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REVIEW ARTICLE

pH in nature, humans and skin

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ABSTRACT

The pH plays an important physiological role in nature and humans. pH varies from 1 to 8 in human organs with tight regulation in blood and epithelia of barrier organs. The physiological pH of the stratum corneum is 4.1–5.8 and several mechanisms contribute to its formation: filaggrin degradation, fatty acid content, sodium-hydrogen exchanger (NHE1) activation and melanosome release. First, the acidic pH of the stratum corneum was considered to present an antimicrobial barrier preventing colonization (e.g. by *Staphylococcus aureus* and *Malassezia*). Later on, it was found that the pH influences skin barrier function, lipid synthesis and aggregation, epidermal differentiation and desquamation. Enzymes of ceramide metabolism (e.g. β-glucocerebrosidase or acid sphingomyelinase) as well as proteases (e.g. chymotryptic enzyme or cathepsin D linked to epidermal differentiation and desquamation) are regulated by the pH. Experimental disruption of the physical barrier leads to an increase of pH, returning to normal levels only after many hours. Inflammatory skin diseases and diseases with an involvement of the epidermis exhibit a disturbed skin barrier and an increased pH. This is known for atopic dermatitis, irritant contact dermatitis, ichthyosis, rosacea and acne, but also for aged and dry skin. Normalizing the pH by acidification through topical treatment helps to establish a physiological microbiota, to repair skin barrier, to induce epidermal differentiation and to reduce inflammation.

Key words: antimicrobial activity, epidermal differentiation, epidermal lipids, skin barrier function, skin pH.

INTRODUCTION

The pH reflects the molar concentration of hydrogen ions in solution. It is a measure of the acidity–alkalinity ratio with a logarithmic scale ranging from 0 (most acidic) to 14 (most alkaline) with 7 as its neutral. pH varies widely in the environment and has different effects. Acid rain caused by atmospheric pollutants can cause serious damage especially to woodland areas. Plants will not grow if the pH drops below the normal soil pH of 6.6–7.3. Carbonate containing buffers keep the pH constant for a long time. Too much fertilizer in agriculture causes acidification of the soil and washing out from fields causes acidic lakes. The pH of the ocean is 7.5–8.4 and acidification is affecting ocean organisms.[1]

PH IN HUMANS

The pH of human organs is tightly regulated by acid-base homeostasis and varies from 1 to 8. Outside the acceptable range, enzymes lose their ability to function. Buffering agents in the body reversibly bind hydrogen ions and impede any change in pH.

pH of the blood and the interstitial fluid is 7.35–7.45 and an acidosis may be life threatening. If one refers to a “physiologic” pH, usually the pH value of blood is meant. Respiratory compensation expelling CO_2 and renal compensation by secretion of hydrogen, bicarbonate and ammonia maintain the blood pH. Extracellular buffers include bicarbonate and ammonia, whereas proteins, in particularly the histidine residues, and phosphate act as intracellular buffers.[2]

The pH of barrier organs is quite variable. The pH of the healthy lung is neutral, while in cystic fibrosis the lung pH is acidic. Reduced pH inhibits the activity of certain endogenous antimicrobials in the lung surfactant leading to bacterial infection.[3,4] This is in contrast to the increased stratum corneum (SC) pH in infected skin and probably related to the different bacterial species and endogenous antimicrobials.

In the stomach, the proton pump hydrogen potassium ATPase exchanges H^+ with K^+ resulting in a highly acidic pH of 1–1.5 if empty.[5] This is important for pre-digestion and bacterial defense. Anacidity leads to gastrointestinal infections; however, too much acid may cause stomach ulcers. Proton pump inhibitors (e.g. omeprazole) effectively increase stomach pH and reduce ulcers.[6]

Urine is slightly acidic in the morning (pH 6.5–7.0), becoming more alkaline (pH 7.5–8.0) as the body digests food. A vegetarian diet leads to higher, whereas meat consumption leads to a lower urine pH; pH of more than 8 indicates bacterial infection.

Tears are more acidic in the morning, taken from an unopened eye than later in the day (average pH 7.25 vs 7.45).[7]

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The vaginal pH in a reproductive woman is 3.8–4.4. Vaginal microbiota is dominated by *Lactobacillus* species degrading glycogen to lactic acid, thus keeping the pH acidic.[8,9] Following menopause, the vaginal pH and susceptibility to infections rise. Vulva pH ranges from 5.0 to 5.5 and, similar to the vagina, a postmenopausal rise in pH due to aging and estrogen deficiency is associated with compromised barrier function against pathogens.[9–11]

PH OF THE HEALTHY SKIN

The "normal" pH of the skin surface (SC) of most body parts is acidic and in the range of pH 4.1–5.8 (95% interval; arithmetic mean, 4.9) with small variations between face, trunk and extremities.[12,13] Highest pH values have been reported to belong to the chin (pH 5.6). Areas with the most acidic pH include the forehead (pH 4.4) and the upper eyelid (pH 4.6). pH of the volar forearm, nose, neck, nasolabial fold, cheek and perioral area are in between those values.[14] Physiological gaps include axillae, groin, toe interdigits and anus exhibiting pH values between 6.1 and 7.4. An increased pH fosters a different microbiome and, therefore, these areas are prone to infection and eczematous reactions.[15]

Racial differences are also important, because it has been shown that darkly pigmented subjects may exhibit a lower pH compared with lightly pigmented individuals (pH 4.6 vs 5.0). Moreover, a superior SC integrity and barrier function was observed in darker skin. These findings were attributed to increased epidermal lipid content and increased lamellar body density. Serine protease activity was reduced in the more acidic environment of the darker pigmented group and increased in the lightly pigmented group.[16]

Stratum corneum pH is higher in newborns (~6.0) than in older children, due to an incomplete acidification, reaching physiological pH after 4 weeks.[17] Thereafter, the pH of the SC remains rather constant until the fifth decade of life. In postmenopausal compared with premenopausal woman the pH increased from 4.7 to 5.0. Well documented are an increased SC pH and a reduced buffer capacity in the elderly.[18–25]

Exogenous factors like soaps, detergents, but more importantly leave-on products (e.g. cosmetics or topical medicinal products) may change the skin surface pH. An elevated pH on the dorsal hand may be a consequence of repeated washing. Even the use of water or a mild detergent solution may lead to an immediate increase in pH in predisposed individuals, with skin pH not returning to normal levels for 6 h after washing. This effect is even more pronounced when alkaline soap is used.[13] Wearing occlusive gloves at the workplace leads to hyperhydration and may also increase pH.[15]

pH is acidic at the SC surface and approaches more neutral values (pH 7–7.4) in its vital layers.[26,27] The average pH of the SC increases with depth because of a decrease in the ratio of acidic microdomains to neutral regions.[28] Surprisingly, in preliminary studies in mice it was found that the very upper surface of the SC has a neutral pH, possibly because of the contact with a neutral environment. This result was obtained by *in vivo* imaging with a pH-sensitive fluorescent protein and confocal microscopy and may have been overlooked by the classic pH electrode. When ear skin was exposed to topical phosphate buffers of different pH, the pH of the upper SC dynamically changed according to the pH applied, while the middle pH maintained its acidity.[29]

PH IN MAMMALIAN SKIN

Mammalian skin SC revealed increased pH values compared with humans. We found a uniform pH of 5.8 on flank skin of hairless mice (10 weeks of age) from the same litter, which increased to approximately 6.8 after barrier disruption by tape-stripping.[30] Others described a pH of 5.4 in young mouse skin, which increased to 5.9 in aged mouse skin.[19] Basic skin pH in dogs was 6–7 and increased in lesional skin of atopic dogs to approximately 8–9.[31,32] Cat skin pH was 6.4–6.9 with higher values in males compared with females.[33] In horse ponies, basic skin pH was 7–8 depending on the body region.[34] The skin pH values for guinea pigs were 5.5, rat 6.5, rabbit 6.7 and monkey 6.4.[35] The fur of animals produces a very important and tight barrier which makes the SC barrier less important compared with humans.

MECHANISMS TO ESTABLISH THE ACIDIC SKIN PH IN HUMAN SKIN

The maintenance of a physiological pH in general is determined by a balance between cellular and metabolic processes generating or consuming protons. Several pathways contribute to skin acidification because of the importance of the acidic SC pH.[11,36–38] The filaggrin–histidine–urocanic acid pathway contributes (urocanic acid has a favorable pK of 4.7 for establishing skin pH), but is probably not essential (Fig. 1).[36,39] Histidase-deficient mice are not able to form urocanic acid[37] as well as genetically modified mice lacking filaggrin; nevertheless, the skin surface pH is unchanged or only slightly decreased.[40,41] Moreover, in atopic dermatitis patients with and without filaggrin mutations, pH was increased but did not differ significantly in the two groups. However, in filaggrin$^{-/-}$ ichthyosis vulgaris patients an increased skin pH was shown.[42,43]

The exocytosis of lamellar bodies, which are lysosomes and maintain an acidic pH of 4.5–5.0 by proton pumps, may lead to acidification of the lower part of the SC.[16,44,45] In addition, the hydrolyzation of free fatty acids from phospholipids by phospholipases (sPLA2) acidifies the SC. Studies with pharmacological inhibitors of sPLA2F and sPLA2F$^{-/-}$ mice showed an increased pH.[46,47] pKa (pKa is the negative base-10 logarithm of the acid dissociation constant [Ka] of a solution; the lower the pKa value, the stronger the acid) of approximately 4.5 for most fatty acids is favorable for SC pH. The buffering capacity of a species or its ability to maintain the pH of a solution is highest when the pKa and pH values are close. Lactic acid could be important for pH,[48,49] but the low pKa of 3.9 stands against a significant role in skin pH. A participation of CO_2/HCO_3^- on skin's pH and buffering capacity has been described; however, pKa of 6.4 argues against an important role.[23] Melanin-containing granules contribute to the reduced pH of the SC, through the release of protons from

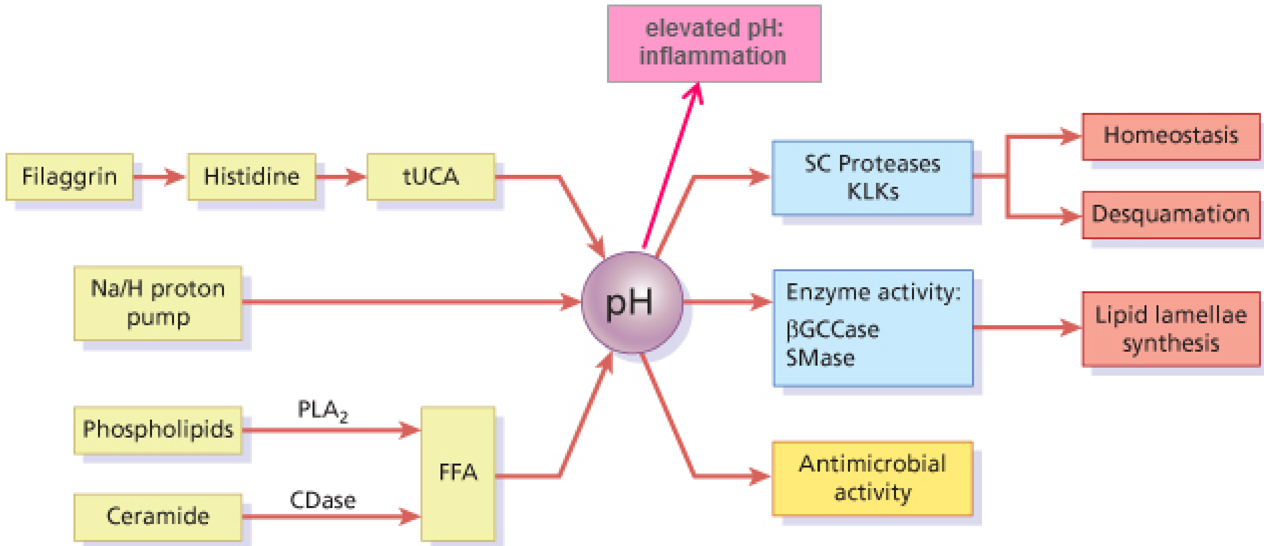

Figure 1. pH generation and function in the skin. FFA, free fatty acids; KLK, kallikrein; SC, stratum corneum; tUCA, trans urocanic acid. Adapted from http://plasticsurgerykey.com/27-the-skin-barrier-in-atopic-dermatitis with permission.

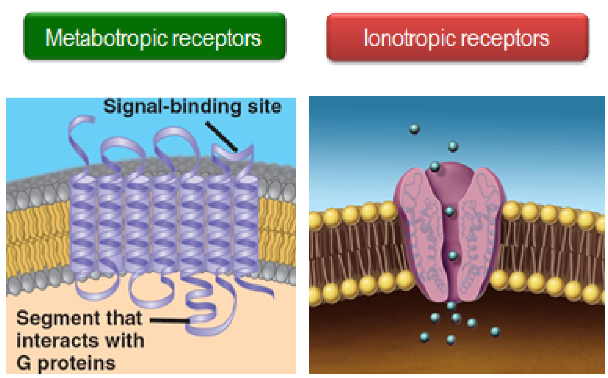

Figure 2. Sensors of extracellular pH. https://www.slideshare.net/mahmoodjassim1/09-ge-lecture-presentation and http://www.yalescientific.org/2013/03/nanochannels-yale-engineers-design-the-first-functional-artificial-ion-channel.

phagolysosomes.[50–52] The sodium-hydrogen exchanger 1 (NHE1) is also involved in SC acidification. In NHE1 knockout mice, pH is slightly increased.[53]

Fluorescence lifetime imaging reveals that neonatal rat SC acidification first becomes evident by postnatal day 3, in extracellular “microdomains” at the SC–stratum granulosum interface, where pH-sensitive lipid processing is known to occur.[53,54] The intracellular space of the corneocytes in mid-SC approaches neutrality.[28]

Endogenous biosensors and transducers are necessary for the maintenance of an optimal skin pH. pH is regulated by metabotropic and ionotropic receptors (Fig. 2). Ion channels include acid-sensing, transient receptor potential (TRP) receptor, pore domain K^+ (K_{2P}) receptor, protein-sensing G-protein-coupled receptors and voltage-dependent ion channels.[55–57] The pH-sensitive G-protein receptor agonists sphingosylphosphorylcholine and lysophosphatidylcholine are activators of transglutaminase and keratinocyte differentiation.[58–61] The impact of receptors and transducers on SC pH has been only partially explored.

PH MEASUREMENT OF THE SKIN

Measurements of the acidity of aqueous solutions with a pH-sensitive glass electrode are of crucial importance in biochemical/medical research. A flat glass electrode is widely used for non-invasive measuring of SC pH and gives reproducible results within seconds.[62] The reliability of this method on the relatively dry SC surface and in a lipid environment has been questioned. However, the SC needs approximately 10% of water to retain its flexibility and there are aqueous pockets within the lipid bilayers. A drop of water on the tip of the glass electrode ensures ionic contact with the skin.

Optical pH-sensitive luminescent sensor foils are available to determine SC pH; the values are in good agreement with the glass electrode. The advantage of the foil method is that small regional differences can be determined by creating a 2-D map.[21] The foil method is more time-consuming and therefore used for special questions only. pH-sensitive fluorescent protein confocal microscopy is used to analyze the pH in different compartments of the SC.[53]

PH AND BUFFER CAPACITY

Stratum corneum acidity can be measured according to two criteria, its value given by pH and its buffer capacity, which represents the ability to resist acidic or alkaline aggression. The buffer system of the skin is widely unrecognized, although it is equally important as the pH. The buffer capacity can be determined by titration with acids or bases.[18,23,63,64] In occupational

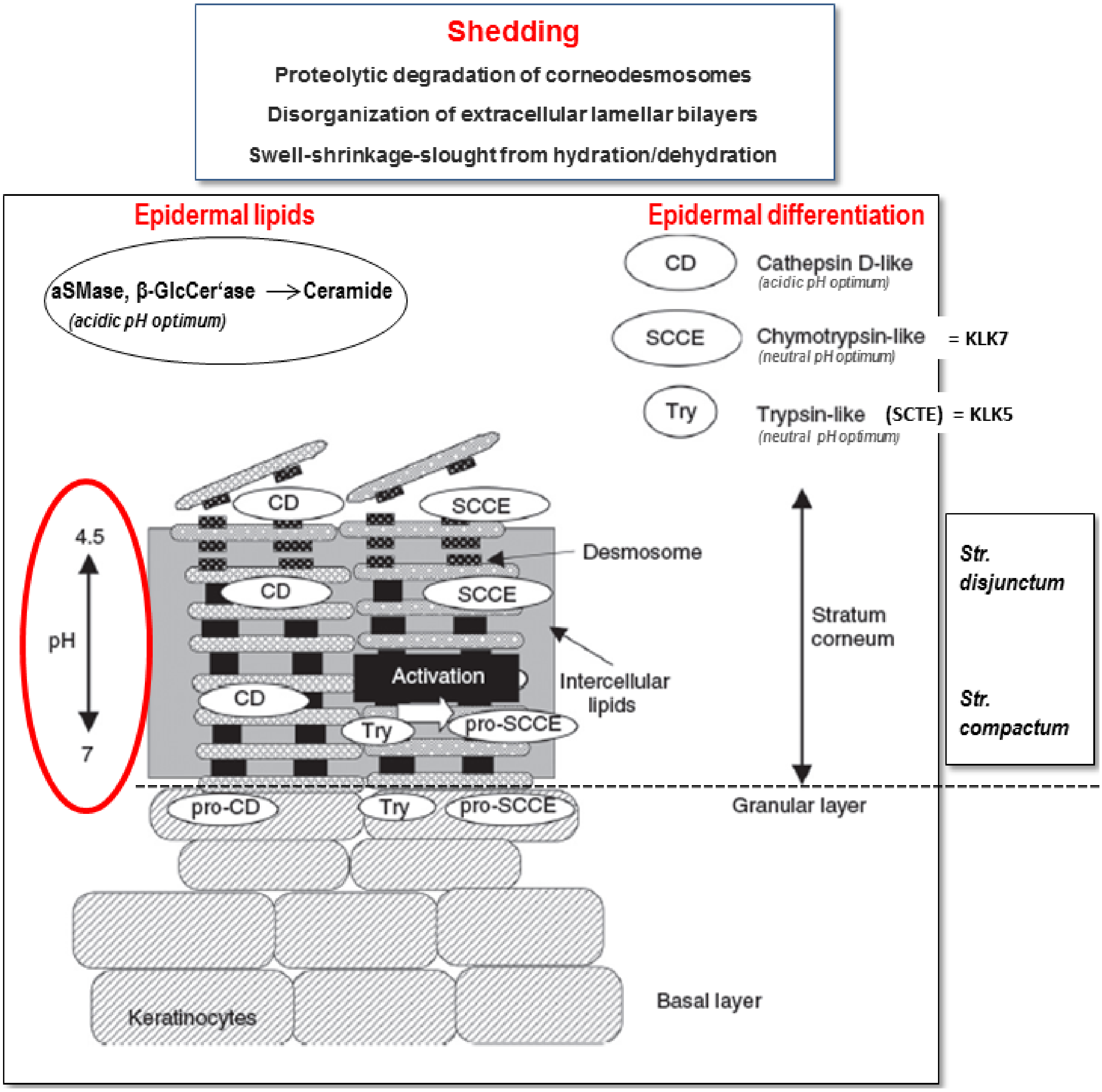

Figure 3. Mechanism of stratum corneum desquamation and shedding. aSMase, acidic sphingomyelinase; β-GlcCer'ase, β-glucocerebrosidase. Adapted from Horikoshi *et al.*[115] and Lin *et al.*[118] with permission.

dermatology, the alkaline-resistance test is used to show whether a patient is prone to irritant contact dermatitis.[63]

The SC buffer system results from differentiated keratinocytes and is formed by weak organic acids, fatty acids, urocanic acid, lactic acid, carbonic acid and the bases with the anions OH^-, COO^- or amines $R\text{-}NH_2$. Also, amino acids, peptides and probably keratins are part of the buffer system.[18,48,63]

The SC has a fairly high buffer capacity. Washing with an alkaline soap (pH of ~9) is well tolerated by many people and only extensive washing may lead to skin diseases.[65] The buffer capacity is reduced by repeated insults, for example, by washing out the buffer components with water and detergent. A low buffer capacity of the skin is reported for babies, aged and diseased skin, explaining an increased sensitivity to irritants and detergents in these groups.[18,23,24]

The buffer capacity of a topically applied preparation is important, because the SC pH following application is the result of the pH and buffer capacity of the topical product and the pH and buffer capacity of the SC. A high buffer capacity of a topically applied product allows for the targeted SC pH to be kept for several hours after application.

PH AND ANTIMICROBIAL EFFECTS

pH of the SC is important for antimicrobial activity, barrier function and desquamation. Acids are well known for their antimicrobial activity. Lactic acid, citric acid and acetic acid are used as antimicrobials in food products. The acidic pH inhibits the colonization of pathogenic bacteria (Fig. 1). Filaggrin breakdown products, which are reduced in atopic dermatitis, demonstrate an inhibitory effect on the growth of *Staphylococcus aureus*.[66] *S. aureus* shows an optimal growth at pH 7.5 and *Propionibacterium acnes* at pH 6.3.[67] Washing with alkaline soaps results in an increased pH and facilitates the growth of these microorganisms. Acidic detergents are favorable for maintaining a low SC pH.[67,68] Moreover, mild acne is significantly improved after application of an acidic leave-on product with pH 4.[69]

Reduction of *S. aureus*, *Clostridium difficile* and *Bacillus subtilis* in atopic skin lesions was achieved by application of acid electrolytic water or peracetic acid, respectively.[70,71] An increased pH in atopic dermatitis leads to enhanced adhesion and multiplication of *S. aureus*. Consequently, acidification by topical application of 0.75% lactic acid reduced the growth of *S. aureus*.[13]

Malassezia, which may aggravate atopic eczema, produced more allergens that elicit an immunoglobulin E response when cultured at pH 6.5 compared with pH 5.5.[72] Skin infection with *Malassezia*, but also with dermatophytes, does not influence the SC pH, in contrast to changed transepidermal water loss (TEWL) and SC hydration.[73] Fungi are able to grow in a wide range of pH values.[74] In addition to the direct effect of the acidity, pH regulates the activity of antimicrobial peptides.[75]

PH, BARRIER FUNCTION, EPIDERMAL LIPIDS, DIFFERENTIATION AND DESQUAMATION

Proper differentiation of corneocytes and regular intercellular lipid lamellae are crucial for the skin barrier. Fatty acids exist as non-ionic acid or in the ionic form depending on the pH. pH 7 in the innermost SC layers will produce 90% ionization of the fatty acids leading to head-group repulsion. At the SC surface, pH of 5 non-ionic fatty acids will cause minimal head-group repulsion and promote a bilayer structure.[76] Increased pH in atopic dermatitis leads to increased head-group repulsion, disturbed epidermal lipid lamellae and thus impaired barrier function.[77]

pH regulates SC barrier formation by activation of ceramide-generating enzymes β-glucocerebrosidase and acid sphingomyelinase, which are active at low pH.[78] Barrier recovery is impaired at neutral compared with acidic pH in parallel with a reduced lipid processing β-glucocerebrosidase activity.[79] A reduced acid sphingomyelinase activity parallels an increased pH in aged skin.[80] Acid sphingomyelinase in term regulates the pH-dependent enzyme cathepsin D involved in epidermal differentiation (Fig. 3).[81] In addition, lamellar bodies contain pH-dependent ceramidases that impact barrier function and desquamation.[82]

pH is important for epidermal differentiation and desquamation. pH regulates the activity of the serine protease chymotryptic enzyme (kallikrein 7) involved in corneodesmosome disintegration and desquamation (Fig. 3).[83,84] Alkalization of the skin induced kallikrein 5 and activates PAR-2 resulting in thymic stromal lymphopoietin secretion, cutaneous T-helper 2 response and finally eczematous reactions. In contrast, weak acidification of eczematous skin in mice reduced kallikrein 5 activity and thus ameliorated dermatitis in this model.[85,86]

After skin barrier disruption by tape-stripping, the SC pH is increased by 0.8–1 units in humans and mice. Experimental barrier disruption by tape-stripping, acetone or sodium lauryl sulfate leads to an injury of keratinocytes and therefore the active process of SC acidification may be disturbed. Application of an acidic solution after barrier disruption leads to a lower increase of pH as compared with application of a neutral or alkaline solution. pH values are normalized during skin barrier repair in parallel with the recovery of the elevated TEWL.[19,30]

PH IN INFLAMMATORY SKIN DISEASES AND ITCH

Inflammatory skin diseases involving the epidermis exhibit an increased pH. In lesional atopic dermatitis compared with non-lesional skin, pH is increased by 0.2–0.3 units and in non-lesional skin compared with healthy controls pH is increased by 0.2 units.[87,88] Increase of 0.3 pH units means half the concentration of H^+-ions, which significantly influences biochemical processes (Fig. 4). pH is also increased in contact dermatitis and radiodermatitis.[89,90]

In ichthyosis vulgaris, in particularly in homozygotes, filaggrin deficiency results in an elevated pH, whereas in X-linked ichthyosis pH is only slightly increased.[89,91,92] The low pH in X-linked ichthyosis is explained by increased SC cholesterol sulfate exhibiting a pKa of 3.1.[93,94] In psoriasis, pH values are increased 0.3–0.4 units. pH is also increased in dry and in sensitive skin.[87,95] Moreover, in diaper dermatitis an increase in pH is proportional to disease severity. Ammonia-induced alkalization activates stool enzymes lipase and tryptase leading to irritation.[89,96] In addition, even in acne and rosacea the mean facial SC pH is significantly increased.[97,98]

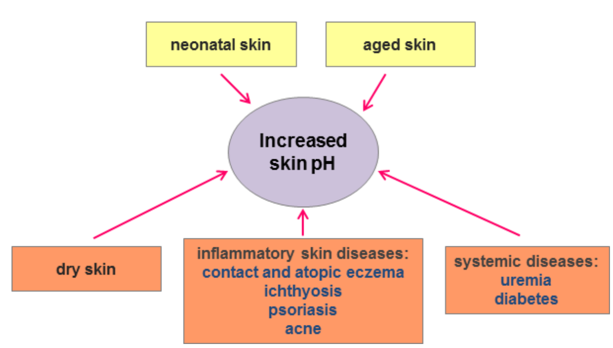

Figure 4. Conditions and diseased with increased skin pH.

Interestingly, the SC pH of hemodialyzed patients is increased despite the fact that these patients have a decreased blood pH. One should note that the SC pH is not related to systemic acid-base balance, although uremia indirectly may affect the skin's ability to secrete acids making the skin susceptible to infections.[99] A reason for the increased pH in uremia may also be the well-known dry skin. Increased pH and dry skin activate proteinase-activated receptor-2 leading to pruritus in these patients, because extra- and intracellular proton concentration modulates afferent (itch and pain) and efferent (cell growth, differentiation and survival) functions (Fig. 4).[16,86]

REDUCING SKIN PH AS A THERAPEUTIC TOOL IN WOUND HEALING, SKIN DISEASES, NEWBORN AND AGED SKIN

Reducing skin pH by acidification is a well-known concept for treating wounds. An acidic environment created by use of acids, such as acetic acid, boric acid, ascorbic acid, alginic acid and hyaluronic acid helps in wound healing by controlling wound infection, increasing antimicrobial activity, altering protease activity, releasing oxygen, reducing toxicity of bacterial end products, and enhancing epithelization and angiogenesis. Most of the pathogenic bacteria associated with infected skin wounds need a pH value of more than 6, while their growth is inhibited at lower pH values.[100] The re-establishment of a functional barrier is the “driver” of healing, and that is how acidification could enhance healing.[101]

Reducing pH has been suggested as a therapeutic or preventive strategy in skin diseases with a more superficial impairment. Products have been developed to alter skin's pH. Several topical skin care products are adjusted to pH 5.4 or 5.5 aimed to preserve the “physiological” skin pH. However, adult skin exhibits a pH range of 4.1–5.8 (mean 4.9). Recently, products with a more acidic pH than 5.4 (e.g. pH 4) and containing a functioning buffer system were introduced to counteract an increased pH. Treatment with an acidic compared with a neutral cream inhibited the occurrence of atopic dermatitis-like skin lesions and respiratory allergy in filaggrin-deficient murine atopic dermatitis models.[102–104] An emollient with a pH of 4.8 altered skin barrier and microbes in infants at risk for developing atopic dermatitis.[105] Skin care products adjusted to pH 4 have been used successfully in acne skin.[106] These products improve the physiological microbial flora, skin barrier and lipid lamellae structure, reduce skin dryness and have been described to be more favorable compared with formulations with a pH of 5.8–6.0.[97,107–110] Newborn and aged skin exhibit an increased SC pH, too. Increased pH and dry skin could be partly related to a decrease of filaggrin content in the aged as described on the aged dry lower leg (Fig. 4).[111] Daily use of moisturizers on newborns and infants with an impaired skin barrier and increased SC pH is helpful in preventing the atopic march.[112,113] A glycolic acid-containing moisturizer with pH 4 reduces the SC pH in healthy, elderly and diabetic subjects,[107–110,114] possibly by influencing cathepsin D-like and chymotrypsin-like proteinases.[115]

It is important to note that not only the pH and the buffer capacity but also the composition of preparations is important for the treatment of skin diseases and conditions. Buffers adjusted to a specific pH may contain citrate, phosphate or glycolate, or a combination. These compounds have several effects on skin integrity, for example, enhancing SC hydration by glycolate. Polyhydroxy acids, lactobionic acid or gluconolactone have been used in hairless mice and reduced the pH at all levels of SC.[116] Polyhydroxy acids and gluconolactone are used as keratolytic compounds in acne treatment.[117]

Therefore, products with a more acidic pH, maintained by an appropriate buffer system and appropriate ingredients may be suitable for several skin conditions like eczema, ichthyosis, dry skin, psoriasis, acne, rosacea and aged skin.

CONCLUSION

The pH plays an important physiological role in ecological systems, in mammals, the human body and in the skin. The role of the SC pH has historically been attributed to antimicrobial defense; however, the latest research points to the regulation of skin barrier function, epidermal differentiation and desquamation. Inflammatory skin diseases, dry, aged and pruritic skin show an increased skin pH. These diseases and conditions may be improved significantly by topical preparations with an acidic pH and appropriate buffer system.

CONFLICT OF INTEREST: The author has participated in an expert panel organized by Dr August Wolff GmbH & Co. KG, Arzneimittel, Germany.

REFERENCES

1 Slessarev E, Lin Y, Bingham N *et al.* Water balance creates a threshold in soil pH at the global scale. *Nature* 2016; **540**: 567.
2 Sabatini S, Kurtzman NA. Bicarbonate therapy in severe metabolic acidosis. *J Am Soc Nephrol* 2009; **20**: 692–695.
3 Nobandegani NM, Mahmoudi S, Pourakbari B *et al.* Antimicrobial susceptibility of microorganisms isolated from sputum culture of patients with cystic fibrosis: Methicillin-resistant Staphylococcus aureus as a serious concern. *Microb Pathog* 2016; **100**: 201–204.
4 Pezzulo AA, Tang XX, Hoegger MJ *et al.* Reduced airway surface pH impairs bacterial killing in the porcine cystic fibrosis lung. *Nature* 2012; **487**: 109–113.
5 Johansson M, Jansson T, Pestov N *et al.* Non-gastric H+/K+ ATPase is present in the microvillous membrane of the human placental syncytiotrophoblast. *Placenta* 2004; **25**: 505–511.
6 Hatlebakk J. Gastric acidity−comparison of esomeprazole with other proton pump inhibitors. *Aliment Pharmacol Ther* 2003; **17**: 10–15.
7 Norn MS. Human tear pH. *Arch Ophthalmol* 1977; **95**: 170.
8 King TL, Brucker MC. Pharmacology for women's health. *J Midwifery Womens Health* 2010; **55**: 394.
9 Kingston A. The postmenopausal vulva. *Obstetrician & Gynaecologist* 2009; **11**: 253–259.
10 Farage MA, Miller KW, Maibach HI. *Textbook of Aging Skin*. New York, NY: Springer Science & Business Media, 2009.
11 Schmid-Wendtner M-H, Korting HC. The pH of the skin surface and its impact on the barrier function. *Skin Pharmacol Physiol* 2006; **19**: 296–302.

12 Segger D, Aßmus U, Brock M *et al.* Multicenter study on measurement of the natural pH of the skin surface. *Int J Cosmet Sci* 2008; **30**: 75.
13 Lambers H, Piessens S, Bloem A *et al.* Natural skin surface pH is on average below 5, which is beneficial for its resident flora. *Int J Cosmet Sci* 2006; **28**: 359–370.
14 Marrakchi S, Maibach HI. Biophysical parameters of skin: map of human face, regional, and age-related differences. *Contact Dermatitis* 2007; **57**: 28–34.
15 Kleesz P, Darlenski R, Fluhr J. Full-body skin mapping for six biophysical parameters: baseline values at 16 anatomical sites in 125 human subjects. *Skin Pharmacol Physiol* 2012; **25**: 25–33.
16 Ali SM, Yosipovitch G. Skin pH: from basic science to basic skin care. *Acta Derm Venereol* 2013; **93**: 261–269.
17 Fluhr J, Darlenski R, Lachmann N *et al.* Infant epidermal skin physiology: adaptation after birth. *Br J Dermatol* 2012; **166**: 483–490.
18 Joseph N, Bourliere F, Molimard R. Titration curves of human epidermis in relation to age. In: Federation Proceedings, Vol. **16**: Federation Amer Soc Exp Biol 9650 Rockville Pike, Bethesda, MD 20814-3998. 1957; 202.
19 Choi E-H, Man M-Q, Xu P *et al.* Stratum corneum acidification is impaired in moderately aged human and murine skin. *J Invest Dermatol* 2007; **127**: 2847–2856.
20 Man M, Xin S, Song S *et al.* Variation of skin surface pH, sebum content and stratum corneum hydration with age and gender in a large Chinese population. *Skin Pharmacol Physiol* 2009; **22**: 190–199.
21 Schreml S, Zeller V, Meier RJ *et al.* Impact of age and body site on adult female skin surface pH. *Dermatology* 2012; **224**: 66–71.
22 Luebberding S, Krueger N, Kerscher M. Age-related changes in male skin: quantitative evaluation of one hundred and fifty male subjects. *Skin Pharmacol Physiol* 2014; **27**: 9–17.
23 Levin J, Maibach H. Human skin buffering capacity: an overview. *Skin Res Technol* 2008; **14**: 121–126.
24 Levin J, Maibach H. pH buffering considerations in mature skin. *Cosmetics & Toiletries* 2011; **126**: 422–428.
25 Luebberding S, Krueger N, Kerscher M. Age-related changes in skin barrier function–Quantitative evaluation of 150 female subjects. *Int J Cosmet Sci* 2013; **35**: 183–190.
26 Schreml S, Meier RJ, Wolfbeis OS *et al.* 2D luminescence imaging of pH *in vivo*. *Proc Natl Acad Sci* 2011; **108**: 2432–2437.
27 Turner NG, Cullander C, Guy RH. Determination of the pH gradient across the stratum corneum. *J Investig Dermatol Symp Proc* 1998; **3**: 110–113.
28 Hanson KM, Behne MJ, Barry NP *et al.* Two-photon fluorescence lifetime imaging of the skin stratum corneum pH gradient. *Biophys J* 2002; **83**: 1682–1690.
29 Furuichi Y, Matsui T, Amagai M. Real time 3D *in vivo* pH imaging of stratum corneum revealed complex morphology-based regulation in mice. *J Dermatol Sci* 2017; **86**: e40.
30 Proksch E, Soeberdt M, Neumann C *et al.* Skin pH and barrier recovery after application of buffers of different pH and composition 45th Annual Meeting of the Arbeitsgemeinscha Dermatologische Forschung (ADF). *Exp Dermatol* 2018.
31 Oh WS, Oh TH. Mapping of the dog skin based on biophysical measurements. *Vet Dermatol* 2010; **21**: 367–372.
32 Zając M, Szczepanik MP, Wilkołek PM *et al.* Assessment of a correlation between Canine Atopic Dermatitis Extent and Severity Index (CADESI-03) and selected biophysical skin measures (skin hydration, pH, and erythema intensity) in dogs with naturally occurring atopic dermatitis. *Can J Vet Res* 2015; **79**: 136–140.
33 Szczepanik MP, Wilkołek PM, Adamek ŁR *et al.* The examination of biophysical parameters of skin (transepidermal water loss, skin hydration and pH value) in different body regions of normal cats of both sexes. *J Feline Med Surg* 2011; **13**: 224–230.
34 Szczepanik M, Wilkołek P, Pluta M *et al.* The examination of biophysical skin parameters (transepidermal water loss, skin hydration and pH value) in different body regions in Polish ponies. *Pol J Vet Sci* 2013; **16**: 741–747.
35 Draize JH. The determination of the pH of the skin of man and common laboratory animals. *J Invest Dermatol* 1942; **5**: 77–85.
36 Rawlings AV, Matts PJ. Stratum corneum moisturization at the molecular level: an update in relation to the dry skin cycle. *J Invest Dermatol* 2005; **124**: 1099–1110.
37 Fluhr JW, Kao J, Ahn SK *et al.* Generation of free fatty acids from phospholipids regulates stratum corneum acidification and integrity. *J Invest Dermatol* 2001; **117**: 44–51.
38 Fluhr JW, Behne MJ, Brown BE *et al.* Stratum corneum acidification in neonatal skin: secretory phospholipase A 2 and the sodium/hydrogen antiporter-1 acidify neonatal rat stratum corneum. *J Invest Dermatol* 2004; **122**: 320–329.
39 Krien PM, Kermici M. Evidence for the existence of a self-regulated enzymatic process within the human stratum corneum–an unexpected role for urocanic acid. *J Invest Dermatol* 2000; **115**: 414–420.
40 Fluhr JW, Elias PM, Man M-Q *et al.* Is the filaggrin–histidine–urocanic acid pathway essential for stratum corneum acidification? *J Invest Dermatol* 2010; **130**: 2141.
41 Kawasaki H, Nagao K, Kubo A *et al.* Altered stratum corneum barrier and enhanced percutaneous immune responses in filaggrin-null mice. *J Allergy Clin Immunol* 2012; **129**(1538–46): e6.
42 Perusquía-Ortiz A, Oji V, Sauerland M *et al.* Complete filaggrin deficiency in ichthyosis vulgaris is associated with only moderate changes in epidermal permeability barrier function profile. *J Eur Acad Dermatol Venereol* 2013; **27**: 1552–1558.
43 Winge MC, Hoppe T, Berne B *et al.* Filaggrin genotype determines functional and molecular alterations in skin of patients with atopic dermatitis and ichthyosis vulgaris. *PLoS ONE* 2011; **6**: e28254.
44 Chapman SJ, Walsh A. Membrane-coating granules are acidic organelles which possess proton pumps. *J Invest Dermatol* 1989; **93**: 466–470.
45 Mindell JA. Lysosomal acidification mechanisms. *Annu Rev Physiol* 2012; **74**: 69–86.
46 Ilic D, Bollinger JM, Gelb M *et al.* sPLA2 and the epidermal barrier. *Biochim Biophys Acta* 2014; **1841**: 416–421.
47 Mao-Qiang M, Feingold KR, Jain M *et al.* Extracellular processing of phospholipids is required for permeability barrier homeostasis. *J Lipid Res* 1995; **36**: 1925–1935.
48 Hoppe U, Kopplow H, Sauermann G. Einfluß von Puffersystemen auf die pHWerte der Erwachsenenhaut. Ärztl. Kosmetok> gie7 1977; **75**.
49 Pascher G, von Steinruck G, Spier H. The water-soluble ingredients of the peripheral horny layer of the skin; quantitative analyses. V. Inhomogeneous distribution of alpha-amino-nitrogen, lactic acid, chloride, potassium (and sodium) in the stratum disjunctum. *Arch Klin Exp Dermatol* 1957; **204**: 140.
50 Man M-Q, Lin T-K, Santiago JL *et al.* Basis for enhanced barrier function of pigmented skin. *J Invest Dermatol* 2014; **134**: 2399–2407.
51 Ancans J, Tobin DJ, Hoogduijn MJ *et al.* Melanosomal pH controls rate of melanogenesis, eumelanin/phaeomelanin ratio and melanosome maturation in melanocytes and melanoma cells. *Exp Cell Res* 2001; **268**: 26–35.
52 Gunathilake R, Schurer NY, Shoo BA *et al.* pH-regulated mechanisms account for pigment-type differences in epidermal barrier function. *J Invest Dermatol* 2009; **129**: 1719–1729.
53 Behne MJ, Meyer JW, Hanson KM *et al.* NHE1 regulates the stratum corneum permeability barrier homeostasis Microenvironment acidification assessed with fluorescence lifetime imaging. *J Biol Chem* 2002; **277**: 47399–47406.
54 Behne MJ, Barry NP, Hanson KM *et al.* Neonatal development of the stratum corneum pH gradient: localization and mechanisms leading to emergence of optimal barrier function. *J Invest Dermatol* 2003; **120**: 998–1006.
55 Weiß KT, Fante M, Köhl G *et al.* Proton-sensing G protein-coupled receptors as regulators of cell proliferation and migration during

tumor growth and wound healing. *Exp Dermatol* 2017; **26**: 127–132.
56 Denda M, Tsutsumi M, Goto M *et al.* Topical application of TRPA1 agonists and brief cold exposure accelerate skin permeability barrier recovery. *J Invest Dermatol* 2010; **130**: 1942–1945.
57 Yang P, Feng J, Luo J, Madison M, Hu H. Neurobiology of TRP Channels. In: Emir TLR, ed. *A Critical Role for TRP Channels in the Skin*, 2nd edn. Boca Raton, FL: CRC Press/Taylor & Francis, 2017.
58 Higuchi K, Kawashima M, Takagi Y *et al.* Sphingosylphosphorylcholine is an activator of transglutaminase activity in human keratinocytes. *J Lipid Res* 2001; **42**: 1562–1570.
59 Okamoto R, Arikawa J, Ishibashi M *et al.* Sphingosylphosphorylcholine is upregulated in the stratum corneum of patients with atopic dermatitis. *J Lipid Res* 2003; **44**: 93–102.
60 Ryborg AK, Johansen C, Iversen L *et al.* Lysophosphatidylcholine induces keratinocyte differentiation and upregulation of AP-1-and NF-κB DNA-binding activity. *Acta Derm Venereol* 2004; **84**: 433–438.
61 Xu Y. Sphingosylphosphorylcholine and lysophosphatidylcholine: G protein-coupled receptors and receptor-mediated signal transduction. *Biochim Biophys Acta* 2002; **1582**: 81–88.
62 Ehlers C, Ivens U, Møller M *et al.* Comparison of two pH meters used for skin surface pH measurement: the pH meter 'pH900'from Courage & Khazaka versus the pH meter '1140'from Mettler Toledo. *Skin Res Technol* 2001; **7**: 84–89.
63 Burckhardt W. Protective function of the skin against the external environment, with special reference to its buffer capacity against alkalis and acids. *Schweiz Med Wochenschr* 1957; **87**: 1525–1529.
64 Lotmar R. Potentiometric titration as a new method for determining the buffer capacity of the human skin. *Arch Klin Exp Dermatol* 1964; **219**: 610.
65 Ayer J, Maibach HI. Human skin buffering capacity against a reference base sodium hydroxide: *in vitro* model. *Cutan Ocul Toxicol* 2008; **27**: 271–281.
66 Miajlovic H, Fallon PG, Irvine AD *et al.* Effect of filaggrin breakdown products on growth of and protein expression by Staphylococcus aureus. *J Allergy Clin Immunol* 2010; **126**(1184–90): e3.
67 Korting H, Bau A, Baldauf P. pH-Abhängigkeit des Wachstumsverhaltens von Staphylococcus aureus und Propionibacterium acnes. *Ärztl Kosmetol* 1987; **17**: 41–53.
68 Korting H, Greiner K, Hübner K *et al.* Changes in skin pH and resident flora by washing with synthetic detergent preparations at pH 5.5 and 8.5. *J Soc Cosmet Chem* 1991; **42**: 147–158.
69 Abels C, Kaszuba A, Michalak I *et al.* A 10% glycolic acid containing oil-in-water emulsion improves mild acne: a randomized double-blind placebo-controlled trial. *J Cosmet Dermatol* 2011; **10**: 202–209.
70 Nerandzic MM, Sankar C, Setlow P *et al.* A cumulative spore killing approach: synergistic sporicidal activity of dilute peracetic acid and ethanol at low pH against Clostridium difficile and Bacillus subtilis spores. *Open Forum Infect Dis* 2016; **3**: ovf206.
71 Sasai-Takedatsu M, Kojima T, Yamamoto A *et al.* Reduction of Staphylococcus aureus in atopic skin lesions with acid electrolytic water-a new therapeutic strategy for atopic dermatitis. *Allergy* 1997; **52**: 1012–1016.
72 Selander C, Zargari A, Möllby R *et al.* Higher pH level, corresponding to that on the skin of patients with atopic eczema, stimulates the release of Malassezia sympodialis allergens. *Allergy* 2006; **61**: 1002–1008.
73 Lee WJ, Kim JY, Song CH *et al.* Disruption of barrier function in dermatophytosis and pityriasis versicolor. *J Dermatol* 2011; **38**: 1049–1053.
74 Brasch J, Zaldua M. Enzyme patterns of dermatophytes. *Mycoses* 1994; **37**: 11–16.
75 Malik E, Dennison SR, Harris F *et al.* pH Dependent Antimicrobial Peptides and Proteins, Their Mechanisms of Action and Potential as Therapeutic Agents. *Pharmaceuticals* 2016; **9**: 67.
76 Lieckfeldt R, Villalaín J, Gómez-Fernández J-C *et al.* Apparent pK a of the fatty acids within ordered mixtures of model human stratum corneum lipids. *Pharm Res* 1995; **12**: 1614–1617.
77 Jensen J-M, Pfeiffer S, Witt M *et al.* Different effects of pimecrolimus and betamethasone on the skin barrier in patients with atopic dermatitis. *J Allergy Clin Immunol* 2009; **124**: R19–R28.
78 Jensen J-M, Schütze S, Förl M *et al.* Roles for tumor necrosis factor receptor p55 and sphingomyelinase in repairing the cutaneous permeability barrier. *J Clin Invest* 1999; **104**: 1761.
79 Mauro T, Grayson S, Gao WN *et al.* Barrier recovery is impeded at neutral pH, independent of ionic effects: implications for extracellular lipid processing. *Arch Dermatol Res* 1998; **290**: 215–222.
80 Jensen JM, Förl M, Winoto-Morbach S *et al.* Acid and neutral sphingomyelinase, ceramide synthase, and acid ceramidase activities in cutaneous aging. *Exp Dermatol* 2005; **14**: 609–618.
81 Egberts F, Heinrich M, Jensen J-M *et al.* Cathepsin D is involved in the regulation of transglutaminase 1 and epidermal differentiation. *J Cell Sci* 2004; **117**: 2295–2307.
82 Jiang YJ, Uchida Y, Lu B *et al.* Ceramide stimulates ABCA12 expression via peroxisome proliferator-activated receptor δ in human keratinocytes. *J Biol Chem* 2009; **284**: 18942–18952.
83 Hachem J-P, Crumrine D, Fluhr J *et al.* pH directly regulates epidermal permeability barrier homeostasis, and stratum corneum integrity/cohesion. *J Invest Dermatol* 2003; **121**: 345–353.
84 Furio L, de Veer S, Jaillet M *et al.* Transgenic kallikrein 5 mice reproduce major cutaneous and systemic hallmarks of Netherton syndrome. *J Exp Med* 2014; **10**: 499–513.
85 Jang H, Matsuda A, Jung K *et al.* Skin pH is the master switch of kallikrein 5-mediated skin barrier destruction in a murine atopic dermatitis model. *J Invest Dermatol* 2016; **136**: 127–135.
86 Steinhoff M, Neisius U, Ikoma A *et al.* Proteinase-activated receptor-2 mediates itch: a novel pathway for pruritus in human skin. *J Neurosci* 2003; **23**: 6176–6180.
87 Ring J, Eberlein-König B, Schäfer T *et al.* Skin surface pH, stratum corneum hydration, trans-epidermal water loss and skin roughness related to atopic eczema and skin dryness in a population of primary school children: clinical report. *Acta Derm Venereol* 2000; **80**: 188–191.
88 Seidenari S, Giusti G. Objective assessment of the skin of children affected by atopic dermatitis: a study of pH, capacitance and TEWL in eczematous and clinically uninvolved skin. *Acta Derm Venereol* 1995; **75**: 429–433.
89 Rippke F, Schreiner V, Schwanitz H-J. The acidic milieu of the horny layer. *Am J Clin Dermatol* 2002; **3**: 261–272.
90 Jang H, Myung H, Lee J *et al.* Impaired skin barrier due to sebaceous gland atrophy in the latent stage of radiation-induced skin injury: application of non-invasive diagnostic methods. *Int J Mol Sci* 2018; **19**: 185.
91 Öhman H, Vahlquist A. The pH gradient over the stratum corneum differs in X-linked recessive and autosomal dominant ichthyosis: a clue to the molecular origin of the "acid skin mantle"? *J Invest Dermatol* 1998; **111**: 674–677.
92 Gruber R, Elias PM, Crumrine D *et al.* Filaggrin genotype in ichthyosis vulgaris predicts abnormalities in epidermal structure and function. *Am J Pathol* 2011; **178**: 2252–2263.
93 Bouwstra JA, Gooris GS, Dubbelaar FE *et al.* pH, cholesterol sulfate, and fatty acids affect the stratum corneum lipid organization. *J Investig Dermatol Symp Proc* 1998; **3**: 69–74.
94 Elias PM. Stratum corneum acidification: how and why? *Exp Dermatol* 2015; **24**: 179–180.
95 Seidenari S, Francomano M, Mantovani L. Baseline biophysical parameters in subjects with sensitive skin. *Contact Dermatitis* 1998; **38**: 311–315.
96 Berg RW, Milligan MC, Sarbaugh FC. Association of skin wetness and pH with diaper dermatitis. *Pediatr Dermatol* 1994; **11**: 18–20.
97 Prakash C, Bhargava P, Tiwari S *et al.* Skin surface pH in acne vulgaris: insights from an observational study and review of the literature. *J Clin Aesthet Dermatol* 2017; **10**: 33.
98 Ní Raghallaigh S, Powell F. Epidermal hydration levels in patients with rosacea improve after minocycline therapy. *Br J Dermatol* 2014; **171**: 259–266.

99 Yosipovitch G, Tur E, Morduchowicz G *et al.* Skin surface pH, moisture, and pruritus in haemodialysis patients. *Nephrol Dial Transplant* 1993; **8**: 1129–1132.
100 Nagoba BS, Suryawanshi NM, Wadher B *et al.* Acidic environment and wound healing: A review. *Wounds* 2015; **27**: 5–11.
101 Elias PM, Ansel JC, La Donna CW *et al.* Signaling networks in barrier homeostasis: the mystery widens. *Arch Dermatol* 1996; **132**: 1505–1506.
102 Hatano Y, Man M-Q, Uchida Y *et al.* Maintenance of an acidic stratum corneum prevents emergence of murine atopic dermatitis. *J Invest Dermatol* 2009; **129**: 1824–1835.
103 Lee HJ, Lee NR, Kim BK *et al.* Acidification of stratum corneum prevents the progression from atopic dermatitis to respiratory allergy. *Exp Dermatol* 2017; **26**: 66–72.
104 Panther DJ, Jacob SE. The importance of acidification in atopic eczema: an underexplored avenue for treatment. *J Clin Med* 2015; **4**: 970–978.
105 Glatz M, Jo J-H, Kennedy EA *et al.* Emollient use alters skin barrier and microbes in infants at risk for developing atopic dermatitis. *PLoS ONE* 2018; **13**: e0192443.
106 Abels C, Reich H, Knie U *et al.* Significant improvement in mild acne following a twice daily application for 6 weeks of an acidic cleansing product (pH 4). *J Cosmet Dermatol* 2014; **13**: 103–108.
107 Abels C, Masur C, Daehnhardt-Pfeiffer S *et al.* 413 Formulation with low pH decreases skin pH, restores disrupted epidermal barrier and improves lipid lamellae structure. *J Invest Dermatol* 2017; **137**: S71.
108 Angelova-Fischer I, Knie U, Zillikens D *et al.* Topical application of a ph 4.0 w/o emulsion improves the epidermal barrier function and recovery in aged skin. *J Dtsch Dermatol Ges* 2016; **14**: 16–17.
109 Blaak J, Dähnhardt D, Dähnhardt-Pfeiffer S *et al.* A plant oil-containing pH 4 emulsion improves epidermal barrier structure and enhances ceramide levels in aged skin. *Int J Cosmet Sci* 2017; **39**: 284–291.
110 Blaak J, Kaup O, Hoppe W *et al.* A long-term study to evaluate acidic skin care treatment in nursing home residents: impact on epidermal barrier function and microflora in aged skin. *Skin Pharmacol Physiol* 2015; **28**: 269–279.
111 Tezuka T, Qing J, Saheki M *et al.* Terminal differentiation of facial epidermis of the aged: immunohistochemical studies. *Dermatology* 1994; **188**: 21–24.
112 Czarnowicki T, Krueger JG, Guttman-Yassky E. Novel concepts of prevention and treatment of atopic dermatitis through barrier and immune manipulations with implications for the atopic march. *J Allergy Clin Immunol* 2017; **139**: 1723–1734.
113 Xu S, Immaneni S, Hazen GB *et al.* Cost-effectiveness of prophylactic moisturization for atopic dermatitis. *JAMA Pediatr* 2017; **171**: e163909.
114 Behm B, Kemper M, Babilas P *et al.* Impact of a glycolic acid-containing pH 4 water-in-oil emulsion on skin pH. *Skin Pharmacol Physiol* 2015; **28**: 290–295.
115 Horikoshi T, Matsumoto M, Usuki A *et al.* Effects of glycolic acid on desquamation-regulating proteinases in human stratum corneum. *Exp Dermatol* 2005; **14**: 34–40.
116 Hachem J-P, Roelandt T, Schürer N *et al.* Acute acidification of stratum corneum membrane domains using polyhydroxyl acids improves lipid processing and inhibits degradation of corneodesmosomes. *J Invest Dermatol* 2010; **130**: 500–510.
117 Tolino E, Skroza N, Mambrin A *et al.* Novel combination for the treatment of acne differentiated according to gender: a new step towards personalized treatment. *G Ital Dermatol Venereol* 2018; https://doi.org/10.23736/S0392-0488.18.05710-3
118 Lin T-K, Crumrine D, Ackerman LD *et al.* Cellular changes that accompany shedding of human corneocytes. *J Invest Dermatol* 2012; **132**: 2430–2439.

