducted to evaluate the effects of glucose on differentiation, high levels of glucose significantly enhanced calcium-induced keratinocyte differentiation, while their proliferation was obviously inhibited (Spravchikov *et al.*, 2001) (Table 2). Because a well-balanced proliferation and differentiation process is one of the critical steps in wound healing, high glucose levels might contribute to impaired wound healing in certain diseases, including diabetes (Spravchikov *et al.*, 2001).

UV irradiation has been suggested as a potent force in skin aging (see details in Vitamin C section) (Takema *et al.*, 1996). Collagen is a major constituent of dermis and is necessary to maintain skin structure (Takema *et al.*, 1996); and exposure to excess UV irradiation dramatically decreases dermal collagen content, resulting in skin aging or delayed wound healing (Takema *et al.*, 1996). Several amino acids have been shown to prevent skin aging by their stimulation of dermal collagen synthesis. Proline and its precursors, glutamate, significantly increase collagen synthesis in human dermal fibroblasts (Karna *et al.*, 2001) (Table 2). While nitric oxide (NO) generated by dermal fibroblasts induces collagen synthesis, some amino acids, *e.g.*, arginine (Stechmiller *et al.*, 2005), ornithine (Shi *et al.*, 2002), and amino acid mixtures from *Mytilus galloprovincialis* and *Rapana venosa* extracts (Badiu *et al.*, 2010), accelerate wound healing *via* increased dermal collagen produced by iNOS/NO-dependent mechanisms (Table 2). Moreover, recent studies suggest that dietary silk protein, sericin, improves epidermal hydration in parallel with increased levels of filaggrin in an animal model of atopic dermatitis (AD) (Kim *et al.*, 2012) (Table 2). These results indicate that amino acids not only protect skin against UV irradiation-mediated damages, including skin aging and delayed wound healing, but amino acid supplements might be useful for treatment of certain skin diseases such as AD.

Major epidermal lipids consist of ceramide, cholesterol, and fatty acids (Uchida and Hamanaka, 2006; Uchida, 2014). Par-

Table 2. Role of macronutrients in skin health and function

Macronutrient	Function	Mechanism	Reference
Glucose			
High concentration	↓ Wound healing	↑ Keratinocyte (KC) differentiation ↓ Proliferation in KC and Fibroblast (FB)	Spravchikov <i>et al.</i> , 2001 Hehenberger <i>et al.</i> , 1998
Amino Acid			
Proline	Protect against UV irradiation-induced skin aging	↑ Collagen synthesis in FB	Karna <i>et al.</i> , 2001
Glutamate			
Arginine	↑ Wound healing	↑ NO production → ↑ Collagen synthesis in FB	Stechmiller <i>et al.</i> , 2005
Ornithine			Shi <i>et al.</i> , 2002
Mixtures from (<i>Mytilus galloprovincialis</i> & <i>Rapana venosa</i>)			Badiu <i>et al.</i> , 2010
Silk protein (sericin)	Improves AD	↑ Filaggrin ↓ TEWL	Kim <i>et al.</i> , 2012
Lipid			
Ceramide	↑ Epidermal Permeability	Serve as a key constituent in epidermal membrane	Uchida, 2014
Cholesterol	Barrier		
Fatty acids			
Ceramide (toxic levels)	↑ Apoptosis	High dose UVB → ↑↑ Ceramide → Caspase-independent mechanism	Uchida <i>et al.</i> , 2010
Ceramide (Subtoxic levels)	↓ Apoptosis	Low dose UVB → ↑ Ceramide → ↑ non-apoptotic metabolites (e.g., Sphingosine-1-Phosphate)	
Sphingosine-1-Phosphate	↑ Innate immunity	NF-κB activation → ↑ Cathelicidin	Park <i>et al.</i> , 2013
Ceramide-1-Phosphate	↑ Innate immunity	STAT1/3 activation → ↑ β-defensin2/3	Kim <i>et al.</i> , 2014

ticularly, ceramide is a key lipid constituent of the epidermal permeability barrier in the extracellular domain of the stratum corneum (Uchida and Hamanaka, 2006; Uchida, 2014) (Table 2). Ceramide and its metabolites also provide signaling roles in modulating multiple cellular functions, e.g., proliferation, differentiation, and apoptosis in epidermal keratinocytes (Uchida and Hamanaka, 2006; Uchida, 2014). While cellular ceramide production is increased in keratinocytes following UV irradiation, high doses (toxic level) of UVB irradiation induce cell apoptosis/death (Uchida *et al.*, 2010). Whereas, subtoxic levels of ceramide, induced by low dose of UVB irradiation, could be restored to normal levels due to its metabolic conversion into non-apoptotic ceramide metabolites, which contribute to protecting cells against ceramide-induced apoptosis (Uchida *et al.*, 2010) (Table 2). In addition, previous studies showed that decreases in ceramide levels occur in certain skin diseases associated with permeability barrier abnormality; i.e., atopic dermatitis and psoriasis (Yamamoto *et al.*, 1991; Motta *et al.*, 1994). Moreover, our recent studies demonstrated that the key ceramide metabolites, ceramide-1-phosphate and sphingosine-1-phosphate, produced in human keratinocytes in response to subtoxic levels of endoplasmic reticulum (ER) stress stimulate production of major epidermal innate immune elements (beta-defensins and cathelicidin antimicrobial peptide) via STAT1/3- or NF-κB-dependent mechanisms, respectively (Park *et al.*, 2013a; Kim *et al.*, 2014) (Table 2).

IMPORTANCE OF KEY MICRONUTRIENTS IN MAINTAINING SKIN HEALTH

Since Dr. James Lind described the importance of vitamin C in the maintenance of skin health (Bartholomew, 2002), other investigators have studied skin abnormalities/diseases due to vitamin deficiencies, such as scurvy and pellagra, which can be corrected with appropriate oral and/or topical vitamin supplementation.

Vitamin A

Vitamin A is a group of unsaturated nutritional organic compounds. Vitamin A and its derivatives, e.g., retinoids and carotenoids, play an important role in regulating proliferation, differentiation, and apoptosis of different cell types, including skin cells (Elias *et al.*, 1981; Goodman, 1984; Lee *et al.*, 2009). Retinoids are mostly found in animal sources, whereas provitamin A carotenoids, including β-carotene, are found in plant products (Goodman, 1984). While the beneficial effects of carotenoids are thought to be due to their role as antioxidants, carotenoids first need to be converted to retinoid forms to provide physiological functionalities in skin (Johnson, 2002). Retinoids mainly mediate their function via nuclear hormone receptors (Fig. 2): the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs), each with three isotypes (α, β, and γ) (Elder *et al.*, 1991; Gann *et al.*, 1996). These receptors form heterodimers (RAR/RXR) or homodimers (RXR/RXR) after activation by selective retinoids. These dimers bind consensus DNA regions (called retinoic acid response elements [RARE] or retinoid X response elements [RXRE]), located in

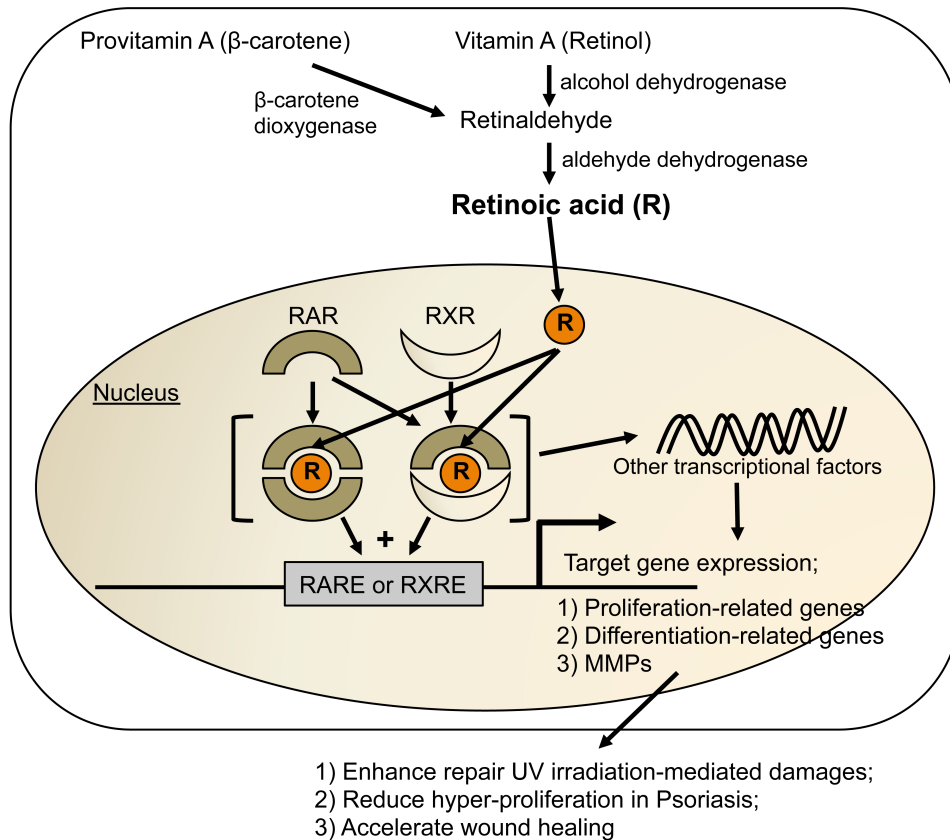


Fig. 2. Signaling of vitamin A to alter cellular functions in epidermal keratinocytes and dermal fibroblasts. RAR, retinoic acid receptor; RXR, retinoid X receptor; RARE, retinoic acid response element; RXRE, retinoid X response element; MMPs, matrix metalloproteinases.

Table 3. Role of key micronutrients in skin health and function

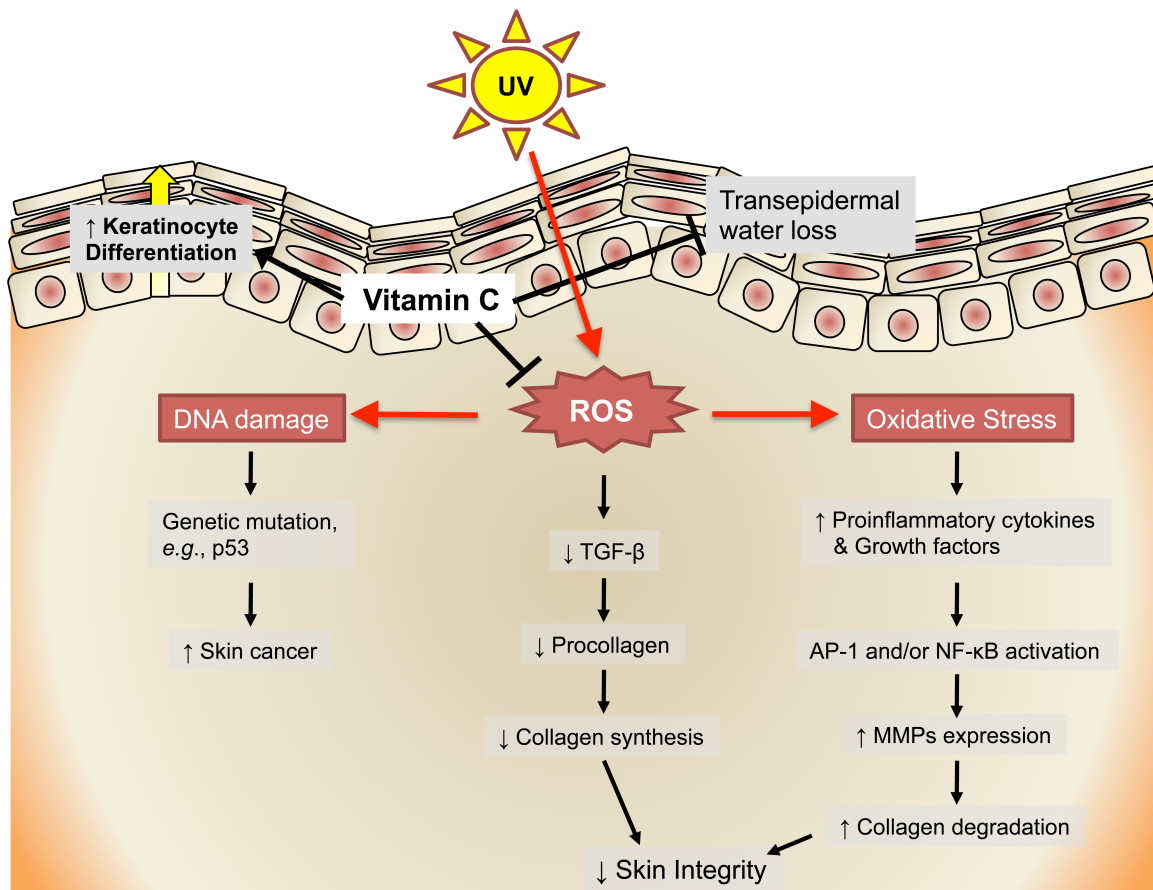
Micronutrients	Roles
Vitamin A	<ul style="list-style-type: none"> • Modulates proliferation of epidermal keratinocytes and dermal fibroblasts (Varani <i>et al.</i>, 1994); • Prevents UV irradiation-mediated skin damage (Fisher <i>et al.</i>, 1997); • Useful for the prevention and treatment of psoriasis (Jean <i>et al.</i>, 2011; van de Kerkhof, 2006), ichthyosis (van Steensel, 2007), skin cancer (Niles, 2002), and acne (Kligman, 1997)
Vitamin C	<ul style="list-style-type: none"> • Suppresses UV irradiation-triggered production of free radicals, protecting cells from oxidative stress (McArdle <i>et al.</i>, 2002); • Attenuates UV irradiation-mediated damages in the skin (McArdle <i>et al.</i>, 2002; Stewart <i>et al.</i>, 1996); • Promotes cutaneous wound healing (Fisher <i>et al.</i>, 1996); • Increases epidermal moisture content, improving skin hydration (Campos <i>et al.</i>, 2008)
Vitamin D	<ul style="list-style-type: none"> • Improve innate immunity (through stimulation of cathelicidin antimicrobial peptide production) (Gombart <i>et al.</i>, 2005); • Modulates inflammation, angiogenesis, wound healing (Frohm <i>et al.</i>, 1997; Koczulla <i>et al.</i>, 2003)
Vitamin E	<ul style="list-style-type: none"> • Suppresses lipid peroxidation (Lopez-Torres <i>et al.</i>, 1998); • Modulates photoaging (Bissett <i>et al.</i>, 1990; Jurkiewicz <i>et al.</i>, 1995) and photocarcinogenesis (Burke <i>et al.</i>, 2000); • Exhibits anti-inflammatory roles (Meydani <i>et al.</i>, 1990; Wu <i>et al.</i>, 2008)
Zinc	<ul style="list-style-type: none"> • Protects from photodamage (Mitchnick <i>et al.</i>, 1999); • Exhibits antimicrobial activity (Mitchnick <i>et al.</i>, 1999);
Copper	<ul style="list-style-type: none"> • Serves as an antioxidant (Pickart <i>et al.</i>, 2012); • Stimulates the maturation of collagen (Pickart, 2008) • Modulates melanin synthesis (Menkes, 1988)
Selenium	<ul style="list-style-type: none"> • Protect skin from UV irradiation-induced oxidative stress (Balagopalakrishna <i>et al.</i>, 1997; Rafferty <i>et al.</i>, 1998); • Useful for the prevention and treatment of psoriasis (Juhlin <i>et al.</i>, 1982)

Table 4. Skin disorders associated with micronutrient deficiencies

Deficiency	Skin disorders
Vitamin A	Atopic dermatitis (Mihaly <i>et al.</i> , 2011); Delayed wound healing (Hunt, 1986)
Vitamin C	Thickening of the stratum corneum, subcutaneous bleeding and delayed wound healing in scurvy (Hodges <i>et al.</i> , 1971)
Vitamin D	Atopic dermatitis (Mesquita Kde <i>et al.</i> , 2013; Peroni <i>et al.</i> , 2011)
Vitamin E	Skin ulcerations (Machlin <i>et al.</i> , 1977); Changes in skin collagen cross-linking (Igarashi <i>et al.</i> , 1989)
Zinc	Epidermolysis bullosa (Fine <i>et al.</i> , 1989); Atopic dermatitis (Ewing <i>et al.</i> , 1991)
Copper	Steely-hair syndrome (Menkes, 1988)
Selenium	Psoriasis (Juhlin <i>et al.</i> , 1982; Naziroglu <i>et al.</i> , 2012); Epidermolysis bullosa (Fine <i>et al.</i> , 2008); Certain skin cancer (McKenzie, 2000)

the promoter of target genes, which mediate transcriptional regulation (Njar *et al.*, 2006). Since epidermal keratinocytes and dermal fibroblasts express both retinoid receptors (Elder *et al.*, 1991), skin is considered as one of the major retinoid-responsive tissues. Retinoids exert effects in the skin through multiple mechanisms (Fig. 2): 1) regulating expression of epidermal structural and functional genes *via* direct binding to RARs and/or RXRs (Tomic-Canic *et al.*, 1996; Radoja *et al.*, 1997); 2) modulating skin-related genes by interfering with the signaling of other transcriptional factors after receptor binding (Lee *et al.*, 2005). Previous investigations have shown that retinoids could enhance repair of UV irradiation-damaged

skin *via* following mechanisms (Table 3); *i.e.*, 1) their ability to increase proliferation of epidermal keratinocytes and dermal fibroblasts (Varani *et al.*, 1994); 2) inhibiting the expression of matrix metalloproteinases (MMPs), matrix-degrading enzymes, leading to increased overall protein and extracellular matrix content (Fisher *et al.*, 1997). In contrast, another studies demonstrated that retinoids modulate epidermal proliferation with anti-proliferative potential in hyper-proliferative skin such as psoriasis (van de Kerkhof, 2006; Jean *et al.*, 2011). Hence, the role of retinoids in regulation of epidermal proliferation may be disease/stress specific (normal skin vs. psoriasis) and/or different expression profiles of unknown cofactors

**Fig. 3.** Vitamin C attenuates UV irradiation-mediated damages in Skin. AP-1, activation protein-1; MMPs, matrix metalloproteinases.

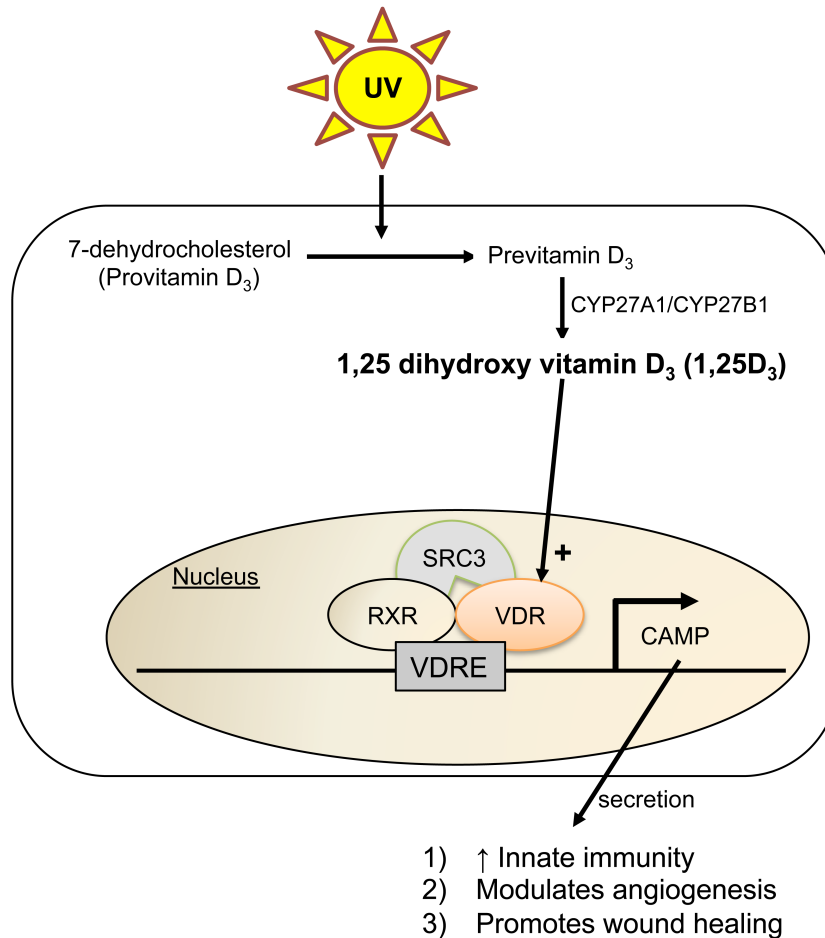


Fig. 4. Vitamin D modulates innate immunity, angiogenesis, and wound healing in skin *via* VDR-dependent mechanism. CAMP, cathelicidin antimicrobial peptide; VDR, vitamin D receptor; RXR, retinoid X receptor; VDRE, vitamin D response element.

required for biological action of retinoids. Moreover, retinoids also have significant potential in the prevention and treatment of other skin diseases, such as ichthyosis (van Steensel, 2007), skin cancer (Niles, 2002), and acne (Kligman, 1997). In particular, topical all-trans-retinoic acid is a safe and effective treatment for mild to moderate acne, while oral 13-cis-retinoic acid (isotretinoin) is used to treat severe acne that is resistant to topical therapies (Kligman, 1997; Verfaillie *et al.*, 2008). More recent results from clinical studies showed the significantly decreased retinoid concentration and dysregulated retinoid-signaling pathway in the skin of patients with atopic dermatitis (AD) (Mihaly *et al.*, 2011) (Table 4), suggesting that abnormal retinoid activity might contribute to pathogenesis of AD. Vitamin A deficiency is also associated with delayed wound healing (Hunt, 1986) (Table 4). However, prolonged topical/oral treatment with vitamin A can cause unwanted side effects, such as retinoid dermatitis that is characterized by erythema, dryness, scaling, pruritus, and variable degrees of irritation (Voorhees, 1990; Mukherjee *et al.*, 2006).

Vitamin C

Exposure to excess UV irradiation induces oxidative stress, impacting the genetic integrity of a living organism, including the skin (Chen *et al.*, 2012). While UVB (wavelengths 280-310

nm) directly damages DNA, UVA (320-400 nm) causes indirect DNA mutations by generating reactive oxygen species (ROS) such as superoxide anion and hydrogen peroxide (Double *et al.*, 2002; Chen *et al.*, 2012) (Fig. 3). Excessive exposure to UV irradiation is associated with photoaging and the development of skin cancer (Chen *et al.*, 2012). UV irradiation triggers the production of pro-inflammatory cytokines and growth factors (Chen *et al.*, 2012). These mediators increase expression of MMPs (MMP-1, -3, -8 and -9) *via* either activation protein-1 (AP-1) and/or NF-κB activation, resulting in degraded collagen and elastin in the skin (Sardy, 2009; Chen *et al.*, 2012) (Fig. 3). Moreover, UV irradiation-induced ROS have been shown to suppress expression of transforming growth factor (TGF)-β, which is a signaling mediator to promote collagen formation (Walraven *et al.*, 2014) (Fig. 3). These results indicate that an increase in production of ROS following exposure to UV irradiation could degrade the structural integrity of skin by altering the collagen and elastin components in the dermis, causing skin aging characterized by deep wrinkles, coarse textures, telangiectasia, and pigmentation. In addition, UV irradiation-induced ROS have been suggested as a mutagen in certain skin cancer; *e.g.*, squamous cell carcinoma (SCC) (Halliday, 2005). ROS induces mutation of p53 gene, driving precursor lesions to malignancy (Halliday, 2005). But the mechanistic

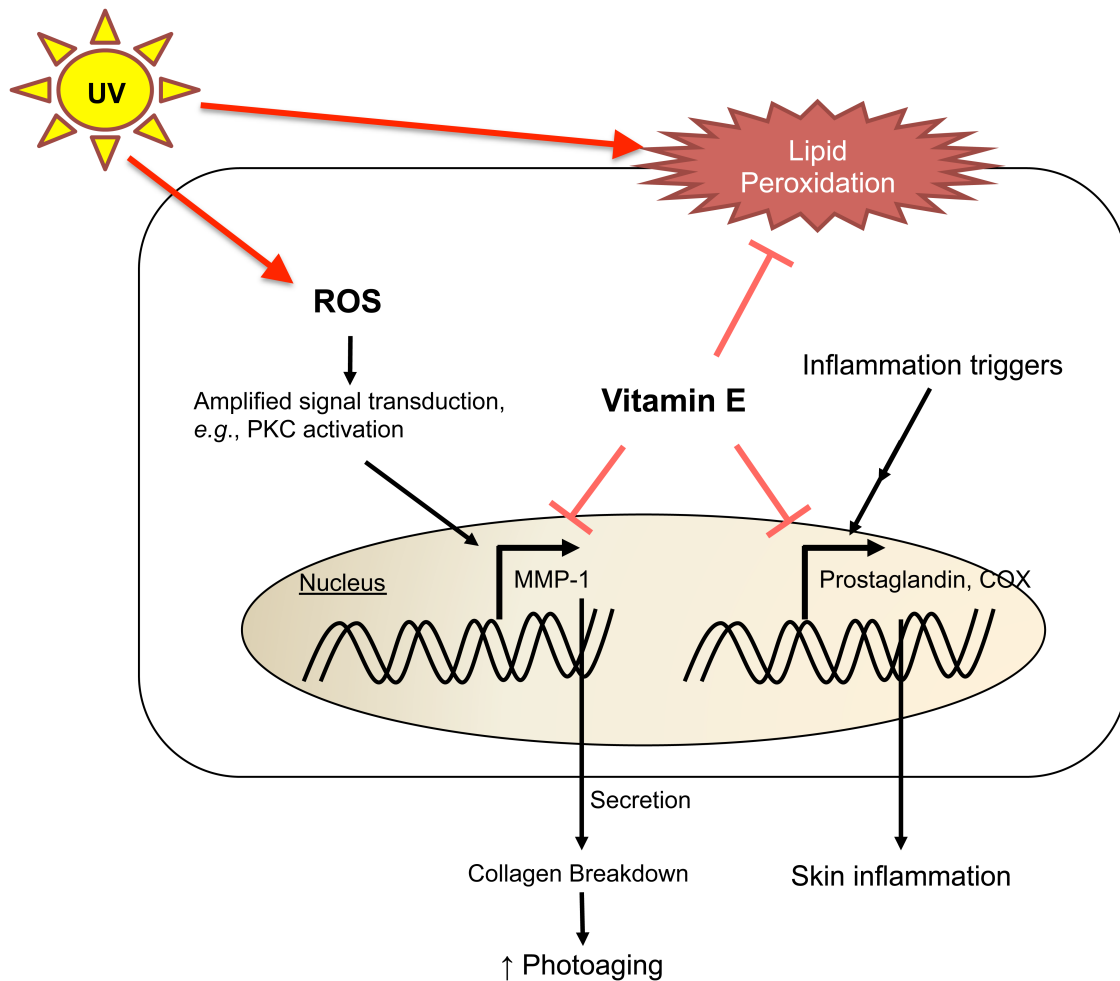


Fig. 5. Vitamin E protects skin from photoaging and inflammation. MMP-1, matrix metalloproteinase-1; PKC, protein kinase C.

connection between ROS and SCC is still unclear. In this regard, vitamin C is a water-soluble, powerful antioxidant that has been shown to attenuate UV irradiation-mediated damages in the skin (Stewart *et al.*, 1996; McArdle *et al.*, 2002). Vitamin C significantly suppresses the UV light-triggered production of free radicals, protecting cells from oxidative stress (McArdle *et al.*, 2002) (Fig. 3). It has an additional role in wound healing by increasing pro-collagen and collagen synthesis (Peterkofsky, 1991; Fisher *et al.*, 1996), which stimulate the formation of the skin barrier (Table 3). In efficacy studies on human skin, vitamin C significantly increased epidermal moisture content, improving skin hydration (Campos *et al.*, 2008) (Table 3). As noted earlier, scurvy is a disease caused by lack of vitamin C. Symptoms of scurvy in the skin include a thickening of the stratum corneum and spots of small subcutaneous bleeding (Hodges *et al.*, 1971). In addition, cutaneous wound healing is delayed due to the scurvy-mediated decrease in mature collagen (Ross and Benditt, 1962) (Table 4).

Vitamin D

Vitamin D is synthesized from 7-dehydrocholesterol by two key enzymes, 25-hydroxylase (CYP27A1) and 25-hydroxyvitamin D₃ 1- α -hydroxylase (CYP27B1), in human skin follow-

ing UVB irradiation (Bikle *et al.*, 2004; Park *et al.*, 2013b). Combined activity of both enzymes is critical in forming active vitamin D, 1,25 dihydroxy vitamin D₃ (1,25D₃). In particular, CYP27B1, which is expressed in keratinocytes, is under the control of signals that occur in bacterial infection or injury (Bikle *et al.*, 2004; Bikle *et al.*, 2010). Activated 1,25D₃ binds to the vitamin D receptor (VDR) to recruit transcriptional co-activator proteins such as steroid receptor coactivator (SRC) 3 (Bikle *et al.*, 2007; Bikle *et al.*, 2010) (Fig. 4). A primary biological role of 1,25D₃ in skin is the stimulation of antimicrobial defense through increasing levels of cathelicidin antimicrobial peptide (CAMP), an innate immune element (Gombart *et al.*, 2005) (Fig. 4). In both cell culture and animal systems, treatment with 1,25D₃ significantly increases CAMP expression *via* VDR-dependent mechanism, stimulating innate immunity (Gombart *et al.*, 2005) (Table 3). In addition to antimicrobial activity, vitamin D₃ significantly inhibits the proliferation of keratinocytes (Bikle, 1995). As such, topical treatment with 1,25D₃ has been used to treat skin diseases linked to hyperproliferation of keratinocytes, including psoriasis (Abramovits, 2009) (Table 3). Vitamin D appears to modulate inflammation, angiogenesis, and wound healing through regulation of CAMP production (Frohm *et al.*, 1997; Koczulla *et al.*, 2003). More-

over, recent studies have shown significantly lower levels of vitamin D in patients with mild AD compared with those with moderate or severe AD, indicating that vitamin D deficiency might be related to the severity of AD (Peroni *et al.*, 2011; Mesquita Kde *et al.*, 2013) (Table 4).

Vitamin E

Vitamin E is a lipid-soluble, membrane-bound antioxidant in multiple tissues (Burke, 2007). Since the level of vitamin E can be depleted even after exposure to a single dose of UV irradiation, it is a sensitive oxidative stress maker in human skin (Thiele *et al.*, 1998). A number of studies have shown that vitamin E treatment modulates UV irradiation-mediated free radical damages in skin; *e.g.*, lipid peroxidation (Lopez-Torres *et al.*, 1998), photoaging (Bissett *et al.*, 1990; Jurkiewicz *et al.*, 1995), immunosuppression (Steenvoorden and Beijersbergen van Henegouwen, 1999), and photocarcinogenesis (Burke *et al.*, 2000). Vitamin E significantly suppresses collagen breakdown by inhibiting MMP-1 expression (Ricciarelli *et al.*, 1999) (Fig. 5). Interestingly, topical application of vitamins C (15%) with E (1%) showed a synergistic protective effect from UV irradiation-induced erythema, compared with either vitamin alone (Lin *et al.*, 2003). In addition to antioxidant properties, vitamin E could downregulate features of skin inflammation; *i.e.*, attenuating production of inflammatory prostaglandin, pro-inflammatory cytokines, cyclooxygenase-2, and NADPH oxidase (Meydani *et al.*, 1990; Wu *et al.*, 2008), suggesting the use of vitamin E as an anti-inflammatory agent in skin (Fig. 5 and Table 3). Vitamin E deficiency in animal has been reported to cause skin ulcerations (Machlin *et al.*, 1977) and changes in skin collagen cross-linking (Igarashi *et al.*, 1989) (Table 4).

Minerals

Minerals, including zinc, copper, and selenium, also have an important role in maintaining skin health. Zinc is an essential cofactor of numerous metalloenzymes. Its main function is to protect the skin against photodamage by absorbing UV irradiation, limiting penetration of radiation into skin (Mitchnick *et al.*, 1999). Co-treatment with zinc and vitamin C exhibits antimicrobial activity that helps to clear bacteria in acne (Mitchnick *et al.*, 1999) (Table 3). Moreover, zinc deficiency has been reported in patients with epidermolysis bullosa (Fine *et al.*, 1989) (Table 4). Although patient with AD also showed a significant decreased level of zinc, zinc supplementation does not result in clinical improvement of AD (Ewing *et al.*, 1991) (Table 4).

Like zinc and vitamins C and E, copper with peptides also serves as an antioxidant, protecting skin from damage that is caused by an UV light-induced increase in free radical levels (Pickart *et al.*, 2012). Furthermore, copper is known to stimulate the maturation of collagen, thus is critical in improving skin elasticity and thickness (Pickart, 2008) (Table 3). While it also plays a role in melanin synthesis enables pigmentation of skin and hair, steely-hair syndrome (white and silver hair) is a severe multisystemic disease caused by copper deficiency/abnormal copper metabolism (Menkes, 1988) (Table 4).

Lastly, selenium protects the skin from UV irradiation-induced oxidative stress by stimulating the activities of the selenium-dependent antioxidant enzymes, glutathione peroxidase and thioredoxin reductase, that are present in the plasma membrane of epidermal keratinocytes (Balagopalakrishna *et al.*, 1997; Rafferty *et al.*, 1998). Selenium also has been

considered for treatment of psoriasis, which shows decreased glutathione peroxidase levels (Juhlin *et al.*, 1982; Naziroglu *et al.*, 2012). Results from human studies showed that selenium supplementation lead to an increase in levels of glutathione peroxidase in patients with psoriasis, resulting in disease improvement (Juhlin *et al.*, 1982) (Table 3). Since selenium deficiency has been detected in patients with recessive dystrophic epidermolysis bullosa, the level of selenium is one marker in this disease (Fine *et al.*, 2008) (Table 4). Moreover, its deficiency is associated with an increased risk of skin cancer (McKenzie, 2000) (Table 4).

CONCLUSIONS

Micronutrients, including vitamins and minerals, are not only essential components of skin structure, but they also modulate multiple biological functions. Although the importance of these micronutrients has been widely characterized, therapeutics utilizing such nutrients have been limited to antioxidants and stimulating wound healing. Like findings which show the novel role of vitamin D in stimulating a major epidermal antimicrobial peptide, cathelicidin, thus stimulating innate immunity (Gombart *et al.*, 2005), further studies are required to better understand previously-undefined roles of micronutrients in order to develop potential therapeutic agents and/or cosmetic products to treat skin diseases and improve barrier function.

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