Review

Desmosomes

Just Cell Adhesion or Is There More?

Ansgar Schmidt¹

Peter J. Koch^{2,*}

¹Institute of Pathology; Philipps University of Marburg School of Medicine; Marburg, Germany

²Department of Dermatology; University of Colorado in Denver and Health Sciences Center (UCHSC); Aurora, Colorado USA

*Correspondence to: Peter J. Koch; Department of Dermatology; University of Colorado in Denver and Health Sciences Center (UCHSC); Aurora, Colorado USA; Tel.: 303.724.0051; Fax: 303.724.3051; Email: Peter.Koch@UCHSC.edu

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KEY WORDS

desmosome, desmoglein, desmocollin, plakoglobin, plakophilin, MAPK, pemphigus, skin appendages

ABBREVIATIONS

Desmoglein	Dsg
Desmocollin	Dsc
Plakoglobin	Pg
Plakophilin	Pkp
Desmoplakin	Dp
Pemphigus Vulgaris	PV
Pemphigus Foliaceus	PF

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ABSTRACT

Desmosomes are cell adhesion structures (junctions) that are particularly abundant in cells derived from the ectodermal lineages. These junctions are required to maintain the integrity of organs subjected to mechanical stress, in particular the skin and the heart. This conclusion is partially based on tissue fragility phenotypes observed in mice with null mutations in certain desmosomal genes. Furthermore, patients have been identified that develop severe skin disorders, and even fatal heart diseases, due to impaired desmosome function. Nevertheless, desmosomes are more than cellular glue. New evidence suggests that these junctions can transmit signals from the extracellular environment to the nucleus, for example by controlling the cytoplasmic pool of transcriptional co-factors that belong to the armadillo family of desmosomal proteins (i.e. plakoglobin, plakophilins). Understanding the signaling properties of desmosomes will provide new insights into developmental processes such as skin and skin appendage development. Furthermore, there is evidence to suggest that abnormal signaling through these junctions contributes to the symptoms of certain skin and heart diseases.

STRUCTURE AND COMPOSITION

Desmosomes are multiprotein complexes, that are assembled at the plasma membrane, connecting adjacent cells and providing anchoring points for the intermediate filament cytoskeleton (see refs. 1 and 2). It is therefore not surprising that these cell junctions are required to maintain tissue cohesion, especially in organs exposed to considerable mechanical stress such as the skin and its appendages, as well as the heart.

Desmosomes of epithelial cells appear as disc-shaped organelles in the electron microscope, with a diameter of 0.1 to 0.5 μm (Fig. 1). Cell-cell adhesion is thought to be established mainly through heterophilic interactions between transmembrane glycoproteins that belong to the desmocollin (Dsc) and desmoglein (Dsg) subfamily of cadherins (calcium-dependent cell adhesion molecules), respectively. The desmosomal cadherins are connected to intermediate filaments through a protein complex consisting of Plakoglobin (Pg), Desmoplakin (Dp) and Plakophilin(s) (Pkp) (Fig. 2).

Both the mouse and the human genome comprise three Dsc genes. Each Dsc gene encodes two different proteins (a- and b-form) that differ only with respect to their COOH-terminal (cytoplasmic) amino acid sequences. The a- and b-forms are translated from mRNAs that are generated by differential splicing. In vitro experiments suggested that only the longer a-form is capable of interacting with desmosomal plaque proteins such as Dp, Pg and Pkp (see ref. 1). The only exception appears to be Dsc3b, which has been shown to bind Pkp3.^{3,4} It is not known whether the b-forms have a specific function in-vivo (see ref. 5 for a discussion of splice variant-specific functions).

Recently, a new transmembrane component of desmosomes has been identified, Perp.^{6,7} The precise function of this protein in desmosomes is not clear yet. However, loss of Perp in knockout mice leads to a severe skin fragility disorder.^{6,7}

The desmoglein family comprises four members in humans (Dsg1-Dsg4¹). Both Dsg and Dsc show complex tissue- and cell type-specific expression patterns in humans. Most notably, all known isoforms of these genes are expressed in the skin and its appendages (see refs. 2 and 5).

Figure 1. The cytoskeleton of epithelial cells. (A) Immunofluorescence microscopy of an epithelial cell line (Caco-2 cells, a human cell line derived from an adenocarcinoma of the colon) stained with antibodies against cyokeratin 18 (green) and desmoplakin (red). The nuclei were stained with DAPI (blue). Note that desmosomes are lined up like pearls on a string along the cell-cell borders (white arrows). Cyokeratin intermediate filaments (black arrows) extend from the cell nucleus to the plasma membrane, where they are anchored at desmosomes. (B) Electron micrograph of a desmosome from mouse epidermis. 1, apparent intercellular space (desmoglea); 2, inner plaque; 3, outer plaque

TISSUE FRAGILITY AND ABNORMAL SIGNALING— HOW DISEASE MODELS ARE SHEDDING NEW LIGHT ON DESMOSOME FUNCTION

Most of the desmosomal genes have been associated with inherited or aquired diseases that affect the skin, its appendages (e.g., hair), and the heart (reviewed in refs. 1, 8 and 9). Table 1 lists disorders linked to specific desmosomal genes. Note that mutations in five desmosomal genes have been linked to heart diseases. It appears that a significant portion of spontaneous deaths due to heart failure are caused by desmosomal defects. Furthermore, important information regarding the role of individual desmosomal genes in normal development and diseases has been gathered by analyzing the phenotypes of mice with null mutations in these genes. As indicated in Table 1, knockout phenotypes often provided the rationale for investigating the role of specific desmosomal genes in human heart and skin disorders (e.g., heart defects in *Pg*, *Dp* and *Pkp2* mutant mice).

Several recent publications have demonstrated an unexpected connection between a group of desmosomal diseases and aberrant cell signaling. The four investigations discussed below focused on the molecular pathology underlying pemphigus disease.

Pemphigus (Pemphigus Vulgaris; Pemphigus Foliaceus) is a group of autoimmune diseases that is characterized by the development of blisters in the epidermis of the skin and in mucous membranes. These blisters are the results of a loss of cell-cell adhesion between keratinocytes in the interfollicular epidermis and/or in mucous membranes (acantholysis). It has been known for a long time that pemphigus patients develop autoantibodies against desmogleins (see ref. 10 for review). The pathogenicity of these antibodies was demonstrated by the fact that injection of purified Dsg antibodies from patients (but not normal immunoglobulin controls) induce

Figure 2. Simplified model of the adhesion complex that forms a desmosome. Heterophilic interactions between the NH₂-terminal extracellular domains of the desmosomal cadherins (desmocollins (Dsc; orange), desmogleins (Dsg; yellow)) are thought to establish cell-cell adhesion. The transmembrane proteins are anchored to the intermediate filament (IF) cytoskeleton (purple) via a complex consisting of the plaque proteins plakophilin (Pkp; blue), plakoglobin (Pg; red) and desmoplakin dimers (Dp; green). Note that the "outer" and "inner" plaques shown in Figure 1 consist of different proteins (see ref. 27). The plasma membrane of adjacent cells is indicated (PM).

intraepidermal blistering in the skin of newborn mice¹¹ (see also ref. 10). The histopathology in these mice and pemphigus patients was identical, demonstrating that the mouse model was ideally suited to investigate disease mechanisms.

In pemphigus vulgaris, Dsg3 autoantibodies cause mucous membrane blistering. A simple explanation for the disease could be that the Dsg autoantibodies somehow neutralize the adhesive function of the Dsg targets. This conclusion is supported by the observation that Dsg3 null mice develop blisters in their mucous membranes. What is the mechanism underlying this loss-of-function phenotype? This question has driven a sometime intense debate in the pemphigus research field for more than a decade. Do these antibodies somehow interfere with heterophilic interactions between Dsg and Dsc proteins by binding to the adhesive interfaces of Dsg? Do they simply deplete the pool of adhesion molecules on the cell surface? Four groups of scientists have recently taken a fresh look at these questions and came up with observations that promise to stimulate a new wave of investigations into desmosomal diseases and functions.

Two groups observed phosphorylation of p38MAPK (p38 mitogen-activated protein kinase) in cultured keratinocytes in response to an exposure to Dsg autoantibodies from pemphigus patients.^{12,13} Interestingly, these research teams identified different down-stream effectors of activated p38MAPK in pemphigus IgG-treated keratinocytes: Waschke et al showed inhibition of the Rho GTPase RhoA in response to autoantibody binding to the cell membrane. Either inhibition of p38MAPK or activation of RhoA abrogated pemphigus IgG-mediated loss of cell adhesion and keratin intermediate filament retraction from desmosomes (two characteristic features of pemphigus). This study suggested a chain of events in which Dsg antibody binding to their targets on the plasma membrane leads to p38MAPK-dependent inactivation of RhoA followed by a loss of cell adhesion. Of note is the fact that Waschke et al. found the same mechanism triggered in PF- and PV-treated keratinocyte cultures. PF sera contain pathogenic Dsg1 antibodies,

Table 1 Impaired desmosome function and human diseases.

Desmosomal Gene/Protein	Disease Association	Cause	Phenotype of Knockout Mouse Models
Dsc1	Subcorneal Pustular Dermatitis ²⁷	Autoantibodies	Skin Fragility, Localized Hair Loss ²⁸
Dsc2	Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) ²⁹	Mutations	ND
Dsc3	ND		Pre-Implantation Embryonic Lethality ³⁰
Dsg1	Striate Palmoplantar Keratoderma (SPPK) ^{31,32} Pemphigus Foliaceus ³³⁻³⁵ Bullous Impetigo & Staphylococcal Scaled-Skin Syndrome ³⁶⁻³⁸	Mutations Autoantibodies Bacterial Toxin	ND Embryonic Lethality ⁴⁰
Dsg2	ARVD/C ³⁹	Mutation	Embryonic Lethality ⁴⁰
Dsg3	Pemphigus Vulgaris ⁴¹	Autoantibodies	Mucous Membrane Blistering and Hair Loss ^{42,43}
Dsg4	Hypotrichosis ⁴⁴	Mutations	Hair Defects ⁴⁵
Dp	SPPK ^{46,47} ARVD/C Carvajal syndrome ⁴⁸⁻⁵¹	Mutations Mutations	Embryonic Lethality ^{52,53} Heart defects in Tetraploid Rescued Mice ⁵²
Pg	Naxos disease, ARVD/C, SPPK ⁵⁴	Mutations	Embryonic Lethality, Heart Defects ^{55,56}
Pkp1	Ectodermal dysplasia ⁵⁷⁻⁵⁹	Mutations	ND
Pkp2	ARVD/C ^{60,61}	Mutations	Embryonic Lethality; Heart Defects ⁶²
Pkp3	ND		Hair Abnormalities (own unpublished observation)

Desmoglein (Dsg), Desmocollin (Dsc), Desmoplakin (Dp), Plakoglobin (Pg), Plakophilin (Pkp). For a detailed discussion of transgenic mouse models with deregulated expression of desmosomal genes see ref. 1.

whereas PV sera contain pathogenic Dsg3 and sometimes Dsg1 antibodies,¹⁰ i.e. suggesting that the same signaling pathway is triggered independent from the Dsg isoform that is targeted.

Berkowitz and colleagues also identified p38MAPK activation as a central event that leads to loss of cell adhesion. However, these authors suggest that phosphorylation of the heat shock protein HSP27 is a key event that ultimately results in a loss of cell adhesion. Most interestingly, Berkowitz et al. demonstrated that inhibitors of p38MAPK activation can prevent PV IgG-induced skin blistering in the passive transfer model for PV (antibody injected newborn mice¹¹). In summary, these data suggest that aberrant MAPK pathway activation is critical for acantholysis in pemphigus.

Williamson et al. focused on another down-stream effector of PV IgG-induced signaling, plakoglobin (Pg).^{14,15} Pg is a member of the armadillo protein family, and is thus sequence-related to β -catenin. Similar to β -catenin, Pg binds to the carboxy-terminal cytoplasmic domains of cadherins. However, unlike β -catenin, Pg can bind to both classical (e.g., E-cadherin) and desmosomal cadherins (Dsc, Dsg; Fig. 2). Plakoglobin has been shown to affect basic cellular behavior of keratinocytes, such as cell migration, proliferation and apoptosis (for example see refs. 8–10). However, Pg can also bind to Tcf/Lef proteins to control gene expression in the nucleus. In at least some instances, it appears that Pg counteracts classical (canonical) Wnt signaling, which uses β -catenin/Tcf/Lef complexes as downstream mediators of transcriptional regulation (see refs. 19 and 20). Nevertheless, β -catenin independent effects of Pg/Tcf/Lef complexes have been described as well (for example see refs. 14 and 21–24).

Williamson et al. found that exposure of keratinocytes to Dsg3-specific PV IgG resulted in an increased turn over of Pg,

leading to a depletion of the cytoplasmic and ultimately nuclear pool of Pg (Fig. 3).^{14,15} Interestingly, this effect appeared to be specific for PV, since Dsg1 autoantibodies from PF patients did not trigger this chain of events. Loss of nuclear Pg led to an increase in *c-Myc* expression and keratinocyte hyperproliferation. In-vitro experiments by these authors demonstrated that Pg forms a complex with Lef-1 that binds to and represses the *c-Myc* promoter, thus demonstrating that a reduction in nuclear Pg and increased *c-Myc* expression are functionally linked. Furthermore, c-Myc inhibitors prevented skin blistering in newborn pups injected with PV IgG, illustrating the biological relevance of the new pathway.

A central role for Pg in desmosomal diseases is also supported by recent experiments published by Garcia-Gras and colleagues.¹⁹ As summarized in Table 1, mutations in four different desmosomal genes can lead to cardiomyopathies [Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C)]. To begin to address the mechanistic basis for these diseases, these authors established a simple in-vitro model for desmosomal defects in cardiomyocytes. Using a siRNA approach, they knocked down Dp expression in these cells. Interestingly, this led to nuclear accumulation of Pg and an increase in the expression of adipogenic and fibrogenic genes. The cells also accumulated fat droplets, a characteristic of adipocytes. The replacement of cardiomyocytes with adipocytes is one hallmark of ARVD/C. The authors found evidence of decreased β -catenin/Tcf/Lef signaling in these cells, and concluded that the increase in nuclear Pg blocks canonical Wnt activity, thereby causing aberrant gene expression patterns and phenotypes reminiscent of ARVD/C. Thus, in contrast to the situation in PV IgG-treated keratinocytes, Pg is predicted to act indirectly through β -catenin in this cell system.

Figure 3. Simplified model of abnormal Pg signaling in Pemphigus Vulgaris (PV) according to Williamson and colleagues (see text for details). The binding of PV autoantibodies to Dsg3 triggers an increase in Dsg3/Pg turnover. As a result, the cytoplasmic and nuclear Pg levels are reduced, leading to a loss of Pg-mediated repression of the c-Myc promoter followed by keratinocyte hyperproliferation. PM, plasma membrane

The examples summarized above demonstrate that at least two signaling molecules, p38MAPK and Pg, are affected when desmosomal functions are impaired. Consequently, it appears that the mechanisms underlying loss of cell adhesion due to impaired desmosome functions are more complex than previously thought. Furthermore, and more importantly, these investigations of desmosomal diseases demonstrate a direct link between desmosomes and signaling pathways, thereby opening new avenues of research.

WHERE DO WE GO FROM HERE—DESMOSOMES AS SIGNALING CENTERS?

The studies described above support the notion that cell adhesion systems are not simply the end point of signaling events that lead to cell migration, cell sorting and the formation of tissue architecture. Instead, it is more likely that these junctions actively participate in these processes by affecting the activity of cytoplasmic signaling cascades and nuclear transcription factors. Our own research demonstrated that Pg can control the expression levels of desmosomal genes, pointing to an auto-regulatory loop that connects desmosomal adhesion with gene expression (own unpublished results).

Desmosomes are particularly abundant in stratifying epithelia, for example in the epidermis of the skin. Gene expression studies and immunohistochemical staining of the developing skin with desmosomal antibodies have demonstrated that the assembly and disassembly of these junctions are tightly controlled during skin appendage formation (e.g. hair follicles and mammary glands^{25,26}). The initial step in appendage formation is the downregulation of desmosomal gene expression followed by the invasion of epithelial cells (keratinocytes) into the dermis. These keratinocytes eventually differentiate into the diverse cell layers that form the appendages. Similarly, in cutaneous wound healing, keratinocytes from the edge of the wound downregulate their cell adhesion system and invade the dermis in order to form a protective epithelial sheet that covers the wound bed. Lastly, during invasive growth of epidermal tumor cells,

a similar process takes place, albeit outside the normal physiological context.

We believe that understanding the connection between cell junctions and cytoplasmic as well as nuclear signaling cascades will shed new light on the pathological processes underlying desmosomal diseases such as pemphigus. Furthermore, identifying these signaling pathways will help us to understand basic developmental processes such as tissue and organ formation, wound healing and invasive growth of epithelial cancer cells.

Reference List

- Cheng X, Koch PJ. In vivo function of desmosomes. *J Dermatol* 2004; 31:171-87.
- Cheng X, Den Z, Koch PJ. Desmosomal cell adhesion in mammalian development. *Eur J Cell Biol* 2005; 84:215-23.
- Bonne S, van Hengel J, Nollet F, Kools P, van Roy F. Plakophilin-3, a novel armadillo-like protein present in nuclei and desmosomes of epithelial cells. *J Cell Sci* 1999; 112:2265-76.
- Bonne S, Gilbert B, Hartzfeld M, Chen X, Green KJ, van Roy F. Defining desmosomal plakophilin-3 interactions. *J Cell Biol* 2003; 161:403-16.
- Cheng X, Mihindukulasuriya K, Den Z, Kowalczyk AP, Calkins CC, Ishiko A, Shimizu A, Koch PJ. Assessment of splice variant-specific functions of desmocollin 1 in the skin. *Mol Cell Biol* 2004; 24:154-63.
- Ihrle RA, Marques MR, Nguyen BT, Horner JS, Papazoglu C, Bronson RT, Mills AA, Attardi LD. Perp is a p63-regulated gene essential for epithelial integrity. *Cell* 2005; 120:843-56.
- Ihrle RA, Attardi LD. A New Perp in the Lineup: Linking p63 and Desmosomal Adhesion. *Cell Cycle* 2005; 4:873-6.
- McGrath JA. Inherited disorders of desmosomes. *Australas J Dermatol* 2005; 46:221-9.
- McGrath JA, Wessagowit V. Human hair abnormalities resulting from inherited desmosome gene mutations. *Keio J Med* 2005; 54:72-9.
- Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N Engl J Med* 2006; 355:1800-10.
- Anhalt GJ, Labib RS, Voorhees JJ, Beals TF, Diaz LA. Induction of pemphigus in neonatal mice by passive transfer of IgG from patients with the disease. *NEJM* 1982; 306:1189-96.
- Berkowitz P, Hu P, Liu Z, Diaz LA, Enghild JJ, Chua MP, Rubenstein DS. Desmosome signaling: Inhibition of p38MAPK prevents pemphigus vulgaris IgG induced cytoskeleton reorganization. *J Biol Chem* 2005; 280:23778-84.
- Waschke J, Spindler V, Bruggeman P, Zillikens D, Schmitt G, Drenckhahn D. Inhibition of Rho A activity causes pemphigus skin blistering. *J Cell Biol* 2006; 175:721-7.
- Williamson L, Raess NA, Caldelari R, Zakher A, de BA, Posthaus H, Bolli R, Hunziker T, Suter MM, Muller EJ. Pemphigus vulgaris identifies plakoglobin as key suppressor of c-Myc in the skin. *EMBO J* 2006; 25:3298-3309.
- Williamson L, Hunziker T, Suter MM, Muller EJ. Nuclear c-Myc: A Molecular Marker for Early Stage Pemphigus Vulgaris. *J Invest Dermatol* 2007; (Epub ahead of print).
- Charpentier E, Lavker RM, Acquista E, Cowin P. Plakoglobin suppresses epithelial proliferation and hair growth in vivo. *J Cell Biol* 2000; 149:503-20.
- Yin T, Getsios S, Caldelari R, Kowalczyk AP, Muller EJ, Jones JC, Green KJ. Plakoglobin suppresses keratinocyte motility through both cell-cell adhesion-dependent and -independent mechanisms. *Proc Natl Acad Sci USA* 2005; 102:5420-5.
- Dusek RL, Godsel LM, Chen F, Strohecker AM, Getsios S, Harmon R, Muller EJ, Caldelari R, Cryns VL, Green KJ. Plakoglobin Deficiency Protects Keratinocytes from Apoptosis. *J Invest Dermatol* 2006; 127:792-801.
- Garcia-Gras E, Lombardi R, Giocondo MJ, Willerson JT, Schneider MD, Khoury DS, Marian AJ. Suppression of Wnt/beta-catenin signaling by nuclear plakoglobin recapitulates phenotype of arrhythmic right ventricular cardiomyopathy. *J Clin Invest* 2006; 116:2012-21.
- Hu P, Berkowitz P, O'Keefe EJ, Rubenstein DS. Keratinocyte adherens junctions initiate nuclear signaling by translocation of plakoglobin from the membrane to the nucleus. *J Invest Dermatol* 2003; 121:242-51.
- Maeda O, Usami N, Kondo M, Takahashi M, Goto H, Shimokata K, Kusugami K, Sekido Y. Plakoglobin (gamma-catenin) has TCF/LEF family-dependent transcriptional activity in beta-catenin-deficient cell line. *Oncogene* 2004; 23:964-72.
- Muller-Tidow C, Steffen B, Cauvet T, Tickenbrock L, Ji P, Diederichs S, Sargin B, Kohler G, Stelljes M, Puccetti E, Ruthardt M, deVos S, Hiebert SW, Koeffler HP, Berdel WE, Serve H. Translocation products in acute myeloid leukemia activate the Wnt signaling pathway in hematopoietic cells. *Mol Cell Biol* 2004; 24:2890-904.
- Simcha I, Shuttman M, Salomon D, Zhurinsky J, Sadot E, Geiger B, Ben-Ze'ev A. Differential nuclear translocation and transactivation potential of beta-catenin and plakoglobin. *J Cell Biol* 1998; 141:1433-48.
- Zhurinsky J, Shuttman M, Ben-Ze'ev A. Differential Mechanisms of LEF/TCF Family-Dependent Transcriptional Activation by beta-Catenin and Plakoglobin. *Mol Cell Biol* 2000; 20:4238-252.
- Nanba D, Nakanishi Y, Hieda Y. Changes in adhesive properties of epithelial cells during early morphogenesis of the mammary gland. *Dev Growth Differ* 2001; 43:535-44.

26. Nanba D, Hieda Y, Nakanishi Y. Remodeling of desmosomal and hemidesmosomal adhesion systems during early morphogenesis of mouse pelage hair follicles. *J Invest Dermatol* 2000; 114:171-7.
27. Hashimoto T, Kiyokawa C, Mori O, Miyasato M, Chidgey MA, Garrod DR, Kobayashi Y, Komori K, Ishii K, Amagai M, Nishikawa T. Human desmocollin 1 (Dsc1) is an autoantigen for the subcorneal pustular dermatosis type of IgA pemphigus. *J Invest Dermatol* 1997; 109:127-31.
28. Chidgey M, Brakebusch C, Gustafsson E, Cruchley A, Hail C, Kirk S, Merritt A, North A, Tselepis C, Hewitt J, Byrne C, Fassler R, Garrod D. Mice lacking desmocollin 1 show epidermal fragility accompanied by barrier defects and abnormal differentiation. *J Cell Biol* 2001; 155:821-32.
29. Syrris P, Ward D, Evans A, Asimaki A, Gandjbakhch E, Sen-Chowdhry S, McKenna WJ. Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Associated with Mutations in the Desmosomal Gene Desmocollin-2. *Am J Hum Genet* 2006; 79:978-84.
30. Den Z, Cheng X, Merched-Sauvage M, Koch PJ. Desmocollin 3 is required for pre-implantation development of the mouse embryo. *J Cell Sci* 2006; 119:482-9.
31. Rickman L, Simrak D, Stevens HP, Hunt DM, King IA, Bryant SP, Eady RA, Leigh IM, Arnemann J, Magee AI, Kelsell DP, Buxton RS. N-terminal deletion in a desmosomal cadherin causes the autosomal dominant skin disease striate palmoplantar keratoderma. *Hum Mol Genet* 1999; 8:971-6.
32. Hunt DM, Rickman L, Whittock NV, Eady RA, Simrak D, Dopping-Hepenstal PJ, Stevens HP, Armstrong DK, Hennies HC, Kuster W, Hughes AE, Arnemann J, Leigh IM, McGrath JA, Kelsell DP, Buxton RS. Spectrum of dominant mutations in the desmosomal cadherin desmoglein 1, causing the skin disease striate palmoplantar keratoderma. *Eur J Hum Genet* 2001; 9:197-203.
33. Amagai M, Koch PJ, Nishikawa T, Stanley JR. Pemphigus vulgaris antigen (desmoglein 3) is localized in the lower epidermis, the site of blister formation in patients. *J Invest Dermatol* 1996; 106:351-5.
34. Warren SJ, Lin MS, Giudice GJ, Hoffmann RG, Hans-Filho G, Aoki V, Rivitti EA, Santos V, Diaz LA. The prevalence of antibodies against desmoglein 1 in endemic pemphigus foliaceus in Brazil. Cooperative Group on Fogo Selvagem Research. *N Engl J Med* 2000; 343:23-30.
35. Arteaga LA, Prisayanh PS, Warren SJ, Liu Z, Diaz LA, Lin MS. A subset of pemphigus foliaceus patients exhibits pathogenic autoantibodies against both desmoglein-1 and desmoglein-3. *J Invest Dermatol* 2002; 118:806-11.
36. Amagai M, Matsuyoshi N, Wang ZH, Andl C, Stanley JR. Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1. *Nat Med* 2000; 6:1275-7.
37. Amagai M, Yamaguchi T, Hanakawa Y, Nishifuji K, Sugai M, Stanley JR. Staphylococcal exfoliative toxin B specifically cleaves desmoglein 1. *J Invest Dermatol* 2002; 118:845-50.
38. Hanakawa Y, Schechter NM, Lin C, Garza L, Li H, Yamaguchi T, Fudaba Y, Nishifuji K, Sugai M, Amagai M, Stanley JR. Molecular mechanisms of blister formation in bullous impetigo and staphylococcal scalded skin syndrome. *J Clin Invest* 2002; 110:53-60.
39. Awad MM, Dalal D, Cho E, Amat-Alarcon N, James C, Tichnell C, Tucker A, Russell SD, Bluemke DA, Dietz HC, Calkins H, Judge DP. DSG2 mutations contribute to arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am J Hum Genet* 2006; 79:136-42.
40. Eshkind L, Tian Q, Schmidt A, Franke WW, Windoffer N, Leube RE. Loss of desmoglein 2 suggests essential functions for early embryonic development and proliferation of embryonal stem cells. *Eur J Cell Biol* 2002; 81:592-8.
41. Arteaga LA, Prisayanh PS, Warren SJ, Liu Z, Diaz LA, Lin MS. A subset of pemphigus foliaceus patients exhibits pathogenic autoantibodies against both desmoglein-1 and desmoglein-3. *J Invest Dermatol* 2002; 118:806-11.
42. Koch PJ, Mahoney MG, Ishikawa H, Pulkkinen L, Uitto J, Shultz L, Murphy GF, Whitaker-Menezes D, Stanley JR. Targeted disruption of the pemphigus vulgaris antigen (desmoglein 3) gene in mice causes loss of keratinocyte cell adhesion with a phenotype similar to pemphigus vulgaris. *J Cell Biol* 1997; 137:1091-102.
43. Koch PJ, Mahoney MG, Cotsarelis G, Rothenberger K, Lavker RM, Stanley JR. Desmoglein 3 anchors telogen hair in the follicle. *J Cell Sci* 1998; 111:2529-37.
44. Rafiq MA, Ansar M, Mahmood S, Haque S, Faiyaz-ul-Haque M, Leal SM, Ahmad W. A Recurrent Intragenic Deletion Mutation in DSG4 Gene in Three Pakistani Families with Autosomal Recessive Hypotrichosis. *J Invest Dermatol* 2003; 123:247-8.
45. Kljuic A, Bazzi H, Sundberg JP, Martinez-Mir A, O'Shaughnessy R, Mahoney MG, Levy M, Montagutelli X, Ahmad W, Aita VM, Gordon D, Uitto J, Whiting D, Ott J, Fischer S, Gilliam TC, Jahoda CA, Morris RJ, Panteleyev AA, Nguyen VT, Christiano AM. Desmoglein 4 in hair follicle differentiation and epidermal adhesion: evidence from inherited hypotrichosis and acquired pemphigus vulgaris. *Cell* 2003; 113:249-60.
46. Whittock NV, Ashton GH, Dopping-Hepenstal PJ, Gratian MJ, Keane FM, Eady RA, McGrath JA. Striate Palmoplantar Keratoderma Resulting from Desmoplakin Haploinsufficiency. 1999; 113:940-6.
47. Armstrong DK, McKenna KE, Purkis PE, Green KJ, Eady RA, Leigh IM, Hughes AE. Haploinsufficiency of desmoplakin causes a striate subtype of palmoplantar keratoderma [published erratum appears in *Hum Mol Genet* 1999 May;8(5):943]. *Hum Mol Genet* 1999; 8:143-8.
48. Turkay S, Odemis E, Karadag A. Woolly hair, palmoplantar keratoderma and arrhythmogenic dilated cardiomyopathy in a 7-year-old Turkish girl: Carvajal syndrome. *Ann Trop Paediatr* 2006; 26:73-7.
49. Yang Z, Bowles NE, Scherer SE, Taylor MD, Kearney DL, Ge S, Nadvoretzkiy VV, DeFreitas G, Carabello B, Brandon LI, Godsel LM, Green KJ, Saffitz JE, Li H, Danieli GA, Calkins H, Marcus F, Towbin JA. Desmosomal dysfunction due to mutations in desmoplakin causes arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Res* 2006; 99:646-55.
50. Norgett EE, Hartsell SJ, Carvajal-Huerta L, Cabezas JC, Common J, Purkis PE, Whittock N, Leigh IM, Stevens HP, Kelsell DP. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum Mol Genet* 2000; 9:2761-6.
51. Lapouge K, Fontao L, Champlaud MF, Jaunin F, Frias MA, Favre B, Paulin D, Green KJ, Borradori L. New insights into the molecular basis of desmoplakin and desmin-related cardiomyopathies. *J Cell Sci* 2006; 119:4974-85.
52. Gallicano GI, Bauer C, Fuchs E. Rescuing desmoplakin function in extra-embryonic ectoderm reveals the importance of this protein in embryonic heart, neuroepithelium, skin and vasculature. *Development* 2001; 128:929-41.
53. Gallicano GI, Kouklis P, Bauer C, Yin M, Vasioukhin V, Degenstein L, Fuchs E. Desmoplakin is required early in development for assembly of desmosomes and cytoskeletal linkage. *J Cell Biol* 1998; 143:2009-22.
54. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastakis A, Coonar A, Norman M, Baboonian C, Jeffery S, McKenna WJ. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). *The Lancet* 2000; 355:2119-24.
55. Ruiz P, Brinkmann V, Ledermann B, Behrend M, Grund C, Thallhammer C, Vogel F, Birchmeier C, Gunthert U, Franke WW, Birchmeier W. Targeted mutation of plakoglobin in mice reveals essential functions of desmosomes in the embryonic heart. *J Cell Biol* 1996; 135:215-25.
56. Bierkamp C, McLaughlin KJ, Schwarz H, Huber O, Kemler R. Embryonic heart and skin defects in mice lacking plakoglobin. *Dev Biol* 1996; 180:780-5.
57. McGrath JA, Hoeger PH, Christiano AM, McMillan JR, Mellerio JE, Ashton GH, Dopping-Hepenstal PJ, Lake BD, Leigh IM, Harper JL, Eady RA. Skin fragility and hypohidrotic ectodermal dysplasia resulting from ablation of plakophilin 1. *British Journal of Dermatology* 1999; 140:297-307.
58. McGrath JA, McMillan JR, Shemanko CS, Runswick SK, Leigh IM, Lane EB, Garrod DR, Eady RA. Mutations in the plakophilin 1 gene result in ectodermal dysplasia/skin fragility syndrome. *Nat Genet* 1997; 17:240-4.
59. Whittock NV, Haftek M, Angoulvant N, Wolf F, Perrot H, Eady RA, McGrath JA. Genomic Amplification of the Human Plakophilin 1 Gene and Detection of a New Mutation in Ectodermal Dysplasia/Skin Fragility Syndrome. 2000; 115:368-74.
60. Awad MM, Dalal D, Tichnell C, James C, Tucker A, Abraham T, Spevak PJ, Calkins H, Judge DP. Recessive arrhythmogenic right ventricular dysplasia due to novel cryptic splice mutation in PKP2. *Hum Mutat* 2006; 27:1157.
61. Syrris P, Ward D, Asimaki A, Sen-Chowdhry S, Ebrahim HY, Evans A, Hitomi N, Norman M, Pantazis A, Shaw AL, Elliott PM, McKenna WJ. Clinical Expression of Plakophilin-2 Mutations in Familial Arrhythmogenic Right Ventricular Cardiomyopathy. *Circulation* 2006; 113:356-64.
62. Grossmann KS, Grund C, Huelsen J, Behrend M, Erdmann B, Franke WW, Birchmeier W. Requirement of plakophilin 2 for heart morphogenesis and cardiac junction formation. *J Cell Biol* 2004; 167:149-60.