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Skin barrier and dry skin in the mature patient

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Abstract Dry skin is the most common clinical manifestation of dermatologic diseases, and it presents with itching, redness, and desquamation—signs and clinical manifestations that are not only physically uncomfortable but also affect patients psychologically. The water content in the stratum corneum is largely dependent on the composition and amount of the intercellular lipids, which regulate the loss of water from the skin, and on the levels of hygroscopic substances of the natural moisturizing factors, which are responsible for retention of water in the stratum corneum. Prevention of water loss and penetration of potentially toxic substances and microorganisms into the body are the most important functions of the skin, which acts as a natural frontier between the inner organism and the environment. Skin barrier defects occur in several skin diseases, but the influence of aging on the skin barrier function is largely unknown and conflicting results have been reported. In this review, the structure and function of the barrier in relation to the aging process are discussed.

Introduction

Skin aging is associated with structural and functional changes, along with increased skin vulnerability and skin dryness.[1] The skin is the largest organ of the human body and constitutes the natural protective interface between the host and external environment.[2] The barrier functions of the skin are believed to be exerted by the epidermis, the most superficial layer of the skin, of which the stratum corneum (SC) is largely responsible for the barrier functions. Dry skin presents with itching, redness, and scaliness, and these signs and clinical manifestations are related to impaired enzymatic processes partly due to decreased SC water content.[3]

There are two elements important for the maintenance of SC humidity: intercellular lipids, which form the main barrier against diffusion of water across the SC, and natural moisturizing factor (NMF), with a key role in the absorption of water in the SC.[3–5] Major NMF components are produced by the enzymatic breakdown of filaggrin (FLG), and the activity of the enzymes responsible for FLG degradation is strongly dependent on the water level in SC and external humidity. The SC of dry skin not only lacks water but also contains reduced levels of NMF, required to bind water in the SC. In this way, a vicious circle has been created.[3–5]

Skin barrier functions

Functions of the skin barrier are numerous, and the skin largely contributes to physical, chemical/biochemical, and

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adaptive immunologic barrier.[6,7] To understand the consequences of barrier impairment, which can occur due to aging or different acquired and/or genetically predisposed skin conditions, it is crucial to understand the mechanisms that underlay skin barrier function.[7] Structural proteins, lipids, various proteases, pH, and innate immunity, along with antimicrobial defense, have distinct impact on barrier function. All these aspects are closely connected and may have great impact on each other.[7] A universally valid definition of "skin barrier" is still elusive. To assess skin barrier function in a more strict sense, commonly the transdermal water loss (TEWL) is used. In a broader sense, SC hydration, sebum level, and pH value are widely accepted as surrogate markers,[3,8] as all of them are related to skin barrier functionality and skin appearance.[3,9] High levels of TEWL are in general associated with low SC hydration, reduced skin surface lipid content, and altered composition and structure of SC lipid bilayers.[2] An increased skin surface pH is accompanied by a reduced buffer capacity, altered activity of skin proteases, and diminished antimicrobial defence.[10–13]

The epidermis generates a set of protective and sensory functions, in part attributable largely to its metabolically active, differentiation endproduct SC.[14,15] Important functions of the epidermal barrier are delivered through complex mechanisms of actions of physical, chemical, and immunologic barriers.[2,3,7,12,13] Defensive function includes the permeability barrier, which retards transepidermal water loss; antimicrobial barrier, which encourages nonpathogenic flora and resists against growth and invasion of pathogens; other protective functions, such as antioxidant and defense against ultraviolet irradiations; and biosensory functions, which place the epidermis as the distal outpost of the nervous system with important regulatory and signaling functions within the epidermis.[2,7,12,13]

The physical barrier, formed by a unique structure of lipids and corneocytes of the SC, is complemented by a very fine, slightly acidic film on the surface of the skin.[2,3] This hydrolipid film is composed of sebaceous gland lipids, corneocyte remains, and sweat and works as an additional biochemical barrier.[3] Acidic pH is important for cutaneous antimicrobial defense and regulation of the activity and expression of epidermal enzymes involved in desquamation, lipid synthesis, and inflammation.[3–5] A physical barrier prevents water loss, microbial invasion, and entrance of allergens and irritants.

The permeability barrier resides in SC, and it retards transcutaneous water loss and allows survival in a potentially desiccating environment. Keratinocyte (KC) cytoskeleton and tight and gap junctions contribute to the physical barrier. Hydrophobic lipids inhibit the outward movement of the water.[16]

The chemical barrier is formed by lipids, the so-called *acid mantle,* antimicrobial peptides (secreted by KCs), and FLG acidic degradation products.[7,14] Acid mantle is provided by free fatty acids, lactic acid from sweat, and urocanic acid, degradation product of FLG.[14] These components act together by ensuring normal keratinization and lipid synthesis, as well as providing antimicrobial protection and proper skin hydration.[14]

Immunologic barrier and antimicrobial defense are important aspects of the skin barrier.[15,17,18] Innate skin immunity is the result of complex interaction of the physical barrier, several immunologically active cell types, action of antimicrobial peptides, cytokines, and encoded proteins, known as pattern recognition receptors.[15]

The skin is colonized by an abundant and diverse community of microbes, which collectively have been referred to as the "microbiome."[19–21]

Epithelial antimicrobial proteins have an essential role in allowing epithelial surfaces to cope with these microbial challenges.[21] These natural antibiotics are evolutionarily ancient innate immune effectors and are members of a diverse array of protein families, all with a function to rapidly kill or inactivate microorganisms.[21]

Function of the barrier is tightly related to the SC structure

When referring to the skin barrier function, mostly the SC is considered.[13] The SC contains multiple layers of anucleated protein-enriched KCs (terminally differentiated KCs) embedded in an intercellular lipid matrix.[2,22] The thickness of the SC differs for different body areas, and the facial skin has the thinnest SC.[23] Cornification is regarded as a specific form of programmed cell death after terminal differentiation of KC; therefore, KCs forming the SC can be viewed as cell skeletons surrounded by lipids and remain tightly connected by corneodesmosomes until degradation done by proteases, which leads to desquamation.[24–26]

Filaggrin

Filaggrin is an important structural protein of the epidermis with several functions involving the skin barrier. It is derived from profilaggrin (proFLG), which forms a major component of the keratohyalin granules within the granular layer.[27,28] FLG is also a component of the protein-lipid cornified envelope, which replaces the plasma membrane of KCs.[24] FLG therefore provides important structural function and mechanical strength of the SC.

FLG deficiency affects the structure of the SC but also affects SC lipids and antimicrobial and protease activity. In addition to the *FLG* genotype, other (genetic, translational, and environmental) factors also can influence FLG and NMF levels.[7,29,30]

A decline in environmental humidities is associated with reduced levels of NMF.[31] Another climatic/environmental influence is UVB radiation. Single dose of UVB exposure downregulates *FLG* expression,[32,33] which may explain why phototherapy induces skin dryness.[33] Exposure to water and irritants also reduces FLG levels. Mechanical disturbance of the barrier, such as scratching, results in intense pruritus in atopic

dermatis (AD) or asteatosis in aged skin. It downregulates FLG expression.[32] Topical therapy also has an impact on FLG expression, as does the prolonged use of topical corticosteroids, unlike topical tacrolimus, which reduces epidermal FLG.[7,34,35]

The important role of lipids in epidermal barrier

Alterations of the structure and composition of SC lipids[7] are an important cause of reduced skin barrier function. Hydrophobic lipids within the extracellular domain inhibit the outward movement of the water.[36] Lipids consist of ceramides, cholesterol, and free fatty acids.[36–41] There is also a link between FLG and lipids, and FLG deficiency is believed to affect also the delivery of lipids.[29]

Importance of maintenance of pH of the skin

The pH value on the skin surface has a great importance for antimicrobial defense and regulation of expression and activity of various proteases.[4–6,10,11,42,43] The pH of the skin follows a sharp gradient across the SC, which is believed to be important in controlling enzymatic activities and skin renewal.[43] The skin pH is affected by a great number of endogenous factors, such as skin moisture, amount and composition of sweat and sebum, anatomic site, genetic predisposition, and age. Also, exogenous factors such as dermal exposure to detergents, application of cosmetic products, occlusive dressings, and topical antibiotics may influence the skin pH. Changes in the pH are reported to play a role in the pathogenesis of skin diseases such as irritant contact dermatitis, AD, ichthyosis, acne vulgaris, and *Candida albicans* infections.[43]

Regardless of the localization or age, most authors agree that men show lower pH values.[42–44] There is an influence of free fatty acids, generated by sebaceous gland lipases and eccrine-gland–derived products, such as lactic acid, on acidification of the skin surface pH. Because men show significantly higher sebum and sweat rates, this may be an explanation for lower pH levels[42]; therefore, the male skin has significantly higher buffering capacity but gets progressively dehydrated with age. Adult pH on the forehead, the temple, and the volar forearm increases slightly with age.[11]

Skin barrier changes with age and aging of the skin

From birth up to 4 weeks of age, functional properties of the barrier gradually mature, SC thickness increases, TEWL decreases, SC hydrates, and skin surface acidifies. There is impaired barrier function in very early age, with elevated protease activity and reduced NMF, which may, in part, explain why infants are predisposed to development of AD. Barrier development takes place through significant structural and functional transitions during the first year of life. The infant skin is 30% thinner and the SC is less organized, with increased cell turnover, smaller and poorly defined corneocyte clusters, and presence of corneodesmosome artifacts, compared with the adult skin.[45–48]

Aging of the skin incorporates two distinct mechanisms: intrinsic (true biological) aging, mainly genetically determined, and extrinsic aging, caused by environmental exposure, especially sunlight-related UV radiation.[6] The latter type of skin aging is also known as "photoaging."[6] Sexual hormones and age have distinct impact on skin aging.[49] With aging, cell replacement in the skin is continuously declining, the barrier function and mechanical protection are decreasing, healing and immune responses are delayed, thermoregulation is compromised, and sweat production and sebum production are decreased[50]; furthermore, KC proliferation and desquamation are decreased, although more recently it has been reported that adherence of KC weakens by age, leading to easier desquamation.[50,51] Barrier recovery is delayed in both murine animals and humans, although baseline TEWL is lower in the aged human skin.[49,52] Also, the aged epidermis displays altered drug permeability, increased susceptibility to irritant contact dermatitis, and often severe xerosis, suggesting alterations of the barrier.[52,53]

Results from a study suggest that differences in TEWL between the younger and mature skin are dependent on body location, as TEWL increases significantly with aging at the décolleté but decreases significantly at forehead and cheek.[3] TEWL is an indicator for the ability of the SC to hold water and is closely related to the sebum content, SC levels of NMF, and the composition and levels of lipids.[3] Increase in TEWL will lead to decreased skin hydration and xerotic skin. Xerosis cutis, associated with roughness, dryness, and scaly skin, is more common in elderly people.[3,54,55] Although most studies show decreased sebum production in the aged skin, results regarding the SC hydration are less consistent and seem to depend on body location and sex.[3,48,55]

The results for lipids are far more congruent. The amount of lipids on the skin surface is higher in younger people and declines with age.[6] The lipid film, which constitutes the main part of residual skin surface components, is essential for skin barrier functions, contributing to water retention, oxidation resistance, and antioxidant transportation, and all these functions decline with age.[6,56,57] The most likely age-related hormonal changes are responsible for reduced sebum production, because androgens stimulate sebocyte proliferation and differentiation.[57,58] There is a decrease in the lipid droplet size in the aged male skin, reflecting declining influence of androgenes.[6]

Hormonal influences

Hormones regulate the structure and composition of the skin in different ways.[44,58] The physiological properties,

including TEWL, SC hydration, sebum content, and pH value, seem to be equal in both sexes in children, but with the beginning of puberty, skin differences become conceivable.[1,42] Skin aging is a result of the synergistic effects of intrinsic aging and photoaging, but in women, there is also an effect of climacteric aging, associated with a reduction in the secretion of progesterone and estrogens.[59] During the menopause, skin temperature and sebum content decrease significantly on the forehead, and also SC hydration declines. The decrease in sebum production is supposed to be a result of changes in the estrogen balance due to menopause.[3] Estrogens are known to affect skin physiology, including skin thickness, capillary blood flow, collagen content, hydrophilic glycosaminoglycans, and water content.[3,60] Hormonal aging of the skin is probably responsible for dermal changes, including reduction of thickness and collagen content, decrease in sebaceous secretion, loss of elasticity, and epidermal changes.[61] Sebum content is mainly influenced by androgens, testosterone, and dehydroepiandrosterone, whereas estrogens exert the opposite effect through downregulation of sebaceous glands[42]; therefore, sebum content is higher in men, at all locations and all age groups, whereas sebum content is progressively decreasing in the female skin from 40 years of age.[42] Changes in the steroid hormone level occur in both sexes, but the female skin suffers more from the negative impact of decreasing estrogen in menopause with a result of drier skin. Sebum lipids have an occlusive effect, and higher sebum content in men may explain lower levels of TEWL in men than in women.[42]

Levels of pH change with age, because sebum levels have the impact to skin pH, and sebum production is affected by hormones. A study found that pH remains unchanged from 20 to 50 years of age, but increases significantly between 50 and 60 years of age; after that decade, the pH decreases to the baseline value or even lower.[3] The skin barrier function partly changes with aging; whereas TEWL and SC hydration (with exception of the décolleté) stay unchanged or improve slightly, sebum production and skin surface pH are significantly affected by menopause. The activity of the sebum glands stays normal until the age of 50 to 60 years and decreases significantly after that.[3]

Impact of comorbidities and chronic disease

The skin barrier may be affected by a large number of intrinsic and environmental factors, including presence of chronic diseases and use of medications.[50] Xerosis cutis is one of the most common diagnoses in dermatology with the prevalence ranging from 30% to 85%.[50,61,62] The prevalence of dry skin–related pruritus also increases with age.[63,64] Treatment of dry skin should be included in the initial therapy for pruritus in all elderly patients.[64] Next to dry skin pruritus, other causes of pruritus should be considered,[64] such as medications as calcium channel blockers and hydrochlorothiazide, which are important causes of pruritic skin eruptions in older patients. Also, neuropathic pruritus is infrequently considered but can be the cause of localized itching (especially in the genital area) and generalized truncal pruritus (especially in patients with diabetes mellitus). Certain skin conditions are also more common in elderly patients, including scabies, bullous pemphigoid, transient acantholytic dermatosis, and mycosis fungoides.[64] Dry skin and pruritus in elderly can be due to more than one condition and more than a consequence of skin aging. In the aging skin, there is also flattening of the dermoepidermal junction and increasing skin stiffness, and so elderly patients are at increased risk of shear-type injuries, such as skin tears or superficial pressure ulcers (prevalence 2% to 40%).[50,65,66] Incontinence-associated dermatitis affects up to 50% of all incontinent patients and it occurs due to excessive moisture from urine and/or stools with a result of overhydration and chemical irritation of the epidermis.[50,67] Cleansing represents physical irritation and contributes to further barrier impairment.[50]

There is also an impact of comorbidities. Decreased SC hydration and altered permeability are found in AD, ichthyosis, psoriasis, malnutrition, and psychological stress.[44,68–73] Malnutrition is commonly found in the elderly population. A low-protein diet induces thinning of the skin epidermis, a decrease of cell proliferative activity in epidermal cells, and a decrease of SC hydration. Protein malnutrition adversely affects the structure and water barrier and reservoir functions of the skin epidermis, and these pathologic changes are associated with the expressions of protein oxidation markers.[68] Hemodialysis patients have higher pH levels and lower SC hydration.[70] A study reported alterations in the recovery of certain residual skin surface components relative to total lipid content in hairless mice with experimentally induced diabetes, and also the quantity of facial skin surface lipids of diabetic patients is significantly lower than that of the control populations.[71]

Acute and chronic effects of UV exposition

Beside the intrinsic part of aging (shortening of telomeres), the skin is affected by extrinsic aging mainly due to substantial exposure to UV light. UVA irradiation (320-400 nm) penetrates deeper into the skin, and approximately 50% of UVA photons enter the dermis, whereas UVB photons (290-315 nm) are mostly absorbed by the epidermis but are far more energetic.[74] UVA irradiation and UVB irradiation damage the skin by different mechanisms involving, for example, ROS elevation, protein and lipid modification and degradation, or direct DNA damage, resulting gradually in photoaging.[75] Solar UV radiation poses a double threat to skin by both increasing the biomechanical driving force for damage and simultaneously decreasing the skin's natural ability to resist, compromising the critical barrier function of the skin.[74]

This occurs in various forms, depending on the individual skin type, skin age, the anatomic site of exposure, the effective frequency of the light source, dose, and wavelength-dependent

response.[75] Disruption of the barrier function due to UV-induced photodamage is largely attributable to the abnormalities in the structures related to the corneocyte adhesion and the disruption of the epidermal permeability function, which accelerate the desquamation process. UV damage causes delayed development of skin barrier abnormality, and the time of restoration is prolonged and proportional to amount of UV exposure.[75]

UVB radiation in particular can be very harmful, and recent *in vivo* studies have shown that UVB radiation affects epidermal morphology, including increasing the mean SC thickness, and disrupts the permeability barrier, causing morphologic changes in SC lipids, increased TEWL, and change of SC hydration.[74] A single UVB irradiation with high minimal erythemal dose (MED) causes not only a significant increase in TEWL but also marked morphologic changes in the SC intercellular spaces.[76]

UVA-related skin barrier damage will facilitate entrance of larger amounts of drugs, toxins, allergens, and carcinogens. Acute UV irradiation induces the decrease in the level of SC intercellular lipids and epidermal synthesis of the major barrier lipid species, vitamin E depletion, and histologically causes delayed and dose-dependent disruption of the permeability barrier by inducing the arrival of a band of lamellar body–incompetent cells at the SC.[76]

Conclusions

Several lines of evidence demonstrate that SC composition and architecture change with aging, manifesting among others in development of dry, less-elastic, and itchy skin, which becomes more prone to infections and inflammation. In addition, the aged skin recovers more slowly after skin irritation.

The aged skin is more prone to irritation, more fragile, easier to develop skin shears and ulcers, and more prone to inflammation and infections, which is largely associated with functional and structural alterations in the SC. The changes in the skin barrier are a result of the synergistic effects of intrinsic aging and photoaging, but in women there is also an effect of climacteric aging.

Aging is copped with comorbidities, painful conditions, lot of psychological stress, and deterioration of other organ systems and immunity, which may further affect the skin barrier; therefore, dry skin in the elderly patient is not just an "old skin," but a complex result of multiple barrier impairments and all other cumulative influences that actually take place in aging. By understanding all these mechanisms and their consequences on the barrier, with adequate skin care and protective measures regarding photoprotection, we can make this condition less pronounced and more bearable to the patient.

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