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ABSTRACT

The integrity of the epidermis depends on the cohesion between keratinocytes, and desmosomes are the main adhesion structures. When cells become cornified, desmosomes are modified and transformed into corneodesmosomes. Mutations in the genes encoding desmosomal components underlie several skin diseases including palmoplantar keratoderma and forms of epidermolysis bullosa, indicating the importance of desmosomes as mechanical stress-bearing structures. Other types of genetic defects in a desmosome component (desmoglein 1), a corneodesmosome component (corneodesmosin), and an inhibitor for proteases involved in corneodesmosome degradation (LEKTI) result in three clinically overlapping conditions: SAM syndrome, an inflammatory type of peeling skin disease, and Netherton syndrome. All three result in allergies to multiple allergens due to severe barrier impairment. Conversely, impaired corneodesmosomal degradation due to matriptase mutations could lead to ichthyosis. By discovering the diverse clinical phenotypes of these diseases, we can enrich our understanding of the multifunctional roles of desmosomes and corneodesmosomes in skin biology.

Contents

1. Introduction

We never know the worth of water till the well is dry.

— Thomas Fuller

We have gained great insights into how our body functions by studying various diseases. The importance of desmosomes, which are adhesive intercellular junctions, was first elucidated by examining autoantibodies against desmogleins (DSGs) from patients suffering from pemphigus, a group of autoimmune blistering diseases affecting desmosomal cadherins. The binding of antibodies against extracellular domains of DSG molecules leads to acantholysis (separation of individual keratinocytes from their neighbours) and intraepithelial blister formation. We have expanded our understanding of desmosomes by studying genetic diseases. A recent important topic has been the discovery of a new severe dermatitis caused by the absence of DSG1 [1]. Thus far, lifelong dysfunction of desmosomes and related structures has been associated with a wide range of clinical phenotypes: alopecia, palmoplantar keratoderma (PPK), generalized erythematosus scaly skin, blistering diseases among others. In this review, we summarize the clinical features and molecular pathology of the spectrum of genetic skin diseases associated with desmosomes and corneodesmosomes, which are the modified form of desmosomes found in the stratum corneum.

2. Desmosomes and the wide spectrum of desmosome related genetic diseases

2.1. Desmosomes

Desmosomes are intercellular attachment sites and anchoring sites for the intermediate filament cytoskeleton, providing the primary resistance to the incessant and strong mechanical forces applied to the skin and cardiac muscle [2,3]. Electron microscopy has been used to reveal characteristic structures: intermediate filaments attached-inner plaque, electron dense outer plaque, plasma membrane, and electron dense midline in the extracellular domain (Fig. 1). Desmosomes are composed of several transmembrane and intracellular molecules. The transmembrane proteins facilitating intercellular adhesion are desmosomal cadherins; DSGs and desmocollins (DSCs). Their

intracellular domains are attached to the intermediate filaments through desmoplakin, plakoglobin, plakophilin and a wide range of other intracellular molecules. Genetic abnormality in desmosomal components could result in diseases of the skin and heart (Table 1) [2,3]. Desmosomes function not only in mechanical cohesion of the tissue, but also in cell signalling and they also play a role in skin barrier functionality. This may at least partially explain the diverse range of clinical phenotypes seen in desmosomal diseases.

2.2. DSG1, palmoplantar keratoderma and generalized erythematosus scaly skin

DSG1 is a member of desmosomal cadherins strongly expressed in the granular and spinous layers of the epidermis [2,3]. DSG1 is also expressed in hair follicles [4]. Heterozygous *DSG1* mutations underlie type I striate palmoplantar keratoderma (PPK), an autosomal dominant condition characterized by marked hyperkeratotic bands on the palms and soles (Table 1, Fig. 2) [5].

Recently, homozygous *DSG1* mutations were found to underlie congenital erythroderma with PPK, hypotrichosis, and hyper-IgE features. This is called SAM syndrome, where the letters S, A and M stand for *s*evere dermatitis, multiple *a*llergies and *m*etabolic wasting (Table 1, Fig. 2) [1]. Patients with these mutations display congenital erythroderma, yellowish papules and plaques arranged at the periphery of the palms, along the fingers and over weight-bearing areas of the feet, skin erosions and scaling, and hypotrichosis. In addition, they exhibit the following characteristics from infancy: severe food allergies, markedly elevated IgE levels and recurrent infections with marked metabolic wasting. The epidermis in these patients showed acantholysis and uneven distribution of desmosomes in the upper spinous layer and granular layer (Fig. 3). Desmosomes at the basal cells and lower spinous cells appeared normal. This reflects the predominant expression of DSG1 in the upper epidermis. Interestingly, heterozygous carriers for this mutation presented with PPK, suggesting that the phenotypic difference is due to a quantitative difference of the same gene defects (Fig. 2). If DSG1 expression is reduced into a half, the damage manifests at mechanically stressed sites only.

2.3. DSG4 mutations cause hypotrichosis 6 and monilethrix

DSG4 is a member of the desmosomal cadherin family expressed in the hair (cortex, cuticle, inner root sheath cuticle) as well as in the upper epidermis [3]. Hypotrichosis 6 or localized autosomal recessive hypotrichosis is an autosomal recessive condition caused by a mutation in *DSG4* (Table 1) [6]. It is characterized by fragile, short, sparse hairs on the scalp, trunk, and extremities. Follicular hyperkeratotic papules and marked pruritus are also prominent. In some patients monilethrix-like hairs have been observed [7]. The reason for the absence of any blistering or PPK may be that DSG1 can compensate for the loss of DSG4 in the epidermis.

2.4. DSC2 and cardiomyopathy with PPK and woolly hair

DSC2 is a member of the desmosomal cadherin family highly expressed in the myocardium, but also present in the lower epidermis [2,3] and hair follicles [4]. All three DSC subtypes are expressed in the epidermis, but DSC2 is the only DSC present in the heart. DSC2 pathology had been described in patients who had arrhythmogenic right ventricular cardiomyopathy (ARVC) without skin pathology. This was assumed to be due to the compensation of DSC1 and DSC3 in the skin. However, a homozygous deletion mutation in *DSC 2* was found to cause not only ARVC, but also mild PPK and woolly hair (Table 1, Fig. 2) [8].

2.5. DSC3 and hypotrichosis and recurrent skin vesicles

DSC3 is predominantly expressed in the basal and first suprabasal cell layers of the epidermis [2,3] and all cell types in the hair follicle [4]. A homozygous nonsense mutation in *DSC3* was reported in patients with hypotrichosis and recurrent skin vesicles in a consanguineous family demonstrating hereditary transmission as an autosomal recessive trait (Table 1) [9]. The patients showed sparse and fragile hair on the scalp, as well as absent eyebrows and eyelashes. However, the validity of their evidence of skin blister was questioned by some [10].

2.6. Desmoplakin and the diverse range of symptoms including cardiomyopathy, PPK, woolly hair, skin fragility and epidermolysis

Desmoplakin is an obligate component of functional desmosomes highly expressed in the heart, epidermis [2,3] and the hair follicle [4]. It anchors intermediate filaments to desmosomal plaques, and also interacts with plakophilin 1 and plakoglobin (Fig. 1 and 2). Desmoplakin haploinsufficiency may underlie type II striate PPK in an autosomal dominant manner (Table 1, Fig. 2) [11]. Absence of other skin, hair or extracutaneous features suggests that a half expression level of desmoplakin is satisfactory for most epidermal functioning in non-palmoplantar skin but insufficient for palms and soles, sites that are subject to considerable mechanical stress. Phenotypes of recessive mutations can be more severe as seen in Carvajal syndrome, in which in addition to striated PPK, woolly hair and left ventricular cardiomyopathy are present [12]. Skin fragility/woolly hair syndrome is caused by another recessive mutation of the desmoplakin gene [13]. Blistering, skin fragility, localized or diffuse PPK, hyperkeratotic plaques on the trunk and extremities, alopecia and woolly hair are typical characteristics; however, cardiac problems have not been associated with this disease. Another mutation which truncates the C-terminus of desmoplakin is associated with lethal acantholytic epidermolysis bullosa (EB), which presents complete alopecia, neonatal teeth, nail loss, extensive skin erosion and neonatal death [14].

2.7. Plakoglobin and the diverse range of symptoms, from PPK to severe EB

Plakoglobin (γ-catenin) is a major cytoplasmic protein and is a constituent common to desmosomes and adherens junctions (Fig. 1) [2,3]. Plakoglobin is mainly expressed in the skin including hair follicles, and the heart, and facilitates the adhesion of desmoplakin to intermediate filaments. Since plakoglobin also constitutes adherens junctions, it may regulate cross-talk between desmosomes and adherens junctions.

In humans, mutations in the gene for plakoglobin, *Junction plakoglobin (JUP),* are associated with either a heart disease, a cardiocutaneous disease in which both skin and heart are affected, or others with only skin manifestations (Table 1, Fig. 2). ARVC type 12 is a heart disease

caused by an autosomal dominant insertion mutation of *JUP*. The other diseases involving the skin are caused by recessive mutations. Naxos disease is caused by a homozygous recessive 2-bp deletion mutation in *JUP* [15]. It is characterized by ARVC, PPK and woolly hair, but skin blistering was absent. Heterozygous carriers usually have no skin or hair abnormalities, but up to 25% have heart involvement. A novel cardiocutaneous disease caused by the homozygous missense mutation in *JUP* was found in patients with ARCV, PPK and alopecia [16]. Clinically, it is similar to Naxos disease, but with alopecia rather than woolly hair. Severity of symptoms in the patients only skin is affected can vary. Some patients suffer from skin fragility, diffuse PPK, and woolly hair [17]. Skin in these patients showed acantholysis and desmosomes were few in number and poorly developed with no clear insertion of the keratin filaments [18]. In other cases, complete lack of plakoglobin expression resulted in extreme skin fragility manifested as lethal congenital EB (Table 1, Fig. 2) which lead to death at perinatal stages [19].

In mice, global deletion of *JUP* results in heart malformations and skin blister formation [20,21]. Ultrastructural analysis revealed that desmosomes were greatly reduced in number and structurally altered [20]. To better understand pathomechanisms of the skin lesions in genodermatosis of plakoglobin, epidermis-restricted *JUP* knock-out mice were generated [22]. In these mice, disrupted desmosome assembly, loose cell-cell contacts, hyperproliferative epidermis, and PPK were seen.

2.8. Plakophilin 1 and ectodermal dysplasia-skin fragility syndrome

Plakophilins are found predominantly in desmosomes (Fig. 1), but also localize to the nucleus [2,3]. Plakophilins interact with multiple partners (desmosomal cadherins, plakoglobin, desmoplakin, and intermediate filament proteins). Plakophilin 1 is expressed in the suprabasal layers of stratified epithelia and hair follicles [23]. Ectodermal dysplasia-skin fragility syndrome or McGrath syndrome is an autosomal recessive dermatosis characterized by skin fragility, PPK, onichodystrophy, perioral fissuring and noncicatricial alopecia [24]. This is caused by recessive mutations in the plakophilin 1 gene (Table 1, Fig. 2). There is no cardiac pathology in these cases

because plakophilin is not expressed in the heart. Skin in these patients showed poorly developed inner and outer desmosomal plaques. Desmosomes were reduced both in size and number in the lower suprabasal layers in the epidermis of affected patients [25].

3. Corneodesmosomes and the unique clinical phenotypes of genetic diseases

3.1. Corneodesmosome and desquamation enzymes

A corneodesmosome is a modified form of desmosome (Fig. 1) [26]. When desmosomes are transformed into corneodesmosomes in the upper stratum granulosum, desmoglea loses its tri-lamellar structure and becomes a homogeneously electron dense ‘plug’. On the cytoplasmic side, components of the desmosomal plaques are cross-linked into and become parts of cornified cell envelopes. Kallikrein-related peptidases (KLKs) and several other proteases are involved in the degradation of corneodesmosomes (Fig. 4) [27].

3.2. Corneodesmosin, peeling skin disease type B and hypotrichosis

Corneodesmosin (CDSN) is a glycoprotein expressed mainly in the epidermis and the inner root sheath of the hair follicles, and constitutes extracellular component of corneodesmosomes (Fig. 1) [26]. In the epidermis, CDSN is secreted by lamellar granules and incorporated into the desmoglea and covalently crosslinked to the cornified cell envelopes, and secure cell-cell adhesion in the stratum corneum (Fig. 1). During corneocyte maturation, corneodesmosin is progressively proteolyzed and desquamation occurs (Fig. 4).

Importance of CDSN in the epidermal cell-cell adhesion was first discovered by lethal phenotypes of mice lacking CDSN expression [28]. In the skin of these mice, corneodesmosomes were structurally abnormal and the stratum corneum was detached from the granular layer. Next in human studies, type B peeling skin disease (PSD) was found to be caused by the absence of functional corneodesmosin expression (Table 1, Fig. 2) [29,30]. PSD is a rare autosomal recessive genodermatosis characterized by continuous superficial exfoliation of the outer epidermis. Several types of PSD have been described. Type A PSD is characterized by noninflammatory and

asymptomatic peeling, and is caused by a mutation in *CHST8* [31]. In type B, there are erythematous migratory patches with a peeling border; pruritus or burning may be conspicuous. Type B may also be associated with several noncutaneous anomalies and various abnormal laboratory findings. In type B PSD, ultrastructural features of corneodesmosomes and skin separation recapitulated those in the CDSN knock-out mice [30].

Dominant nonsense mutations in *CDSN* that produce a truncated form of CDSN underlie hypotrichosis simplex of the scalp, a rare disease that leads to complete baldness in young adults [32]. In this disease, the epidermis is not affected. Since hair phenotype is very mild or absent in type B PSD patients, hair-restricted phenotype in human hypotrichosis simplex is likely to be due to a dominant negative effect of the truncated form of CDSN on hair follicle integrity.

3.3. LEKTI and Netherton syndrome

Lympho-epithelial Kazal-type-related inhibitor (LEKTI) is an inhibitor for the desquamation-associated KLKs (Fig. 4) [33]. LEKTI is expressed in the granular layer of the epidermis and secreted into the extracellular space [34]. Its fragments inhibit epidermal KLK5, -7, and -14 forming a tight binding complex [35]. LEKTI2 is a KLK5-specific inhibitor highly expressed in the palmoplantar epidermis [36,37]. Still another KLK inhibitor found recently is Spink6 [38]. While it is most prominently expressed at the palmoplantar sites, Spink6 is expressed in the epidermal granular cells at the different body sites including the face, arms, trunk, and legs inhibiting KLK5, KLK7 and KLK14.

Mutations in *SPINK5* encoding LEKTI underlie Netherton syndrome (NS), a rare autosomal recessive disorder characterized by severe ichthyosis, hair-shaft defects (bamboo hair) and atopic features (Table 1, Fig. 2) [39]. Insufficient LEKTI activity results in increased proteolytic activity of KLKs, activated degradation of DSG1, and premature desquamation [40]. Matriptase initiates disease onset in a mouse model of NS by activating epidermal KLKs (Fig. 4) [41]. Ablation of matriptase from NS-model mice prevented detachment of stratum corneum and improved the

barrier function of the epidermis. This adds new insights into development of effective treatment for NS.

3.4. Clinical overlapping between SAM, NS and type B PSD

There are overlapping features between SAM, NS and type B PSD (Fig. 2)[42]. Clinically, they all have autosomal recessive inheritance, lifelong skin shedding with erythema, pruritus, epidermal hyperplasia, and increased serum IgE levels. Histopathologically, cell-cell adhesion is disturbed in the spinous and granular cells in SAM and in the upper granular and cornified cells in NS and type B PSD. Although there are some differences, such as characteristic hair abnormalities and double-edged scales of NS having not found in PSD and SAM, these three diseases can be categorized into one group characterized by less adhesiveness of upper epidermal cells. This results in compromised barrier function, skin inflammation and multiple allergies. Since there are more proteins which constitute desmosomes or regulate corneodesmosomal degradation, more diseases might be found in this category in future.

3.5. Matriptase and ichthyosis with hypotrichosis

Matriptase or ST14 is a type II transmembrane serine protease expressed in the skin [43], and is an efficient activator of epidermal KLKs (Fig. 4) [41]. Its genetic mutations cause congenital ichthyosis associated with abnormal sparse hair (Table 1, Fig. 2) [44]. In the ichthyotic skin, corneodesmosome degradation is impaired, which is in line with the function of matriptase in activation of epidermal KLKs involved in corneodesmosome degradation. It should be kept in mind that both the diseases with decreased desquamation as seen in this disease and the diseases with accelerated desquamation such as SAM, NS and type B PSD can be categorized into a group of diseases “ichthyosis” and can be misleading.

4. Future prospects

What else could be found in genodermatosis of desmosomes? DSG3 is expressed mainly in the basal and the immediate suprabasal cell layers of the epidermis and oral mucosa, and in the outer root sheath of the hair follicle. Since targeted disruption of *DSG3* in mice causes oral mucosal erosions, trauma-induced skin erosions and hair loss due to acantholysis [45,46], a *DSG3* mutation might cause human diseases affecting oral mucosa, skin and/or hair. Mice lacking DSC1, which is normally expressed in the upper epidermis, exhibited flaky skin, granular layer acantholysis and defective barrier function [47]. This is somewhat reminiscent of SAM suggesting that similar human diseases might be caused by *DSC1* mutations. Since plakophilin 3 deficient mice develop hair coat abnormalities and cutaneous inflammation [48], there might be a human plakophilin 3 disease of the epidermis and hair. As being serine protease inhibitors highly expressed in the palmoplantar skin, LEKTI2 and Spink6 might be relevant to the pathogenesis of some forms of PPK [36,37,38]

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Figure legends.

Fig. 1. Ultrastructures of desmosome and corneodesmosome and their schematic representation. (A) Tri-lamellar structure of the desmoglea of desmosomes is sandwiching an electron dense midline. Desmoglea of corneodesmosome (arrowhead) is homogeneously electron dense. Corneodesmosin is localized at the desmoglea of corneodesmosome, but not that of desmosome. Cytoplasmic parts of corneodesmosomes are incorporated into the cornified envelope (arrows). (B) Immunoelectron microscopy showing different localization patterns of desmosome and corneodesmosome molecules. Desmoglein 1 labels are seen at the desmoglea and desmoplakin labels are at the desmosomal plaques. Corneodesmosin is localized at the desmoglea of corneodesmosome.

Fig. 2. Pathological mechanisms for desmosome and corneodesmosome related genetic skin diseases. Increased adhesiveness of corneocytes (blue arrow) is seen in matriptase abnormalities presenting as ichthyosis. Reduced adhesiveness of keratinocytes (red arrow) leads to a wide spectrum of disease phenotypes depending on the severity of adhesion defect. In mild conditions, symptoms only appear at the mechanical stress sites as PPK. If cell-cell adhesion is deeply compromised, skin fragility and widespread skin detachment occurs spontaneously or with minor trauma. If cell-cell adhesion is moderately compromised, skin inflammation and pruritus become prominent due to defective

outside-in skin barrier function.

Fig. 3. Ultrastructure of the upper spinous layer of a patient with SAM. Note that desmosome distribution is uneven and some areas are devoid of desmosomal contact (red arrows). Characteristic half-split desmosomes are also noted (black arrow). Panels B and C are higher magnification views of the areas indicated in panels A and B, respectively.

Fig. 4. Schematic representation of the proteolytic cascade of corneodesmosomes. The extracellular components of corneodesmosomes consisting of DSG1, DSC1 and CDSN are proteolysed by KLKs. KLKs constitute a family of 15 (chymo) trypsin-like serine proteases (KLK1-15) and function through proteolytic cascades. In the skin, KLKs are expressed and secreted into the extracellular space at the transition point between the granular and cornified layers. KLK14 is uniquely expressed to a greater extent in the plantar epidermis. Activated KLK5, KLK7, and KLK14 can degrade corneodesmosomal components. KLK5, -7, and -14 are inhibited by LEKTI. KLK5 is activated by matriptase.

Table 1. Desmosome and Corneodesmosome related genetic skin diseases

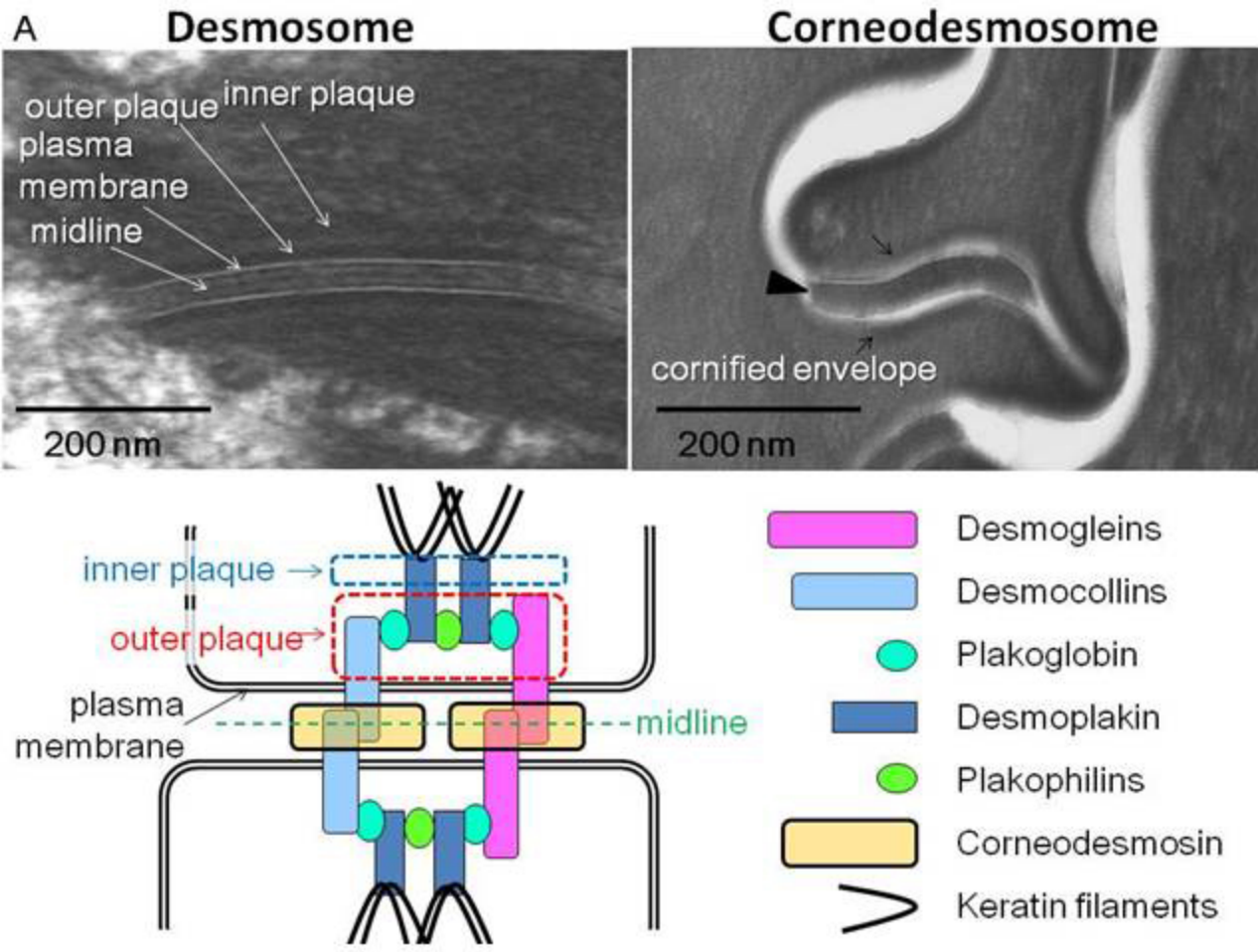
Molecules	Diseases	OMIM number	Inheritance
Desmoglein 1	Type I striate PPK	148700	AD
	SAM syndrome	615508	AR
Desmoglein 4	Hypotrichosis 6	607903	AR
Desmocollin 2	ARVC11	610476	AR, AD
	ARVC11 with mild PPK and woolly hair	610476	AR
Desmocollin 3	Hypotrichosis and recurrent skin vesicles	613102	AR
Desmoplakin	Type II striate PPK	612908	AD
	ARVC8	607450	AR
	Carvajal syndrome	605676	AR
	Skin fragility/woolly hair syndrome	607655	AR
	Lethal acantholytic EB	609638	AR
Plakoglobin	ARCV12	611528	AD
	Naxos disease	601214	AR
	ARVC, PPK & total alopecia		AR
	Focal and diffuse PPK & wooly hair		AR
	Lethal congenital EB		AR
Plakophilin 1	Ectodermal dysplasia-skin fragility syndrome	604536	AR
Corneodesmosin	PSD type B	270300	AR
	Hypotrichosis simplex	146520	AD
LEKTI	Netherton syndrome	256500	AR
Matriptase	Ichthyosis with hypotrichosis	610765	AR

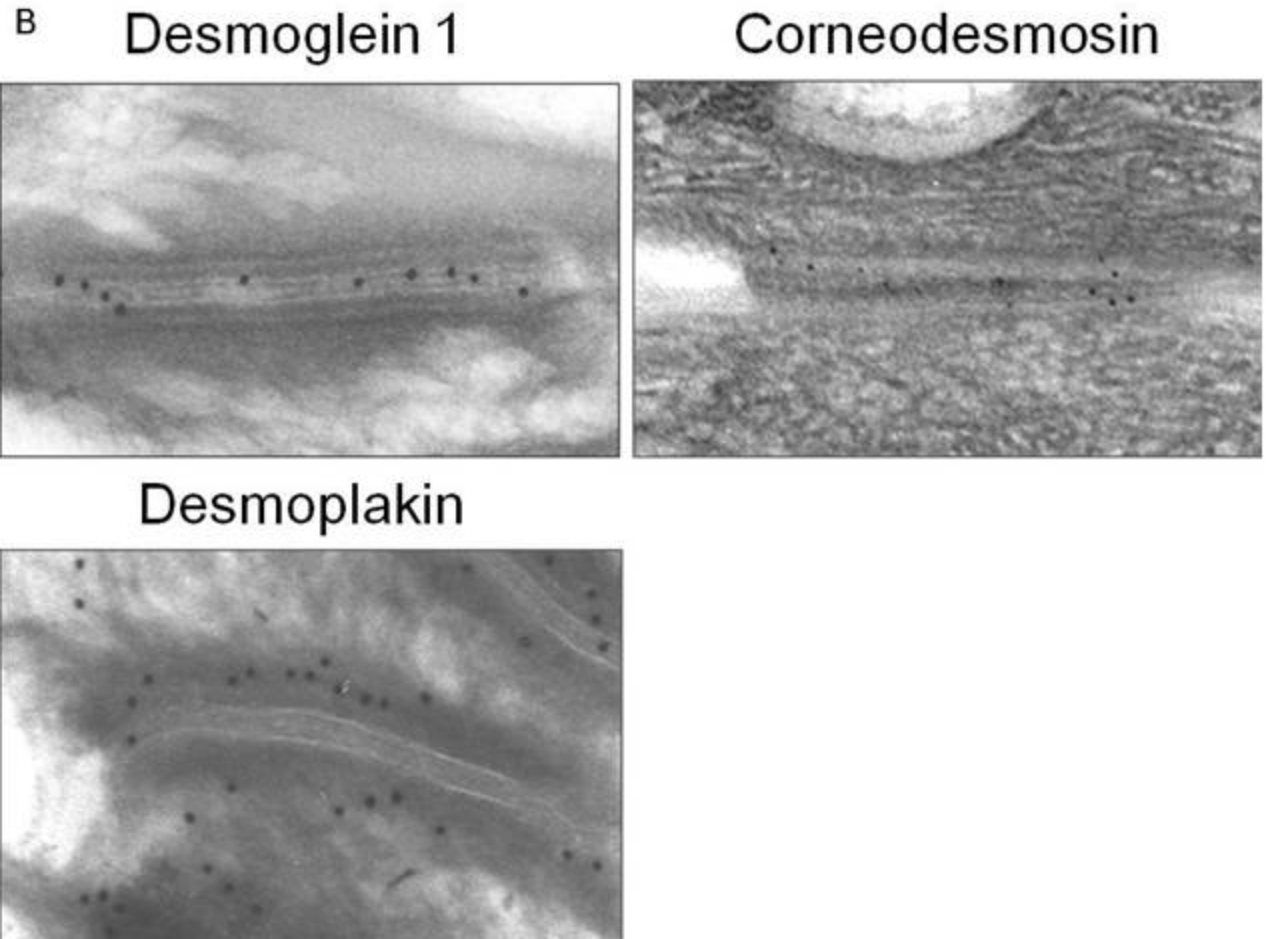
AD, autosomal dominant

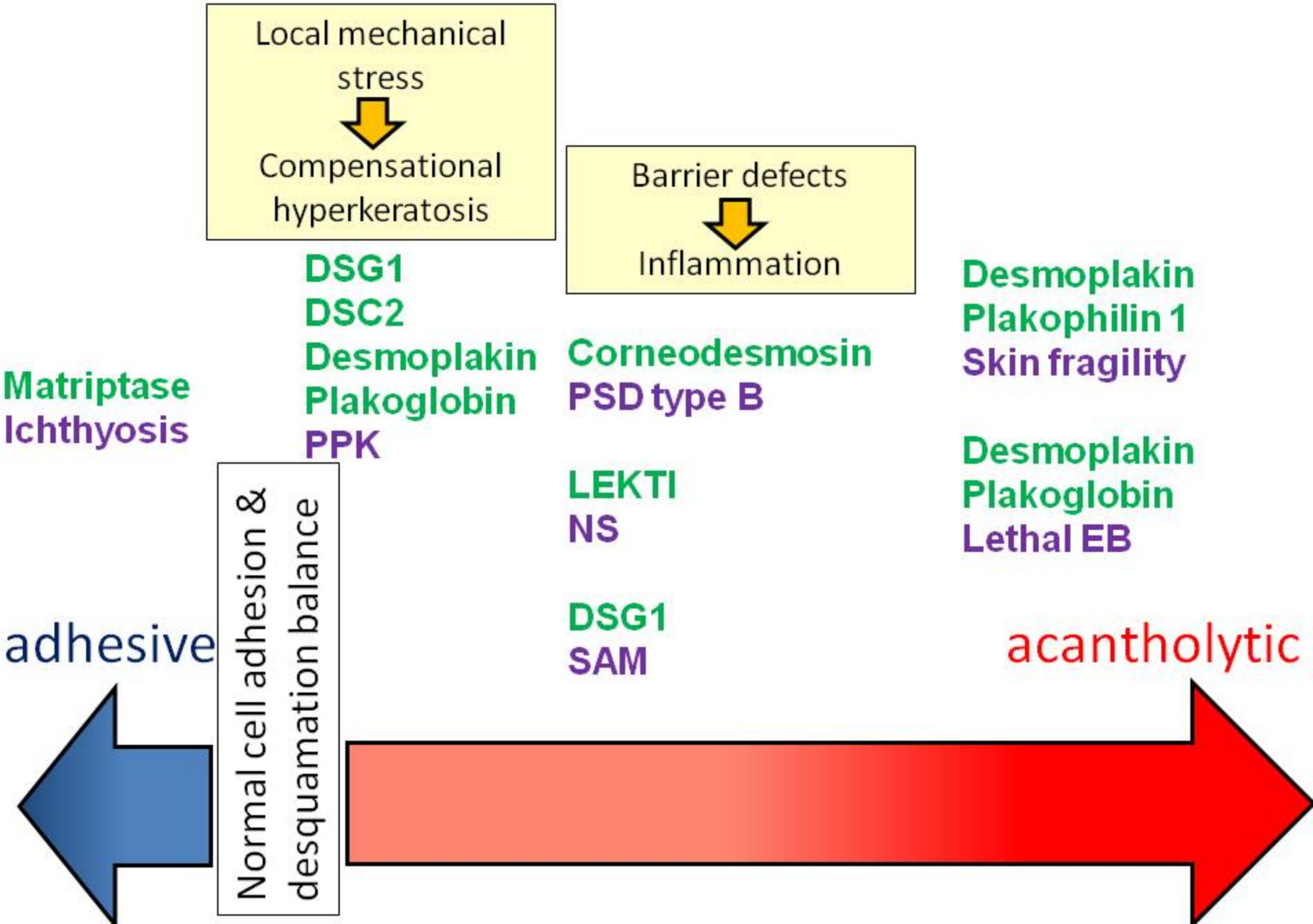
AR, autosomal recessive

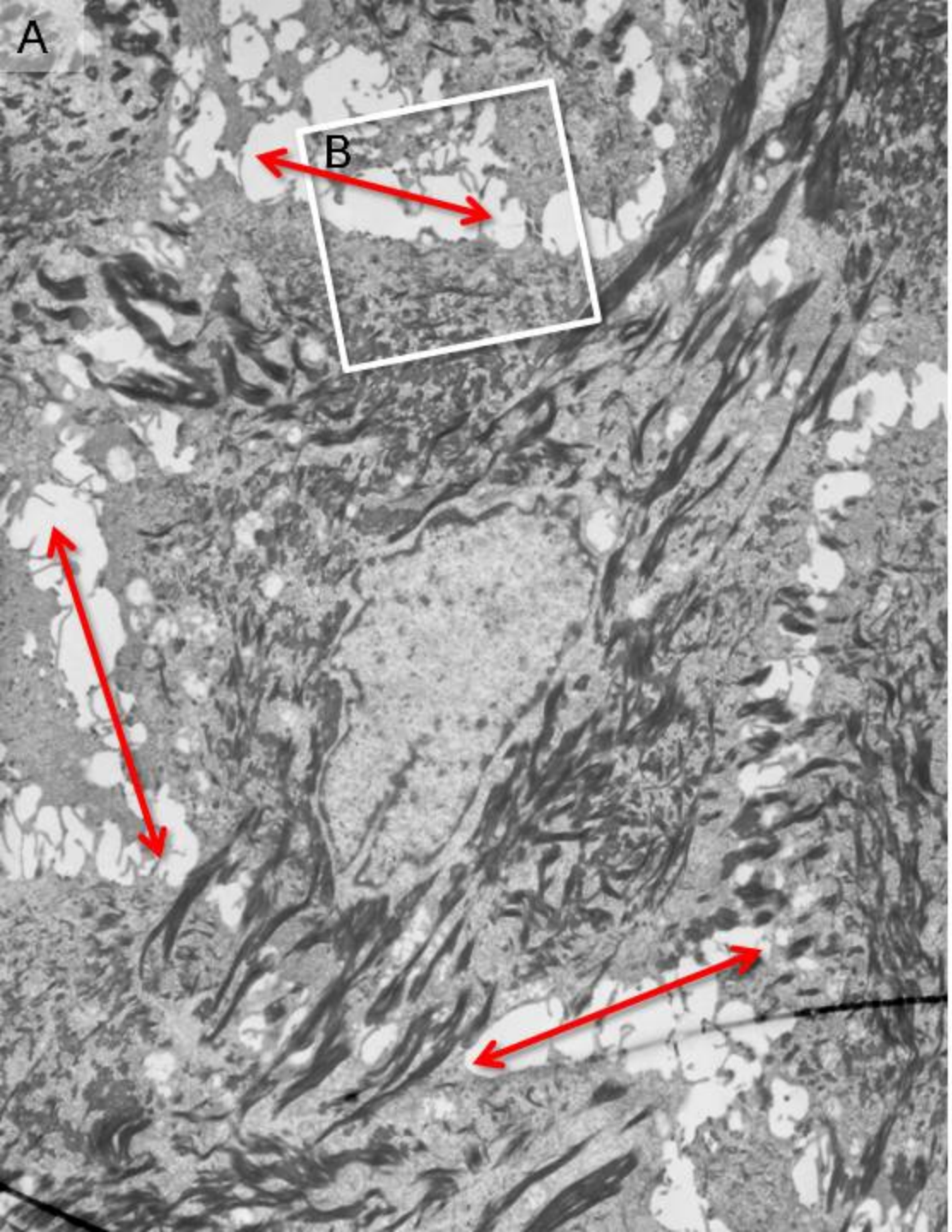
ARVC, Arrhythmogenic right ventricular cardiomyopathy

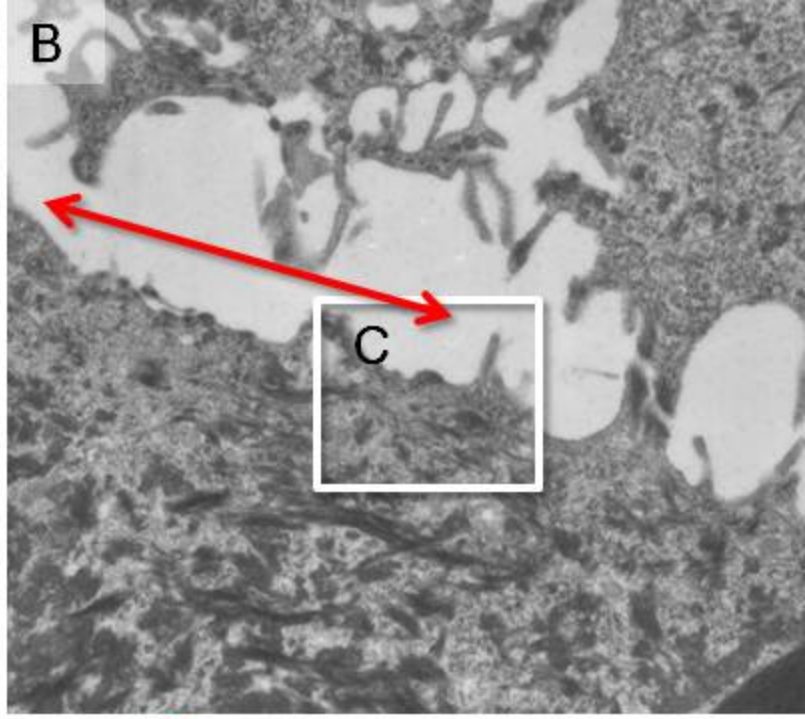
EB, epidermolysis bullosa


A
Desmosome
Corneodesmosome
outer plaque
inner plaque
plasma membrane
midline
200 nm
cornified envelope
200 nm
inner plaque
outer plaque
plasma membrane
midline
Desmogleins
Desmocollins
Plakoglobin
Desmoplakin
Plakophilins
Corneodesmosin
Keratin filaments


B
Desmoglein 1
Corneodesmosin
Desmoplakin


Local mechanical stress
Compensational hyperkeratosis
Barrier defects
Inflammation
DSG1
DSC2
Desmoplakin
Plakoglobin
PPK
Corneodesmosin
PSD type B
LEKTI
NS
DSG1
SAM
Desmoplakin
Plakophilin 1
Skin fragility
Desmoplakin
Plakoglobin
Lethal EB
Matriptase
Ichthyosis
adhesive
Normal cell adhesion & desquamation balance
acantholytic


A
B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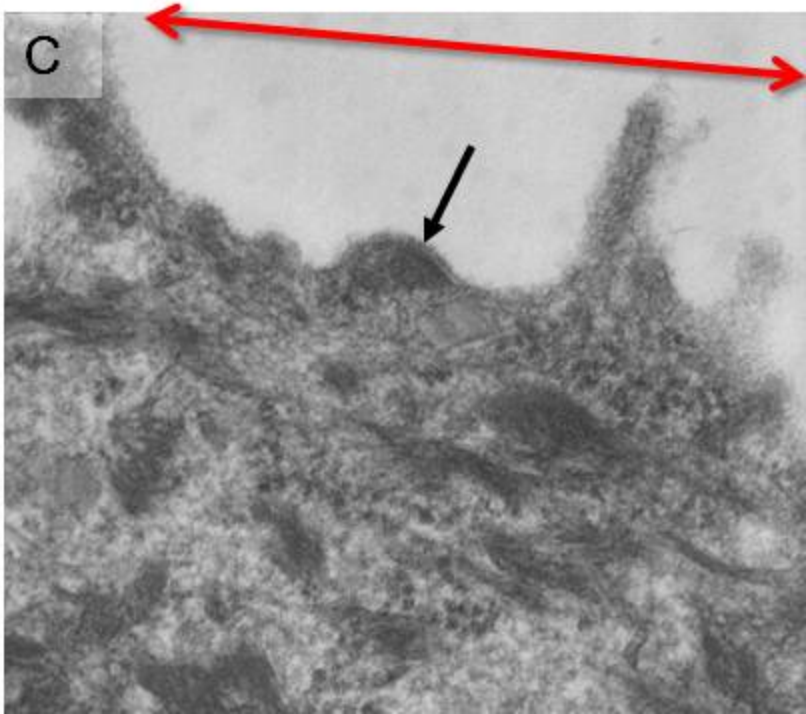
C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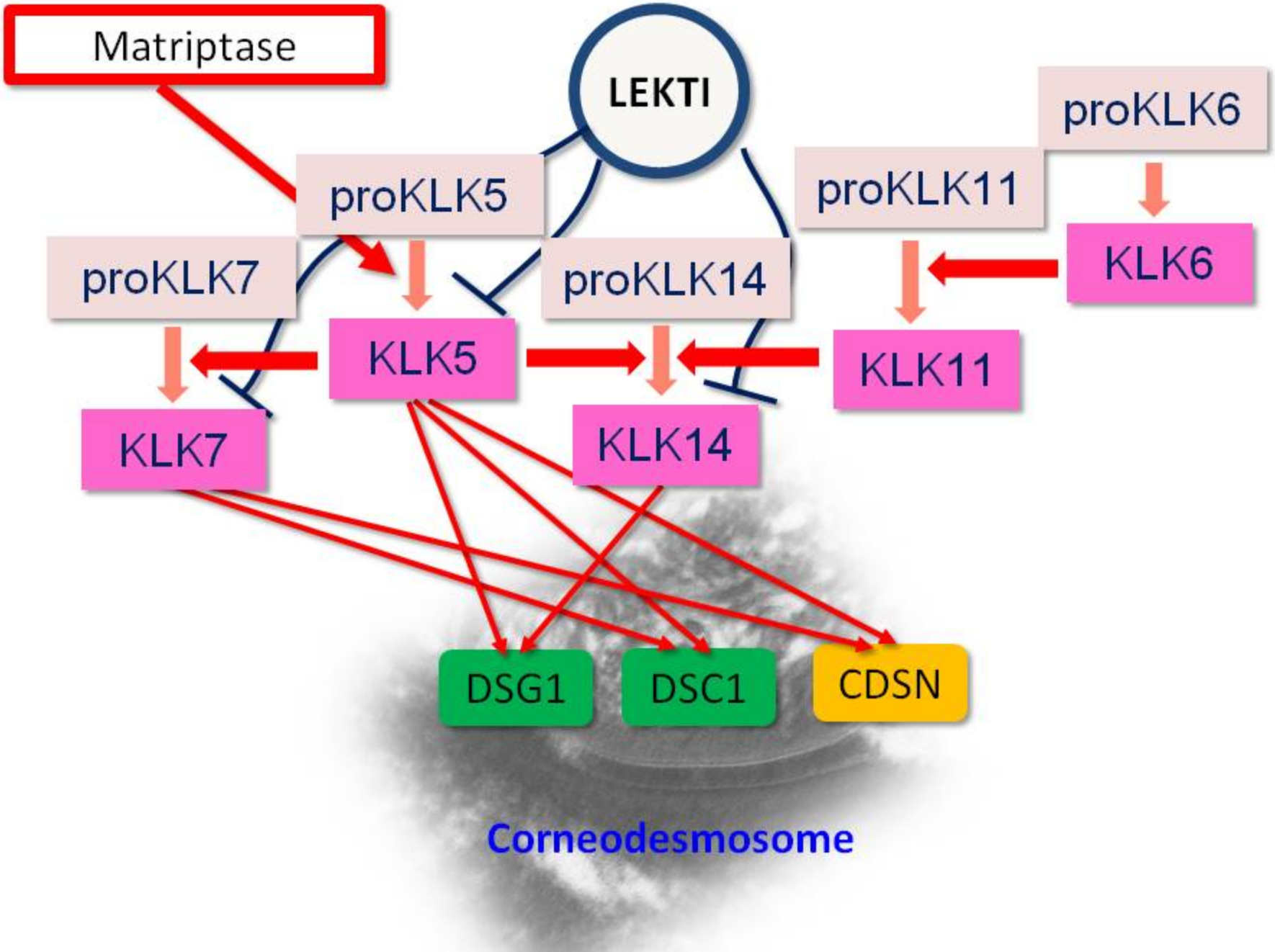
Matriptase
LEKTI
proKLK6
proKLK5
proKLK11
proKLK7
proKLK14
KLK6
KLK5
KLK11
KLK7
KLK14
DSG1
DSC1
CDSN
Corneodesmosome