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REVIEW

The skin barrier as an innate immune element

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Abstract Since life in a terrestrial environment threatens mammals continuously with desiccation, the structural, cellular, biochemical, and regulatory mechanisms that sustain permeability barrier homeostasis have justifiably comprised a major thrust of prior and recent research on epidermal barrier function. Yet, the epidermis mediates a broad set of protective 'barrier' functions that includes defense against pathogen challenges. Permeability and antimicrobial function are both co-regulated and interdependent, overlapping through the dual activities of their lipid/protein constituents. Most of the defensive (barrier) functions of the epidermis localize to the stratum corneum (SC), which limits pathogen colonization through its low water content, acidic pH, resident (normal) microflora, and surface-deposited antimicrobial lipids (1° free fatty acid). These various barrier functions are largely mediated by either the corneocyte or the extracellular matrix, and it is both the localization and the organization of secreted hydrophobic lipids into characteristic lamellar bilayers that is critical not only for permeability barrier function, but also for antimicrobial function through its contribution to the maintenance of SC integrity. Low constitutive levels of antimicrobial peptides under basal conditions emphasize the key role of epithelial structure in antimicrobial defense. But antimicrobial peptide synthesis and delivery to the SC interstices accelerates after external insults to the barrier.

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Epidermis mediates multiple protective functions

Because life in a terrestrial environment threatens mammals continuously with desiccation, the structural, cellular, biochemical, and regulatory mechanisms that sustain permeability barrier homeostasis have justifiably comprised a major thrust of prior and recent research on epidermal barrier function [28, 32]. Yet, the epidermis mediates a broad set of protective (barrier) functions against; for example, microbial pathogen challenges, oxidant stress, including ultraviolet light, foreign chemical exclusion, mechanical insults, frictional resistance, and it serves as a distal outpost of the cutaneous inflammatory interface (Table 1).

It is now generally accepted that most of the defensive (barrier) functions of the epidermis localize to the stratum corneum (SC) [28]. These various barrier functions are largely mediated by either the corneocyte or the extracellular matrix, and they further localize to specific subcompartments in each (e.g., corneocyte envelope vs cytosol; Table 1). It is both the localization and the organization of the secreted hydrophobic lipids into characteristic lamellar bilayers that is critical not only for permeability barrier function but also for several other defensive functions through its contribution to the maintenance of SC integrity [30].

A key concept to emerge in recent years emphasizes the SC not as a dead tissue, but rather as possessing multiple types of catalytic (primarily catabolic) activity in both the cytosolic and membrane/extracellular compartments [25].

Table 1 Multiple protective functions of mammalian stratum corneum

Function	Principal compartment	Structural basis	Chemical basis	Regulatory signals (receptors)
Permeability[a,b]	Extracellular matrix	Lamellar bilayers	Ceramides, cholesterol, nonessential FA in proper ratio	IL-1α, Ca^{++}, nuclear hormone receptors, SP activation (PAR2)
Antimicrobial[a,b]	Extracellular matrix	Lamellar bilayers	Antimicrobial peptides, FFA, Sph	1,25 (OH)2D3; IL-1α
Antioxidant[b]	Extracellular matrix	Lamellar bilayers	Chol., FFA; secreted vit. E, redox gradient	?
Cohesion (integrity) →desquamation[a,b]	Extracellular matrix	Corneodesmosomes (CD)	Intercellular DSG1/DSC1 homodimers	pH, Ca^{++} (TPRV)
Mechanical/rheological[b]	Corneocyte	Cornified envelope; keratin filaments	γ-Glutamyl isopeptide bonds	Ca^{++}, CholSO4, nuclear hormone receptors
Chemical (antigen exclusion)[a,b]	Extracellular matrix	Extracellular lacunae	Hydrophilic products of CD	?
Psychosensory interface[b]	Extracellular matrix	Lamellar bilayers	Barrier lipids	Glucocorticoids, pH, heat osmotic Δs (TPRV1-3)
Hydration[b]	Corneocyte	Cytosol	Filaggrin proteolytic products; glycerol	Δs in relative humidity (TPRV4)
Electromagnetic radiation	Corneocyte	Cytosol	Cis-urocanic acid (histidase activity)	Δs in relative humidity
Initiation of inflammation (1° cytokine activation)[a,b]	Corneocyte	Cytosol	Proteolytic activation of pro-IL-1α/β	pH (TPRV1), SP activation

[a] Regulated by stratum corneum pH
[b] Abnormal in atopic dermatitis

Much of this activity either (1) generates the various 'barriers' described above, (2) regulates desquamation, (3) results in the generation of endogenous UV filters and osmotically active ingredients, and (4) results in the activation of primary cytokines.

Integrative aspects of various epidermal barriers

While each protective function of the skin can be considered as a discrete activity, these activities are often linked and even co-regulated [29]. For example, one type of external stressor, an increase in SC pH, can impact several defensive functions of the SC (Table 2). While an acidic pH is hostile to bacterial, yeast, and dermatophytic pathogens, elevations in pH instead support the growth of *Staphylococcus aureus*, *S. pyogenes*, and other pathogenic species [52]. In contrast, the negative impact of an increased pH on permeability barrier homeostasis, SC integrity/cohesion, and initiation of inflammation results from the activation of serine proteases, followed by signalling of diverse downstream mechanisms [39, 40].

A second type of stressor, which displays negative consequences for several epidermal functions, is psychological stress (PS; Table 2). PS, through an increase in endogenous glucocorticoids (GC), compromises permeability barrier homeostasis, SC integrity/cohesion [20, 50], and antimicrobial defense [2]. A mechanism that can largely account for these alterations comprises GC-mediated inhibition of epidermal lipid synthesis, resulting in a decline in lamellar body (LB) production [16, 50]. Ultimately, less LB contents get delivered to the SC interstices, protein into LB requires prior or concurrent lipid sequestration [71], antimicrobial peptide (AMP) cargo are not delivered to nascent LB [2]. For example, human β-defensin 2 (hBD2) and its murine homologue, mBD3, as well as the carboxyterminal product of human cathelicidin, LL-37, and its murine homologue, cathelicidin-related antimicrobial peptide (CRAMP), are first packaged within, and then secreted from LB [2, 10, 68]. Further, the negative effects of PS on the SC integrity/cohesion are also linked to the GC-induced lipid synthesis/secretory abnormality, although the responsible pathophysiologic mechanisms have not yet been elucidated. The proof of the link between decreased lipid generation and these three functional abnormalities could be demonstrated by the ability of topical physiologic lipid replenishment to largely or completely normalize these functions in the face of ongoing PS/GC [2, 14, 50].

Another type of functional interaction occurs when perturbations in one key function of the SC alter other defensive functions (Table 2), demonstrating that they are clearly-intertwined. For example, changes in SC hydration, resulting from either prolonged exposure to extremes of

Table 2 Linkage between multiple barrier functions

A. SINGLE STRESSOR CAN ALTER MULTIPLE FUNCTIONS

1) ↑ Psychological stress → ↑ Endogenous steroids →	↓ Permeability barrier ↓ SC Integrity/Cohesion ↓ Antimicrobial barrier
2) ↑ pH → ↑ Serine protease activity →	↓ Permeability barrier ↓ SC Integrity/Cohesion ↑ Cytokine activation ↓ Antimicrobial barrier by allowing pathogen colonization and ↑ Degradation of antimicrobial peptides
3) ↑ or ↓ SC hydration →	↑ or ↓ Permeability and antimicrobial barriers in parallel

B. ALTERATIONS IN 1 FUNCTION CAN ALTER ANOTHER FUNCTION

1) ↓ Mechanical strength → ↓ permeability barrier

2) Permeability barrier insults → ↑ antimicrobial and permeability barriers;
↓ resistance to percutaneous chemical/antigen/pathogen ingress
↑ inflammation

external humidity, or due to sudden shifts in extremes of humidity, produce significant alterations in permeability barrier function (Fig. 1). A further example pertinent to this review would be that barrier perturbations sufficient to accelerate transcutaneous water loss simultaneously allow ingress of xenobiotes [80], and likely antigens and pathogenic microorganisms, as well (Table 2). Moreover, while external insults to the permeability barrier can provoke inflammation by initiating the 'cytokine cascade,' some of these signalling molecules also signal certain physiologic production by epidermal keratinocytes (see below). The initiation of IL-1α and IL-1β activation at the level of the SC appears to occur through a pH-induced increase in the activity of at least one serine protease that is resident primarily within the SC (kallikrein 7 or SC chymotryptic enzyme) [67]. A further example of one function impacting another that is also relevant for antimicrobial defense, comprises the permeability barrier abnormalities that result from structural defects of the corneocyte [27, 74]. As a result of an inadequate scaffold, the organization of extracellular lipids into lamellar bilayers is disturbed. Indeed, an intact lamellar membrane system that completely engorges the SC extracellular domains is critical not only for permeability barrier homeostasis but also for antimicrobial defense (see below).

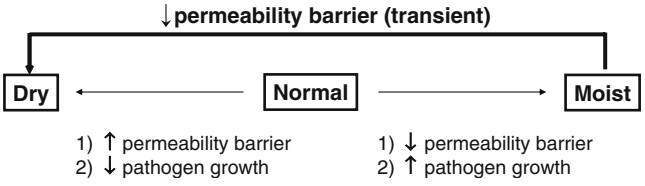

Fig. 1 Changes in external humidity alter permeability and antimicrobial barriers

Co-regulation of permeability and antimicrobial barriers

Of the several important protective functions of the epidermis that are linked and co-regulated, perhaps most integrated are antimicrobial defense and the permeability barrier through the multiple mechanisms listed in Table 3. With the notable exception of dermatophytes and *Candida albicans* that elaborate proteases that allow these pathogens to enter corneocytes [65, 72, 82], ultrastructural studies suggest that the extracellular matrix is the pathway through which bacterial pathogens, such as *S. aureus*, breach the SC [64] (Fig. 2). Therefore, the lamellar bilayers serve as an important physical as well as a chemical barrier. As noted above, epidermal LB deliver a family of lipids that form the permeability barrier and certain of these lipids, most notably free fatty acids (FFA) and sphingosine, that themselves exhibit potent activity against a variety of bacterial, yeast, and viral pathogens [9, 64, 85].

In addition, LBs deliver several non-lipid proteins that display AMP activity (Tables 3 and 4), including LL-37

Table 3 How permeability and antimicrobial barriers are linked

1) Co-localization in extracellular (mortar) domains
2) Pathogens attempt to invade through SC extracellular domains
3) Some permeability barrier lipids (e.g., free fatty acids and sphingosine) exhibit potent antimicrobial activity
4) Antimicrobial peptides (AMP) localize to lamellar bodies (along with lipids) and are co-delivered to SC extracellular domains
5) AMP expression and secretion of AMP both accelerate after permeability barrier disruption, paralleling increased lipid synthesis
6) At least one AMP (LL-37) is required for permeability barrier homeostasis

[10] and hBD2 [68] to the SC interstices (see below for further details).

The close relationship between permeability and antimicrobial function is most convincingly demonstrated by the recent demonstration that AMP expression increases after disruption of the permeability barrier [1]. Although this relationship is readily explained by the fact that barrier disruption removes extracellular AMP along with the lipids required for permeability barrier maintenance [29], the relationship between these two functions is more complex than simply a response to the co-removal of extracellular lipids and peptides. In fact, AMP appear to be important for permeability barrier homeostasis because transgenic mice that fail to express CRAMP, the murine homologue of LL-37, exhibit not only increased cutaneous streptococcal infections [66], but also a significant permeability barrier abnormality [1]. Ultrastructural studies suggest further that LL-37 (and perhaps other AMP) contribute to the supramolecular organization of the extracellular matrix into lamellar domains (op cit), perhaps through the requirement of relatively hydrophilic molecules for lamellar membrane organization. Thus, the AMP have a third set of functions in the epidermis that extends beyond their well-established dual roles as antimicrobial and signaling molecules; i.e., they are structural constituents of the epidermal permeability barrier.

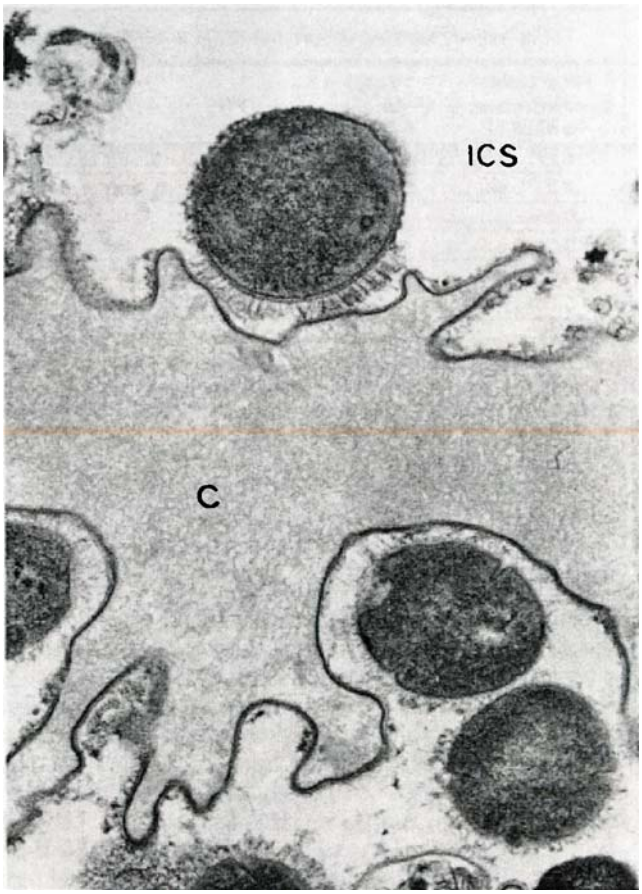

Fig. 2 Transmission electron microscopic study of biopsy specimen from culture-positive *Staphylococcus aureus* skin infection. Gram-positive cocci may be seen intercalating between corneocytes (C) within the stratum corneum, i.e., via intercellular spaces (ICS) occupied by the stratum corneum lipids (see text and [15, 16, 23]). Note that corneocytes do not appear damaged and are not traversed by bacteria (42,000×) (reprinted from [64], with permission)

The epidermal surface as an antimicrobial shield

Since AMP are expressed at only low levels under basal conditions, the importance of epithelial integrity in the protection against pathogen assault cannot be overemphasized. Intact SC deploys not only lipids with substantial antimicrobial activity, but also corneocyte 'bricks' with their chemically resistant cornified envelopes, as well as complex interdigitations with neighboring corneocytes, forming a formidable physical barrier to pathogen ingress (Table 5). In addition, the low water content and highly acidic surface pH (≈5.0) of non-occluded (non-intertriginous) SC presents a hostile milieu for common pathogens, such as *S. aureus* [3]. Yet, the acidic surface pH of normal SC provides ideal growth conditions for the normal cutaneous microflora, including both corynebacteriae and micrococceae, such as *S. epidermidis* [51, 52]. Recent studies have elucidated the origin of the SC's acidic pH, demonstrating critical roles for three endogenous mechanisms, including the sodium–proton antiporter, NHE1, phospholipase A_2-catalyzed generation of bulk FFA from LB-derived phospholipids, and a further likely contribution from filaggrin-derived amino acids, which after deimination, generate a variety of acidic metabolites, such as urocanic acid and pyrrolidone carboxylic acid (see below).

Table 4 Spectrum of stratum corneum antimicrobial peptides

Chemicals	Killing mechanism	Organism class			
		Gram+ Bacteria	Gram− Bacteria	Yeast	Viruses
Lipids					
(FFA, Sph)	? Detergent activity	+	+	+	(+ FFA)
Proteins					
LL-37	Pore formation	+	+	+	+
hBD2	Pore formation	−	+	−	?
Psoriasin	Trace element (Zn^{++}, Cu^{++}) sequestration	Minimal	+ (*E. coli*)		?
RNase7	Unknown	+	+ (*S. fecalis*)	+	?
Dermcidin	Unknown	+	+	+	?

1) Defensive characteristics of SC structural organization: Mammalian epidermal differentiation culminates in the formation of the anucleate layer, the SC, comprised of interlocking, vertical columns of 10–20 polyhedral corneocytes that interdigitate with several comparable neighboring stacks [18, 55, 63]. In frozen sections stained with fluorescent or non-fluorescent lipophilic reagents, individual corneocytes appear to be embedded within a highly hydrophobic lipid-enriched matrix, which on freeze–fractive replication, or after post-fixation with the highly reactive electron-dense reagent, ruthenium tetroxide, appears organized into a series of broad lamellar membranes of unique subcellular organization [22, 46]. In the lower SC, these extracellular membranes are bridged at regular intervals by specialized junctions, corneodesmosomes (CD) [42], containing the e-cadherins, desmoglein 1, and desmocollin 1, and an external coating of a novel, secreted protein, corneodesmosin [42, 77]. CD progressively disintegrate into lenticular lacunae as corneocytes migrate apically toward the cell surface [62]. While under low ambient humidities, these lacunae remain as isolated foci; with hydration, the lacunae expand until they interconnect, forming a potential 'pore pathway' across the SC [62] (Fig. 3). Although ultrastructural studies have shown that pathogens, such as *S. aureus*, bypass corneocytes as they attempt to penetrate the SC [64] (Fig. 2), whether they selectively traverse the interconnected pore pathway that is created in hydrated SC is not yet known. But the expansile nature of the lacunar network under hydrated/superhydrated conditions could provide a structural mechanism that bypasses the lamellar bilayers, thereby, facilitating pathogen invasion.

The two-compartment organization of the SC, i.e., of corneocytes embedded in a lipid-enriched extracellular matrix, has been analogized to a brick wall [23]. While corneocytes result from a specialized form of terminal differentiation 'physiologic apoptosis,' the matrix lipids and several extracellular structural, antimicrobial (see below) and enzymatic proteins are delivered to the SC interstices through epidermal LB secretion (Fig. 3). LB are relatively small (1/3–1/2 μm) ovoid organelles that are produced in abundance in the outer nucleated layers of the epidermis and secreted by compound exocytosis (i.e., end-to-end and side-to-side fusion) at the stratum granulosum (SG)–SC interface [26]. Within minutes of perturbation of the SC, much of the preformed pool of LB is deposited into the SG–SC interface [26], followed by amplified production and further secretion of nascent LB [61]. The net result is rapid on-going delivery of the full complement of LB contents to the SC interface as part of a rapid multi-pronged metabolic response to barrier insults (reviewed in Feingold [32]).

Table 5 Multiple levels of cutaneous antimicrobial defense

Levels	Activity
1) Epidermal (SC) surface	Microflora and products; ↓ pH; desiccation; sweat/sebum products (e.g., LL-37, dermcidin, RNase 7); SC and sebaceous lipids (e.g., free fatty acids); protease inhibitors
2) Epidermis →SC	Secreted and inducible antimicrobial proteins (LL-37, hBD2; psoriasin, RNase 7)
3) Epidermis+dendritic cells	Keratinocyte phagocytic activity; toll-like receptors (TLRs 2, 4, 7); cytokines (e.g., IL-18, IFNγ); chemokines
4) Mast cells	LL-37
5) Neutrophils	Lysozyme, α-defensins (hNP1-3)
6) Circulating T-cells (adaptive immunity)	TH1 induction

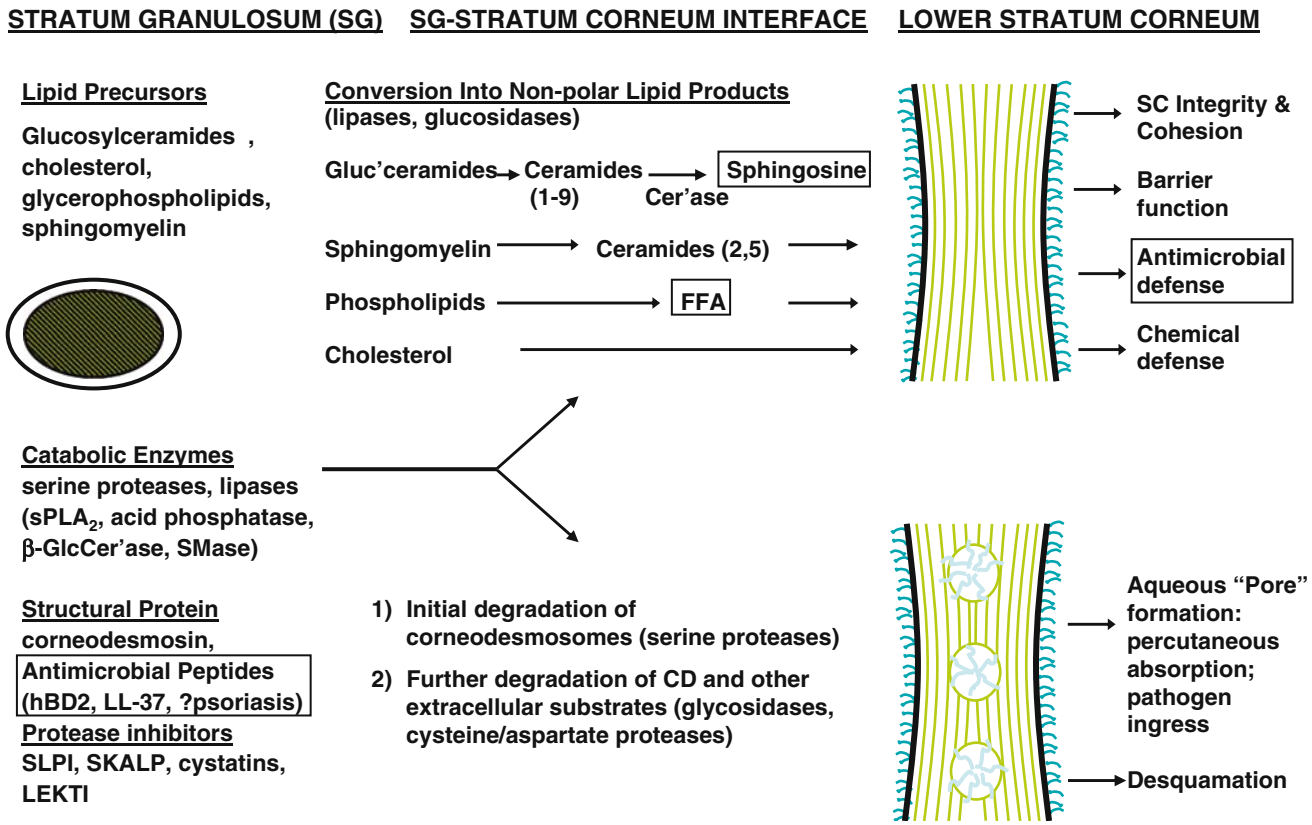

Fig. 3 Processes involved in generating the microbial barrier of stratum corneum

2) Normal cutaneous microflora: Because the SC lies at the interface with the external environment, it is continually threatened with xenobiotic assault. Yet, through a variety of mechanisms characteristic of epithelia in general and epidermis in particular (Table 5), it staunchly (and successfully) defends itself against the overwhelming majority of attempts by exogenous pathogens to colonize and invade. Epidermis has evolved multiple, largely tissue-specific strategies that deal with pathogen challenges (Table 5). Despite their overwhelming quantitative importance for cutaneous antimicrobial defense, these inherently "less-sexy" strategies have elicited very little systematic inquiry in comparison with epidermal AMP, toll-like receptors, and regulatory signalling mechanisms (Table 6), but undoubtedly, as each of these mechanisms is scrutinized further, their origins, biochemical basis, and regulation will become increasingly intriguing.

Perhaps, most important, yet least understood on a mechanistic level, is the substantial carriage of normal cutaneous flora in the outer SC and on the skin surface (about 10^2–10^3/cm^2 of micrococceae and propiononobacteriae [corynebacteriae]), first acquired during the birthing process, which rapidly spread to coat the skin surface (reviewed in Schröder and Harder [75]). It is widely assumed that the density of the normal flora is restricted by the process of epidermal cell renewal, which terminates in the desquamation of superficial corneocytes (with their resident organisms) from the skin surface. Yet, the presence of the cutaneous flora predicts a key role in antimicrobial defense through (a) competition with potential pathogens for niche occupancy, and (b) the limited availability of nutrients on the skin surface. Moreover, some strains of the normal flora can also secrete molecules, such as azelaic

Table 6 Basis for antimicrobial defense at the skin surface under basal conditions

Conditions
Intrinsic to stratum corneum
Geometry of intact SC layer
Replete lamellar bilayers
SC lipids; e.g., FFA, sphingosine
Acidic pH, low water content
Low, constitutive levels of hBD2 and LL-37 within extracellular matrix
From normal microbial flora
Niche occupancy; competition for nutrients
Secrete inhibitory metabolic products; e.g., acetic and propionic acids
Produce specific antimicrobial compounds; e.g., penicillin, azelaic acid
Surface-deposited antimicrobials
Sweat; e.g., dermcidin, ll-37
Sebum (lysozyme, FFA, RNase 7)

acid, propionic acid, and penicillin, which themselves inhibit pathogen colonization (Table 6). In vitro studies have shown that normal flora proliferate at a pH that duplicates the acidic milieu of the SC (≈5) [52], and through elaboration of acidic metabolites (azelaic and propionic acids), they could, in part, create the acidic conditions that favor their own persistence (see also below). Conversely, growth of the normal microflora is inhibited as skin surface pH rises [3], as is the case in chronic inflammatory dermatoses, such as atopic dermatitis (reviewed in [34]), although the neutral pH of inflamed skin instead favors the proliferation of microbial pathogens, most notably *S. aureus* and *S. pyogenes* [3, 52]. Finally, despite the presence of a spectrum of AMP with broad activities against multiple pathogens, there is evidence that the normal flora are resistant to AMP molecules [75].

3) The 'acid mantle' of the stratum corneum: The acidic character of skin surface pH has been long appreciated [59], and both in vitro [51, 52] and in vivo studies [3, 8, 64] suggest a teleological role for the 'acid mantle' in antimicrobial defense [34]. Yet, the origin of SC acidity and the functions that it impacts have only recently been methodically assessed. Previously assumed to be attributable to the surface deposition of (a) microbial metabolites (see above), (b) FFA from sebum, and/or (c) acidic eccrine gland products, such as lactic acid (reviewed in [34, 75]), recent studies have shown instead that these metabolites are not necessary for formation of an acidic surface pH [36]. Instead, SC acidity results largely from two or more endogenous mechanisms. Complete hydrolysis of epidermal phospholipids into FFA by one or more secretory PLA_2 ($sPLA_2$) occurs as the outer nucleated cell layers of the epidermis transition into the SC [57, 58]. The resultant largely non-essential FFA are not only critical structural components of the extracellular lamellar bilayers of the SC [57, 58], which physically exclude pathogens, but inhibitor studies have also shown that they contribute about 1 pH unit to the bulk acidic pH of SC [33]. Thus, by contributing to the bulk acidity and integrity of SC, the hydrolysis of PL into FFA helps form the compact acidic milieu that is so hostile to invading pathogens [57, 58]. Yet in addition, FFA are themselves potent antimicrobial species (see also below).

A second, endogenous source of the acidic pH of SC is the non-energy-dependent, sodium–proton exchange mechanism, NHE1. In the epidermis, this ubiquitous transporter localizes to the outer nucleated layers, where it acidifies extracellular domains at the granular layer (SG)–SC interface and in the lower SC [6]. Although it is a minor contributor to the bulk pH of SC, by selectively acidifying membrane microdomains in the lower SC, it impacts at least one key epidermal function that becomes established at this level, i.e., permeability barrier homeostasis [6, 7]. The age-associated decline in NHE1 activity, with a resultant net increase in SC pH, accounts, in part, for the decline in both permeability barrier function and SC integrity/cohesion in aging skin [17], and it could also account in part for the increased risk of pathogen invasion in aged skin.

Yet another, still-unproven source of SC acidification could be the filaggrin proteolytic pathway that culminates in the downstream generation of multiple, deiminated carboxylic acids, such as trans-transurocanic acid (UCA) [53]. Because the surface pH of hisidase-deficient (Peruvian) mice is normal [36] and humans with the common inherited disorder, histidinemia, who lack histidase activity exhibit no known cutaneous abnormalities, the importance of this mechanism for skin function remains uncertain. Moreover, the proteolytic step that initiates filaggrin proteolysis is humidity sensitive; i.e., it is inhibited at external relative humidities above 80% [76]. Because UCA would not be generated in a humid environment, it would be an inconstant contributor to SC pH. Yet, the increased propensity for *S. aureus* and gram-negative cutaneous infections to occur in superhydrated skin could, in theory, be linked to the down-regulation of this mechanism.

Recent studies have explored the functions of SC acidification in both humans and animals. Using topical applications of either 'superbases' (more basic than 1 N NaOH) or 'superacids' (more acidic than 1 N H_20 SO_4), such as the polyhydroxylacids (PHA), lactobionic acid, and gluconolactone, it is possible to modulate pH selectively at all levels of SC without evidence of toxicity to the underlying nucleated layers of the epidermis [39, 40]. This approach allows the manipulation of pH without the coexistence of other experimental variables, such as hydration or occlusion, which confounded earlier in vivo studies [3]. Accordingly, 'superbase'-induced elevations in SC pH in hairless mice modify both permeability barrier homeostasis and SC integrity/cohesion, largely through increased activity of SPs [3] which exhibit neutral pH optima [12]. Conversely, hyperacidification of SC with PHA generates a 'super' barrier and an even more cohesive SC than present in normal human and murine skin [41]. Yet, whether the pH-dependent changes in permeability barrier function and SC integrity/cohesion directly impact antimicrobial function, i.e., resistance to pathogen adhesion/invasion, has not yet been addressed. Because of the positive correlations between the permeability and antimicrobial barriers (Table 3), one would expect, however, that the antimicrobial barrier would change in parallel to alterations in permeability barrier function.

4) Hydration status: The water content of SC drops precipitously towards the surface of SC [83], creating

desiccating conditions that normally inhibit pathogen colonization [3]. Yet, the normal cutaneous microflora seem to thrive under similar conditions for reasons that are largely unknown. Conversely, pathogen colonization, particularly by *S. aureus* and *S. pyogenes*, is favored by the superhydration of SC [8], explaining the increased propensity for clinical infections in intertrigenous or occluded skin sites, such as the axillae, inframammary folds, groin, and plantar surfaces (reviewed in [34]). Likewise, the common occurrence of staphylococcal and streptococcal infections in tropical climates can be explained, in part, by the increased hydration of SC at these ambient humidities. Finally, as noted above, filaggrin proteolysis is inhibited under these conditions, resulting not only in an increased surface pH, but also in altered SC hydration. Filaggrin proteolysis generates not only the histidine metabolite, trans-UCA, but also a broad range of deiminated metabolites, often termed together as 'natural moisturizing factor' (NMF). Abundant glycerol, a potent endogenous humectant, is generated and surface-deposited through both the high rates of triglyceride turnover that occur in sebaceous glands [15, 35] and the importation from the circulation via the activities of one or more aquaporin channels (e.g., AQP3) that are expressed on keratinocyte cell membranes [43]. Finally, eccrine glands surface deposit other osmotically active ingredients, such as lactic acid. It is intriguing to consider the possibility that not only humidity-sensitive downregulation of filaggrin proteolysis but also, perhaps, AQP3 activity could be downregulated at high humidities in response to the broad requirements for a desiccated SC for antimicrobial defense.

5) Biochemical basis for SC antimicrobial defense—lipids: Even in hydrated SC, invading pathogens encounter and must overwhelm an impressive array of antimicrobial lipids and proteins that reside in the extracellular matrix (chemical defensive shield; Tables 4, 5, 6 and 7). SC lamellar lipids primarily comprise three major species: a family of nine ceramides (Cer), cholesterol, and essential/non-essential FFA present in an approximately equimolar ratio. Cer derive from the hydrolysis of glucosylCer and sphingomyelin [81], while FFA result from epidermal phospholipid hydrolysis [57, 58], as well as in sebaceous gland-enriched regions, and from the surface deposition of FFA derived from triglyceride catabolism [35]. The three major lipids are secreted from epidermal LB, largely as their precursors, but hydrolysis is completed in the lower SC, eventually resulting in the extracellular lamellar membranes unique to the epidermis (Fig. 3) [24]. Further, the partial hydrolysis of Cer into sphingosine (Sph) and FFA, catalyzed by two isoforms of ceramidase (Cer'ase), the acidic and alkaline forms, occurs more distally in SC [47]. This pathway doubtlessly impacts antimicrobial defense, as Sph and FFA are the two most potent antimicrobial lipid species in SC [9, 64, 85], and again, there could be a further contribution of Cer'ase-generated FFA to the acidic bulk pH of SC. In vitro studies have demonstrated a wide array of antimicrobial activity for both Sph and FFA against *S. aureus*, *pyogenes*, *C. albicans*, and dermatophytes, with lesser potency against gram negative organisms, such as pseudomonas [4, 9, 64, 85]. Other work has demonstrated additional antiviral activity of FFA, as well [79]. In the case of FFA, anti-staphylococcal activity is also chain-length dependent, with species less than or equal to 16 exhibiting greater potency more than or equal to C18 [64]. Further, the antimicrobial activities of FFA persist at low micromolar concentrations that are relevant for the absolute quantities of these FFA that are present within the SC interstices (whether levels of Sph are sufficient to mediate antimicrobial defense in vivo is not known). Finally, GlucCer also exhibit considerable in vitro activity against the same pathogens [64], but in intact cells, these lipids largely reside in focal lipid-raft domains of cell membranes, where they instead facilitate pathogen adherence to cells and could instead facilitate colonization and invasion [70].

These observations appear to be clinically relevant for atopic dermatitis (AD), where activity of a still-incompletely characterized sphingolipid deacylase degrades the two Cer precursors, glucosyl Cer and sphingomelin, resulting not only in Cer and FFA deficiency but also in a paucity of its downstream product, Sph [4], the most potent endogenous antimicrobial lipid [9]. The net result of a decrease in Cer and FFA content is a paucity of extracellular lamellar bilayers in AD [13, 31], with further abnormalities in lamellar membrane organization due to disturbed lipid

Table 7 Principal antimicrobial peptides of the skin surface

	β-Defensin2	hCAP product (LL-37)	Psoriasin	Dermcidin	RNase 7
Epidermis	Inducible (low → high abundance)	Inducible	Constitutive; focal high abundance	–	Constitutive and inducible (low → high)
Eccrine glands	–	Constitutive (low abundance)	–	Constitutive, abundant	–
Sebaceous glands	–	–	Constitutive and inducible (abundant)	–	–

distribution (i.e., not only is there a reduction in total extracellular lipids but also abnormalities in the molar ratio of the three key lipids critical for bilayer formation) [56]. While together these indirect observations strongly suggest that SC lipids are critical for antimicrobial defense, further in vivo studies using either inhibitors or genetic deletions of lipid-generating enzymes, e.g., one or more isoforms of secretory phospholipase A_2 or ceramidase, followed by microbial pathogen challenges, are still needed.

6) Biochemical basis for antimicrobial defense—proteins: Human epidermis and its appendages elaborate several proteins that exhibit antimicrobial activity [11, 37, 48, 54, 75]. In light of the skin's continuous risk of exposure to pathogenic microbes from the environment, it is not surprising that, where known, these proteins largely localize to the outer epidermis [75]. These include at least two members of the RNaseA100 superfamily, RNase 7 and psoriasin, as well as members of the supergene family that encodes β-defensins (hBD1–4) and one product of the epidermal cathelicidin, hCAP18, i.e., its carboxyterminal fragment, LL-37 (and its murine homologue, CRAMP). The carboxy- and amino-terminal products of hCAP display distinctive (non-overlapping) spectra of antimicrobial activity (Table 4). Both LL-37 and hBD2 are small, evolutionarily conserved, cationic, highly hydrophobic, cysteine-enriched that, because of their dual role as signalling molecules, are distal members of the innate immune system (reviewed in [11, 37, 54], and elsewhere in this volume). Both of these peptides appear to kill pathogens by disrupting the hydrophobic core of the organisms' lipid bilayers (e.g., [69]).

Recent studies suggest that these two molecules also have a third, previously unrecognized structural role, i.e., in maintaining epidermal integrity [72], as do related AMP in the gastrointestinal and alveolar epithelium [78]. hBD2 and 3, as well as hCAP, are expressed only at low levels in human epidermis under basal conditions [19], emphasizing the highly effective and sufficient role of the SC barrier under most circumstances (see above). Surface-deposited sebaceous and eccrine products, including not only LL-37, but also the eccrine products, dermcidin (DCD), a tissue-specific constitutively expressed eccrine gland protein, and its 31, 30, and 20 kDa catabolic products (reviewed in [75]) also contribute to basal antimicrobial defense (Tables 5 and 6). Sebaceous glands deposit not only FFA, but also the RNaseA100 protein, psoriasin, as well as lysozyme, a non-specific protease whose role in antimicrobial defense in vivo remains uncertain (Tables 6 and 7). Yet, the expression of both hBD2 and hCAP increases markedly after external injury, UV exposure, and pathogen challenge in certain inflammatory dermatoses and/or during wound healing [11, 37, 48, 75]. While hBD2 expression in keratinocytes is upregulated by several cytokines [37, 54], hCAP expression is regulated conversely by the class II nuclear hormone receptor ligands, retinoic acid, and 1,25 $(OH)_2$ vitamin D3 [45, 84].

The RNase superfamily of S100 proteins includes several proteins with inherent antimicrobial activity, such as eosinophil-derived cationic protein, calgranulin-β, eosinophil-derived neurotoxin, angiogenin, and psoriasin (S100A7). Only calgranulin-β and psoriasin are known to be upregulated in psoriasis [38, 60]. An additional, novel AMP, RNase7 is constitutively expressed in normal SC [44] and is further inducible by bacterial challenge and cytokines, such as IFNγ, TNFα, and IL-1β. RNase7 is a highly basic 14.5 kDa cysteine-enriched protein with multiple disulfide bridges, but with broad activity against yeast, as well as against both gram+ and gram− bacteria. Because its greatest activity is against *S. faecalis* (including vancomycin-resistent organisms), its major role may be to protect against infections originating in the gut [75]. Yet, not only is RNase7's killing mechanism unknown, both its mode of delivery to and sub-cellular localization within SC remain unknown [44].

Five members of the RNase S100A family fall under the rubric psoriasin, but only the S100C variant is present in normal SC, while S100A1S is the predominant variant in psoriatic scales [38]. Psoriasin is an 11-kDa protein with a terminal acyl group rendering this protein the most hydrophobic of all epidermal AMP. Although it is a multifunctional protein [21], it is readily extracted from normal SC by acetone washing, and therefore, it could be similarly secreted and co-sequestered with barrier lipids within the SC interstices, like hBD2 (mBD3) and LL-37 (CRAMP). Yet, psoriasin is not uniformly distributed over the skin surface—its preferential expression in hydrated and peri-orificial skin sites (e.g., nose and around openings of pilosebaceous ducts), coupled with its unusual antibacterial spectrum (primarily *Escherichia coli*, with lesser activity against other gram− organisms and *S. aureus*), suggest a specialized role in antimicrobial defense, specifically against gut-derived *E. coli* (Tables 4 and 7). In contrast to RNase 7, more is known about the molecular mechanism of psoriasin's microcidal activity, which includes not only perforating activity, like cathelicidins and β-defensins, but also Zn^{++} and/or Ca^{++} sequestration [75].

Finally, the SC must contend with an array of hydrolytic enzymes, elaborated by pathogens as they attempt to attach, colonize, and invade. In response, the outer epidermis elaborates and secretes via the LB secretory mechanism, an array of serine and cysteine protease inhibitors (SPI), which exhibit net antimicrobial activity by interdicting exogenous proteases [72] that not only can facilitate invasion but also can degrade AMP, such as LL-37 [73]. Yet, certain of these hydrolases could also be required to process AMP

precursor pro-peptides into their active fragments, while their inhibitors could regulate the kinetics of such activation. To date, little is as yet known about the regulation or localization of these processes in mammalian SC.

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