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Review Article

Genetic skin diseases related to desmosomes and corneodesmosomes☆

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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.

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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 *DSC2* 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 (Figs. 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