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Aging of the skin barrier

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Abstract The skin barrier is mainly present in the stratum corneum (SC), composed of corneocytes surrounded by intercellular lipid lamellae, and attached by corneodesmosome. The tight junction attached to the lateral walls of keratinocytes in the upper part of the stratum granulosum is also included in the skin barrier. During aging, the following structures and functions of the skin barrier are changed or disturbed: (1) skin barrier structure, (2) permeability barrier function, (3) epidermal calcium gradient, (4) epidermal lipid synthesis and SC lipid processing, (5) cytokine production and response after insults, (6) SC acidity, (7) SC hydration, and (8) antimicrobial barrier. Patients with diabetes also show changes in the skin barrier similar to those in aged skin, and the characteristics of the skin barrier are very similar. Understanding the pathogenic mechanisms of the skin barrier in aging will permit us to develop therapeutic strategies for aged or diabetic skin.

Skin barrier structural changes with aging

A basic concept of the skin barrier has been developed after an introduction of the two-compartment organization, such as the "bricks and mortar" model.[1] The skin barrier mainly resides in the stratum corneum (SC), composed of corneocytes ("the bricks"), surrounded by intercellular lipid lamellae ("the mortar"), and attached by corneodesmosome (CD) ("the rivets"). Recently, the tight junction (TJ) attached to lateral walls of keratinocytes in the upper part of the stratum granulosum (SG) was included in the skin barrier. Corneocytes contribute to structural stability and elasticity due to their main composition, mainly keratin fibrils. The SC intercellular lipids, composed of ceramides, cholesterol, and free fatty acids, function as a blocker of transepidermal water loss (TEWL) and barrier to transcutaneous penetration of external harmful agents.[2] Keratin filaments occupy 80% to 90% of the corneocytes and form the macrofibrils by crosslinking with the cornified envelope (CE) of the corneocytes. The SC lipid layer is covalently attached to the external surface of the CE proteins of fully differentiated corneocytes. This cornified lipid envelop (CLE) consisted of ω-hydroxyceramide covalently attached to CE proteins such as involucrin.[3] The ω-hydroxyl group on the ceramides is required for CLE formation[4]; thus, the CE is an effective physical and water impermeable barrier. TJ proteins, the major regulators of barrier function in simple epithelium, were identified in the human skin.[5] TJs localize in the SG[6] and contribute to epidermal barrier formation (Figure 1).

Structural changes in aged skin resulted from combined and cumulative effects of intrinsic and extrinsic aging.[7] Skin aging has been divided into intrinsic and extrinsic. Intrinsic aging (chronologic aging) presents functional rather than morphologic changes. Extrinsic aging (photoaging) presents structural and physiologic changes due to chronic sun exposure.

In aged epidermis, the number of SC layers is significantly increased compared with that in younger skin. The epidermis

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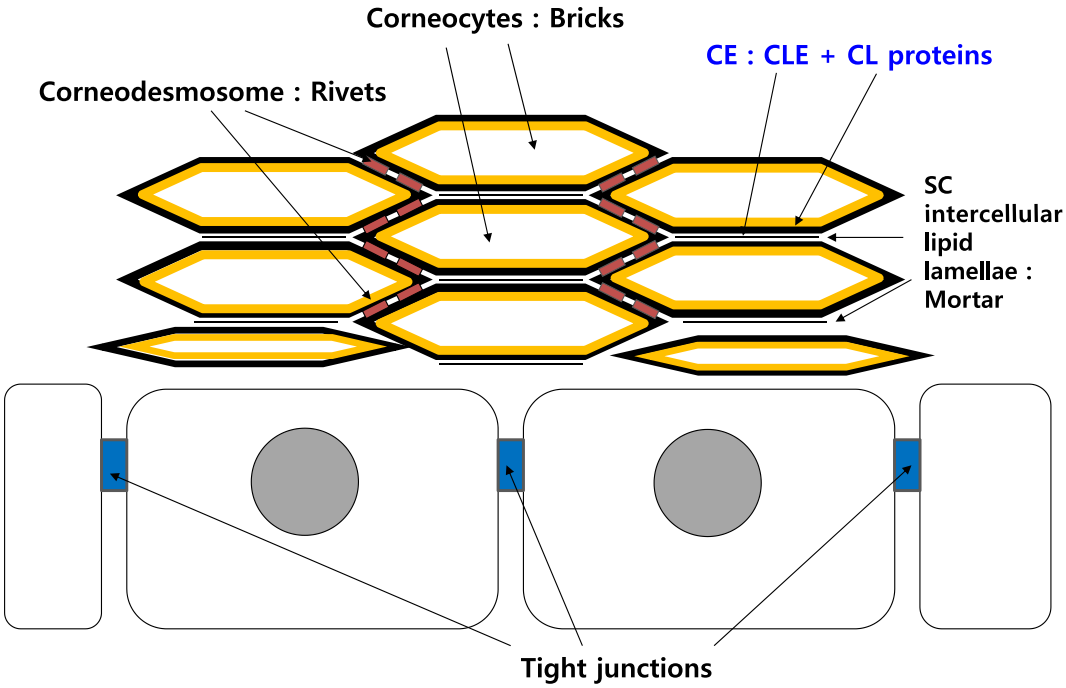

Fig. 1 Basic structure of the skin barrier. The skin barrier mainly resides in the stratum corneum (SC) composed of corneocytes (the bricks) surrounded by intercellular lipid lamellae (the mortar) and attached by corneodesmosome (CD) (the rivets). Recently, the tight junction (TJ) attaching to lateral walls of keratinocytes in the upper stratum granulosum (SG) was included in the basic skin barrier structure. Keratin filaments form the macrofibrils by crosslinking with the cornified envelope (CE) of the corneocytes. The SC lipid layer is covalently attached to the external surface of the CE proteins of fully differentiated corneocytes, which forms the cornified lipid envelop (CLE).

shows remarkable structural changes with aging, which include epidermal thinning, flattening of the rete ridges, and orthokeratosis. A photoaged epidermis presents more disorganized cellular maturation with some cytologic atypia, a significant decrease in Langerhans cells, and an uneven distribution of melanocytes in the basal layer.[8] Individual keratohyalin granules are much smaller and more broadly distributed throughout the SG cells with aging. An aged epidermis shows various changes that imply skin barrier impairment, such as increased transdermal drug delivery, increased sensitivity to irritants, aggravation of xerosis, and development of pruritus.[7,9] In aged skin, TJ components such as claudin-1 and occludin are also decreased.[10]

Changes in skin barrier function with aging

In humans, significant anatomic variability was noted for basal TEWL, SC hydration, skin surface pH, and sebum content in aged skin as well as in young skin. Among all measured factors, only basal TEWL was significantly lower in the aged group compared with that in the young group. Comparing men and women volunteers, none of the four factors showed significant differences.[11] The epidermal permeability barrier function, as assessed by TEWL rates, is normal or even supernormal under basal condition in aged skin, presumably due to a decrease in sweating and microcirculation or an increase in corneocyte cell surface area; however, its functional problems are revealed only after an insult. SC integrity is impaired, and the barrier recovery after acute perturbation with tape stripping is delayed. The time required to reconstitute competent SC is more than double in the elderly population. The aged skin barrier is disrupted more easily and repaired more slowly compared with the young skin barrier. These defects mainly originate from an overall deficiency in all key epidermal lipids (especially cholesterol), focal decrease in SC intercellular lamellae, and diminished lamellar body (LB) secretion (Figure 2).[12,13]

Whereas these alterations are detectable in chronologically aged skin, they are further aggravated in the human skin with superimposed photoaging.[8] The effects of ultraviolet B (UVB) wave on both epidermal barrier function and proliferation with chronologic aging showed that a single UVB exposure (7.5 minimal erythema dose) promoted the development of a barrier abnormality (increased TEWL) and DNA synthesis, which were significantly diminished in intrinsically aged versus young mouse epidermis. The transient barrier abnormality at 2 to 3 days after UVB exposure is attenuated in aged skin compared with young skin, presumably as a result of a decreased mitogenic response.[14]

Epidermal calcium gradient is disrupted in aged skin

Epidermal calcium gradient in normal and young skin is characterized by low calcium ion levels in both the basal

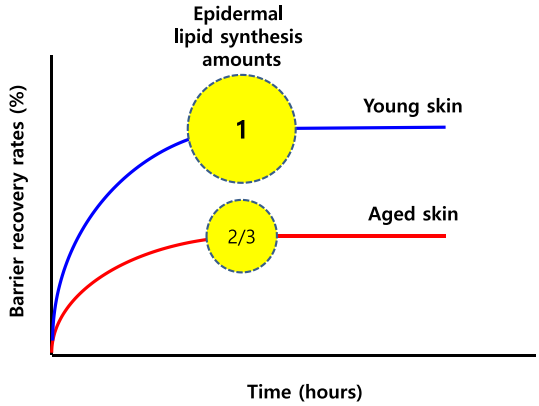

Fig. 2 Recovery rate after acute barrier perturbation is delayed in aged skin. Functional problems of aged skin barrier are revealed only after an insult. Barrier recovery after acute perturbation, such as tape stripping, is delayed in aged skin compared with that in young skin. That is, the aged skin barrier is disrupted more easily and repaired more slowly. These defects mainly originate from an overall deficiency in all key epidermal lipids, which comprise two-thirds.

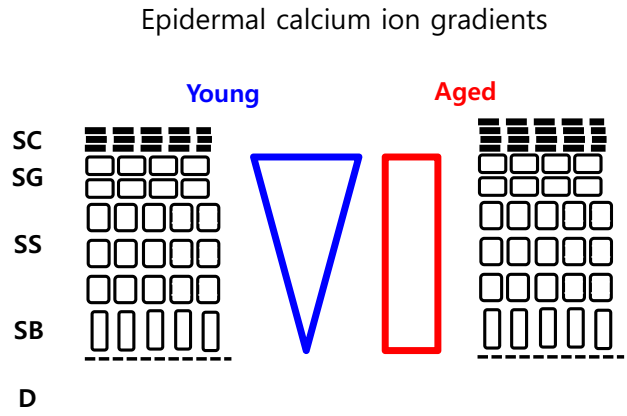

Fig. 3 Epidermal calcium ion gradient is disturbed in aged skin. Epidermal calcium gradient in normal and young skin is characterized by low calcium ion levels in both the basal and spinous layers, with an increase in extracellular and intracellular calcium ion that peaks in the outer SG (blue). This calcium ion gradient serves many functions in the epidermis, which include the induction of terminal differentiation, formation of the CE, epidermal lipid synthesis, exocytosis of lamellar bodies (LBs), and regulation of the last events of terminal differentiation. Distribution of calcium in the epidermis becomes abnormally broad with aging. Calcium ion was distributed throughout the epidermis of elderly subjects (red).

and spinous layers and a peak increase in extracellular and intracellular calcium ion levels in the outer SG.[15] This calcium ion gradient serves many functions in the epidermis, which include the induction of terminal differentiation,[16] formation of the CE, epidermal lipid synthesis, exocytosis of LBs, and regulation of the last events of terminal differentiation that together form the barrier.[17–19] The epidermal permeability barrier is regulated by the change in epidermal calcium ion.[20] After the skin barrier is disrupted by external physicochemical stress, TEWL occurs, and in turn, loss of epidermal calcium ion follows. Loss of epidermal calcium ion acts as a signal for the homeostasis of the skin barrier. Immediately after barrier disruption, preformed LBs that include lipid precursors for SC intercellular lipid membranes are secreted, and in turn, new LBs are produced and replenish the disrupted lamellar structures to restore a normal barrier.[17]

As the differentiation of keratinocytes is strictly calcium dependent, the calcium ion also plays an important role in the aged epidermis.[21] The permeability barrier abnormality in aged skin results from the reduced delivery of secreted lipids to the SC. The decrease in lipid secretion, in turn, results in a reduction in the number of SC intercellular lamellar bilayers shown in electron microscope findings. Finally, the extracellular matrix of the SC could be more porous in the aged skin.[12] The mechanism responsible for this decreased LB secretion has been suggested as the loss of the epidermal calcium gradient. The distribution of calcium in the epidermis becomes abnormally broad with aging.[22] There is an alteration of calcium distribution in the epidermis after examination of young (13, 26, 29, and 34 years), middle-aged (48 years), and elderly (70, 71, 77, and 79 years) patients.[23] The researchers observed that the calcium ion was distributed throughout the epidermis in elderly patients. In addition, the epidermal calcium gradient in middle-aged patients appeared intermediate compared with that of the young and elderly patients (Figure 3).[23] Epidermal calcium gradient loss may originate from a decreased number of ion pumps, ion channels, or ionotropic receptors in aged skin.[24] The alteration of epidermal calcium distribution in the aged skin negatively influences the epidermal permeability barrier by impeding the delivery of LBs to the SC, which results in a decrease in extracellular lipid bilayers.

Epidermal lipid synthesis and SC lipid processing in aged skin

SC intercellular lipid membrane originates from LB produced from the Golgi complex in keratinocytes. Lipid precursors, such as phospholipids, sphingomyelin, cholesterol sulfate, glucosylceramide, and acylglucocylceramide that are stored in the LB, are then secreted into the SC-SG interspace. Following this event, lipid precursors are processed to ceramide (about 50% by weight), cholesterol (25%), and free fatty acids (25%) by hydrolases to form the mature multilamellar structure.[25] They are equal in molar ratio of about 1:1:1.[26]

A report on the biochemical changes of epidermal lipids in the aged skin has revealed that the content of three major lipid species, such as ceramide, cholesterol, and fatty acids, was reduced.[12] The structural abnormality of the SC intercellular lipid membrane was best explained by a global reduction in SC lipids in the aged skin (about one-third less lipid weight percentage than in young SC) (Figure 2). In contrast, a more profound decrease in cholesterol or ceramide species was reported.[27] Selective changes in specific SC ceramide

species such as ceramide 2 (N-lingocerylsphingosine), with concurrent increases in ceramide 3 (nonhydroxy N-acyl fatty acid and phytosphingosine) relative to total ceramide content, have also been noted in the aged epidermis.[28]

Alteration of SC lipid processing has been reported in epidermal aging. Acid sphingomyelinase (aSMase) activity is reduced in aged human epidermis (eighth decade) compared with that in young adults (second decade).[29] aSMase generates long- (C24) and short- (C16) chain-containing ceramide species. This becomes critical for epidermal barrier function.[30,31] The activities of aSMase and ceramide synthase were reduced only in the inner epidermis of aged (15-18 months) versus young (2-3 months) hairless mice, which correlated with reduced capacity for barrier repair in aging. aSMase was normal in the outer epidermis, which correlates with normal barrier function under basal condition.[31]

The metabolic basis for barrier abnormality in aged skin could be explained by the reduced activity of the rate-limiting enzymes for each of these lipids, such as serine palmitoyltransferase, 3-hydroxy-3-methylglutaryl-coenzyme A reductase, and acetyl coenzyme A carboxylase.[32] Collectively, lipid synthesis and enzyme activity in the aged epidermis not only are reduced under basal condition, but also fail to upregulate sufficiently after acute barrier disruption. Lipid synthesis in the aged epidermis does not reach the level in the young epidermis after comparable insults.

The molecular basis for the epidermal lipid synthetic abnormality observed in aged skin has been partially explored. One possible mechanism is that the content or activation of the sterol regulatory element binding proteins, which transcriptionally regulate several key enzymes of cholesterol and fatty acid syntheses, is abnormal.[33] The other mechanism is that autocrine or paracrine signaling responsible for the epidermal lipid metabolic pathway is partly abnormal.[34]

Cytokine production and response are decreased in aged epidermis

Epidermal keratinocytes secrete proinflammatory cytokines that directly stimulate epidermal proliferation and dermal inflammatory cells. Cytokines secreted from dermal inflammatory cells indirectly provoke epidermal proliferation due to an increase in DNA synthesis of keratinocytes.[35] Homeostasis of skin barrier function is maintained through this mechanism. Treatment of interleukin 1 alfa (IL-1α) in cultured human keratinocytes stimulates epidermal lipid synthesis.[36] There are few studies on local cytokine levels in the skin during aging. IL-1α decreases in various tissues in the aged skin, including a decrease in cytokine production in the aged human cultured keratinocytes[37] and lower mRNA levels in aged mice and humans.[38] There are not only age-dependent changes in cytokine expression but also a decreased response to cytokines with aging.[39,40] Aged transgenic mice with a knockout of the functional IL-1α receptor displayed a barrier abnormality versus age-matched, wild-type littermates.[40] Topical treatment in the aged skin with an immunomodulator, imiguimod, normalizes barrier recovery rates in aged mice.[39] Collectively, the reduction of cytokine production or downstream biologic reactivity is a common feature of the aging tissues that could explain the functional abnormalities in the aging skin.

SC acidity breaks in the aged skin

SC normally has an acidic pH, referred to as the "acid mantle."[41] This acidic pH contributes to the protective functions of the skin, such as permeability barrier homeostasis,[41–43] SC integrity and cohesion,[41,42] epidermal antimicrobial defense,[41,44] and primary cytokine activation.[45] Three endogenous pathways as well as exogenous insults contribute to the acidic environment of the SC: (1) sodium ion/hydrogen ion (Na^+/H^+) antiporter-1 (NHE1)[46]; (2) free fatty acids generated from phospholipids by secretory phospholipase A_2[42,47]; and (3) urocanic acid degraded from histidine by histidase.

Deterioration of any of these pathways can increase SC pH, which is linked to the alteration of permeability barrier homeostasis and SC integrity and cohesion. Maintenance of SC acidity contributes to permeability barrier homeostasis by increasing the activity of the two key ceramide-generating enzymes, namely, β-glucocerebrosidase and aSMase,[48–50] and supports SC integrity and cohesion by decreasing the activity of serine proteases (SPs). SPs not only inactivate lipid-processing enzymes,[49] but also degrade the CDs[41] and inhibit LB secretion.[51] Lysis of CD is involved in the desquamation of corneocytes, which are influenced by pH in the SC. In the normal epidermis, the upper SC presents with pH 4.5 to 5.0, but the lower SC presents with pH 6.5 to 7.0, which normally makes a pH gradient in the SC.[13] SPs, specific enzymes in the epidermis, such as stratum corneum chymotryptic enzyme encoded by *KLK7* and stratum corneum tryptic enzyme encoded by *KLK5*, are activated under an environment of neutral pH and then contribute to the corneocyte desquamation and skin barrier disruption.[52] In summation, women, younger patients, and those with black skin have a lower skin pH compared with men, older individuals, and those with white skin.[53]

In aged skin, an increased skin surface pH has been reported repeatedly. One group found that the skin surface pH was significantly higher in the advanced aged group (>80 years) compared with the younger group.[54] A positive correlation between age and pH was also reported.[55] In a large Chinese cohort, skin surface pH on the forehead of both men and women older than 70 years was higher than that in younger groups.[56] In humans and mice of advanced age (>75 years in humans or >18-24 months in mice), skin barrier defects are linked to reduced epidermal lipid synthesis.[12] In comparison, skin barrier defects in moderately aged humans

(50-80 years) or mice (12-15 months) are linked, instead, to defective SC acidity. In the epidermis of moderately aged mice, the abnormal acidification is linked to decreased NHE1 expression. Decreased NHE1 levels, in turn, lead to increased SC pH, which results in defective lipid processing and delayed maturation of SC lipid lamellar membranes, due to suboptimal activation of the pH-sensitive essential, lipid-processing enzyme, β-glucocerebrosidase. In moderately aged skin, the SC integrity is impaired due to increased pH-dependent activation of SPs, which contributesto premature degradation of CD.[13]

Although various factors such as humidity, androgen excess, and psychologic stress are known to negatively affect barrier homeostasis in young skin, it is not known whether these factors aggravate barrier homeostasis in aged skin. A dry environment induces epidermal proliferation and scaling in both young and aged murine skin; however, no remarkable difference was found in the skin barrier recovery of aged mice in a dry environment.[57] Important factors maintaining skin barrier function include SC hydration, SC pH, SC integrity and cohesion, and antimicrobial properties. All of these are compromised to some degree in aged skin, in part as a result of the faulty lipid synthetic pathway (Figure 4).

SC hydration is decreased in aged skin

Maintenance of optimal SC hydration is an important function of the epidermis and is dependent on several factors. These include the lamellar structure of SC intercellular lipids, which traps water within the corneocytes; the amount of natural moisturizing factors (NMFs), which are a complex mixture of low molecular-weight produced within corneocytes by filaggrin degradation, and SC glycerol content.[58] In the aged epidermis, all three factors are compromised. Decreased lipid content in the aged SC coupled with disorganized lamellar structures and enlarged corneocytes impairs SC water retention. There is a significant age-related decline in the level of NMF. Electron microscope examination showed a decrease in keratohyalin granules in senile xerosis, which would lead to reduced synthesis of profilaggrin and subsequently low NMF.[59] The NMF decrease in the aged SC likely results from reduced synthesis of profilaggrin.[60] The decline in NMF production may reflect the cumulative effects of actinic damage as it was observed only in photoaged skin. The two possible mechanisms of low glycerol level in the aged SC could be explained as follows:

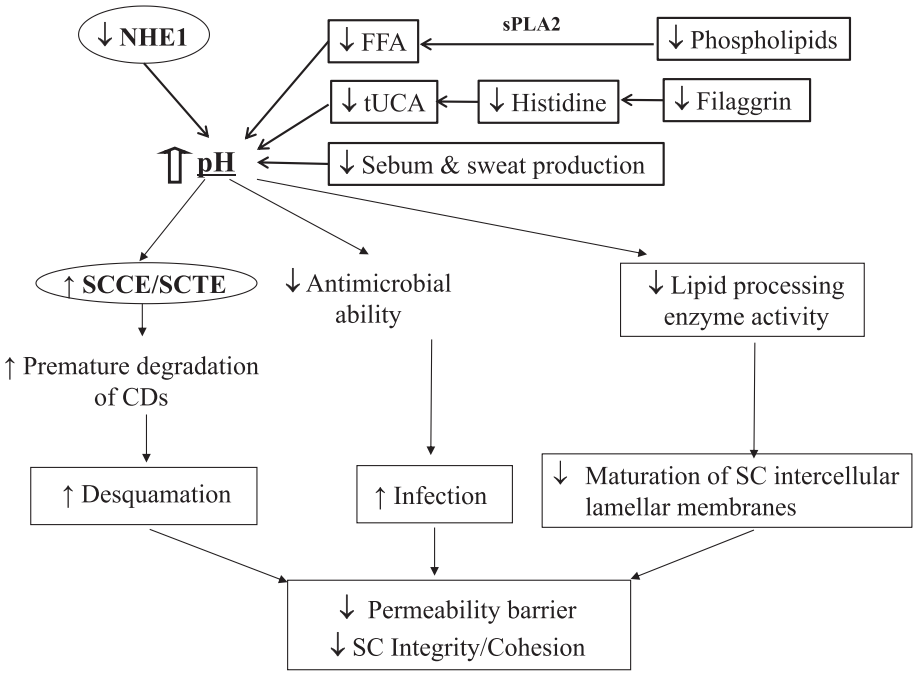

Fig. 4 SC acidity breaks in aged skin. Three endogenous pathways as well as exogenous insults contribute to the acidic environment of the SC: (1) sodium ion/hydrogen ion (Na^+/H^+) antiporter-1 (NHE1); (2) free fatty acids generated from phospholipids by secretory phospholipase A_2 ($sPLA_2$); and (3) urocanic acid degraded from histidine by histidase. Deterioration of any of these pathways can increase SC pH, which is linked to the alteration of permeability barrier homeostasis and SC integrity and cohesion. Maintenance of SC acidity contributes to permeability barrier homeostasis by increasing the activity of the two key ceramide-generating enzymes and supports SC integrity and cohesion by decreasing the activity of serine proteases (SPs). SPs not only inactivate lipid-processing enzymes, but also degrade the CDs and inhibit LB secretion. In the aged skin, skin surface pH increases due to the disturbance of all of the above pathways.

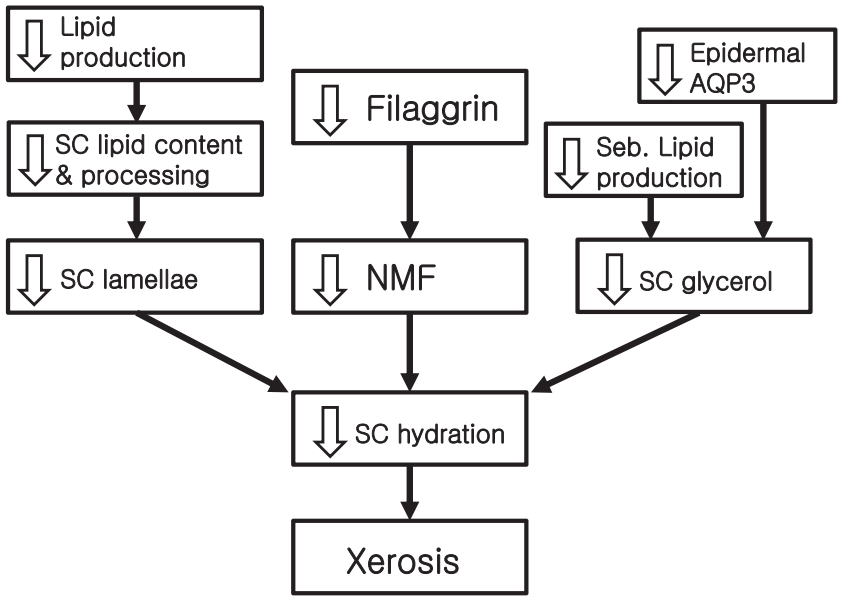

Fig. 5 SC hydration is decreased in aged skin. Maintenance of optimal SC hydration is an important function of the epidermis and is dependent on several factors. Decreased lipid content in the aged SC coupled with disorganized lamellar structures impairs SC water retention. There is a significant age-related decline in the natural moisturizing factor level. The two possible mechanisms of low glycerol level in the aged SC could be explained: (1) decrease in sebaceous lipid production and (2) decreased levels of epidermal water or a glycerol transporter, aquaporin-3 (AQP3).

- The decrease in sebaceous lipid production in the aged skin could result in decreased glycerol generation from triglycerides.
- Aged skin exhibits decreased levels of the epidermal water and glycerol transporter, aquaporin-3. Aquaporin-3–deficient mice display defective skin hydration, elasticity, and barrier function,[61] which are corrected by glycerol replacement, suggesting that diminished glycerol transport to the SC generates the observed functional defects of the skin (Figure 5).

Antimicrobial barrier is also disturbed in aged skin

The antimicrobial property and epidermal permeability barrier function are the main roles of the skin barrier. These are considered as discrete, protective functions of mammalian skin.[2] Although permeability barrier homeostasis and outer antimicrobial shield are both localized to the SC, the structural and biochemical basis for each differs.[62] The outermost antimicrobial shield is attributed to low water content, acidic surface pH,[63] resident microflora, and certain proteins of eccrine and sebaceous gland origin.[64] Human SC also contains at least four antimicrobial peptides (AMPs), such as S100 protein, psoriasin (S100A7), RNase7, cathelicidin (hCAP18) carboxy-terminal fragment, LL-37, and human β-defensin 2 (HBD-2).[65] AMPs are located in the intercellular lipid domain of the SC, which functions as the permeability barrier.[62,66] HBD-2 is stored in the LBs of epidermal keratinocytes as well as in the intercellular spaces, suggesting that HBD-2 is released along with the contents of LB to provide an antimicrobial shield for the epidermis.[67] HBD-2 and LL-37 are inducible by UVB, chronic inflammation, pathogen challenge, and wound healing, although they expressed at low levels under basal conditions.[68] Both HBD-2 and LL-37 are within the LB in the epidermis.[67,69] As a result, the epidermal permeability and the antimicrobial barriers are linked[62] and do not have disparate but rather interdependent processes.[68]

As HBD-2 is under transcriptional control of IL-1α and IL-1β,[70] alterations in IL-1α signaling with aging could decrease the upregulation of AMPs. The decreased IL-1 signaling with aging reduces the inflammatory response exhibited by the aged skin,[40] while defective IL-1α signaling in the aged epidermis could increase the risk of infections by not only altering the antimicrobial properties of the barrier but also diminishing the inflammatory response to pathogens.

Skin barrier in diabetic skin similar to aged skin

Diabetes mellitus (DM) that shows a chronic hyperglycemic condition is clinically classified into types 1 and 2. Type 2 DM accounts for >80% of all DM and shows a complex pathophysiology, such as insulin resistance and inadequate insulin production, typically in old and obese individuals.[71] Chronic uncontrolled hyperglycemia contributes to various complications. At least 30% of patients with DM have some type of skin involvement related to the disease.[72] Dryness, pruritus, cutaneous infection, and delayed wound healing

Table 1 The skin barrier in diabetes is similar to aged skin

	Aged	Diabetes mellitus
Basal TEWL	↓	↓
SC hydration	↓	↓
SC integrity/cohesion	↓	↓
SC pH	↓	↓
Barrier recovery	↓	↓
Total epidermal lipids	↓	↓
Epidermal lipid synthesis	↓	↓
LB number	↓	↓
LB secretion	↓	↓
SC intercellular lipid bilayer	↓	↓
IL-1α	↓	↓

IL-1α, interleukin 1 alfa; TEWL, transepidermal water loss.

are commonly observed in patients with type 2 DM as well as people of advanced age.[73] All of these skin problems result from an impaired skin barrier.

A current hypothesis states that long-standing hyperglycemic condition accelerates the skin aging process; namely, the skin in chronic hyperglycemia shows a more advanced aged skin barrier in Otsuka Long-Evans Tokushima Fatty (OLETF) rats. OLETF rats have typical characteristics of type 2 DM.[74,75] OLETF rats exhibited decreased epidermal lipid synthesis and AMP expression with increased age. Decreased epidermal lipid synthesis accounted for decreased LB production. In addition, there were significantly higher serum advanced glycation endproducts (AGEs) levels and increased AGE receptors in the epidermis. They concluded that long-standing hyperglycemia impairs skin barrier function, including permeability and antimicrobial barriers, by accelerating the skin aging process in proportion to the duration of hyperglycemia.[74]

Patients with type 2 DM have presented with epidermal barrier impairments, including SC hydration, which were influenced by blood glucose control (the hemoglobin A1c level). In the lipid analysis of SC, ceramides, fatty acids, and cholesterol were significantly decreased in patients with type 2 DM compared with controls. Type 2 DM murine models showed similar skin barrier state with chronic hyperglycemic models. Impairment of the skin barrier was observed in type 2 DM, which results in part from a decrease in epidermal proliferation. Serum AGE and its epidermal receptors were increased in type 2 diabetic mice, which display impaired skin barrier parameters such as epidermal lipid synthesis, LB production, epidermal AMP, and SC lipids.[76] Because diabetic skin shows similar changes in the skin barrier as those of aged skin, both have very similar characteristics in the skin barrier (Table 1).

Therapeutic strategies for aging skin barrier

Equimolar mixtures of the three key lipids, such as ceramide, cholesterol, and fatty acids, allow normal barrier recovery rates in young skin.[47] The three component mixtures to 3:1:1 molar ratios as physiologic lipid mixture significantly accelerate barrier recovery.[77] In the young skin, any of the three key lipids can predominate.[26] In the aged epidermis, only topical cholesterol alone could accelerate barrier recovery.[32] Additionally, equimolar mixtures of the three key lipids could also accelerate barrier recovery if cholesterol is the predominant lipid.[77] These reports emphasize the profound effect of a decrease in cholesterol synthesis in the aged epidermal permeability barrier.[78] Topical mevalonic acid has been shown to have a role in acute barrier repair in aged skin but not in young skin. Mevalonic acid is an intermediate

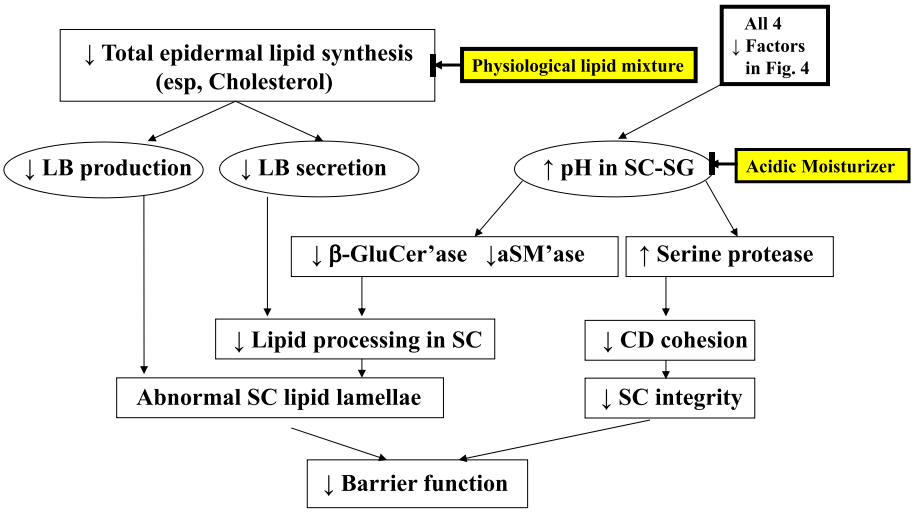

Fig. 6 Therapeutic strategies for aging skin barrier. Mixtures of three key lipids such as ceramide, cholesterol, and fatty acids at 3:1:1 molar ratios as physiologic lipid mixture could be used for aged epidermis. Considering a decreased skin surface acidity in the aged skin, the acidic moisturizer could be beneficial.

substrate generated early in cholesterol biosynthesis. Similar to that with cholesterol, topical treatment of mevalonic acid in aged murine skin enhances the rate of barrier repair after acute disruption.[79]

Considering a decreased skin surface acidity in the moderately aged skin as well as the advanced aged skin, an acidic moisturizer could be beneficial for the aged skin (Figure 6). The barrier abnormalities in the aged skin were normalized by acidifying the SC exogenously, suggesting a basis for the well-known acidification therapies that are widely used to treat pathologic xerosis or eczema seen in moderately aged humans.[13] Results of a small-sized clinical study showed that a 4-week treatment of pH 4.0 skin care products significantly improved the SC integrity of the elderly patients. The reduction in the baseline skin surface pH of elderly patients is accompanied by improved SC integrity. The authors concluded that skin care products for the elderly population have to be adjusted in the pH range of 3.5 to 4.0.[80] The skin barrier in diabetic conditions exhibits many similar characteristics comparable with that in the aged skin. Therefore, therapeutic strategies for the aged skin might be helpful for the diabetic skin.

Conclusions

Restoration of the antioxidant barrier of the SC may be another therapeutic strategy for the aged skin barrier. Topical antioxidants are recommended. Among lipid-soluble antioxidants, tocopherol has photoprotective properties[81] and may stabilize SC lamellar membrane.[82] Theoretically, α-tocopherol (free vitamin E) may be more efficient in antioxidant production of skin surface lipids and skin barrier constituents compared with vitamin E esters. Photoprotection is also an important antioxidant strategy to prevent damage to SC lipids and proteins. Chemical peelings using fruit acids, β-hydroxy acid, trichloroacetic acid, and phenolic compounds and nonablative (intense pulsed light, pulsed dye laser, neodymium-doped yttrium aluminum garnet (Nd:YAG)) and ablative (carbon dioxide, erbium-doped yttrium aluminium garnet (Er:YAG)) light-assisted methods are also suggested.[83]

Acknowledgements

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