The Molecular Basis of Keratinizing Disorders

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Abstract: Technological advances in molecular biology have brought about a number of major scientific achievements in the field of normal and abnormal epidermal differentiation. This article reviews the molecular defects that cause many types of keratinizing disorders, and highlights the roles of affected genes encoding a variety of epidermal proteins.

Key words: Keratinizing disorders; Pathogenic gene; Mutation

Introduction

Keratinizing disorders are conditions in which qualitative or quantitative abnormality based on a certain genetic background affects the pathway of epidermal differentiation from the birth of basal cells in the epidermis to their exfoliation as cornified cells at the skin surface. This paper reviews biological aspects of pathogenic genes encoding cytoskeletal proteins (keratins), desmosomal proteins (desmoplakin, desmoglein, plakoglobin, and plakophilin), gap junction proteins (connexins), cornified envelope protein (loricrin), and certain enzymes/enzyme inhibitors

Keratinizing Disorders and Pathogenic Genes (Table 1)

1. Enzymes and their inhibitors
   (1) Lipoxygenase

   Nonbullous ichthyosiform erythroderma is caused by the mutation of the lipoxygenase-3 (ALOXE3) or the 12R-lipoxygenase (ALOX12B) gene.1) ALOXE3 and ALOX12B are both enzymes involved in the metabolism of arachidonic acid. The loss of activity of these enzymes results in a shortage of essential fatty acids and compromises the hydration ability of the horny layer.

   (2) Transglutaminase 1 (TGase 1)

   Lamellar ichthyosis, a condition resembling nonbullous ichthyosiform erythroderma, is caused by the mutation of the TGase 1 gene.2) TGase 1 catalyzes the bridging of proteins at the γ-carboxyl groups in glutamine residues and at the lysine residues. Through these reactions, TGase 1 bridges the components of the cornified cell envelope, which is a structure that lines the cell membrane, and plays an important role in maintaining the construction of cornified cells. In this disease, the activity of
TGase 1 is reduced, and the ability to bridge the cornified cell envelope precursor proteins is insufficient. As a result, the ceramide that normally binds to the cornified cell envelope components is accumulated in intercellular spaces, and the decomposition of desmosomes by protease is inhibited.

(3) Sarco/endoplasmic reticulum Ca\(^{2+}\) ATPase (SERCA)

Darrier’s disease is caused by the mutation
of the sarco/endoplasmic reticulum Ca\(^{2+}\)-ATPase type 2 isoform (SERCA2) gene.\(^3\) SERCA2 belongs to the large family of P-type cation pumps that couple ATP hydrolysis with cation transport across membranes. SERCA pumps specifically maintain low cytosolic Ca\(^{2+}\) concentrations by actively transporting Ca\(^{2+}\) from the cytosol into the sarco/endoplasmic reticulum lumen. In this disease, the level of SERCA2b that has a normal pump function is reduced by half, and this results in the impairment of Ca\(^{2+}\)-mediated signal transduction and cell adhesion.

(4) 3beta-hydroxysteroid dehydrogenase

CHILD (congenital hemidysplasia with ichthyosiform erythroderma and limb defects) syndrome is caused by the mutation of the 3beta-hydroxysteroid dehydrogenase gene.\(^4\) This enzyme functions in the pathway for cholesterol biosynthesis. Since cholesterol is important in embryonic development controlled by the hedgehog signaling pathway, this led to the notion that a cholesterol precursor without the potential to form esters might impair signaling through hedgehog proteins and thus explain the dysplasias observed in CHILD syndrome.

(5) Cathepsin C

Papillon-Lefèvre syndrome is caused by the mutation of the cathepsin C gene.\(^5\) Cathepsin C is a cysteine protease of the papain family and is a dipeptidyl aminopeptidase capable of removing dipeptides from amino terminus of proteins. The Cathepsin C knockout mice show insufficiency in the cytotoxic activity of CTL cells and NK cells through activation impairment of serine proteases called granzymes A and B. In this disease, the immune response to infections becomes abnormal via the same mechanism seen in the knockout mice and characteristically induces severe periodontitis.

(6) Steroid sulfatase (STS)

X-linked ichthyosis vulgaris is caused by the mutation of the STS gene.\(^6\) STS is an enzyme hydrolyzing the sulfate group at the sterol ring 3β position in steroid hormones and cholesterol. In this disease, the degradation of cholesterol sulfate, the substrate for this enzyme, to cholesterol, does not take place, and cholesterol sulfate accumulates in the spaces between cornified cells. As a result, cholesterol sulfate inhibits the activity of chymotrypsin-type serine proteases and hinders the decomposition of desmosome components.

(7) Fatty aldehyde dehydrogenase (FALDH)

Sjögren-Larsson syndrome is caused by the mutation of the FALDH gene.\(^7\) FALDH is a component of the fatty alcohol: NAD oxidoreductase enzyme complex that catalyzes the sequential oxidation of fatty alcohol to aldehyde and fatty acid. In this disease, FALDH deficiency causes the accumulation of fatty alcohol and wax esters in the intercellular membrane lamella, which may disrupt the epidermal water barrier.

(8) Phytanoyl-CoA hydroxylase (PAHX)

Refsum syndrome is caused by the mutation of the PAHX gene.\(^8\) PAHX is involved in the α-oxidation of phytanic acid. In this disease, PAHX deficiency leads to the accumulation of phytic acid followed by replacement of essential fatty acid with phytic acid in the lipid moieties of various tissues.

(9) LEKTI (lymphoepithelial Kazal-type-related inhibitor)

Netherton syndrome is caused by the mutation of the SPINK5 (serine protease inhibitor, Kazal-type 5) gene, which codes LEKTI, a serine protease inhibitor.\(^9\) LEKTI is involved in T-cell differentiation in thymic epithelium as well as anti-inflammatory and bactericidal activities in mucosal epithelium. Defective LEKTI expression may cause unbalanced Th2 immune response with markedly elevated IgE levels, increased susceptibility to infection and impaired desquamation of cornified cells.

2. Adhesion Molecules

(1) Desmosome components

Striate palmoplantar keratoderma, Naxos disease, and skin fragility syndrome are caused by mutations of the desmoplakin gene or the desmoglein 1 gene, the plakoglobin gene, and
the plakophilin gene, respectively. Desmosomes are intracellular adhesion apparatuses occurring in epithelial cells and myocardial cells. The protein component of a desmosome is composed of a group of transmembrane glycoproteins and a group of attachment plaque proteins binding to them on the cytoplasm side. Desmoglein 1 belongs to the former group, and desmoplakin, plakoglobin, and plakophylin belong to the latter. Mutations in these desmosome components are considered to cause abnormalities in cell adhesion, but little is known about their relation to palmoplantar keratosis, the common clinical manifestation of the above-mentioned diseases.

(2) Connexins

Erythrokeratoderma variabilis, Clouston syndrome, Vohwinkel’s syndrome with deafness and KID (keratitis-ichthyosis-deafness) syndrome are caused by mutations of the connexin 31 gene, the connexin 30 gene and the connexin 26 gene, respectively. Connexins are the main protein components of the gap junction. Six connexin molecules assembled in a ring form a doughnut-shaped structure. The tunnel at the center of this structure opens and closes to adjust the transportation of small molecules between adjacent cells, which play an important role in intercellular interaction. Mutant connexins are likely to be incapable not only of forming the normal gap junction but also of playing a crucial role in epithelial homeostasis and differentiation.

3. Cornified Cell Envelope Proteins

(1) Loricrin

Both Vohwinkel syndrome with ichthyosis and progressive erythrokeratodermia are caused by the mutation of the loricrin gene. Loricrin deposits on the 15-nm-thick layer of the cytoplasmic surface of the cell periphery (cornified cell envelope). Frameshift mutations in the loricrin gene produce amino acid sequences that contain motifs resembling nuclear localization signals. As a result, the mutant loricrin moves into the nucleus being associated with normal loricrin, and the formation of the cornified cell envelope is impaired.

4. Cytoskeletal Proteins (Table 1)

(1) Keratins

Various diseases collectively called keratin diseases are caused by the mutation of various keratin genes. Keratins are an extremely diversified group of proteins that play an important role in cell shape maintenance. In keratin diseases, the ability of keratins to maintain cell shape is weakened, and cells are easily destroyed by even slight external force.

5. Others

(1) Dyskerin and telomerase RNA

X-linked recessive dyskeratosis congenita and autosomal dominant dyskeratosis congenita are caused by mutations of the dyskerin gene and telomerase RNA gene, respectively. These components are suspected to play a role in the activity adjustment of telomerase, which governs the life span of cells. However, their functional significance in these diseases is unknown.

(2) SLURP-1 (secreted Ly6/uPAR-related protein 1)

Mal de Meleda type of palmoplantar keratosis is caused by the mutation of the SLURP-1 gene. SLURP-1 belongs to the leukocyte antigen-6 (Ly6)/urokinase-type plasminogen activator (uPAR) protein family, and the structure of SLURP-1 suggests its relationship with snake and frog toxins. SLURP-1 receptors are assumed to play an important role in signal transduction, cell growth, cell adhesion, etc., but their functional significance in this disease is unknown.

6. Diseases Being Studied for Identification of Pathogenic Genes

The genes for harlequin fetus and palmoplantar keratoderma Howel-Evans map to chromosomes 18q21.3 and 17q25, respectively.
Conclusion
These findings of genes responsible for keratinizing disorders are expected to provide valuable information in the elucidation of pathogenic mechanisms and the search for new treatment modalities.

REFERENCES


