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REVIEW ARTICLE

An integrated view of the epidermal environmental interface

Peter M. Elias*, Joan S. Wakefield

Dermatology Service, VA Medical Center, San Francisco and Department of Dermatology, UC San Francisco, San Francisco, CA, USA

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ABSTRACT

The harsh realities of life in a terrestrial environment demand that the epidermis must respond quickly to many types of external stressors that threaten the internal milieu. We review herein how the individual protective functions of the skin (e.g., permeability barrier, antimicrobial barrier, antioxidant defense, integrity, hydration, and mechanical integrity) appear to be integrated into a broad defensive shield. Then, we will review how the epidermis responds to external perturbations through a network of extracellular signaling mechanisms and second messengers, as well as the pathophysiology of these responses in diseases such as atopic dermatitis and psoriasis. Finally, we will briefly discuss the potential therapeutic implications of this new functional paradigm.

Introduction

Too long viewed as a mere battleground for the immune system, the epidermis is asserting its rightful place at the center of cutaneous biology and pathophysiology. Although immunologists seek ever-finer distinctions between T cell subsets in inflammatory lesions, it is now increasingly clear that the protective requirements of the skin dictate virtually every metabolic process (including adaptive immune responses) in its underlying layers. True, there are "outside-to-inside-back-to-outside" vicious cycles, whereby immune responses further compromise epidermal function, and there are also examples of primary immune disorders, such as autoimmune and bullous diseases, human immunodeficiency virus (HIV) infections, and superantigen-initiated flares of erythrodermic psoriasis, where a primary inflammatory infiltrate can produce downstream abnormalities in epidermal function (e.g., for HIV, see Gunathilake et al[1]). But, as the example of filaggrin-deficient atopic dermatitis (AD) eloquently demonstrates, most cutaneous immune phenomena occur downstream of primary epidermal insults, whether inherited or acquired, and these responses are recruited only when epidermal homeostatic responses fail to promptly reestablish normal cutaneous function. In this review, we consider: (1) a new "holistic" view of epidermal defense; (2) a concise review of the structural basis for the barrier with an update on tight junctions (TJs) and the corneocyte lipid envelope; (3) intraepidermal metabolic processes that are regulated by barrier requirements; (4) the role of homeostatic signaling mechanisms in regulating these responses; and (5) interrelated processes that impact disease pathogenesis.

Brief review of barrier structure and function

Two-compartment model

The protective functions of the skin, including the permeability barrier, largely localize to the outer epidermis and stratum corneum (SC; Table 1; Figure 1). The SC is an a nucleate structure, arranged in a "brick-and-mortar" mosaic of flattened corneocytes ("bricks"), embedded in lipid-enriched extracellular matrix ("mortar") that is organized into parallel stacks of lamellar bilayers, enriched in ceramides, cholesterol, and free fatty acids (FFAs).[2] These water-repellent lipids restrict the outward flow of water, while also impeding the inward absorption of toxins, allergens, and microbial pathogens.[3] It is the secretion of the contents of multiple, small ovoid lamellar bodies (LBs)[2] that delivers both lipid precursors and hydrolytic "processing" enzymes that generate the hydrophobic species, ceramides (Cer), FFAs, and cholesterol, that

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* Corresponding author. Dermatology Service, VA Medical Center, San Francisco and Department of Dermatology, UC San Francisco, 4150 Clement Street, MS 190, San Francisco, CA 94121, USA.
E-mail address: eliasp@derm.ucsf.edu (P.M. Elias).

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Table 1 Defensive gradients in outer epidermis.

Functions	Outer surface (sebaceous glands)	Stratum corneum	Stratum granulosum
Antimicrobial	AMP, FFA (↓ pH)	FFA (↓ pH), AMP, SPI	AMP, TLR
Permeability barrier	—	Cholesterol, Cer, FFA in lamellar bilayers	Tight junction (larger xenobiotes)
Antioxidant	Vitamin E	Vitamin E, Sprr2d, Sprr2h, Slpi	SOD, CoQ, catalase, GluTR
UV-B	—	t-UCA (melanin)	Melanin
Mechanical	—	Cornified envelopes	—
Cohesion	—	Lipids, corneodesmosomes	Desmosomes, adherens junctions
Cytokine activation	—	IL-1α/β release	TNFα, IL-1α/β, GMCSF, IL-6, NGF, AR, VEGF
Neurosensory	—	—	TRPVs, TRPM8
Hydration	Glycerol	FLG → NMF; glycerol, urea	AQP channels Urea transporters

AMP = antimicrobial peptide; Cer = ceramide; CoQ = coenzyme Q; FFA = free fatty acid; GM-CSF = granulocyte-macrophage colony-stimulating factor; GluTR = glutamyl tRNA reductase; IL = interleukin; NGF = nerve growth factor; NMF = natural moisturizing factor; Slpi = serine leukocyte protease inhibitor; SOD = superoxide dismutase; SPI = serine protease inhibitor; TLR = Toll-like receptor; TNF = tumor necrosis factor; TRPM8 = transient receptor potential melastatin-8; TRPV = transient receptor potential vanilloid; t-UCA = trans-urocanic acid; VEGF = vascular endothelial growth factor.

mediate the permeability barrier (Figure 2).[4] These two lipids, along with as-yet-unidentified amphiphilic molecules, are required for the organization of the secreted lipids into mature lamellar bilayers.[2]

Corneocyte-bound lipid envelope

The external surface of the cornified envelope (CE) is coated with a monolayer of ω-hydroxyceramides (ω-OH-Cer) that are covalently bound to peptides (1° involucrin) within the CE.[5–7] Both the origin and the function of this structure are still uncertain. Although most workers believe that it is formed from a pool of secreted acylCer, the corneocyte-bound lipid envelope (CLE) could also derive from the insertion of a myriad of LB limiting membranes during the exocytosis of these organelles.[4] We noted that the CLE fails to form in several inherited and acquired disorders that compromise steps that either generate acylCer or oxidize the ω-OH-linoleate moiety of acylCer (Figure 2). Because all of these disorders are characterized by a faulty permeability barrier, poor SC hydration, and impaired desquamation, it is a tempting (but still not certain) prospect that the CLE is linked to one or more of these functions.[4]

TJ controversy

How should we interpret an ever-expanding literature that proclaims a potential role for TJ in normal permeability barrier function (e.g., see Brandner et al[8] and Kubo et al[9]), as well as a potential role for abnormal TJ function in AD?[10] We will attempt to navigate this heavily invested subject as follows. First, complex TJ structures, such as those found in the kidney and gastrointestinal tract, do not occur in adult keratinizing epithelia.[11] Second, with the exception of highly complex TJs in renal collecting tubules, where they comprise multitiered, overlapping sites of membrane fusion ("zonulae occludentes"), in other tubular epithelia, such as the trachea and gastrointestinal tract, these junctions provide a relatively poor barrier against paracellular water movement.[12,13] Much of the confusion in the skin-related literature has occurred because "TJ proteins" are widely equated with "TJ".[8,9,14] Certainly, multiple TJ proteins heavily decorate the apical–lateral plasma membranes of cells in the outer stratum granulosum (SG) of normal adult epidermis, forming "kissing points." However, these focal attachments—i.e., "maculae occludentes"[11]—do not comprise true zonulae occludentes (= TJ), as occur in tubular epithelia. The most compelling evidence that these putative TJs play no direct role in the paracellular water barrier comes from solvent extraction studies, where removal of SC lipids by repeated, gentle, lipid solvent swabbing completely abrogates the permeability barrier.[15] It should be noted that this observation also excludes a possible "backup" role for TJ-like structures in the water barrier, although it remains possible that true TJs eventually could begin to form in response to such repeated solvent wipes. Moreover, these incomplete structures could suffice to interdict the paracellular passage of

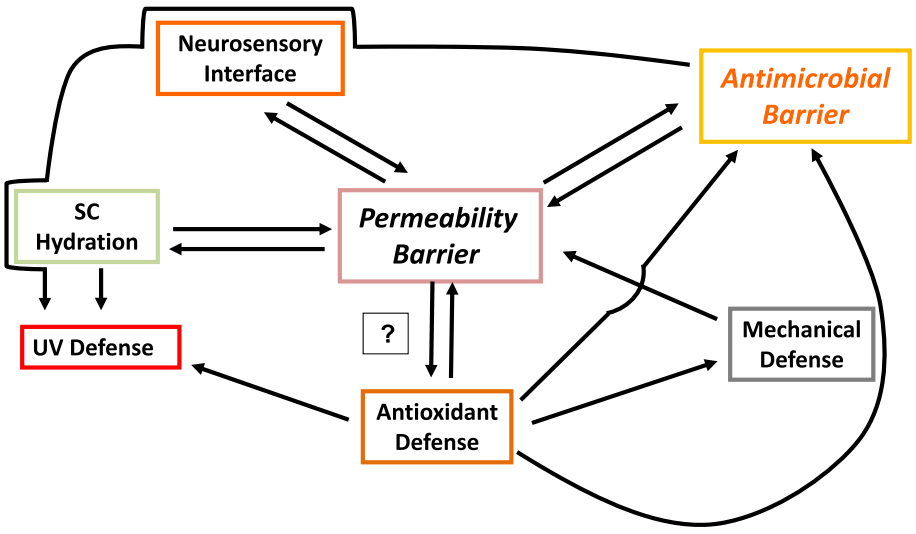

Figure 1 Protective (defensive) functions are related, coregulated and interdependent.