

# The how, why and clinical importance of stratum corneum acidification

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## Abstract

In this article, I review the multiple endogenous mechanisms that contribute to the highly acidic pH of normal stratum corneum (SC). Then, I describe how each mechanism potentially impacts specific defensive functions of the SC. Finally, I review the rapidly expanding, clinical implications and potential therapeutic applications of SC acidification.

## KEYWORDS

acidification, barrier function, pH, stratum corneum

## 1 | INTRODUCTION

While long suspected to be an important regulator of cutaneous antimicrobial defense, the “acid mantle” of the stratum corneum (SC) is also a critical regulator of at least three other critical functions—permeability barrier homeostasis, the integrity/cohesion (desquamation) of the SC and restriction of pro-inflammatory cytokine signalling (ie dampening of inflammation).<sup>[1,2]</sup> As a result, topical products increasingly are being developed at a reduced pH to exploit these advantages. The pH of normal human SC ranges from 4.5 to 5.5, with the lowest levels occurring in darkly pigmented individuals, independent of race or ethnicity.<sup>[3]</sup> Moreover, the extracellular domains of normal SC are even more acidic than the corneocyte cytosol, with pH levels of <5.<sup>[4]</sup> The question often arises as to how one can measure pH in such lipid-enriched domains. Although these domains contain abundant hydrophobic lipids in the form of lamellar bilayers, these membranes possess hydrophilic head-group domains. Moreover, corneodesmosomes, which are hydrophilic, traverse the extracellular spaces, and as they are proteolytically degraded, they form lacunae filled with the hydrolytic products that also are hydrophilic. Finally, we have shown that the lacunar domains imbibe water and expand to encompass up to 40% of SC volume.<sup>[5]</sup> We consider herein (i) how and why these sites become selectively acidified; (ii) the functional impact of site-specific acidification; (iii) the clinical implications of

this emerging area of research; and (iv) still unresolved questions about SC acidification.

## 2 | ORIGINS OF THE ACID MANTLE

For several decades after its discovery, it was widely assumed that the low pH of the SC resulted from the deposition of sebaceous gland (SG)-derived free fatty acids (FFA) on the skin surface. But it is now evident that secreted SG products are not required for SC acidification and may not even impact the pH of the skin surface. For example, the pH of SG-depleted (asebia) mice is as acidic as in wild-type mice,<sup>[6]</sup> and SG-impooverished skin sites of humans are as acidic as adjacent, SG-enriched sites.<sup>[7]</sup>

Instead, at least four and likely five endogenous mechanisms account for the global reduction in the pH of the SC, as well as the further selective acidification of extracellular vs cytosolic SC compartments (Table 1). Yet, in assessing the role of each mechanism, it is essential to know whether they selectively impact extracellular vs cytosolic domains, or whether they more broadly impact both compartments. This distinction is critical, because certain SC functions, such as SC cohesion/desquamation and barrier function, are mediated by extracellular mechanisms, while in contrast, antimicrobial defense and the dampening of inflammation instead may largely localize to the corneocyte cytosol (note: inflammation in disorders associated with acute or chronic barrier abnormalities begins with the pH-dependent, enzymatic activation of interleukins 1 $\alpha$  and 1 $\beta$ , which are stored as their 33-kDa pro-forms in the corneocyte cytosol—see below). Here, I

**Abbreviations:** AD, atopic dermatitis; CSO<sub>4</sub>, cholesterol sulphate; FFA, free fatty acids; FLG, filaggrin; KLK, kallikrein; NHE1, sodium-hydrogen antiporter type 1; SC, stratum corneum; SG, sebaceous gland; sPLA, secretory phospholipase.

**TABLE 1** Endogenous SC acidifying mechanisms localize to different SC domains; are differentially expressed during development; and regulate different epidermal functions

Acidifying mechanisms	Change in bulk pH	Localization	Impact on epidermal functions	Changes during development
PL → FFA (PLA2G2F)	≈1 unit	?	Barrier, Cohesion+?	↓ Neonatal
NHE1	≈¼ unit	Extracellular domains of SG-SC interface	Barrier+?	↓ Aged
FLG → PCA (t-UCA)	≈1 unit	?	Barrier+?	?
Melanin persistence/extrusion	Transient	Extracellular domains of SG-SC interface	Barrier, Cohesion+?	?
CSO <sub>4</sub> ionization	?	Likely extracellular spaces of SC	Cohesion+?	?

Chol, cholesterol; CSO<sub>4</sub>, cholesterol sulphate; FFA, free fatty acid; FLG, filaggrin; NHE1, Na<sup>+</sup>/H<sup>+</sup> antiporter 1; PCA, polycarboxylic acid; PL, phospholipids; SC, stratum corneum; SG, stratum granulosum; SO<sub>4</sub>, sulphate; t-UCA, transurocanic acid?, unknown.

review the four established, endogenous mechanisms and then present evidence in support of a likely fifth mechanism.

## 2.1 | Mechanism 1

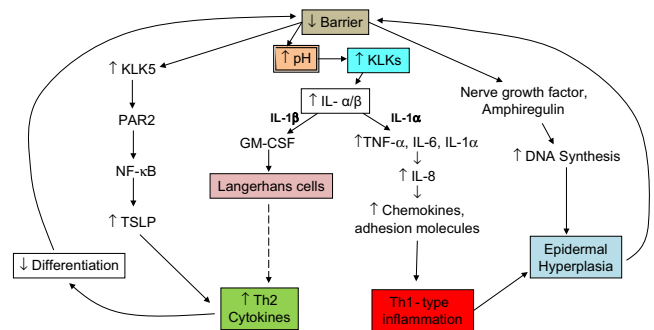
During terminal differentiation, *phospholipids* are fully hydrolysed to their constituent FFA by secretory phospholipases (sPLA2). Studies with pharmacologic inhibitors<sup>[8]</sup> and in transgenic mice with deletions in the *pla2g2f* isoform of sPLA2<sup>[9]</sup> show that phospholipid-derived FFA account for ≈one unit of SC bulk pH, but also that these FFA simultaneously become necessary components of the lamellar bilayers that mediate the permeability barrier.<sup>[8]</sup> Yet, whether the sPLA2 mechanism selectively acidifies only extracellular domains and/or whether it also impacts the pH within the corneocyte cytosol is not known.

## 2.2 | Mechanism 2

In transgenic mice with a selective knockout of the sodium-hydrogen antiporter type 1 (NHE1), the bulk pH of the SC increases by only ≈1/4 pH unit.<sup>[4]</sup> Yet, this mechanism selectively acidifies extracellular domains in the lower SC, the key site where both barrier function and SC cohesion initially become established, and where the earliest events leading to desquamation also are initiated.<sup>[10]</sup> Pertinently, the enzymes that regulate these functions all are lamellar body-derived products that are delivered to extracellular domains as the contents of these organelles are secreted. Of these enzymes, two are ceramide-generating hydrolases, β-glucocerebrosidase and acidic sphingomyelinase, which both require an acidic pH for optimal activity. Conversely, the extracellular kallikreins (KLKs) that initiate desquamation remain inactive at a reduced pH.<sup>[11]</sup> Together, the colocalization of a low pH along with secreted hydrolytic enzymes explains the impact of this acidifying mechanism on barrier function, SC cohesion and desquamation.

## 2.3 | Mechanism 3

The catabolism of filaggrin (FLG) into its constituent amino acids, followed by the further, downstream deimination of these amino



**FIGURE 1** pH-dependent, barrier-initiated cytokine cascades provoke inflammation and further barrier defects in inflammatory dermatoses (modified from Elias & Wakefield<sup>[15]</sup>). GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-1, interleukin-1; KLKs, kallikreins; NF-κB, nuclear factor kappa B; TNF-α, tumor necrosis factor alpha; TSLP, thymic stromal lymphopoietin

acids into polycarboxylic acids,<sup>[6]</sup> including trans-urocanic acid, accounts for about ½ unit of the bulk pH of the SC. The best evidence for this link is the pH changes that accompany loss-of-function mutations in *FLG* in ichthyosis vulgaris (IV), where single-allele mutations result in a ¼ unit increase in pH, while double-allele loss of function results in a ½ unit increase in surface pH.<sup>[12]</sup> If the protons generated via this mechanism remain largely localized to the corneocyte cytosol, they likely would suppress one or more KLKs, which exhibit neutral to alkaline pH optima. These KLKs in turn activate IL-1α and IL-1β as the pH of the SC increases following external insults,<sup>[13,14]</sup> or in inflammatory dermatoses.<sup>[15]</sup> The 33-kDa pro-forms of IL-1α/β are hydrolysed into their 17-kD active forms by these KLKs, initiating a series of cytokine cascades that eventually provoke inflammation (Fig. 1). The reduced pH of the corneocyte cytosol likely is also critical for antimicrobial defense (S1), because penetrating microorganisms are diverted from the cytosol, preferentially invading via the SC interstices, rather than across corneocytes (Fig. S1). However, the prevailing, higher-than-normal pH of IV renders these patients a “time bomb,” ready to develop inflammation (ie atopic dermatitis [AD] with any additional acquired insults to the

epidermal barrier; eg further elevations in pH from the use of alkaline soaps or surfactants).

## 2.4 | Mechanism 4

In darkly pigmented skin, single, large melanin granules are transferred from melanocytes to keratinocytes, which persist into the outer epidermis within highly acidic phagolysosomes. When these organelles eventually disperse, they likely release a pool of protons, which likely account for the further reductions in pH of the outer SC in darkly vs lightly pigmented skin, explaining its superior barrier function and cohesion.<sup>[3]</sup> In contrast, lightly pigmented individuals display an inferior permeability barrier, which is directly linked to an elevated pH, supported by the observation that exogenous acidification of lightly pigmented human skin with topical acidifying agent, lactobionic acid, “resets” barrier function to levels found in darkly pigmented individuals.<sup>[3]</sup>

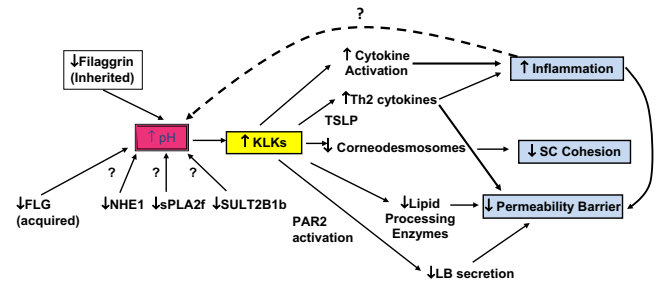
## 2.5 | A possible additional, fifth mechanism

Because mechanisms 1-4 account for only  $\approx 1.5$  to 2 units of SC pH, I am tentatively identifying a possible additional (“missing”) mechanism here: that is, cholesterol sulphate ( $\text{CSO}_4$ ) ionization and/or hydrolysis could account for the “missing” protons. This hypothesis is based first upon the lower-than-normal pH of SC in patients with X-linked ichthyosis (who have  $\approx 10$ -fold higher levels of  $\text{CSO}_4$ ). As noted above, while the extracellular domains are largely composed of lipid-enriched lamellar bilayers, SC extracellular domains also contain expandable hydrophilic domains, which expand further along the polar leaflets of the membrane bilayers, and at sites where corneodesmosomes are proteolytically degraded.<sup>[5]</sup> In normal SC,  $\text{CSO}_4$  ionization to  $\text{Chol} + \text{H}_2\text{SO}_4$  should also occur initially, but it also is possible that the progressive, steroid sulphatase-mediated degradation of  $\text{CSO}_4$  into cholesterol plus  $\text{SO}_4^-$  ions could also generate  $\text{H}_2\text{SO}_4$  in situ within hydrophilic extracellular domains of normal SC. Hence, two related,  $\text{CSO}_4$ -related mechanisms, that is ionization and hydrolysis, could contribute to the further acidification of normal SC.

## 3 | CLINICAL IMPLICATIONS OF SC ACIDIFICATION

### 3.1 | Developmental pH abnormalities

The elevated pH of neonatal SC, in combination with increased hydration, likely accounts for the tendency of neonates to develop both diaper dermatitis and perinatal skin infections (S2). But it also is possible that the increased propensity of neonatal skin to blister could also contribute to the faulty cohesion of neonatal epidermis. Conversely, treatment with PPAR $\alpha$ , PPAR $\beta/\delta$  or LXR activators, or by exogenous acidification with topical lactobionic acid or gluconolactone, accelerates the maturation of barrier function and SC cohesion in neonatal rat skin (S3, S4).



**FIGURE 2** Inherited/acquired elevations in pH activate kallikreins (KLKs), impacting multiple stratum corneum (SC) functions in atopic dermatitis. Multiple conditions, either inherited or acquired, elevate SC pH. Abnormal SC activity, in turn, acts through KLKs to impair multiple epidermal functions. Finally, inflammation could feed back to further negatively impact SC pH (dotted arrow) (modified from Elias & Wakefield<sup>[15]</sup>)

At the other end of the spectrum, moderately aged human SC (ages 50-65) exhibits an elevated pH, with proven adverse consequences for both barrier function and SC cohesion.<sup>[16]</sup> In analogous mouse models, the pH abnormality has been linked to decreased expression/activity of the NHE1 antiporter and sPLA2.<sup>[16]</sup> Here again, the importance of the pH abnormality was shown by the normalization of these functions with exogenous acidification.<sup>[16]</sup> Yet, whether this abnormality becomes even more pronounced with more advanced ageing is not known. Nonetheless, the pH abnormality could explain the increased propensity of chronologically aged skin to severe xerosis, excessive scaling and cutaneous infections.

### 3.2 | Elevated pH in inflammatory dermatoses

The pH of the SC inevitably increases towards neutrality in inflammatory dermatoses, due to the association with a barrier abnormality,<sup>[17]</sup> such as that occurs in AD,<sup>[18]</sup> disorders that are inevitably accompanied by abnormalities in permeability barrier homeostasis, SC cohesion, defective antimicrobial defense and increased cytokine-initiated inflammation (Fig. 1). AD is a “waste basket” of different genetic disorders that converge on the lamellar body secretory system (Fig. S2). As noted above, AD-prone patients with FLG mutations (ichthyosis vulgaris) exhibit allele-dependent elevations in pH ( $\approx$  half-unit increase), even in the absence of inflammation.<sup>[12]</sup> But it should be noted that FLG levels also decline in AD patients, even in those patients who are wild-type for FLG mutations, due in part to a Th2 cytokine-driven decline in the expression of differentiation-related proteins, including FLG (Fig. 2). Then, as inflammation supersedes “the IV scaling phenotype,” a further increase in pH creates a vicious circle of abnormalities that predispose atopics to a host of functional abnormalities, including the development of *Staphylococcus aureus* superinfections (Fig. 2). Conversely, maintenance of acidic pH alone largely prevents the development of AD in mouse models, likely by multiple salubrious mechanisms.<sup>[15]</sup> Moreover, exogenous acidification, when combined with other anti-inflammatory modalities, provides synergistic

benefits and prevents development of rebound flares of AD in hapten-induced, murine AD. The barrier abnormality accompanying FLG deficiency in turn allows the transcutaneous penetration of food and aeroallergens, predisposing affected children to the “atopic march” of AD asthma and then allergic rhinitis. Yet, as reported recently in this journal, Eung Ho Choi’s group at Yonsei University now show that topical acidification prevents the progression from AD towards aeroallergen-provoked asthma in three AD models (hapten-challenged, Nc/Nga mice); and as described in a recent issue of *Experimental Dermatology*, aeroallergen-induced asthma in flaky mice bearing two FLG mutations.<sup>[19]</sup>

### 3.3 | Future applications of acidification

Because the clinical benefits of acidification are becoming increasingly evident, wherever possible or appropriate, reduced pH emollients and cleansers should be deployed to prevent and treat AD. Moreover, it should also be noted that while classical (flexural) AD tends to disappear after adolescence, the underlying genetic predispositions persist into adulthood. Indeed, many types of eczematous dermatitis in adults occur more frequently in subjects with a prior history of AD than in the general population. Hence, comparable topical acidification strategies should also benefit adults with inflammatory dermatoses, who have a prior history of AD. It is important to note that acidification can be impacted either directly or indirectly, for example, by topical agents, such as PPARs and bioflavonoids that we have shown enhance NHE1 and sPLA2 expression.<sup>[20-23]</sup>

Wound healing represents another clinical arena where acidifying approaches could be useful. Wound beds, which are in contact with underlying tissues, likely exhibit a neutral pH, and this elevation in pH in turn would inevitably favour KLK-activated inflammatory mechanisms that could benefit the early stages of wound healing. But the ongoing, elevated pH in these wounds would inevitably favour colonization by pathogenic microbes and delay formation of a competent barrier in parallel with re-epithelialization. Hence, topical dressings, if applied in an acidic solution, should accelerate healing and prevent secondary infections in wounds.

Finally, an acidic approach could help prevent and treat incontinence-associated dermatitis, common in both hospitals and long-term care facilities. Urea and ammonia, the by-products of urine incontinence, as well as the proteases present in faecal incontinence, likely contribute to a higher pH environment and deterioration of skin barrier function, cohesion and inflammation. Consequently, topical acidification of affected skin could offer an intriguing new therapeutic approach (technology of this type already is being deployed in hospitals and long-term care facilities [eg TheraWorx<sup>®</sup> dressings; Avadim Technologies, Asheville, NC USA]).

### CONFLICT OF INTERESTS

The author is a consultant to Avadim Technologies, Inc., Asheville, NC.

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**SUPPORTING INFORMATION**

Additional Supporting Information may be found online in the supporting information tab for this article.

**DATA S1** References

**FIGURE S1** Exogenous *S. aureus* are diverted from a transcellular to an extracellular route as they attempt to penetrate the stratum corneum (SC) (Modified from Elias, PM. *Semin Immunopathol* 29: 3-14, 2007)

**FIGURE S2** How inherited abnormalities converge to produce defective permeability and antimicrobial barriers in AD

**How to cite this article:** Elias PM. The how, why and clinical importance of stratum corneum acidification. *Exp Dermatol.* 2017;26:999-1003. <https://doi.org/10.1111/exd.13329>