Synopsis of Original Research Paper

Studies on the developmental processes of human cornified cell envelope and the pathogenesis of its dysfunction

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Terminally differentiated stratified squamous epithelium forms a lining of the plasma membrane called the cornified cell envelope (CCE), a thick layer of several covalently cross-linked precursor proteins including involucrin, small proline-rich proteins (SPRPs) and loricrin. Their cross-linking isodipeptide bonds are formed by epidermal transglutaminases (TGases) 1, 2 and 3. The formation of CCE and sequential expression of major CCE precursor proteins, TGases, and 25-kD lamellar granule-associated protein (LGP) were studied in human embryonic and fetal skin. Ultrastructurally, membrane thickening has already started in periderm cells of the two-layered epidermis and an electron dense, thickened cell envelope similar to CCE in adult epidermis is observed in periderm cells at the three-layered and later stages of skin development. In the two-layered epidermis (49-65 days EGA), immunoreactivities of involucrin, SPRPs, all the TGases and LGP were present only in the periderm. In the three-layered epidermis and thereafter (66-160 days EGA), loricrin became positive in the periderm cells, TGases extended to the entire epidermis, and LGP was detected in intermediate cells as well as periderm cells. Immunoelectron microscopy demonstrated that all three major CCE precursor proteins, involucrin, SPRPs and loricrin, were restricted to the CCE in periderm cells at this stage of development. After 160 days EGA, the periderm had disappeared and CCE proteins and LGP were expressed in the spinous, granular and cornified cells and TGases were detected in the entire epidermis. These findings indicate that CCE precursor proteins, TGases, and LGP are expressed in coordination in periderm cells during human epidermal development and suggest that periderm cells form CCE in the process of regression.

As a next step, five patients with non-bullous congenital ichthyosiform erythroderma (NBCIE), one patient with lamellar icthyosis and two patients with mutilating palmoplantar keratoderma (MPPK) were studied.

In one patient out of five NBCIE cases, expression of TGase 1 molecule was markedly reduced in the patient's epidermis. Electron microscopy revealed incomplete thickening of CCE during keratinization in the epidermis. Sequencing of the entire exons and exon-intron borders of TGase 1 gene (TGM1) revealed that the proband was a compound heterozygote for two novel mutations, 9008delA and R388H. These findings indicate that the compound heterozygote for missense mutation (R388H) in the core domain and the frameshift mutation (9008delA) resulting in a premature termination codon at the tail of the TGase 1 peptide leads to the NBCIE phenotype. TGM1 mutations were also found in the lamellar ichthyosis patient.

In the patients with MPPK, ultrastructural, immunohistochemical, and immunoelectron microscopic analyses revealed malformed CCE and reduced deposition of loricrin to CCE. Sequencing of the entire exons and exon-intron borders of loricrin gene of the patients excluded a mutation in loricrin DNA sequence. These data confirm the presence of MPPK phenotype with abnormal loricrin cross-linking at the final stage of CCE formation that is not caused by mutations in the epidermal differentiation complex region.