Evolving Concepts of Neonatal Skin

Carrie C. Coughlin, M.D.,* and Alain Taieb, M.D., Ph.D.†

*Division of Dermatology, Department of Medicine, Washington University, St. Louis, Missouri, †Department of Dermatology and Pediatric Dermatology, Bordeaux University Hospitals, University of Bordeaux, Bordeaux, France

Abstract: Skin barrier function is crucial to health. Importantly, the skin operates as an air-liquid, a liquid-liquid, and an immunological barrier. The skin’s physical and chemical structures, as well as its microbiome, function to create, maintain, and repair this complex barrier.

Evolving knowledge of neonatal skin development has advanced knowledge of skin function in neonates. Specifically, insights into permeability, transepidermal water loss (TEWL), absorption, and epithelial turnover have influenced patient care and technology of items such as diapers and diaper wipes. Knowledge of neonatal skin function affects care of normal and abnormal skin, which is relevant to parents and physicians alike.

EPIDERMAL DEVELOPMENT IN THE EMBRYO AND FETUS—AN OVERVIEW

Skin begins as a single cell layer of ectoderm in an embryo. The next stage in epidermal development involves two layers of cells (a basal cell layer and periderm layer), which evolve to three layers with the addition of an intermediate layer in the third month of development. By the middle of the second trimester, the epidermis and dermis are formed but are thin and immature. The periderm sloughs by the end of the second trimester and becomes part of the vernix caseosa (1). The epidermis differentiates in the third trimester to contain the stratum corneum, stratum granulosum (granular cell layer), stratum spinosum (spinous layer), and stratum germinativum (basal and germinative cell layer), all of which are composed of keratinocytes (2). Langerhans cells and melanocytes do not form from the epidermis during development; instead, they migrate into the epidermis near the end of the first trimester (1).

SKIN AS AN AIR–LIQUID BARRIER

Multiple components of the epidermis contribute to its function as a barrier. The stratum corneum provides an air–liquid barrier and blocks physical agents from entering the skin. Corneocytes, lipid bilayers, and desmosomes in the stratum corneum work together to form a physical barrier to irritants. Antimicrobials, such as lysozyme and lactoferrin, are present in the stratum corneum and provide resistance to penetration by bacteria. The normal stratum corneum is an acid mantle; low pH and temperature are essential for functional regulation of enzymes located there.

Profilaggrin, the precursor protein to filaggrin, is located in keratohyalin granules in cells of the granular layer. It is processed into filaggrin between the granular cell layer and the stratum corneum. Filaggrin has keratin-binding functions. It is degraded...
into free amino acids, urocanic acid, and pyrrolidine carboxylic acid, otherwise known as natural moisturizing factors (NMFs), as it travels through the epidermis. The NMFs affect hydration of the stratum corneum and reduce local pH (3). Low pH is not entirely dependent on filaggrin, as shown in flaky tail mouse and filaggrin null mouse models (4,5). Recent work has shown direct results of a disrupted physical barrier in individuals with mutations in filaggrin. These mutations cause ichthyosis vulgaris and can increase risk of atopic dermatitis (6–8).

Desquamation of the stratum corneum is a tightly regulated process. Proteases, protease inhibitors, and skin pH interact to cause desquamation. Netherton syndrome, caused by loss of function of the serine peptidase inhibitor, Kazal type 5 (SPINK5) gene, is a well-studied example of how a mutation can cause disruption of the barrier function by interrupting normal desquamation. Corneodesmosome cleavage is increased, and the stratum corneum detaches from the granular cell layer abnormally in patients with Netherton syndrome (9,10). A similar, but milder, phenotype can be seen in patients with atopic dermatitis with polymorphisms of SPINK5 (9).

SKIN AS A LIQUID–LIQUID BARRIER

Tight junctions in the granular layer of the epidermis create a liquid–liquid barrier that is important for regulating TEWL. The rate of TEWL is a measure of skin barrier permeability and is faster in patients with a damaged barrier. TEWL changes in neonates throughout the first weeks after birth. A study by Fluhr et al (11) examined this change in detail. TEWL, pH, and capacitance (representing skin hydration state) were examined in full-term newborns, babies 5 to 6 weeks old and 5 to 7 months old, children 1 to 2 years old and 4 to 5 years old, and adults. All participants had TEWL of normal skin. Skin surface pH varied with age, being highest in the newborns (6.0), decreasing to 5.1 in babies 5 to 6 weeks old, and then staying approximately stable. Capacitance was lowest in newborns. Thus, although full-term infants have a competent barrier and normal rates of TEWL, permeability, pH, and hydration are dynamic and evolve as people age.

VERNIX CASEOSA: COMPOSITION AND FUNCTION

In addition to the skin itself, babies are born with a coating of vernix caseosa. The primary constituent of the vernix is water (80.5%); (12) proteins, barrier lipids (cholesterol, free fatty acids, phospholipids, ceramides), other lipids, and antimicrobial peptides are also present. The vernix has been shown to promote moisture accumulation in the skin and contribute to a higher baseline hydration, and vernix retention has been associated with lower pH than vernix removal (13). Thus, retention of the vernix contributed to the development of the skin’s acid mantle. Vernix retention was not noted to affect temperature (13). Numerous antimicrobial, antifungal, and antiparasitic agents have been identified in the vernix (14). Potential advantages of vernix retention have led to discussions of the benefit of not immediately removing it from newborns at birth.

SKIN AS AN IMMUNOLOGICAL BARRIER

The third element of the barrier function of the epidermis is the immunological barrier. Langerhans cells (which are antigen-presenting cells) are the critical components of this system. Antigenic stimuli can increase in the setting of a dysfunctional barrier; disrupted epidermal barrier function has an affect on allergy and allergic predisposition. Novak et al (15) found an association between filaggrin mutations and contact sensitivity to nickel in a group of more than 1,000 adults, especially in women. In addition, children with a filaggrin mutation and well-controlled asthma were shown to be more likely to have asthma exacerbations than children with asthma without the filaggrin mutation (16). Thus, filaggrin mutations have multiple clinical effects.

Innate immunity of the newborn also involves the skin. Several antimicrobial peptides have been measured in significant amounts in neonatal skin. Dorschner et al (17) investigated levels of cathelicidin and beta-defensins in neonatal foreskin. Cathelicidin and human beta-defensin 2 were present in substantial amounts. Walker et al (18) examined proteins obtained by tape disc sampling of neonates’ forehead and back skin during the first 24 hours of life and were able to measure lysozyme and lactoferrin. Therefore, although neonatal immunity is not advanced, cell-mediated and innate pathways contribute to host defense mediated by the skin (19).

The cutaneous microbiome also plays a role in the barrier function of the skin. Diversity increases with age, and components are site specific. Method of delivery (vaginal birth vs Cesarean section) also influences a baby’s microbiome. Three of four neonates delivered via vaginal delivery developed skin microflora similar to that cultured in their mothers’
vagina (20). The microflora seen early in these babies were *Lactobacillus, Prevotella, Atopobium,* and *Sneathia* species. Babies delivered via Cesarean section developed colonization similar to adult skin, including *Staphylococcus* species (20). Capone et al (21) showed that a child’s microbiome evolves over at least the first year of life across multiple sites. Thus, susceptibility to infection changes as well. As the cutaneous microbiome continues to be explored, knowledge of these changes is likely to have a direct effect on infant skin care.

Initial skin colonization could affect microbial communities of other sites, including the gut (20). Breastfeeding has also been shown to influence gut colonization (22). Populations of anaerobes can reach adult-like levels within the first week of life (23).

Fungal colonization is also present early in neonates. *Malassezia* species were shown to be transmitted from mother to baby (24). Similar to bacterial species, *Malassezia* colonization evolved with time, with differing proportions of *M. restricta* and *M. globosa*. In neonates, the ratio of these species was relatively equal. The proportion of *M. restricta* was greater at day 30 of life, which was more similar to findings in adults (24). The overgrowth of *Malassezia* is associated with neonatal cephalic pustulosis.

**CONCLUSION**

In summary, the skin acts as a barrier to water loss, irritants, and allergens; works to control infection, in immunosurveillance, and to allow enzyme function; and becomes an acid mantle. Knowledge of normal and abnormal barrier states has a clear role in disease treatment and prevention.

**CONFLICTS OF INTEREST**

The authors have declared no conflicts of interest.

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