



Pachyonychia Congenita Project

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We hope that making available the relevant information on Pachyonychia Congenita will be a means of furthering research to find effective therapies and a cure for PC.

antigenic determinants (12), have led to correct conclusions about the topology of LamB (see figure). Most of the residues detected as part of the maltodextrin binding site are located within the channel, although often in the inward parts of loops. Secondary structure predictions, by themselves, were poor in establishing correct topology; recent methods based on the three-dimensional structures of other porins were more successful (8) but still predicted 16 transmembranous strands instead of 18.

This model raises interesting questions. How does the helical path work? How do other sugars that appear to rely on LamB for growth in limiting conditions (13) diffuse? How would a filter work? Is it an early weak binding site? The notion that the general porins may generate a local electric field near the channel constriction, sufficient to orient small hydrophilic molecules and repel hydrophobic ones (2), suggests that there is only a quantitative difference between binding sites and filters. What is the

role of the umbrella? Does it protect the channel and binding site from noxious agents or from phages (the loops of the umbrella are the parts of LamB that are the most variable between bacterial species)? Do the loops move in vivo and thus contribute to the motion of the sugar? Is there a structural connection between LamB and other components of the maltose transport system? What exactly is the phage receptor—a binding site for the phage or an accessibility gate to the real, possibly yet undetected, binding site (14)? How does this fast, tight interaction succeed in firmly attaching two large structures such as a bacteria and a phage? Is there a relation between the pathway followed by the phage DNA upon infection and LamB organization? As usual, a nice achievement in science provides at least as many questions as answers.

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Defects in the Barrier

Dennis Roop

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The skin is a physical barrier at the interface between an organism and its environment—preventing water loss and withstanding mechanical, chemical, and microbial assaults. To perform these functions, the outer layer of the skin (the epidermis) undergoes keratinization, a process in which epidermal cells progressively mature from basal cells with proliferative potential to lifeless flattened squames of the stratum corneum. During this differentiation, certain genes are activated while others are down-regulated—leading to changes in both structural proteins and in the expression and activation of enzymes that control posttranslational modifications, metabolic changes, and lipid synthesis. A defect in any one of these structural components or enzymatic processes has the potential to impair the barrier function of the skin and cause disease.

Surprisingly, the phenotypic consequences of defects in many of these diverse processes can be very similar—resulting in the keratinization disorders known as the ichthyoses, characterized by thickened and scaly skin (1): Recessive X-linked ichthyosis (RXLI) is caused by a deficient enzyme of cholesterol metabolism (steroid sulfatase) (2); the epidermolytic ichthyoses—epiderm-

olytic hyperkeratosis (EHK), epidermolytic palmoplantar keratoderma (EPPK), and ichthyosis bullosa of Siemens (IBS)—are caused by defects in structural proteins (keratins) (3); and as reported in this issue of *Science* by Huber et al. (4), lamellar ichthyosis (LI) is due to defects in an enzyme that catalyzes cross-linking of proteins in the upper layers of the epidermis (a transglutaminase). How can defects in genes that encode proteins with such different functions produce skin disorders that are clinically so similar?

The epidermis is a perpetually renewing tissue, comprised of four histologically distinct cellular layers, each with a distinct maturation state of the keratinocyte, the major cell type of the epidermis (see figure). Keratinocytes arise from stem cells in the basal layer, and move through a series of differentiation events until they are finally sloughed into the environment (desquamation). Thus in the normal epidermis, there is a balance between the processes of proliferation and desquamation that results in a complete renewal approximately every 28 days. In the ichthyoses, the rate of desquamation may decrease, leading to epidermal cell retention (hyperkeratosis), or there may be an increase in proliferation, which further exacerbates the build up of skin cells in these patients (or both processes may occur simultaneously.)

Keratins are major structural proteins synthesized in keratinocytes. They assemble

into a weblike pattern of intermediate filaments (IFs) that emanate from a perinuclear ring, extend throughout the cytoplasm, and terminate at junctional complexes called desmosomes and hemidesmosomes (5). Keratin IFs are essential for maintaining the integrity of the epidermis; mutations in six keratin genes result in four distinct epidermal diseases (3). All of these disorders are characterized by blistering, with lesions originating at the site of synthesis of the mutant keratin: Epidermolysis bullosa simplex (EBS) shows mutations in the basal layer keratins K5 or K14; EHK has spinous layer K1 or K10 defects; IBS has granular layer K2e defects; and EPPK has granular layer K9 defects that are restricted to palmar and plantar epidermis. Interestingly, only those diseases with defects in upper layer keratins (EHK, IBS, EPPK) exhibit hyperkeratosis, or a thickening of the stratum corneum. Why keratinization disorders only result from defects in keratin genes expressed in the differentiated layers of the epidermis is not clear, but there are some clues. Lysis of differentiated keratinocytes may release cytokines involved in the wound response such as transforming growth factor α (TGF- α). Given that TGF- α and its receptor are up-regulated in EHK lesions (6) and that overexpression of TGF- α in the epidermis of transgenic mice produces a marked hyperkeratosis (7), it is likely that TGF- α contributes to this aspect of the disease. In addition, during the final stages of normal differentiation, keratin IFs are aligned into highly ordered and condensed arrays through interactions with filaggrin, a matrix protein (8). In the keratin disorders, the IF networks collapse around the nucleus, preventing at-

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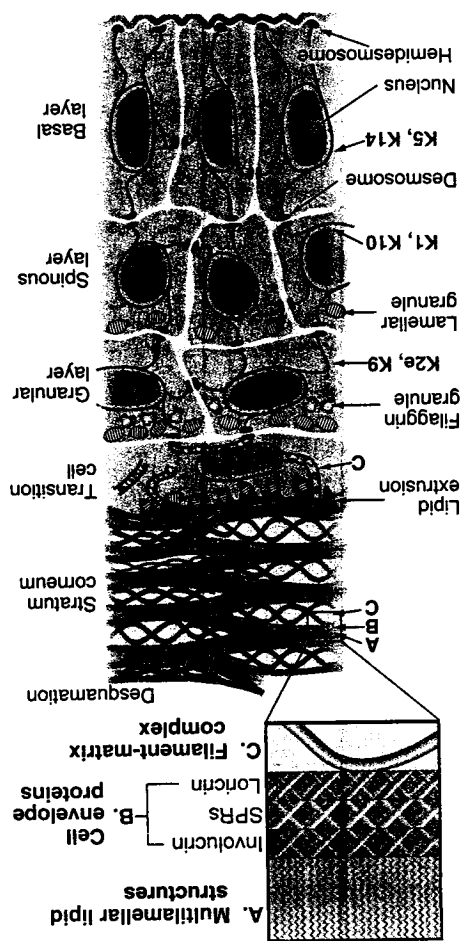
Ichthyotic side effects from hypolipidemic drugs are thought to result from direct effects on epidermal lipogenesis (15), but in the case of retinoids, the underlying mechanism is not known (17). However, recent transgenic studies may provide clues. Selective inhibition of the retinoid signaling pathway in the epidermis produces a transgenic mouse that fails to form lipid multilamellar structures and exhibited a defective barrier function (18). Lipid analysis confirmed a defect in lipid processing and suggests that retinoids are able to directly modulate epidermal lipid metabolism.

The formation and maintenance of skin barrier function is never ending. It is the product of the highly organized and regulated process of epidermal differentiation. Defects in structural components, either protein or lipid, or the enzymes responsible for their synthesis, processing, or assembly can disrupt the barrier or alter the process of renewal. Perhaps it is not so unexpected after all that the resultant phenotypes are similar—a thickened, scaly skin that places patients at increased risk for infection and desiccation.

extrude their contents into the intracellular spaces at the transition to the stratum corneum. The extruded lipids are enzymatically processed into the intercellular multilamellar structures which are covalently linked via ester bonds to the carboxyl groups of the CE (10), perhaps to involucrin (14). The successive stages of assembly of the CE result in conformational changes that permit covalent attachment of extracellular lipids to the exterior surface of CE; these processes would be altered in LI.

Changes in the lipid composition of the stratum corneum, either as a result of altered synthesis or processing, can produce scaling disorders (15). In fact, the first ichthyosis to be defined at the molecular level was RXLI, a steroid sulfatase deficiency (2). Several other inborn errors in lipid metabolism have been implicated in scaling disorders (4), defects in the lipid portion of the CE could cause the ichthyotic phenotype. The lipid component of the stratum corneum originates from lamellar granules, membrane-bound organelles that first appear in the spinous and granular layers and

Barrier development. Schematic illustrating the synthesis and assembly of products that contribute to epidermal barrier function. Inset shows the components of the composite cell envelope.



complex and the inner surface of squames and altering interactions (desmosomal contacts) between neighboring cells, thereby potentially affecting desquamation.

In LI, Hohl, Huber, and co-workers (4) have identified mutations that result in loss of activity of transglutaminase K (TCK), an enzyme that cross-links proteins to form the cell envelope (CE). The CE, a specialized structure that replaces the plasma membrane of terminally differentiating keratinocytes (9), consists of proteins cross-linked by covalent bonds into a rigid scaffold, with lipids covalently attached to its external surface (10) and the filament-matrix complex interacting with its internal surface (11). The cross-links between proteins are mainly disulfide bridges and highly stable covalent cross-links, catalyzed by transglutaminases, between glutamine and lysine residues.

The formation of a structurally mature CE occurs in several steps (9). In the last stages of differentiation, TCK, a membrane-bound keratinocyte-specific enzyme cross-links a membrane-bound protein with a cytosolic precursor protein (most likely involucrin). This initial scaffold is further strengthened by cross-linking other less abundant components, for example, cornifins and other small proline-rich proteins (SPRs) until the inner surface of the cell membrane is covered. This inner surface envelope is then reinforced by the attachment of loricin by TCK or by transglutaminase E, a cytosolic enzyme. Keratin filaments, which have been aggregated by filaggrin, are then thought to interact with the thickened protein envelope to strengthen the cytoskeleton. Finally, lipids are covalently bound to the outer surface of the protein cell envelope to complete the barrier. The ichthyotic phenotype of LI may occur as a direct result of an abnormal CE, due to incomplete cross-linking of the major protein components. In fact, the failure of these granular cells to localize Hohl et al. (12) the first clue that TCK might be defective in LI and an ultrastructural examination of LI skin revealed thin or absent CE (13). If a defective CE can cause LI, one would predict that the failure to synthesize the major protein components of the CE—loricin, involucrin, or the SPRs—might result in the development of a phenotypically similar disease.

Similarly, as pointed out by Huber and co-workers (4), defects in the lipid portion of the CE could cause the ichthyotic phenotype. The lipid component of the stratum corneum originates from lamellar granules, membrane-bound organelles that first appear in the spinous and granular layers and

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