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Desmosomes in Human Disease

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Abstract

Tissue integrity is crucial for maintaining the homeostasis of living organisms. Abnormalities that affect sites of cell-cell contact can cause a variety of debilitating disorders. The desmosome is an essential cell-cell junctional protein complex in tissues that undergo stress, and it orchestrates intracellular signal transduction. Desmosome assembly and junctional integrity are required to maintain the overall homeostasis of a tissue, organ, and organism. This review discusses the desmosome and the human diseases associated with its disruption.

INTRODUCTION

Tight junctions: form a tight seal between two cells, provide polarity, and are often linked with barrier functions; also known as occluding junctions

Gap junctions: specialized channels between two neighboring cells; also known as communicating junctions

Adherens junctions: cell junctional protein complexes that extracellularly interact with adherens junctional components of a neighboring cell and intracellularly link to the actin cytoskeleton network

Genodermatoses: genetic skin diseases

Cardiocutaneous disorders: diseases that display cardiac and skin phenotypes

The development of multicellular organisms occurred 3.8 billion years ago in a series of events that gave rise to cellular specialization, differentiation, and morphogenesis. The ability of multicellular eukaryotes to develop specialized tissues is dependent on cellular adhesion in establishing connections between neighboring cells at intercellular junctions. Investigations of these critical structures have provided essential information for understanding tissue architecture and cell polarity. Multicellular organisms contain a variety of specialized junctional complexes, which predominately include tight junctions, gap junctions, adherens junctions, and desmosomes. The latter has been identified as the cell adhesion complex that is essential for tissue integrity. Historically, desmosomes were first described as small dense nodules and named nodes of Bizzozero by the pathologist Giulio Bizzozero (1) in the mid-1800s (2–7). In the 1920s, it had been assigned the term desmosome based on the Greek terminology for bond (*desmo*) and body (*soma*) (4, 6, 8, 9).

Today, the desmosome is classified as a calcium-dependent anchoring junction that tethers cells together through its extracellular contacts and internally links to the intermediate filament (IF) cytoskeleton. Through this linkage between cells, the desmosome provides tissues with the ability to resist mechanical forces (10). This anchoring complex is composed of three gene superfamilies: the desmosomal cadherins, the armadillos, and the plakins. Within each family, there are multiple isoforms that can constitute a desmosome, with the exception of the obligate desmosomal component, desmoplakin (Dp), from the plakin family, which also consists of periplakin, plectin, and envoplakin. The cadherin family consists of desmogleins (Dsg1–4) and desmocollins (Dsc1–3), whereas the armadillo family consists of plakophilins (Pkp1–3) and plakoglobin (Pg). Desmosomes are found in a variety of tissue types and are particularly notable in tissues that undergo a high degree of mechanical stress, such as the myocardium, bladder, gastrointestinal mucosa, and epidermis (8, 11). Intracellularly, the desmosome links to the IF cytoskeleton, which can further be classified depending on the cell type. For example, most epithelial cells contain type I acidic keratins and type II basic keratins. Myocardial cells are rich in the type III IF, known as desmin, and subsequently, leukocytes, fibroblasts, and follicular dendritic cells of lymph nodes contain the most widely distributed of all IF proteins, vimentin (type III) (12). The IF family of proteins is extensive and large, but only the members mentioned above have been found to associate with desmosomes (**Figure 1**).

Because multiple isoforms of the desmosomal components exist, the precise desmosomal composition depends on the type of tissue and the relative degrees of differentiation within that tissue. The exact transcriptional program underlying desmosomal isoform expression is largely unknown; however, tight regulation of specific desmosomal isoforms is required for homeostasis within a tissue. Some research has been able to link transcriptional regulators to the desmosomal components, but the differences in cell types within these reports must be noted (see 13). The importance of desmosomal compositions is underscored by the presence of specific mutations identified in diseases that gives rise to a spectrum of histological abnormalities. Disorders range from genetic skin diseases (genodermatoses) to cardiomyopathies, including skin and heart (cardiocutaneous) disorders, and some cancers. In the following sections, the desmosome is reviewed in a normal state and a disease-associated state for each protein family within this cell junctional complex. We have yet to gain much information in terms of understanding the desmosome in either context. By analyzing the desmosome in normal tissues, we can gain insight into diseased states and vice versa, which will provide an appreciation for how the desmosome contributes to the integrity and homeostasis of tissue structure and function.

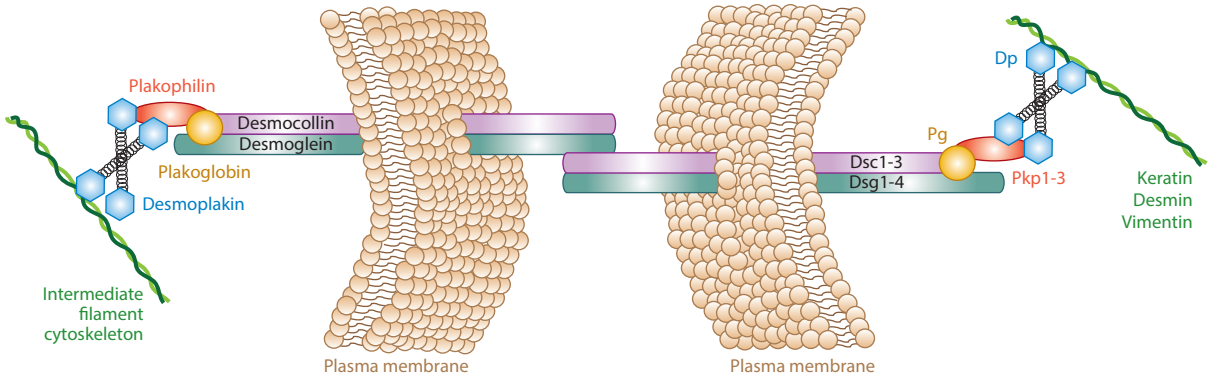

Figure 1

Desmosome structure and organization. The cell on the left displays the basic components and structure of a desmosome, which extracellularly tethers to desmosomes on neighboring cells and intracellularly links to the intermediate filament (IF) cytoskeleton. The proteins that make up the desmosome fall under three gene superfamilies: the desmosomal cadherins [desmogleins (Dsg1-4) and desmocollins (Dsc1-3)], the armadillo family [plakophilins (Pkp1-3) and plakoglobin (Pg)], and the plakin family [desmoplakin (Dp)]. The cell on the right displays the different types of isoforms that exist for certain desmosomal components and also displays the IF cytoskeleton networks (keratin, desmin, vimentin) that have been shown to associate with the desmosome.

DESMOSOME ASSEMBLY

Early reports noted that keratinocytes grown in media without calcium did not develop cell contacts. In response to an elevation of extracellular calcium, desmosomal cadherins clustered and became more stabilized (14). It is thought that Dscs may initiate desmosome assembly, and Dsgs arrive later to stabilize the complex (15). Regardless, desmosomal cadherins are constantly synthesized and delivered to the plasma membrane (16, 17), following the classic cadherin secretory route, which begins with the synthesis and folding of the cadherins in the endoplasmic reticulum, then with further protein processing via the Golgi apparatus, and ends with sorting into post-Golgi carriers via a microtubule-dependent motor (18, 19). Desmosomal cadherins, specifically the Dsg family and Dsc family, are synthesized as soluble proteins and it is only upon their incorporation into cell contacts that they become insoluble (20). Additionally, posttranslational modifications may contribute to desmosomal cadherin insolubility, specifically glycosylation, which is a modification that largely occurs in the endoplasmic reticulum and Golgi apparatus, whereby a glycosyl group (a carbohydrate) is attached to a molecule (21).

The desmosomal cadherins, Dsgs and Dscs, are closely related to the family of classic cadherins, which consists of E-cadherin (E-cad), P-cadherin (P-cad), and N-cadherin (N-cad) known to incorporate in adherens junctions. Whereas classical cadherins typically undergo homophillic interactions to effect adhesions, it remains unclear whether heterophilic or homophilic interactions are required for desmosomes (22–25). Because desmosomal cadherins are the portions of the desmosome that transverse the plasma membrane, one might question the extent to which membrane dynamics may play a role in desmosome assembly. In fact, it has been shown that desmosomal cadherins can localize to cholesterol-rich raft domains and may rely on this membrane association for their assembly and compartmentalization into functional junctions (26). Interestingly, the same question can be asked whether interactions with other desmosomal components affect the dynamics and trafficking of desmosomal cadherins. Research has shown that Pkp2 is required for kinesin-2-dependent trafficking of Dsc2 (19), further supporting the notion that the construction of the desmosome is not just a sum of its parts but rather a multistep process with intricate lines of

communication among all parties. Within the armadillo family of proteins, Pkp3 has been found to associate with dynamin-like protein DNMIL, which is involved in vesicle trafficking (27). Another armadillo protein, Pg, can associate with the classic cadherins found in adherens junctions or with the desmosomal cadherins in desmosomes. Pg serves as a regulator molecule in desmosome formation because it temporally switches its binding partner interactions with either cell junction protein complex, depending on the presence of Pg-associated E-cad or P-cad (28). Additionally, insoluble pools of newly synthesized Pg associated with Dsg are required for its stabilization and incorporation in desmosomes (29).

Basal layer: cells directly in contact with basement membrane, which retain proliferative/mitotic potential

Spinous layer: cells found immediately superior to the basal layer; cells have entered the process of epidermal differentiation

Suprabasal layer: all layers of the skin superior to the basal layer, including the spinous, granular, and corneal layers

The armadillo family of proteins has also been shown to participate in the temporal regulation of Dp dynamics. This large plakin protein member is an obligate component of the desmosome and is the key linker between IF and the plasma membrane (30–33). When observing newly formed contacts, Dp accumulates within 5 min. Shortly thereafter, within 15–20 min, non-membrane-bound Dp-containing particles appear in the cortical region of the cell. This pool is also found to be associated with the IF cytoskeleton. Finally, Dp-IF precursors translocate to cell-cell contacts to bolster the desmosomal plaque in a microtubule-independent manner (34). The armadillo family member Pkp2 has been found to colocalize with Dp precursors to assist in the promotion of Dp's translocation by scaffolding a complex containing Dp and protein kinase C alpha (35). Whereas some interactions among armadillo proteins, desmosomal cadherins, and Dp have been identified, the full extent of the cross talk among these proteins during recruitment to sites of cell contact has not been fully defined (reviewed in 6).

DESMOSOMAL EXPRESSION PATTERN

Desmosomes have been observed in a variety of tissue types, and they are particularly predominant in tissues that experience mechanical stress. Desmosome structures have been found in the skin, heart, intestine, gallbladder, uterus, oviduct, liver, pancreas, stomach, salivary glands, thyroid glands, and the epithelial cells of nephrons (11, 36, 37). Multiple isoforms exist within the desmosomal cadherin and armadillo families. It is known that tight regulation and control of the isoform patterns are required for tissue homeostasis. However, why certain isoforms exist in specific tissues or why certain isoforms predominate in specific regions of tissue is still largely unknown.

Desmosomal cadherins consist of Dsg and Dsc proteins, of which Dsg2 and Dsc2 are found widely in multiple tissues, whereas the other desmosomal cadherins are present predominantly in stratified epithelia. Most notable among stratified epithelia is the epidermis, which expresses the seven desmosomal cadherins (Dsg1–4, Dsc1–3). Dsg2, Dsg3, Dsc2, and Dsc3 are found in the basal layer of the epidermis, whereas the distribution of some of these isoforms decreases in the upper layers of the skin. Specifically, Dsg3, Dsc2, and Dsc3 are found in the basal and spinous layers of the skin, and Dsg2 is restricted to the basal layer. In contrast, Dsg1 and Dsc1 begin to appear in the spinous layers of the skin, with increasing protein expression through each subsequent layer of the skin, and reaching the highest abundance of protein expression in the uppermost suprabasal layers. A role for Dsg1's predominance in the suprabasal layers has been underscored through the finding that it promotes epidermal differentiation. It has been reported that Dsg1 drives epidermal differentiation through the attenuation of epidermal growth factor receptor (EGFR) and downstream signaling effectors such as Erk1/2 (extracellular signal–regulated kinase 1, 2), which did not require the adhesive ectodomain of Dsg1 (38).

Additionally, reports have identified novel interactions of Dsg1 that are required to inhibit EGFR directly and downstream signaling events of EGFR (39, 156). These reports highlight an emerging concept that the desmosome may function as a signaling hub, opposed to its historically known "spot-welding" function. Moreover, these reports also provide insight into

why desmosomal isoforms may predominate in certain tissues or in certain regions of tissues. For example, forced expression of Dsg3 in suprabasal layers via a keratin 1–driven promoter in mice resulted in epidermal hyperproliferation and abnormal differentiation (40). Moreover, Dsg3 expression in suprabasal layers via an alternative promoter, involucrin, resulted in a more severe aberration of skin morphogenesis (41). Given the specific functions of each desmosomal component, individual desmosomal isoforms may not be able to compensate for the absence or disruption of a particular component. This is revealed by diseases associated with certain desmosomal components, further supporting that the complexity of the desmosome is not solved by redundancy of individual components. Together, these reports suggest that the tight regulation of the expression pattern of desmosomal isoforms is required for proper tissue morphogenesis.

Hyperkeratosis: thickening of the stratum corneum

DESMOSOMAL CADHERINS

The desmosomal cadherin family is closely related to the classic cadherin family (E-cad, P-cad, and N-cad); both families are type 1 integral membrane glycoproteins that contain five extracellular subdomains (ECs) (42). The ECs are connected by flexible linkers that form calcium-binding pockets for up to three calcium ions, all of which allow desmosomes to display calcium-dependent assembly and adhesion. Following the extracellular portion, desmosomal cadherins contain a domain most proximal to the membrane called the extracellular anchor (43). The desmosomal cadherins cross the plasma membrane once through their transmembrane domain, and on the cytoplasmic side contain an intracellular anchor domain and an intracellular cadherin-typical sequence (ICS) domain. The Dsgs have additional unique sequences defined by an intracellular proline-rich linker domain, a repeating units domain, and a Dsg terminal domain (**Figure 2**). The desmosomal cytoplasmic domains exhibit a high degree of divergence from the classical cadherins, with the exception of the ICS domain, which is required for Pg binding (44–47). Desmosomal cadherins consist of Dsg1-4 and Dsc1-3, of which the *DSC* genes give rise to variants a and b via alternative splicing where Dsc-b is the shorter form (48, 49) (**Figure 2**).

DESMOSOMAL CADHERIN GENODERMATOSES

The importance of cadherin components in the desmosome is underscored by the adhesive ectodomain. The first human cadherin gene mutation was reported in the *DSG1* gene in 1999 in a Dutch family; this mutation led to a dominantly inherited skin disease, striate palmoplantar keratodermas (SPPKs). Within the family of inherited palmoplantar keratodermas (PPKs), there are four patterns of hyperkeratosis (striate, focal, diffuse, and punctate). Phenotypically, these Dsg1-haploinsufficient individuals displayed hyperkeratotic bands on their palms and soles (50). Subsequently, numerous other *DSG1* mutations were identified that had features of SPPK, but without hair and nail abnormalities (51–54). Additionally, two homozygous mutations in *DSG1* were shown to result in severe skin dermatitis, multiple allergies, and metabolic wasting syndrome (55, 56). One of these mutations was more severe than the others and led to loss of Dsg1 expression versus cytoplasmic mislocalization of Dsg1. The differences in the phenotypic consequences of these two mutations could indicate that nonjunctional cytoplasmic Dsg1 may be partially functional, suggesting that in a normal state the protein maintains adhesive and signaling functions. More recently, unrelated American, African, and European families were found to have one recurrent and five novel *DSG1* mutations, causing an autosomal dominant PPK that displayed phenotypic variation despite molecular similarities (57).

Mutations in other Dsg isoforms can also have devastating effects. Dsg4, which is expressed in the more differentiated layers of stratified epithelium, is also predominately expressed in the

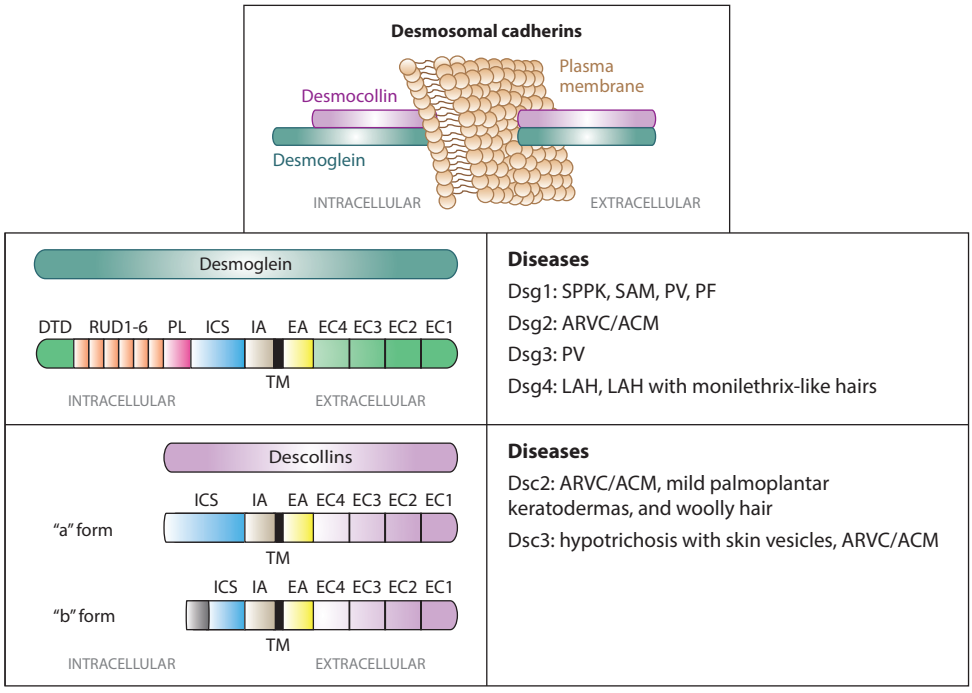

Figure 2

Desmosomal cadherins and associated diseases. (*Top*) Desmosomal cadherins, Dsg and Dsc, are depicted crossing a plasma membrane. Dsg1 and Dsc1 contain four highly conserved ECs, followed by an EA. Both types of desmosomal cadherins cross the plasma membrane once through the TM. Intracellularly, Dsgs and Dscs contain an IA and an ICS. Dsgs contain an additional PL and up to five RUDs, which are isoform-dependent. Dsc-a and Dsc-b isoforms contain an IA and ICS domain, with Dsc-b possessing a unique cytoplasmic sequence depicted in gray. The diseases associated with desmosomal cadherins are listed on the right. Abbreviations: ARVC/ACM, arrhythmogenic right ventricular cardiomyopathy/arrhythmogenic cardiomyopathy; Dsc, desmocollin; Dsg, desmoglein; DTD, desmoglein terminal domain; EA, extracellular anchor; EC, extracellular domain; IA, intracellular anchor; ICS, intracellular cadherin-like sequence; LAH, localized autosomal recessive hypotrichosis; PF, pemphigus foliaceus; PL, proline-rich linker; PV, pemphigus vulgaris; RUD, repeated unit domain; SAM, skin dermatitis, multiple allergies and metabolic wasting syndrome; SPPK, striate palmoplantar keratoderma; TM, transmembrane domain.

hair follicle (5). Various mutations in the *DSG4* gene have been shown to cause localized autosomal recessive hypotrichosis (LAH), which is characterized by short, sparse, coarse, brittle hair on the scalp, trunk, extremities, eyebrows, and eyelashes, but sparing beard, pubic, and axillary hairs (58–62). Other *DSG4* mutations have displayed LAH with monilethrix-like hairs. Monilethrix is an autosomal dominant hair shaft disorder in which hair displays a beaded appearance (63–66). Additionally, nonsense mutations in *DSC3* were identified in an Afghan family with hereditary hypotrichosis and recurrent skin vesicles; family members also presented with an absence of eyebrows and eyelashes (67). Human diseases with mutations in *DSG3* and *DSC1* have yet to be identified. Regardless, the importance of these desmosomal cadherins is underscored by mouse knockout experiments, which displayed epidermal abnormalities and hair loss in *dsg3*-deficient mice (68), and epidermal fragility with localized hair loss in *dsc1*-deficient mice (69).

DESMOSOMAL CADHERIN CARDIOMYOPATHIES

Dsg1, Dsg3, Dsg4 and Dsc1 are predominately expressed in the epidermis, which is why genetic mutations in these components cause a variety of skin and hair abnormalities. Interestingly, whereas Dsg2 and Dsc2 are present in the epidermis, they are also highly expressed in the myocardium (70). Mutations in these desmosomal cadherins have been shown to cause arrhythmogenic right ventricular cardiomyopathy/arrhythmogenic cardiomyopathy (ARVC/ACM) (71–75), a hereditary disorder of cardiac muscle. ARVC/ACM can result in ventricular arrhythmias, cardiac failure, and sudden cardiac death, and is characterized by the fibrofatty replacement of normal cardiac tissue in the right ventricle (76). The right ventricle usually predominates; however, left ventricle involvement is increasingly recognized (77). Mutations in these desmosomal cadherins have also been shown to lead to skin and heart defects, termed cardiocutaneous disorders. Specifically, a homozygous mutation of *DSC2* led to ARVC/ACM with mild PPK and woolly hair (78).

Woolly hair: tightly coiled hair

Acantholysis: loss of intracellular connections

AUTOIMMUNE-TARGETED DESMOSOMAL CADHERIN DISORDERS

The two major autoimmune diseases known to target desmosomal cadherins are pemphigus foliaceus (PF) and pemphigus vulgaris (PV). Early reports of these diseases in the 1960s found that IgG autoantibodies targeting the cell surface of keratinocytes were present in the sera of individuals harboring these diseases (79). It was not until approximately 20 years later that researchers found the target antigens of pemphigus (80–82). IgG autoantibodies produced against Dsg3, with later stages of the disease targeting Dsg1, cause PV (83–90), which is characterized by suprabasal acantholysis, mucous membrane erosion, and epidermal blisters (91). Individuals with the disease PF have antibodies against only Dsg1, which causes superficial blisters, without mucous membrane involvement (90). Phenotypic differences of pemphigus diseases could be due to tissue localization and distribution (92). The basic pathophysiology of pemphigus is the inhibition of cellular adhesion in which the pathogenic autoantibodies attach to EC1 and EC2 domains of Dsgs in both PF (93) and PV (94). While pemphigus is a rare disease found in five out of 1 million individuals per year, these research findings give key insight into mechanisms of acantholysis.

Additionally, bacteria such as *Staphylococcus aureus* and *Streptococcus pyogene* have been shown to cause a variety of blistering disorders classified as bullous impetigo and nonbullous impetigo. Bullous impetigo is a common infection caused by *S. aureus* strains that produce an exfoliative toxin. Staphylococcal scalded skin syndrome is a generalized form of bullous impetigo that more commonly affects young children. The exfoliative toxin that induces blisters in these disorders can circulate throughout the body and cause blisters at distant sites (95, 96). Both of these diseases share a clinical resemblance to PF (97), which is largely due to the fact that Dsg1 is targeted by the exfoliative toxin. Collectively, the diverse clinical manifestations of these genetic mutations, autoimmune disorders, and bacterial infections highlight the importance of individual desmosomal cadherin isoforms to desmosomal function and cellular adhesion.

ARMADILLO FAMILY

The first human sequence encoding a desmosomal component to be published was in 1989 for Pg, an armadillo family protein (98). The other armadillo family members found in desmosomes are the Pkps, which are also members of the p120-catenin subfamily. The armadillo proteins found in desmosomes, Pg and Pkp1–3, are placed within this family because they contain arm repeats, which are composed of 42 amino acids forming three short α-helices. Pg is encoded by the *JUP* gene and contains 12 arm repeats flanked by short N- and C-terminal domains, whereas Pkps

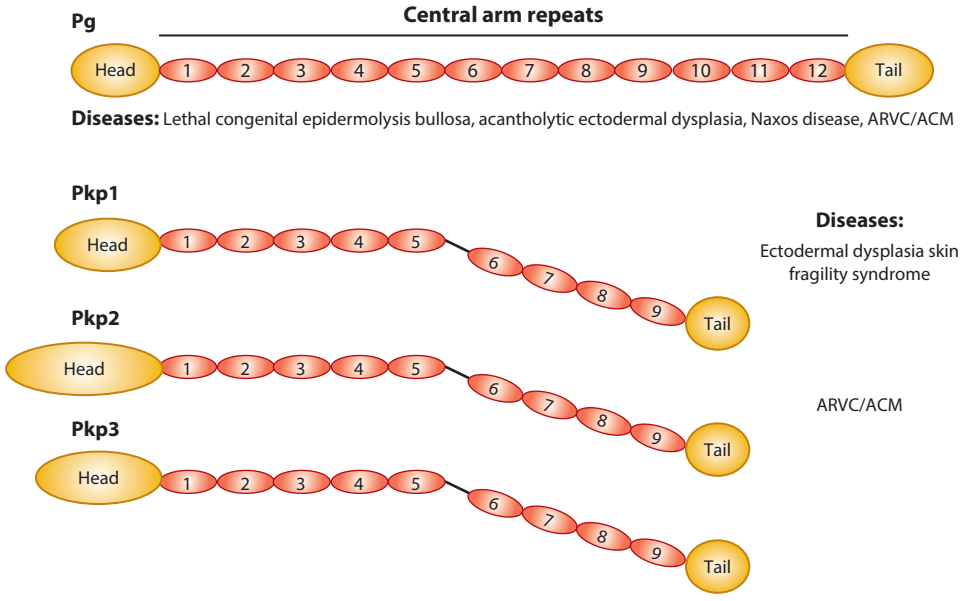

Figure 3

Armadillo proteins and associated diseases. Pg contains 12 arm repeats that are flanked by a short amino terminal (head) domain, and carboxyl terminal (tail) domain, whereas Pkps have 9 arm repeats. The Pkp arm domain is interrupted between repeats five and six by a sequence, introducing a kink into the overall structure. Abbreviations: ARVC/ACM, arrhythmogenic right ventricular cardiomyopathy/arrhythmogenic cardiomyopathy; Pg, plakoglobin; Pkp, plakophilin.

have 9 arm repeats. The Pkp arm domain is interrupted between repeats five and six by a sequence that introduces a kink into the overall structure (**Figure 3**) (10, 99, 100). Similar to desmosomal cadherins, Pkps also display a differentiation-specific expression pattern in stratified epithelia. Pkp1, similar to Dsg1, is found in the suprabasal layers of the epidermis, whereas Pkp2 expression decreases in the most differentiated layers of the epidermis. Pkp3 and Pg display the most uniform expression in simple and stratified epithelia (13), and the latter is known to interact with the ICS domain of desmosomal cadherins as well as the amino terminal domain of Dp, functioning as a structural connection between the plasma membrane and IF (5, 10, 11, 101). Pkps have been shown to interact with many of the desmosomal proteins, including desmosomal cadherins, Pg, and Dp (5, 10, 11, 100).

ARMADILLO PROTEIN GENODERMATOSES

Pg and Pkps have been implicated in a variety of skin abnormalities. Pkp1 was the first desmosomal protein to be linked to a genetic skin disorder. In 1997, it was found that an autosomal recessive mutation led to a loss of Pkp1, in which the phenotypic characterization presented skin fragility and blistering upon trauma (102). This disease is called ectodermal dysplasia skin fragility syndrome, and various mutations in *PKP1* have since been identified with ranging phenotypes of skin fragility (103–105). Cross talk among desmosomal components is expected, and recent research supports the clinical implications of this. In the autoimmune disease PV (discussed in the section titled Autoimmune-Targeted Desmosomal Cadherin Disorders), Pkp1 overexpression protects keratinocytes by forming calcium-independent desmosomes (106). This finding

demonstrates that manipulating the expression of a desmosomal plaque protein can block the pathogenic effects of targeting the desmosomal cadherins.

Additional armadillo genodermatoses include lethal congenital epidermolysis bullosa, which has been identified in one patient and is caused by a homozygous nonsense mutation in the *JUP* gene. This disorder results in no cardiac dysfunction but causes total alopecia, severe congenital skin fragility, generalized epidermolysis, and massive transcutaneous fluid loss. The mutation was identified in a patient who died 12 days after birth due to respiratory failure caused by compression of the thorax caused by infected and stiffened skin (107). Very few desmosomes formed in this patient, and these altered desmosomes displayed abnormal formation. Additionally, the expression and distribution of desmosomes were severely affected, suggesting an essential role for Pg in desmosome assembly. Because Pg can also interact with adherens junction components, these researchers also analyzed this cell-cell junctional protein complex and found that it was localized to the plasma membrane of keratinocytes but did not assist properly in establishing cellular adhesion (107). This is likely due to the classical cadherins of the adherens junctions binding to Pg and β-catenin, whereas desmosomal cadherins associate exclusively with Pg (11). Acantholytic ectodermal dysplasia is another genetic skin disease associated with Pg mutations that is caused by homozygous loss of function mutation in *JUP*. This disease is characterized by skin fragility, trauma-induced blisters, diffuse PPK, hyperkeratotic-fissured plaques in skin covering flexor and extensor joints, and woolly hair (108).

Alopecia: hair loss

ARMADILLO CARDIOMYOPATHIES

Because desmosomal proteins are predominately found in tissues that undergo mechanical stress, it is not surprising that mutations can cause skin and heart phenotypes. Naxos disease is caused by a homozygous recessive mutation in *JUP* and manifests as cardiomyopathy, PPK, and woolly hair (109). This triad of phenotypes begins with woolly hair at birth, with PPK developing in the first year of life. Cardiomyopathy will manifest in the adolescent years of the patient with ventricular tachycardia or sudden death (110).

Pg's role in maintaining desmosomal integrity was underscored in 2007, when the first dominantly inherited ARVC/ACM-linked mutation was reported in *JUP* (111). It has been proposed that nuclear Pg is necessary for the differentiation of cardiac cells into adipocytes (112). This is an important finding because ARVC/ACM is characterized by fibrofatty replacements and fibrosis. One possible explanation of this phenotype is that a Pg, β-catenin, Yes-associated protein complex can promote adipogenesis through Hippo signaling (113).

PKP mutations have also been identified in ARVC/ACM, most notably in the Pkp2 isoform, which is the only Pkp expressed in cardiomyocytes. Whereas dominant and recessive *PKP2* mutations have been identified, the most common genetic mutations to cause ARVC/ACM are heterozygous mutations in *PKP2*, which lead to abnormal gap junctions at intercalated discs (114). Through the disruption of gap junctions, pathways for ions between cardiomyocytes are negatively affected due to the defects in electrical communication, further emphasizing why ARVC/ACM disorders are detrimental. Other mutations have also been identified in *PKP2*, which include missense mutations and truncating mutations (115).

DESMOPLAKIN

Dp is considered to be the obligatory desmosomal component linking desmosomes to the IF cytoskeletal system. There are two splice variants of Dp, *DPI* and *DPII*, which have different lengths of their α-helical coiled-coil domain but retain the same globular amino and carboxyl termini

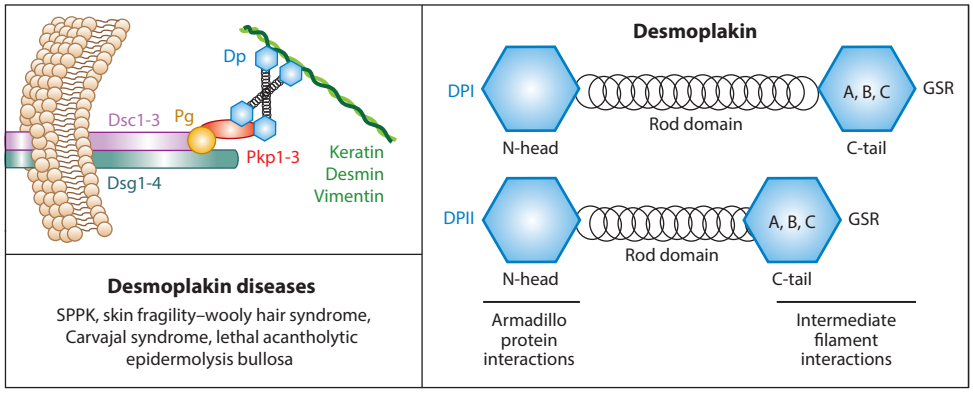

Figure 4

Desmoplakin domains and associated diseases. (*Top left*) Dimerized Dp within the context of a desmosome. (*Right*) The domains of Dp, indicating the N-head mediating interactions with armadillo family proteins, and indicating the C-tail, which regulates intermediate filament interactions through a GSR. Abbreviations: C-tail, carboxy terminal tail; Dp, desmoplakin; Dsc, desmocollin; Dsg, desmoglein; GSR, glycine/serine-rich domain; N-head, amino terminal globular head; SPPK, striate palmoplantar keratoderma.

(**Figure 4**). The protein product of the longer splice variant, *DPI*, is detectable among almost all desmosome-containing tissues. Previously, *DPII* messenger RNA was thought to be undetectable in cardiomyocytes (116). However, it was more recently shown to exist in cardiac tissue (117). The central coiled-coil domain is responsible for the dimerization of Dp and the amino terminal domain of Dp, which interacts with armadillo family proteins, which in turn target Dp to the desmosomal components at the plasma membrane. The carboxyl terminal domain contains three plakin repeat domains (A, B, and C) and is thought to mediate Dp-IF interactions (reviewed in 5, 11).

DESMOPLAKIN GENODERMATOSES

Owing to Dp's obligate role as a linker to the IF cytoskeleton, it is not surprising that genetic mutations in the Dp gene, *DSP*, manifest in a variety of clinical phenotypes. The first human *DSP* mutation, identified in 1999, was characterized by a null allele and haploinsufficiency. The disease was classified as SPPK with a linear pattern of skin thickening on the fingers and palms of the hands and circumscribed areas of skin thickening on the soles of the feet. The affected skin demonstrated loosening of intercellular connections and a disruption of desmosome-IF interactions (118, 119). Compound heterozygous or homozygous mutations in *DSP* with amino terminal missense mutations and carboxyl terminal nonsense mutations have been found in a disease termed skin fragility–wooly hair syndrome. Specifically, individuals with Dp haploinusfficiency in combination with missense mutations on the other allele display more severe keratodermas than those who are just Dp haploinsufficient. Additional phenotypes that have been found in skin fragility–wooly hair syndrome are skin blistering, woolly hair, degrees of alopecia, nail dystrophy, and focal or diffuse PPK. Biopsies from these individuals indicated intraepidermal blisters with acantholysis. Additionally, it was noted that Dp mostly localized to the cytoplasm, but some punctate molecules were visible at the cell periphery (120–122).

DESMOPLAKIN CARDIOCUTANEOUS MYOPATHIES

Mutations in *DSP* can also result in heart pathologies. Because *DPII* messenger RNA was not found in cardiomyocytes until recently, these mutations are mainly identified in the *DPI* splice variant.

Carvajal syndrome, caused by mutations in the *DSP* gene, is found to display three phenotypes: SPPK, left ventricular dilated cardiomyopathy, and woolly hair (123, 124). Individuals with these mutations can develop skin and heart phenotypes separately or in combination. The first autosomal recessive mutation in *DSP* causing Carvajal syndrome was identified in 2000 (125) with the triad of clinical features. The mutation in *DSP* for these individuals caused a truncated version of Dp that lacked part of the carboxyl terminal tail domain.

Other autosomal recessive mutations in *DSP* have been shown to cause severe skin and mucosal fragility at birth, total alopecia, possible cardiomyopathy, and stillbirth or early neonatal lethality due to transcutaneous fluid loss because of extensive skin erosion. This *DSP* mutation was first reported in 2005 and was termed lethal acantholytic epidermolysis bullosa (LAEB) (126). The compound heterozygous mutation caused a truncated carboxyl terminus of Dp (126). Other mutations causing LAEB have also been identified causing shortening of the Dp rod domain and carboxyl terminal truncations (127).

IMPLICATIONS FOR DESMOSOMES IN CANCER

Potential roles of adherens junctions in tumor progression have been noted (128–132), which is not surprising because metastasis of many tumors requires breaking the junctions that hold cells together in a tissue. With more than 90% of cancers being of epithelial origin, it is plausible that other cell junctional protein complexes could be implicated in the progression of cancer, including the desmosome. Recent research highlights a potential role for desmosomes in driving cancer progression and, specifically, for their disassembly in cancer progression.

EGFR and ADAM (a disintegrin and metalloprotease) sheddase cooperate to regulate endocytic trafficking of the desmosomal cadherin Dsg2, exposing a mechanism for weakening intercellular adhesion in oral cancer cells (133). Additionally, knockdown of Dsg2 in intestinal cancer cells leads to decreased EGFR and downstream Erk1/2 signaling and suppresses cell proliferation (134). Dsg2 is one of four Dsg cadherins and is predominant in the basal cells of the epidermis, whereas Dsg1 is expressed in more differentiated layers. A quantitative study showed that in 78 head and neck squamous cell carcinomas, Dsg1 protein was decreased and was associated with worse disease-specific survival (135). These and other studies have demonstrated that desmosome downregulation may contribute to early invasion and tumor progression. Specifically, Dsg1–3, Dsc2, Dsc3, Pg, and Pkp1–3 are downregulated in gastric, colorectal, prostate, bladder, breast, skin, head/neck, cervical, and endometrial cancer, which correlates with advanced tumor grade, increased metastasis, and poor prognosis (136). Other examples have also shown decreases in desmosomal components, such as human malignant chondrosarcoma cells, which have decreased Dsg1, Dp, and Pg that are all rescued by overexpression of proline-rich polypeptide-1 (137). Conversely, studies have shown that overexpression of Dsg2 in the suprabasal layers of the mouse epidermis induced tumor development (138). Dsg2, Dsg3, and Pkp3 were found to be elevated in lung, prostate, head/neck, and skin cancers and were associated with disease progression and reduced patient survival (27, 139–142). This research supports the concept that the desmosome is abrogated in many cancer types and further highlights its complexity due to evidence supporting both upregulation and downregulation of certain components.

Recently, a global proteomic analysis of digested peptides and RNA expression profiles of oral cavity squamous cell carcinoma was performed to identify changes that reflect patient outcomes. Three patient outcomes were assessed, two of which were distant metastasis and disease-specific death. Patients who developed distant metastases and disease-specific death had significantly lower Dp at the RNA and protein levels. Low levels of Pkp1 protein and RNA were also associated with distant metastases and disease-specific death (143). Pkp1, which is in the family of armadillo proteins, has a direct effect on cellular proliferation by regulating protein synthesis via eIF4A1 in an

adhesion-independent manner (144), which is significant because protein translation pathways are often deregulated in cancer (100). Pkp1 has been shown to be downregulated in head/neck cancer and esophageal adenocarcinoma (145–147). Also, Pkp1 levels were largely reduced in aggressive prostate cancer and were associated with lymph node metastases (142, 148). Additionally, the loss of Pkp1 has been shown to upregulate an extracellular matrix-related gene, *SPOCK1*, in prostate adenocarcinomas, which suggests that Pkp1 has a role in prostate tumor progression (149). Whereas Pkp1 has been found to be downregulated in multiple cancers, a study of bladder cancer found Pkp2 to be upregulated.

Additionally, whereas Pkp3 is downregulated in bladder cancers correlated with invasiveness (150), it was also identified as a potential prognostic marker in lung cancer (27, 151, 152). Recently, it was shown that reactive oxygen species trigger c-Src kinase–mediated phosphorylation of Pkp3 at Tyr-195. EGFR can also phosphorylate Pkp3 at Tyr-195, which sheds light on how a pathway known to be overactive in cancer (EGFR) may communicate with the desmosome. Further supporting this notion, it was shown that Pkp3 phosphorylation occurs in adenocarcinomas of the prostate and may contribute to tumor progression (153).

To resolve some of the reported discrepancies in the proposed roles of various components of desmosomes in cancer, researchers have turned to mouse models. A mouse model of pancreatic islet cell tumorigenesis has shown a reduction in gene expression of *DP*, *DSG2*, *DSC2*, and *PKP2* in highly invasive tumors compared to noninvasive tumors, suggesting that desmosome downregulation may contribute to malignant progression (154). This group further found that the deletion of *DSP* resulted in an increase in local tumor invasion, independent of adherens junction status. Dp has also been found to be decreased in non-small-cell lung cancer (NSCLC). Additionally, ectopic expression of Dp resulted in the inhibition of cell proliferation, migration, and invasion (155). This group found that Dp expression promoted an increased expression of Pg, which resulted in decreased canonical Wnt signaling, which supports the role of Dp as a tumor suppressor in NSCLC through the inhibition of Wnt/β-catenin signaling (155).

The differences in the roles of desmosomes and their components in the array of cancer types discussed here may be due to the differences among the actual cancer types. Because there are research reports that support a dual role for the desmosome as a tumor suppressor and an oncogene, additional studies will be critical to more fully understand the complexities of the roles of desmosomes in cancer.

CONCLUDING REMARKS

This review highlights the features of the desmosome and describes the human diseases that result when the desmosome is disrupted. Although this cell junctional protein complex was first identified in the 1800s, a remarkable amount of knowledge has been gained since then. In earlier days, the desmosome was classically thought of as a structural "spot weld." Research has expanded how we think about this adhesion complex, which is now known to display a high level of structural organization and assembly. Through identification of novel binding partners and signaling events associated with the desmosome, researchers have re-defined the desmosome's functions. While research has uncovered how the desmosome assists in the promotion of epidermal differentiation, it is still unclear whether there are any implications for tissue patterning and development. Further research is required to shed light on this understudied new area of desmosomal biology.

Additionally, the exact mechanisms regulating differentiation dependent protein expression patterns of the desmosome have yet to be identified. It is clear that tight regulation of protein expression pattern is required, and in some instances forced expression of desmosomal components at points where they are not normally expressed can cause negative effects. This partially explains

why desmosomal diseases and disorders can be so debilitating, as other components are unable to compensate for their loss. In addition to understanding the communication and cross talk among desmosomal components and isoforms, another area that has been poorly researched is the communciation between desmosomes and other cell junctional protein complexes. The importance of this communication is underscored by the critical roles of gap junctions in cardiomyocyte physiology. If certain desmosomal mutations are able to cause a variety of disorders and diseases, one must also question the homeostasis of neighboring protein complexes such as tight junctions, adherens junctions, and gap junctions, as well as the cross talk between those protein complexes. While exciting and important research is continuing to emerge on the desmosome, future studies will be critical in providing scientists and physicians with sufficient additional understanding of the desmosome to permit the development of potential therapeutics.

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LITERATURE CITED

1. Bizzozero G. 1905. *Le opere scientifiche 1862–1896*. Milan: Hoepli
2. Mazzarello P, Calligaro AL, Calligaro A. 2001. Giulio Bizzozero: a pioneer of cell biology. *Nat. Rev. Mol. Cell Biol.* 2:776–81
3. Calkins CC, Setzer SV. 2007. Spotting desmosomes: the first 100 years. *J. Investig. Dermatol.* 127(Suppl. 3):E2–3
4. Waschke J. 2008. The desmosome and pemphigus. *Histochem. Cell Biol.* 130:21–54
5. Delva E, Tucker DK, Kowalczyk AP. 2009. The desmosome. *Cold Spring Harb. Perspect. Biol.* 1:a002543
6. Harmon RM, Green KJ. 2013. Structural and functional diversity of desmosomes. *Cell Commun. Adhes.* 20:171–87
7. Stahley SN, Kowalczyk AP. 2015. Desmosomes in acquired disease. *Cell Tissue Res.* 360:439–56
8. Getsios S, Huen AC, Green KJ. 2004. Working out the strength and flexibility of desmosomes. *Nat. Rev. Mol. Cell Biol.* 5:271–81
9. Cirillo N. 2014. 150th anniversary series: desmosomes in physiology and disease. *Cell Commun. Adhes.* 21:85–88
10. Kowalczyk AP, Green KJ. 2013. Structure, function, and regulation of desmosomes. *Prog. Mol. Biol. Transl. Sci.* 116:95–118
11. Holthofer B, Windoffer R, Troyanovsky S, Leube RE. 2007. Structure and function of desmosomes. *Int. Rev. Cytol.* 264:65–163
12. Green KJ, Gaudry CA. 2000. Are desmosomes more than tethers for intermediate filaments? *Nat. Rev. Mol. Cell Biol.* 1:208–16
13. Johnson JL, Najor NA, Green KJ. 2014. Desmosomes: regulators of cellular signaling and adhesion in epidermal health and disease. *Cold Spring Harb. Perspect. Med.* 4:a015297
14. Watt FM, Mattey DL, Garrod DR. 1984. Calcium-induced reorganization of desmosomal components in cultured human keratinocytes. *J. Cell Biol.* 99:2211–15
15. Burdett ID, Sullivan KH. 2002. Desmosome assembly in MDCK cells: Transport of precursors to the cell surface occurs by two phases of vesicular traffic and involves major changes in centrosome and Golgi location during a Ca^{2+} shift. *Exp. Cell Res.* 276:296–309

16. Penn EJ, Burdett ID, Hobson C, Magee AI, Rees DA. 1987. Structure and assembly of desmosome junctions: biosynthesis and turnover of the major desmosome components of Madin-Darby canine kidney cells in low calcium medium. *J. Cell Biol.* 105:2327–34
17. Pasdar M, Nelson WJ. 1989. Regulation of desmosome assembly in epithelial cells: kinetics of synthesis, transport, and stabilization of desmoglein I, a major protein of the membrane core domain. *J. Cell Biol.* 109:163–77
18. Bryant DM, Stow JL. 2004. The ins and outs of E-cadherin trafficking. *Trends Cell Biol.* 14:427–34
19. Nekrasova OE, Amargo EV, Smith WO, Chen J, Kreitzer GE, Green KJ. 2011. Desmosomal cadherins utilize distinct kinesins for assembly into desmosomes. *J. Cell Biol.* 195:1185–203. Erratum. 2013. *J. Cell Biol.* 201:1085
20. Gloushankova NA, Wakatsuki T, Troyanovsky RB, Elson E, Troyanovsky SM. 2003. Continual assembly of desmosomes within stable intercellular contacts of epithelial A-431 cells. *Cell Tissue Res.* 314:399–410
21. Shore EM, Nelson WJ. 1991. Biosynthesis of the cell adhesion molecule uvomorulin (E-cadherin) in Madin-Darby canine kidney epithelial cells. *J. Biol. Chem.* 266:19672–80
22. Chitaev NA, Troyanovsky SM. 1997. Direct Ca^{2+}-dependent heterophilic interaction between desmosomal cadherins, desmoglein and desmocollin, contributes to cell-cell adhesion. *J. Cell Biol.* 138:193–201
23. Syed SE, Trinnaman B, Martin S, Major S, Hutchinson J, Magee AI. 2002. Molecular interactions between desmosomal cadherins. *Biochem. J.* 362:317–27
24. Waschke J, Bruggeman P, Baumgartner W, Zillikens D, Drenckhahn D. 2005. Pemphigus foliaceus IgG causes dissociation of desmoglein 1–containing junctions without blocking desmoglein 1 transinteraction. *J. Clin. Investig.* 115:3157–65
25. Al-Amoudi A, Frangakis AS. 2008. Structural studies on desmosomes. *Biochem. Soc. Trans.* 36:181–87
26. Resnik N, Sepcic K, Plemenitas A, Windoffer R, Leube R, Veranic P. 2011. Desmosome assembly and cell-cell adhesion are membrane raft-dependent processes. *J. Biol. Chem.* 286:1499–507
27. Furukawa C, Daigo Y, Ishikawa N, Kato T, Ito T, et al. 2005. Plakophilin 3 oncogene as prognostic marker and therapeutic target for lung cancer. *Cancer Res.* 65:7102–10
28. Lewis JE, Wahl JK 3rd, Sass KM, Jensen PJ, Johnson KR, Wheelock MJ. 1997. Cross-talk between adherens junctions and desmosomes depends on plakoglobin. *J. Cell Biol.* 136:919–34
29. Pasdar M, Li Z, Chlumecky V. 1995. Plakoglobin: kinetics of synthesis, phosphorylation, stability, and interactions with desmoglein and E-cadherin. *Cell Motil. Cytoskelet.* 32:258–72
30. Mueller H, Franke WW. 1983. Biochemical and immunological characterization of desmoplakins I and II, the major polypeptides of the desmosomal plaque. *J. Mol. Biol.* 163:647–71
31. Gallicano GI, Kouklis P, Bauer C, Yin M, Vasioukhin V, et al. 1998. Desmoplakin is required early in development for assembly of desmosomes and cytoskeletal linkage. *J. Cell Biol.* 143:2009–22
32. Bornslaeger EA, Corcoran CM, Stappenbeck TS, Green KJ. 1996. Breaking the connection: Displacement of the desmosomal plaque protein desmoplakin from cell-cell interfaces disrupts anchorage of intermediate filament bundles and alters intercellular junction assembly. *J. Cell Biol.* 134:985–1001
33. Vasioukhin V, Bowers E, Bauer C, Degenstein L, Fuchs E. 2001. Desmoplakin is essential in epidermal sheet formation. *Nat. Cell Biol.* 3:1076–85
34. Godsel LM, Hsieh SN, Amargo EV, Bass AE, Pascoe-McGillicuddy LT, et al. 2005. Desmoplakin assembly dynamics in four dimensions: multiple phases differentially regulated by intermediate filaments and actin. *J. Cell Biol.* 171:1045–59
35. Godsel LM, Dubash AD, Bass-Zubek AE, Amargo EV, Klessner JL, et al. 2010. Plakophilin 2 couples actomyosin remodeling to desmosomal plaque assembly via RhoA. *Mol. Biol. Cell* 21:2844–59
36. Farquhar MG, Palade GE. 1963. Junctional complexes in various epithelia. *J. Cell Biol.* 17:375–412
37. Staehelin LA. 1974. Structure and function of intercellular junctions. *Int. Rev. Cytol.* 39:191–283
38. Getsios S, Simpson CL, Kojima S, Harmon R, Sheu LJ, et al. 2009. Desmoglein 1–dependent suppression of EGFR signaling promotes epidermal differentiation and morphogenesis. *J. Cell Biol.* 185:1243–58
39. Harmon RM, Simpson CL, Johnson JL, Koetsier JL, Dubash AD, et al. 2013. Desmoglein-1/Erbin interaction suppresses ERK activation to support epidermal differentiation. *J. Clin. Investig.* 123: 1556–70

40. Merritt AJ, Berika MY, Zhai W, Kirk SE, Ji B, et al. 2002. Suprabasal desmoglein 3 expression in the epidermis of transgenic mice results in hyperproliferation and abnormal differentiation. *Mol. Cell Biol.* 22:5846–58
41. Elias PM, Matsuyoshi N, Wu H, Lin C, Wang ZH, et al. 2001. Desmoglein isoform distribution affects stratum corneum structure and function. *J. Cell Biol.* 153:243–49
42. Nollet F, Kools P, van Roy F. 2000. Phylogenetic analysis of the cadherin superfamily allows identification of six major subfamilies besides several solitary members. *J. Mol. Biol.* 299:551–72
43. Garrod DR, Merritt AJ, Nie Z. 2002. Desmosomal cadherins. *Curr. Opin. Cell Biol.* 14:537–45
44. Mathur M, Goodwin L, Cowin P. 1994. Interactions of the cytoplasmic domain of the desmosomal cadherin Dsg1 with plakoglobin. *J. Biol. Chem.* 269:14075–80
45. Troyanovsky SM, Troyanovsky RB, Eshkind LG, Krutovskikh VA, Leube RE, Franke WW. 1994. Identification of the plakoglobin-binding domain in desmoglein and its role in plaque assembly and intermediate filament anchorage. *J. Cell Biol.* 127:151–60
46. Troyanovsky SM, Troyanovsky RB, Eshkind LG, Leube RE, Franke WW. 1994. Identification of amino acid sequence motifs in desmocollin, a desmosomal glycoprotein, that are required for plakoglobin binding and plaque formation. *PNAS* 91:10790–94
47. Roh JY, Stanley JR. 1995. Plakoglobin binding by human Dsg3 (pemphigus vulgaris antigen) in keratinocytes requires the cadherin-like intracytoplasmic segment. *J. Investig. Dermatol.* 104:720–24
48. Parker AE, Wheeler GN, Arnemann J, Pidsley SC, Ataliotis P, et al. 1991. Desmosomal glycoproteins II and III. Cadherin-like junctional molecules generated by alternative splicing. *J. Biol. Chem.* 266:10438–45
49. Collins JE, Legan PK, Kenny TP, MacGarvie J, Holton JL, Garrod DR. 1991. Cloning and sequence analysis of desmosomal glycoproteins 2 and 3 (desmocollins): cadherin-like desmosomal adhesion molecules with heterogeneous cytoplasmic domains. *J. Cell Biol.* 113:381–91
50. Rickman L, Simrak D, Stevens HP, Hunt DM, King IA, et al. 1999. N-terminal deletion in a desmosomal cadherin causes the autosomal dominant skin disease striate palmoplantar keratoderma. *Hum. Mol. Genet.* 8:971–76
51. Hunt DM, Rickman L, Whittock NV, Eady RA, Simrak D, et al. 2001. Spectrum of dominant mutations in the desmosomal cadherin desmoglein 1, causing the skin disease striate palmoplantar keratoderma. *Eur. J. Hum. Genet.* 9:197–203
52. Kljuic A, Gilead L, Martinez-Mir A, Frank J, Christiano AM, Zlotogorski A. 2003. A nonsense mutation in the desmoglein 1 gene underlies striate keratoderma. *Exp. Dermatol.* 12:523–27
53. Dua-Awereh MB, Shimomura Y, Kraemer L, Wajid M, Christiano AM. 2009. Mutations in the desmoglein 1 gene in five Pakistani families with striate palmoplantar keratoderma. *J. Dermatol. Sci.* 53:192–97
54. Hershkovitz D, Lugassy J, Indelman M, Bergman R, Sprecher E. 2009. Novel mutations in *DSG1* causing striate palmoplantar keratoderma. *Clin. Exp. Dermatol.* 34:224–28
55. Samuelov L, Sarig O, Harmon RM, Rapaport D, Ishida-Yamamoto A, et al. 2013. Desmoglein 1 deficiency results in severe dermatitis, multiple allergies and metabolic wasting. *Nat. Genet.* 45:1244–48
56. Has C, Jakob T, He Y, Kiritsi D, Hausser I, Bruckner-Tuderman L. 2015. Loss of desmoglein 1 associated with palmoplantar keratoderma, dermatitis and multiple allergies. *Br. J. Dermatol.* 172:257–61
57. Lovgren ML, McAleer MA, Irvine AD, Wilson NJ, Tavadia S, et al. 2016. Mutations in desmoglein 1 cause diverse inherited palmoplantar keratoderma phenotypes: implications for genetic screening. *Br. J. Dermatol.* 176:1345–50
58. Kljuic A, Bazzi H, Sundberg JP, Martinez-Mir A, O'Shaughnessy R, et al. 2003. Desmoglein 4 in hair follicle differentiation and epidermal adhesion: evidence from inherited hypotrichosis and acquired pemphigus vulgaris. *Cell* 113:249–60
59. Rafique MA, Ansar M, Jamal SM, Malik S, Sohail M, et al. 2003. A locus for hereditary hypotrichosis localized to human chromosome 18q21.1. *Eur. J. Hum. Genet.* 11:623–28
60. Moss C, Martinez-Mir A, Lam H, Tadin-Strapps M, Kljuic A, Christiano AM. 2004. A recurrent intragenic deletion in the desmoglein 4 gene underlies localized autosomal recessive hypotrichosis. *J. Investig. Dermatol.* 123:607–10

61. Rafiq MA, Ansar M, Mahmood S, Haque S, Faiyaz-ul-Haque M, et al. 2004. A recurrent intragenic deletion mutation in DSG4 gene in three Pakistani families with autosomal recessive hypotrichosis. *J. Investig. Dermatol.* 123:247–48
62. Wajid M, Bazzi H, Rockey J, Lubetkin J, Zlotogorski A, Christiano AM. 2007. Localized autosomal recessive hypotrichosis due to a frameshift mutation in the desmoglein 4 gene exhibits extensive phenotypic variability within a Pakistani family. *J. Investig. Dermatol.* 127:1779–82
63. Schaffer JV, Bazzi H, Vitebsky A, Witkiewicz A, Kovich OI, et al. 2006. Mutations in the desmoglein 4 gene underlie localized autosomal recessive hypotrichosis with monilethrix hairs and congenital scalp erosions. *J. Investig. Dermatol.* 126:1286–91
64. Shimomura Y, Sakamoto F, Kariya N, Matsunaga K, Ito M. 2006. Mutations in the desmoglein 4 gene are associated with monilethrix-like congenital hypotrichosis. *J. Investig. Dermatol.* 126:1281–85
65. Ullah A, Raza SI, Ali RH, Naveed AK, Jan A, et al. 2015. A novel deletion mutation in the *DSG4* gene underlies autosomal recessive hypotrichosis with variable phenotype in two unrelated consanguineous families. *Clin. Exp. Dermatol.* 40:78–84
66. Wang JM, Xiao YJ, Liang YH. 2015. Novel D323G mutation of *DSG4* gene in a girl with localized autosomal recessive hypotrichosis clinically overlapped with monilethrix. *Int. J. Dermatol.* 54:1163–68
67. Ayub M, Basit S, Jelani M, Ur Rehman F, Iqbal M, et al. 2009. A homozygous nonsense mutation in the human desmocollin-3 (*DSC3*) gene underlies hereditary hypotrichosis and recurrent skin vesicles. *Am. J. Hum. Genet.* 85:515–20
68. Koch PJ, Mahoney MG, Ishikawa H, Pulkkinen L, Uitto J, et al. 1997. 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.* 137:1091–102
69. Chidgey M, Brakebusch C, Gustafsson E, Cruchley A, Hail C, et al. 2001. Mice lacking desmocollin 1 show epidermal fragility accompanied by barrier defects and abnormal differentiation. *J. Cell Biol.* 155:821–32
70. Li J, Radice GL. 2010. A new perspective on intercalated disc organization: implications for heart disease. *Dermatol. Res. Pract.* 2010:207835
71. Pilichou K, Nava A, Basso C, Beffagna G, Bauce B, et al. 2006. Mutations in desmoglein-2 gene are associated with arrhythmogenic right ventricular cardiomyopathy. *Circulation* 113:1171–79
72. Syrris P, Ward D, Evans A, Asimaki A, Gandjbakhch E, et al. 2006. Arrhythmogenic right ventricular dysplasia/cardiomyopathy associated with mutations in the desmosomal gene desmocollin-2. *Am. J. Hum. Genet.* 79:978–84
73. Heuser A, Plovie ER, Ellinor PT, Grossmann KS, Shin JT, et al. 2006. Mutant desmocollin-2 causes arrhythmogenic right ventricular cardiomyopathy. *Am. J. Hum. Genet.* 79:1081–88
74. Awad MM, Dalal D, Cho E, Amat-Alarcon N, James C, et al. 2006. *DSG2* mutations contribute to arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Am. J. Hum. Genet.* 79:136–42
75. Awad MM, Calkins H, Judge DP. 2008. Mechanisms of disease: molecular genetics of arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Nat. Clin. Pract. Cardiovasc. Med.* 5:258–67
76. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, et al. 1982. Right ventricular dysplasia: a report of 24 adult cases. *Circulation* 65:384–98
77. Sen-Chowdhry S, Syrris P, Ward D, Asimaki A, Sevdalis E, McKenna WJ. 2007. Clinical and genetic characterization of families with arrhythmogenic right ventricular dysplasia/cardiomyopathy provides novel insights into patterns of disease expression. *Circulation* 115:1710–20
78. Simpson MA, Mansour S, Ahnood D, Kalidas K, Patton MA, et al. 2009. Homozygous mutation of desmocollin-2 in arrhythmogenic right ventricular cardiomyopathy with mild palmoplantar keratoderma and woolly hair. *Cardiology* 113:28–34
79. Beutner EH, Jordon RE. 1964. Demonstration of skin antibodies in sera of pemphigus vulgaris patients by indirect immunofluorescent staining. *Proc. Soc. Exp. Biol. Med.* 117:505–10
80. Stanley JR, Yaar M, Hawley-Nelson P, Katz SI. 1982. Pemphigus antibodies identify a cell surface glycoprotein synthesized by human and mouse keratinocytes. *J. Clin. Investig.* 70:281–88
81. Eyre RW, Stanley JR. 1988. Identification of pemphigus vulgaris antigen extracted from normal human epidermis and comparison with pemphigus foliaceus antigen. *J. Clin. Investig.* 81:807–12

82. Hashimoto T, Ogawa MM, Konohana A, Nishikawa T. 1990. Detection of pemphigus vulgaris and pemphigus foliaceus antigens by immunoblot analysis using different antigen sources. *J. Investig. Dermatol.* 94:327–31
83. Amagai M, Klaus-Kovtun V, Stanley JR. 1991. Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion. *Cell* 67:869–77
84. Amagai M, Karpati S, Prussick R, Klaus-Kovtun V, Stanley JR. 1992. Autoantibodies against the amino-terminal cadherin-like binding domain of pemphigus vulgaris antigen are pathogenic. *J. Clin. Investig.* 90:919–26
85. Amagai M. 1996. Pemphigus: autoimmunity to epidermal cell adhesion molecules. *Adv. Dermatol.* 11:319–52; discussion 353
86. Amagai M, Koch PJ, Nishikawa T, Stanley JR. 1996. Pemphigus vulgaris antigen (desmoglein 3) is localized in the lower epidermis, the site of blister formation in patients. *J. Investig. Dermatol.* 106:351–55
87. Ding X, Aoki V, Mascaro JM Jr., Lopez-Swiderski A, Diaz LA, Fairley JA. 1997. Mucosal and mucocutaneous (generalized) pemphigus vulgaris show distinct autoantibody profiles. *J. Investig. Dermatol.* 109:592–96
88. Amagai M. 1999. Autoimmunity against desmosomal cadherins in pemphigus. *J. Dermatol. Sci.* 20:92–102
89. Amagai M. 2002. Pemphigus as a paradigm of autoimmunity and cell adhesion. *Keio J. Med.* 51:133–39
90. Payne AS, Hanakawa Y, Amagai M, Stanley JR. 2004. Desmosomes and disease: pemphigus and bullous impetigo. *Curr. Opin. Cell Biol.* 16:536–43
91. Stanley JR, Amagai M. 2006. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. *N. Engl. J. Med.* 355:1800–10
92. Mahoney MG, Wang Z, Rothenberger K, Koch PJ, Amagai M, Stanley JR. 1999. Explanations for the clinical and microscopic localization of lesions in pemphigus foliaceus and vulgaris. *J. Clin. Investig.* 103:461–68
93. Chan PT, Ohyama B, Nishifuji K, Yoshida K, Ishii K, et al. 2010. Immune response towards the amino-terminus of desmoglein 1 prevails across different activity stages in nonendemic pemphigus foliaceus. *Br. J. Dermatol.* 162:1242–50
94. Ohyama B, Nishifuji K, Chan PT, Kawaguchi A, Yamashita T, et al. 2012. Epitope spreading is rarely found in pemphigus vulgaris by large-scale longitudinal study using desmoglein 2–based swapped molecules. *J. Investig. Dermatol.* 132:1158–68
95. Amagai M. 2003. Desmoglein as a target in autoimmunity and infection. *J. Am. Acad. Dermatol.* 48:244–52
96. Amagai M. 2009. The molecular logic of pemphigus and impetigo: the desmoglein story. *Vet. Dermatol.* 20:308–12
97. Amagai M, Matsuyoshi N, Wang ZH, Andl C, Stanley JR. 2000. Toxin in bullous impetigo and staphylococcal scalded-skin syndrome targets desmoglein 1. *Nat. Med.* 6:1275–77
98. Franke WW, Goldschmidt MD, Zimbelmann R, Mueller HM, Schiller DL, Cowin P. 1989. Molecular cloning and amino acid sequence of human plakoglobin, the common junctional plaque protein. *PNAS* 86:4027–31
99. Choi HJ, Weis WI. 2005. Structure of the armadillo repeat domain of plakophilin 1. *J. Mol. Biol.* 346:367–76
100. Hatzfeld M, Wolf A, Keil R. 2014. Plakophilins in desmosomal adhesion and signaling. *Cell Commun. Adhes.* 21:25–42
101. Kowalczyk AP, Bornslaeger EA, Borgwardt JE, Palka HL, Dhaliwal AS, et al. 1997. The amino-terminal domain of desmoplakin binds to plakoglobin and clusters desmosomal cadherin-plakoglobin complexes. *J. Cell Biol.* 139:773–84
102. McGrath JA, McMillan JR, Shemanko CS, Runswick SK, Leigh IM, et al. 1997. Mutations in the plakophilin 1 gene result in ectodermal dysplasia/skin fragility syndrome. *Nat. Genet.* 17:240–44
103. Ersoy-Evans S, Erkin G, Fassihi H, Chan I, Paller AS, et al. 2006. Ectodermal dysplasia-skin fragility syndrome resulting from a new homozygous mutation, 888delC, in the desmosomal protein plakophilin 1. *J. Am. Acad. Dermatol.* 55:157–61
104. Tanaka A, Lai-Cheong JE, Cafe ME, Gontijo B, Salomao PR, et al. 2009. Novel truncating mutations in *PKP1* and *DSP* cause similar skin phenotypes in two Brazilian families. *Br. J. Dermatol.* 160:692–97

105. Zheng R, Bu DF, Zhu XJ. 2005. Compound heterozygosity for new splice site mutations in the plakophilin 1 gene (*PKP1*) in a Chinese case of ectodermal dysplasia-skin fragility syndrome. *Acta Derm. Venereol.* 85:394–99
106. Tucker DK, Stahley SN, Kowalczyk AP. 2014. Plakophilin-1 protects keratinocytes from pemphigus vulgaris IgG by forming calcium-independent desmosomes. *J. Investig. Dermatol.* 134:1033–43
107. Pigors M, Kiritsi D, Krumpelmann S, Wagner N, He Y, et al. 2011. Lack of plakoglobin leads to lethal congenital epidermolysis bullosa: a novel clinico-genetic entity. *Hum. Mol. Genet.* 20:1811–19
108. Cabral RM, Liu L, Hogan C, Dopping-Hepenstal PJ, Winik BC, et al. 2010. Homozygous mutations in the 5′ region of the *JUP* gene result in cutaneous disease but normal heart development in children. *J. Investig. Dermatol.* 130:1543–50
109. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, et al. 2000. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). *Lancet* 355:2119–24
110. Protonotarios N, Tsatsopoulou A, Fontaine G. 2001. Naxos disease: keratoderma, scalp modifications, and cardiomyopathy. *J. Am. Acad. Dermatol.* 44:309–11
111. Asimaki A, Syrris P, Wichter T, Matthias P, Saffitz JE, McKenna WJ. 2007. A novel dominant mutation in plakoglobin causes arrhythmogenic right ventricular cardiomyopathy. *Am. J. Hum. Genet.* 81:964–73
112. Lombardi R, da Graca Cabreira-Hansen M, Bell A, Fromm RR, Willerson JT, Marian AJ. 2011. Nuclear plakoglobin is essential for differentiation of cardiac progenitor cells to adipocytes in arrhythmogenic right ventricular cardiomyopathy. *Circ. Res.* 109:1342–53
113. Chen SN, Gurha P, Lombardi R, Ruggiero A, Willerson JT, Marian AJ. 2014. The hippo pathway is activated and is a causal mechanism for adipogenesis in arrhythmogenic cardiomyopathy. *Circ. Res.* 114:454–68
114. Fidler LM, Wilson GJ, Liu F, Cui X, Scherer SW, et al. 2009. Abnormal connexin43 in arrhythmogenic right ventricular cardiomyopathy caused by plakophilin-2 mutations. *J. Cell Mol. Med.* 13:4219–28
115. Broussard JA, Getsios S, Green KJ. 2015. Desmosome regulation and signaling in disease. *Cell Tissue Res.* 360:501–12
116. Angst BD, Nilles LA, Green KJ. 1990. Desmoplakin II expression is not restricted to stratified epithelia. *J. Cell Sci.* 97(Pt. 2):247–57
117. Uzumcu A, Norgett EE, Dindar A, Uyguner O, Nisli K, et al. 2006. Loss of desmoplakin isoform I causes early onset cardiomyopathy and heart failure in a Naxos-like syndrome. *J. Med. Genet.* 43:e5
118. Armstrong DK, McKenna KE, Purkis PE, Green KJ, Eady RA, et al. 1999. Haploinsufficiency of desmoplakin causes a striate subtype of palmoplantar keratoderma. *Hum. Mol. Genet.* 8:143–48
119. Whittock NV, Ashton GH, Dopping-Hepenstal PJ, Gratian MJ, Keane FM, et al. 1999. Striate palmoplantar keratoderma resulting from desmoplakin haploinsufficiency. *J. Investig. Dermatol.* 113:940–46
120. Whittock NV, Wan H, Morley SM, Garzon MC, Kristal L, et al. 2002. Compound heterozygosity for non-sense and mis-sense mutations in desmoplakin underlies skin fragility/woolly hair syndrome. *J. Investig. Dermatol.* 118:232–38
121. Al-Owain M, Wakil S, Shareef F, Al-Fatani A, Hamadah E, et al. 2011. Novel homozygous mutation in DSP causing skin fragility-woolly hair syndrome: report of a large family and review of the desmoplakin-related phenotypes. *Clin. Genet.* 80:50–58
122. Smith FJ, Wilson NJ, Moss C, Dopping-Hepenstal P, McGrath J. 2012. Compound heterozygous mutations in desmoplakin cause skin fragility and woolly hair. *Br. J. Dermatol.* 166:894–96
123. Carvajal-Huerta L. 1998. Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy. *J. Am. Acad. Dermatol.* 39:418–21
124. Rao BH, Reddy IS, Chandra KS. 1996. Familial occurrence of a rare combination of dilated cardiomyopathy with palmoplantar keratoderma and curly hair. *Indian Heart J.* 48:161–62
125. Norgett EE, Hatsell SJ, Carvajal-Huerta L, Cabezas JC, Common J, et al. 2000. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum. Mol. Genet.* 9:2761–66
126. Jonkman MF, Pasmooij AM, Pasmans SG, van den Berg MP, Ter Horst HJ, et al. 2005. Loss of desmoplakin tail causes lethal acantholytic epidermolysis bullosa. *Am. J. Hum. Genet.* 77:653–60

127. Bolling MC, Veenstra MJ, Jonkman MF, Diercks GF, Curry CJ, et al. 2010. Lethal acantholytic epidermolysis bullosa due to a novel homozygous deletion in *DSP*: expanding the phenotype and implications for desmoplakin function in skin and heart. *Br. J. Dermatol.* 162:1388–94
128. Bremnes RM, Veve R, Gabrielson E, Hirsch FR, Baron A, et al. 2002. High-throughput tissue microarray analysis used to evaluate biology and prognostic significance of the E-cadherin pathway in non-small-cell lung cancer. *J. Clin. Oncol.* 20:2417–28
129. Rakha EA, Abd El Rehim D, Pinder SE, Lewis SA, Ellis IO. 2005. E-cadherin expression in invasive non-lobular carcinoma of the breast and its prognostic significance. *Histopathology* 46:685–93
130. Syrigos KN, Krausz T, Waxman J, Pandha H, Rowlinson-Busza G, et al. 1995. E-cadherin expression in bladder cancer using formalin-fixed, paraffin-embedded tissues: correlation with histopathological grade, tumour stage and survival. *Int. J. Cancer* 64:367–70
131. Wijnhoven BP, Pignatelli M, Dinjens WN, Tilanus HW. 2005. Reduced p120ctn expression correlates with poor survival in patients with adenocarcinoma of the gastroesophageal junction. *J. Surg. Oncol.* 92:116–23
132. Zheng Z, Pan J, Chu B, Wong YC, Cheung AL, Tsao SW. 1999. Downregulation and abnormal expression of E-cadherin and beta-catenin in nasopharyngeal carcinoma: close association with advanced disease stage and lymph node metastasis. *Hum. Pathol.* 30:458–66
133. Klessner JL, Desai BV, Amargo EV, Getsios S, Green KJ. 2009. EGFR and ADAMs cooperate to regulate shedding and endocytic trafficking of the desmosomal cadherin desmoglein 2. *Mol. Biol. Cell* 20:328–37
134. Kamekura R, Kolegraff KN, Nava P, Hilgarth RS, Feng M, et al. 2014. Loss of the desmosomal cadherin desmoglein-2 suppresses colon cancer cell proliferation through EGFR signaling. *Oncogene* 33:4531–36
135. Wong MP, Cheang M, Yorida E, Coldman A, Gilks CB, et al. 2008. Loss of desmoglein 1 expression associated with worse prognosis in head and neck squamous cell carcinoma patients. *Pathology* 40:611–16
136. Dusek RL, Attardi LD. 2011. Desmosomes: new perpetrators in tumour suppression. *Nat. Rev. Cancer* 11:317–23
137. Galoian K, Qureshi A, Wideroff G, Temple HT. 2015. Restoration of desmosomal junction protein expression and inhibition of H3K9-specific histone demethylase activity by cytostatic proline-rich polypeptide-1 leads to suppression of tumorigenic potential in human chondrosarcoma cells. *Mol. Clin. Oncol.* 3:171–78
138. Brennan D, Hu Y, Joubeh S, Choi YW, Whitaker-Menezes D, et al. 2007. Suprabasal Dsg2 expression in transgenic mouse skin confers a hyperproliferative and apoptosis-resistant phenotype to keratinocytes. *J. Cell Sci.* 120:758–71
139. Kurzen H, Munzing I, Hartschuh W. 2003. Expression of desmosomal proteins in squamous cell carcinomas of the skin. *J. Cutan. Pathol.* 30:621–30
140. Chen YJ, Chang JT, Lee L, Wang HM, Liao CT, et al. 2007. DSG3 is overexpressed in head neck cancer and is a potential molecular target for inhibition of oncogenesis. *Oncogene* 26:467–76
141. Brennan D, Mahoney MG. 2009. Increased expression of Dsg2 in malignant skin carcinomas: a tissue-microarray based study. *Cell Adhes. Migr.* 3:148–54
142. Breuninger S, Reidenbach S, Sauer CG, Strobel P, Pfitzenmaier J, et al. 2010. Desmosomal plakophilins in the prostate and prostatic adenocarcinomas: implications for diagnosis and tumor progression. *Am. J. Pathol.* 176:2509–19
143. Harris TM, Du P, Kawachi N, Belbin TJ, Wang Y, et al. 2015. Proteomic analysis of oral cavity squamous cell carcinoma specimens identifies patient outcome-associated proteins. *Arch. Pathol. Lab. Med.* 139:494–507
144. Wolf A, Krause-Gruszczynska M, Birkenmeier O, Ostareck-Lederer A, Huttelmaier S, Hatzfeld M. 2010. Plakophilin 1 stimulates translation by promoting eIF4A1 activity. *J. Cell Biol.* 188:463–71
145. Papagerakis S, Shabana AH, Depondt J, Gehanno P, Forest N. 2003. Immunohistochemical localization of plakophilins (PKP1, PKP2, PKP3, and p0071) in primary oropharyngeal tumors: correlation with clinical parameters. *Hum. Pathol.* 34:565–72
146. Sobolik-Delmaire T, Katafiasz D, Keim SA, Mahoney MG, Wahl JK 3rd. 2007. Decreased plakophilin-1 expression promotes increased motility in head and neck squamous cell carcinoma cells. *Cell Commun. Adhes.* 14:99–109

147. Kaz AM, Luo Y, Dzieciatkowski S, Chak A, Willis JE, et al. 2012. Aberrantly methylated PKP1 in the progression of Barrett's esophagus to esophageal adenocarcinoma. *Genes Chromosomes Cancer* 51:384–93
148. Yang C, Strobel P, Marx A, Hofmann I. 2013. Plakophilin-associated RNA-binding proteins in prostate cancer and their implications in tumor progression and metastasis. *Virchows Arch*. 463:379–90
149. Yang C, Fischer-Keso R, Schlechter T, Strobel P, Marx A, Hofmann I. 2015. Plakophilin 1-deficient cells upregulate SPOCK1: implications for prostate cancer progression. *Tumour Biol*. 36:9567–77
150. Takahashi H, Nakatsuji H, Takahashi M, Avirmed S, Fukawa T, et al. 2012. Up-regulation of plakophilin-2 and down-regulation of plakophilin-3 are correlated with invasiveness in bladder cancer. *Urology* 79:240.e1–8
151. Kundu ST, Gosavi P, Khapare N, Patel R, Hosing AS, et al. 2008. Plakophilin3 downregulation leads to a decrease in cell adhesion and promotes metastasis. *Int. J. Cancer* 123:2303–14
152. Demirag GG, Sullu Y, Yucel I. 2012. Expression of Plakophilins (PKP1, PKP2, and PKP3) in breast cancers. *Med. Oncol.* 29:1518–22
153. Neuber S, Jager S, Meyer M, Wischmann V, Koch PJ, et al. 2015. c-Src mediated tyrosine phosphorylation of plakophilin 3 as a new mechanism to control desmosome composition in cells exposed to oxidative stress. *Cell Tissue Res*. 359:799–816
154. Chun MG, Hanahan D. 2010. Genetic deletion of the desmosomal component desmoplakin promotes tumor microinvasion in a mouse model of pancreatic neuroendocrine carcinogenesis. *PLOS Genet*. 6:e1001120
155. Yang L, Chen Y, Cui T, Knosel T, Zhang Q, et al. 2012. Desmoplakin acts as a tumor suppressor by inhibition of the Wnt/β-catenin signaling pathway in human lung cancer. *Carcinogenesis* 33:1863–70
156. Najor NA, Fitz GN, Koetsier JL, Godsel LM, Albrecht LV, et al. 2017. Epidermal growth factor receptor neddylation is regulated by a desmosomal-COP9 (constitutive photomorphogenesis 9) signalosome complex. *eLife*. In press. **https://doi.org/10.7554/eLife.22599**