Desmosomes are intercellular junctions that mediate cell-cell adhesion and anchor the intermediate filament network to the plasma membrane, providing mechanical resilience to tissues such as the epidermis and heart. In addition to their critical roles in adhesion, desmosomal proteins are emerging as mediators of cell signaling important for proper cell and tissue functions. In this review we highlight what is known about desmosomal proteins regulating adhesion and signaling in healthy skin—in morphogenesis, differentiation and homeostasis, wound healing, and protection against environmental damage. We also discuss how human diseases that target desmosome molecules directly or interfere indirectly with these mechanical and signaling functions to contribute to pathogenesis.

Desmosomes are intercellular junctions that strengthen mechanically challenged tissues by linking intermediate filaments of adjoining cells. They are crucial for both embryonic development and adult tissue integrity. Insults against or mutations in desmosomal proteins lead to potentially lethal skin and heart diseases (Bazzi and Christiano 2007; Amagai and Stanley 2012; Petrof et al. 2012; Kowalczyk and Green 2013).

Members of three protein families make up the core components of the desmosome (Figs. 1 and 2): cadherins including desmogleins and desmocollins (Dsgs, Dscs), armadillo proteins including plakoglobin and plakophilins (Pg and Pkps), and a plakin, desmoplakin (Dp) (Green and Simpson 2007; Delva et al. 2009). Other tissue-specific desmosome proteins include Perp (p53 apoptosis effector related to PMP-22) (Ihrie and Attardi 2005) and the outer epidermal cornified envelope components corneodesmosin, perilakin, enoplakin, involucrin, and kazrin (Groot et al. 2004; Sonnenberg and Liem 2007; Leclerc et al. 2009). The desmosomal cadherins join cells together through their extracellular domains and associate with Pg and the Pkps through their intracellular domains. The cadherin–armadillo complex binds in turn to Dp, which tethers the intermediate filament network to the junctional plaque (Green and Simpson 2007; Kowalczyk and Green 2013). The ability to confer mechanical strength through interaction with flexible, mechanically resilient intermediate filaments...
distinguishes desmosomes from a similar cadherin-based organelle, the adherens junction, which interacts with the more rigid actin cytoskeleton (Chu et al. 2004; Mucke et al. 2004; Gardel et al. 2008).

Desmosomal components change as keratinocytes differentiate and stratify (Fig. 2). For instance, Dsg2 is concentrated in the basal proliferating layers, whereas Dsg1 is first expressed as cells transit out of the basal layer and becomes progressively concentrated in suprabasal layers during stratification. Different desmosomal cadherins have inherent differences in adhesive strength (Hartlieb et al. 2013). Therefore, switching components in each layer may allow cell plasticity in the lower, proliferative layers and increased strength and barrier function in the upper layers. In addition to their adhesive functions, desmosomal components regulate intracellular signaling (Green and Gaudry 2000; Green and Simpson 2007; Kowalczyk and Green 2013), and forced expression of a cadherin in

Figure 1. Desmosome structure and organization. Electron micrograph of a desmosome from bovine tongue epithelium overlaid with a representation of the membrane and plaque components. Desmosomes are composed of cadherins (Desmoglein, Dsg; Desmocollin, Dsc), armadillo proteins (Plakoglobin, Pg; Plakophilin, Pkp), and a plakin (Desmoplakin, Dp), which act as a cytolinker to tether the desmosome to the intermediate filaments (IF).
the “wrong” layer can lead to alterations in proliferation/survival and differentiation (Henkler et al. 2001; Hanakawa et al. 2002; Merritt et al. 2002; Hardman et al. 2005; Brennan et al. 2007, 2010). The naturally diverse expression of desmosomal components in each epidermal layer allows desmosomes to serve not only as nuts and bolts to hold cells together but also as a tool kit to modulate form and function of the highly specialized tissue.

In the sections that follow, we review transcriptional programs that dictate where and when desmosomal cadherins are expressed and the functional implications of the resulting expression patterns in health and disease. We conclude by introducing how desmosomal protein expression might be manipulated pharmacologically, taking advantage of natural turnover processes that control junction homeostasis.

**Figure 2.** Desmosome differential protein expression pattern in epidermis and the transcription factors linked to their regulation. Several of the desmosomal components display a unique spatial pattern of expression within the epidermis (depicted as triangles and rectangles). We have summarized the transcriptional regulation of the desmosomal components from multiple cell types in Table 1. Desmosomal regulators that have been verified in the epidermis (no asterisk) are distinguished from those verified in other tissues (asterisk). Transcription factors regulating Pkp1, Dsg3, and Dsg2 are putative or unknown.

**TRANSCRIPTIONAL REGULATION OF DESMOSONAL COMPONENTS**

The mechanisms responsible for establishing the spatial patterning of desmosomal components in stratified epithelia are not yet well understood. Desmosomal cadherin genes group together on chromosome 18, whereas Pkp1-3, Pg, and Dp genes map to chromosomes 1, 12, 11, 17, and 6, respectively (Arnemann et al. 1991; Wang et al. 1994; Simrak et al. 1995; Cowley et al. 1997a,b; Bonne et al. 1998; Whittock and Bower 2003). The chromosomal grouping of the desmosomal cadherins may allow for sequential expression in which, for example, Dsc1 follows Dsg1 expression in epidermal differentiation, although a mechanism has not yet been elucidated (Getsios et al. 2009).

Signaling pathways involved in epidermal differentiation regulate keratin and desmosomal...
al protein expression in keratinocytes, such as Notch, transforming growth factor β (TGF-β), IκB kinase (IKK), Ras/mitogen activated protein kinase (MAPK), phosphoinositide-3-kinase (PI3K), Wnt, protein kinase C or A (PKC, PKA), and Rho GTPases (Dong and Chen 2009; Leitner et al. 2011; Lopez-Pajares et al. 2013). However, links between these signaling pathways and the specific downstream transcription factors that regulate desmosomal protein expression have only been elucidated in a few instances. It has long been known that PKC signaling regulates expression of desmosomal cadherins in keratinocytes (Denning et al. 1998). Suppression of PKC-α or PKC-δ isoforms increases Dsg3 expression, whereas suppression of PKC-δ and PKC-ε isoforms either decreases or increases Dsg1 levels, respectively (Szegedi et al. 2009). However, the specific transcription factors which act downstream of PKC isoforms to induce or inhibit desmosomal protein expression have not yet been directly shown, even though Dsg1, Dsg3, Dsc2, and Pg promoters all have putative binding sites for PKC-regulated transcription factors (Table 1). Recently, the Ephrin family of receptors and ligands has emerged as regulating expression of differentiation-associated proteins, including Dsg1 (Lin et al. 2010; Walsh and Blumenberg 2011) but, similarly to PKC, the specific transcription factors controlled by this pathway have not yet been determined.

More direct links between desmosomal component expression and transcriptional regulators downstream of Notch, Rho, and Wnt pathways have recently been shown. Notch and the transcription factor p63 regulate each other (Roemer 2012) and p63 has been shown by chromatin immunoprecipitation (ChIP) to bind and activate Dsg1, Dsc3, and Dp promoters (Ferone et al. 2013; Johnson et al. 2014). Rho-mediated changes in the actin cytoskeleton lead to changes in Srf-dependent transcription (Miralles et al. 2003) and Srf controls the expression of Pkp2 and Dsg1, which in turn drives a program of terminal differentiation (Leitner et al. 2011; Dubash et al. 2013). The Wnt-regulated TCF/Lef transcription complex has been implicated in regulation of Dsg4, Dsc2, Dsc3, and Pg expression but direct binding of these transcription factors to desmosomal component promoters has only been shown in a few instances (Table 1) (Bazzi et al. 2009; Bailey et al. 2012; Tokonza et al. 2013). Pg itself complexes with TCF/Lef-1 to regulate the balance of Dsc2 and Dsc3 expression (Tokonza et al. 2013).

Desmosomal cadherin distribution within the stratified epidermis may in part be regulated by the differential activity of transcription factor isoforms. For instance, the more basally concentrated Dsc3 is activated by the β form of CCAAT/enhancer-binding protein, whereas Dsc1 is activated by the α isoform. This isoform specificity suggests one potential mechanism for switching between basal and suprabasal desmosomal cadherins during differentiation. Expression of desmosomal components and keratins can be regulated by the same transcription factors. For example, Ap2, HoxC13, Lef-1 and Foxn1, which up-regulate or repress keratin expression, have also been implicated as putative or shown regulators of Dsgs, Dscs, armadillo proteins, and the associated desmosomal components periplakin and envoplakin (Byrne et al. 1994; Silos et al. 1996; Marsden et al. 1997; Adams et al. 1998; Aho et al. 1999; Maatta et al. 2000; Potter et al. 2001; Bazzi et al. 2009).

Understanding how transcriptional programs coordinate the expression of cytoarchitectural building blocks during differentiation will help us better understand epidermal development, hair follicle cycling, wound healing, and responses to environmental exposure.

Desmosomal components can be transcriptionally repressed by factors such as Slug and Zeb, which promote epithelial-to-mesenchymal (EMT) transition and wound re-epithelialization (Savagner et al. 2005; Vandewalle et al. 2005; Aigner et al. 2007). Epigenetic mechanisms, including promoter methylation and histone deacetylation (HDAC), also repress the expression of desmosomal proteins, which may contribute to carcinogenesis (Potter et al. 2001; Cui et al. 2011; Kaz et al. 2012; Yang et al. 2012). The consequent loss of desmosome-mediated adhesion can be restored in part by HDAC inhibitors (Shim et al. 2004; Simpson et al. 2010). Furthering our understanding of the transcriptional programs that regulate desmosomal pro-
Table 1. Transcriptional regulators of desmosomal components, representative upstream signaling pathways regulating those transcription factors, and biological processes impacted

<table>
<thead>
<tr>
<th>Component</th>
<th>Transcription factor</th>
<th>Upstream regulator</th>
<th>Biological process reported or potentially implicated from other references</th>
<th>Method</th>
<th>References</th>
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<td>Dsg1</td>
<td>AP-1</td>
<td>PKC, MAPK</td>
<td>Proliferation, differentiation, development, tumorigenesis</td>
<td>Putative</td>
<td>Adams et al. 1998</td>
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<td>Putative</td>
<td>Adams et al. 1998</td>
</tr>
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<td>0ct-2</td>
<td>MAPK</td>
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<td>Putative</td>
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<td>Adams et al. 1998</td>
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<td>IKK</td>
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protein expression will be an important prerequisite for pharmacologically intervening in disorders involving these molecules.

**ROLES FOR DESMOSOME MOLECULES IN MORPHOGENESIS AND HOMEOSTASIS OF STRATIFIED TISSUES**

Desmosomal protein expression patterning contributes not just to tissue integrity, but also to signaling that controls morphogenesis and homeostasis. Interfering with desmosomal cadherin expression patterns can upset the balance between proliferation and differentiation during embryogenesis and in the adult (Allen et al. 1996; Chidgey et al. 2001; Elias et al. 2001; Merritt et al. 2002; Kljuic et al. 2003; Hardman et al. 2005). Forced expression of basally concentrated Dsg3 in the suprabasal layers of mouse epidermis increases the Dsg3:Dsg1 ratio and distribution to resemble that of oral epithelium (Elias et al. 2001). These mice show alterations in the stratum corneum and die shortly after birth because of excessive transepidermal water loss. Dsg2, the most broadly expressed Dsg, is required for embryonic stem cell proliferation.

<table>
<thead>
<tr>
<th>Component</th>
<th>Transcription factor</th>
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<td></td>
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</table>

The method by which the transcription factor was determined to interact with the desmosomal component promoter is listed as either putative (the cloned promoter contained a binding site for the transcription factor, but direct association between them has not been shown), confirmed by electrophoretic mobility shift assay (EMSA) or reporter assay (such as luciferase, referred to as Rep), or confirmed by chromatin immunoprecipitation (ChIP). Dsg2 was excluded from the table as there is currently no published information for its transcriptional regulation.

AP-1/2, activator protein 1/2; Oct, octamer binding; SP1, specificity protein 1; NF-κB, nuclear factor κ-light-chain-enhancer of activated B cells; TCF/LEF, high mobility group transcription factors; C/EBP, CCAAT-enhancer-binding protein; E2A, E box binding protein, Klf, Kruppel-like factor; RE, responsive element; SMAD, bone morphogenetic protein (BMP) pathway; Hox, homeobox transcription factor; Fox, forkhead box; Pit, pituitary-specific positive transcription factor; Cdx, homeobox transcription factor; NFY, CCAAT binding nuclear factor; pea, Ets family member; MyoD, myogenic regulatory factor; Nkx, homeobox domain transcription factor; Brn, Pit-Oct-Unc family member isolated from brain; Mal/MRTF, myocardin related transcription factor; SRF, serum response factor; Zeb, zinc finger E-box-binding homeobox.

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Further, its misexpression in upper epidermal layers results in hyperplasia by engaging growth factor signaling cascades that promote proliferation and survival including PI3K/AKT, MEK-MAPK, STAT3, and NF-κB (Brennan et al. 2007; Brennan and Mahoney 2009). In contrast, Dsg3 knockdown reduces cell proliferation in vitro (Mannan et al. 2011) and Dsg3 knockout mice do not show enhanced epidermal carcinogenesis compared with controls (Baron et al. 2012). Dsg1, which first emerges as cells stratify, is important for promoting differentiation through suppression of epidermal growth factor receptor (EGFR) and Erk-1/2 signaling (Getsios et al. 2009). The adhesive ectodomain of Dsg1 is dispensable for this function, which instead requires interaction with a newly identified binding partner Erbin (ERBB2IP) (Harmon et al. 2013). Erbin blocks Erk signaling by disrupting Ras–Raf complexes mediated by a scaffolding protein called SHOC2. Misexpression or interference with other desmosomal cadherins has similarly been reported to affect epidermal or hair follicle differentiation (Chidgey et al. 2001; Kljuic et al. 2003). These data support the idea that basal and suprabasal desmosomal cadherins play a “yin–yang” role to control the proper balance of proliferation and differentiation in tissue.

Desmosome molecules may control tissue homeostasis in part through armadillo protein-dependent signaling. Dscs1-3, Pg, Pkp2, and Dp suppress β-catenin, which is pro-proliferative, through altering β-catenin subcellular localization, competing for β-catenin DNA binding sites to alter its transcriptional function, and regulating β-catenin expression and stability (Chen et al. 2002; Hardman et al. 2005; Thoma son et al. 2010; Kolegraff et al. 2011; Aktary and Pasdar 2012; Yang et al. 2012). Pg has also been shown to reduce the proliferative capacity in both normal epidermis and cancer cells, and can act directly on transcriptional targets or indirectly by competing for β-catenin binding factors (Parker et al. 1998; Charpentier et al. 2000; Aktary and Pasdar 2012).

Cadherin-associated proteins also regulate growth factor effector signaling. For instance, Dp either supports (Gallicano et al. 1998) or inhibits proliferation depending on cell type, the latter through suppression of Erk and Akt (Wan et al. 2007). In turn, growth factor signaling can convert desmosomal components from adhesive to pro-proliferative functions as in the case of insulin signaling via Akt2 causing Pkp1 to promote proliferation and migration (Wolf et al. 2013). Collectively, these observations suggest that the core building blocks of desmosomes are tailored to support specific functions within complex tissues and are important for controlling epidermal homeostasis.

**DESMOSOMES AND THE EPIDERMAL BARRIER**

To help maintain the skin’s barrier against the environment, desmosomes become modified into structures called corneodesmosomes in the outermost epidermal layers. Differentiation-specific components are incorporated into corneodesmosomes including Dsg1, Dsc1, envoplakin, periplakin, and corneodesmosin (CDSN). CDSN is thought to support suprabasal adhesion through a glycine-rich domain within its amino terminus. The cornified envelope forms along the plasma membrane between desmosomes through transglutaminase-mediated cross-linking of involucrin to itself and to Dp, periplakin, and envoplakin (Ruhberg et al. 1997; Steinert and Marekov 1999). A differentiation-specific periplakin binding protein called kazrin assists in promoting differentiation and formation of the cornified envelope, acting to scaffold multiple cytoskeletal elements (Groot et al. 2004) and to regulate cell shape through Rho GTPases (Sevilla et al. 2008; Nachat et al. 2009). Thus, just as the early stages of epidermal differentiation require proper expression and distribution of desmosomal cadherins, so do later differentiation states require specialized desmosome functions to ensure proper barrier formation.

Desmosomes are subject to regulation by environmental interactions, yet at the same time participate in epidermal responses to stressors like humidity and heat. Dry conditions increase the number of corneodesmosomes and Dsg1 content, associated with decreased desqua-
Desmosomes are affected by exposure to carcinogens including tobacco smoke, air pollution, and UV light (White and Gohari 1984; Tachikawa et al. 1986). UV-induced sunburn cells (defined by pyknotic nuclei and eosinophilic cytoplasm) stain negatively for Dsgs and Dps (Bayerl et al. 1995) and reduced desmosome molecule transcripts are frequently observed in UV-exposed keratinocytes (Li et al. 2001; Murakami et al. 2001; Sesto et al. 2002; Rundhaug et al. 2005). UVC (below 290 nm wavelength) results in caspase-dependent cleavage of Dsg1 and redistribution of Dsg1 from cell borders into the cytoplasm (Dusek et al. 2006). In line with these findings, Dsg1 and Dsc1 are reduced by UVB (290- to 320-nm wavelengths) exposure in keratinocytes beginning to differentiate. Importantly, ectopic Dsg1 expression counteracts UVB-induced loss of differentiation markers (Johnson et al. 2014) indicating that desmosomal components contribute directly to epidermal responses to carcinogenic exposure.

Desmosome molecules are also involved in apoptosis associated with UV exposure and other environmental stresses (Dusek et al. 2006, 2007; Nava et al. 2007; Baron et al. 2012). Whereas loss of Dsg1 protects keratinocytes against UVC-mediated apoptosis, Dsg3 knockout mice show no changes in apoptosis following chronic UVB exposure (Dusek et al. 2006; Baron et al. 2012). Pg has been reported to be both pro- and antiapoptotic (Aktary and Pasdar 2012). For instance, loss of the GTPase Rnd3 protects keratinocytes from cisplatin-induced apoptosis; sensitivity to cisplatin is restored when Pg, but not Dp, is knocked down in a Rnd3-deficient background (Ryan et al. 2012). The mechanisms linking Pg to cell survival are not clear, although the authors speculate it may be through regulation of cell survival effectors such as Bcl-2. Another study indicates that keratinocytes derived from Pg null mice are protected from apoptosis, with null cells showing delayed mitochondrial cytochrome c release and activation of caspase-3 as well as increased Bcl-XL expression (Dusek et al. 2007). The role of desmosome molecules in cell survival or death may thus be stimulus and/or context dependent. Together these results suggest that whereas desmosomes are frequently targeted by environmental factors, desmosome molecules also aid epidermal recovery following stress.
Attardi 2011) suggesting that desmosomal components suppress both early and late stages of carcinogenesis. Expression of desmosomal cadherins in the proper epidermal layer is an important factor in suppressing carcinogenesis. Supporting this idea, misexpression of Dsg2 in the upper epithelial layers in transgenic mice leads to an increase in precancerous papillomas and susceptibility to chemically induced carcinogenesis (Brennan et al. 2007; Brennan and Mahoney 2009). Multiple signaling pathways are increased by misexpression of Dsg2 including EGFR and NF-κB, PI3K/AKT, MEK/MAPK, and STAT3, suggesting that regulation of signaling by desmosomal components is important for prevention of tumorigenesis. Whereas misexpression of normally basal Dsg2 promotes EGFR and other growth-related pathways, loss of suprabasal Dsg1 results in a failure to down-regulate EGFR/MAPK signaling required for normal differentiation. Through its association with the scaffolding protein Erbin, Dsg1-dependent inhibition of Ras-Raf signaling could be important for cancer prevention because aberrant Ras signaling is oncogenic. In line with this, Dsg1’s loss during head and neck cancer progression has been reported as a better indicator of poor prognosis than loss of E-cadherin (Wong et al. 2008). Because Perp and Dsc3 are transcriptionally regulated by p53 (Oshiro et al. 2003; Reczek et al. 2003), p53 mutation during carcinogenesis could lead to defective desmosomes, reduced intercellular adhesion, and altered desmosome component-mediated cell signaling. Collectively, these data suggest that desmosomes suppress cancer-promoting signaling pathways that drive proliferation and metastasis in multiple epithelia.

DESMOSOMES IN EPIDERMAL AUTOIMMUNE DISORDERS AND UNDER ATTACK BY TOXINS

The autoimmune skin disorders pemphigus and paraneoplastic pemphigus are associated with the presence of circulating autoantibodies attacking desmosomal components including Dsg1, Dsg3, Dsc3, and possibly Pkp3, bullous pemphigoid antigen 1, envoplakin, periplakin, and Perp (Koulu et al. 1984; Amagai et al. 1991; Nguyen et al. 2009; Mao et al. 2010; Yong and Tey 2012; Kalantari-Dehaghi et al. 2013) and reviewed recently by several groups (Amagai and Stanley 2012; Grando 2012; Cirillo and Al-Jandan 2013). Although a potential role for antibodies directed against cytoplasmic components in disease pathogenesis has been suggested, the majority of data point to Dsg3 and Dsg1 as the primary targets in pemphigus vulgaris and folliculosis (see Fig. 4). Steric hindrance caused by antibody binding has been suggested to interfere with desmosomal cadherin ectodomain interaction to cause skin blistering in pemphigus; however, autoantibody binding also promotes Dsg internalization and activates signaling pathways, most notably p38/MAPK. Dsg3 loss and/or autoantibody-dependent increases in p38/MAPK signaling decrease the activity of the small GTPase RhoA, thus destabilizing victronectin-dependent or fibronectin-dependent src signaling (Todorovic et al. 2010; Franzen et al. 2012) and Dp by inhibiting the Wnt/β-catenin signaling pathway (Yang et al. 2012).

Finally, Perp, a p53/p63 regulated protein that promotes desmosome assembly and strength, promotes UVB-induced apoptosis and suppresses UV-induced tumorigenesis in mice (Beaudry et al. 2010). Because Perp and Dsc3 are transcriptionally regulated by p53 (Oshiro et al. 2003; Reczek et al. 2003), p53 mutation during carcinogenesis could lead to defective desmosomes, reduced intercellular adhesion, and altered desmosome component-mediated cell signaling. Collectively, these data suggest that desmosomes suppress cancer-promoting signaling pathways that drive proliferation and metastasis in multiple epithelia.
the actin cytoskeleton (Spindler and Waschke 2011). Accordingly, direct RhoA inhibition leads to pemphigus skin blistering (Waschke et al. 2006). In addition to its negative effects on desmosome function, Dsg3 internalization also promotes loss of E-cadherin through Src, possibly thereby having a more general effect on cell–cell adhesion (Tsang et al. 2010, 2012b). However, others report that siRNA-mediated silencing of Dsg1 and/or Dsg3 does not significantly affect the observed IgG-dependent increase in Src and EGFR signaling, suggesting that other targets may be involved in activating these tyrosine kinases (Grando 2012).

Dsg1 is a target for Staphylococcus exfoliative toxin in staphylococcal scalded skin syndrome (SSSS) (Amagai and Stanley 2012; Kowalczyk and Green 2013). Pg and Dsg2 expression reduces the blistering associated with attack by these toxins (Brennan et al. 2010; Simpson et al. 2010). Use of therapeutic agents that increase expression of desmosomal cadherins and Pg such as EGFR inhibitors, histone deacetylase inhibitors, or tyrosine phosphatase inhibitors like sodium pervanadate (Lorch et al. 2004; Garrod et al. 2008; Simpson et al. 2010; Aktery and Pasdar 2012) may lessen the severity of blistering in pemphigus and Staphylococcal infections.

The cellular responses to pemphigus antibodies and Dsg-specific toxins have facilitated a better understanding of fundamental signaling/assembly circuits that are likely to make important contributions to cell homeostasis. However, much is yet to be done to determine the relative contribution of signaling-dependent and -independent mechanisms to disease pathogenesis in vivo (Mao et al. 2011, 2013; Saito et al. 2012).

ROLE OF DESMOSOMES IN PATHOGENESIS OF INHERITED SKIN AND HEART DISEASE

Mutation of desmosomal components in humans leads to skin and heart diseases including skin fragility-ectodermal dysplasia syndrome, lethal congenital epidermolysis bullosa, striate palmoplantar keratoderma (SPPK) and other keratodermas, hypotrichosis, wooly hair, arrhythmogenic cardiomyopathy (ARVC), and dilated cardiomyopathy (Kowalczyk and Green 2013). Several of these diseases are lethal in humans and embryos from a number of animal models of desmosome diseases die before birth or shortly thereafter because of skin and heart defects (Thomason et al. 2010; Kowalczyk and Green 2013). Only Pkp3 and Dsc1 have so far not been associated with mutations leading to human disease. However, Dsc1 and Dsg1 in corneodesmosomes are targeted for degradation by hyperactive proteases and kallikrein peptidases when the protease inhibitor LEKT1 (lympho-epithelial Kazal-type related inhibitor) is mutated in Netherton syndrome. Skin allergy, inflammation, scaling, and hypotrichosis are the result (Descargues et al. 2006; Hovnanian 2013).

Phenotypes resulting from mutations in desmosomal proteins may arise not only from defective adhesion, but also from alterations in cell signaling cascades. In normal skin, the cytoplasmic tail of Dsg1 binds Erbin-Shoc2 complexes to keep Shoc2 away from Ras (Fig. 3). However, in tissue biopsies taken from SPPK patients with Dsg1 haploinsufficiency, increased Ras-SHOC2 and decreased Erbin-SHOC2 co-localization occurs, offering a possible explanation for the observed impairment of differentiation and epidermal hyperplasia (Fig. 4) (Harmon et al. 2013). Dsg1-mediated regulation of Erk/MAPK signaling may also play a role in ectodermal dysplasias because a transcriptional regulator of Dsg1, p63, is frequently mutated or misregulated in ectodermal dysplasias (Ferone et al. 2013).

Mutations in Dsg2, Dsc2, Pkp2, Pg, and Dp have all been implicated in ARVC, which presents with or without accompanying cutaneous symptoms (Fig. 4). It is not yet clear whether ARVC results from the response to mechanical stress imposed on weakened cell–cell junctions, or whether more direct desmosome-dependent signaling contributes to cardiac myocyte apoptosis, fibrofatty deposition, and lethal arrhythmias. The existing data would support the idea that both can occur. Pg loss is a diagnostic feature of ARVC (Asimaki et al. 2009) and its trans-
location to the nucleus interferes with β-catenin signaling and promotes adipogenic/fibrotic transcriptional pathways in a Dp knockout mouse model (García-Gras et al. 2006). It is speculated that Pg nuclear functions may also account for defects in hair follicles, which leads to the wooly hair seen in some patients (MacRae et al. 2006). A Pg truncation mutation leads to skin abnormalities but still allows normal heart development (Cabral et al. 2010). Further, only keratoderma and not heart defects are observed in a conditional Pg knockout mouse model where Pg nuclear localization cannot occur (Li et al. 2012). In spite of the fact that alterations in Wnt/β-catenin signaling are not observed in this model, alterations in cell proliferation,
apoptosis, differentiation, and the epidermal immune system occur. It is possible that other signaling pathways previously associated with loss of Pg (e.g., EGFR) (Pan et al. 2007) or Src/Rho signaling (Todorovic et al. 2010; Franzen et al. 2012) contribute to these changes. It is notable that another armadillo protein, Pkp2, is the most commonly mutated target in ARVC (Kowalczyk and Green 2013). Alterations in RhoA and PKC-α signaling occur following Pkp2 knockdown in keratinocytes (Godsel et al. 2010), raising the possibility that similar signaling deficits may contribute to ARVC pathogenesis.

REGULATION OF DESMOSOME DYNAMICS, REMODELING, AND TURNOVER

Although cell adhesion is imperative for maintaining tissue integrity, adhesive contacts cannot remain static during processes like epidermal development, differentiation, wound healing, and apoptosis. Desmosomes are degraded or internalized in response to EGFR signal-
ing, ADAM sheddases, matrix metalloproteases (MMPs), caspases, and kallikrein peptidases (Bektaş et al. 2010; Green et al. 2010; Kowalczyk and Green 2013). The ubiquitin proteosome may reduce cell adhesion by keeping Dp from cell contacts. Proteosome inhibition stabilizes Dp at keratinocyte borders and strengthens cell–cell contacts (Löffek et al. 2012). However, it remains to be seen whether the proteosome regulates desmosomal adhesion under physiological conditions.

Desmosomes in adult tissues show a unique property termed “hyperadhesion,” characterized by enhanced stability and adhesive strength even in the context of extracellular calcium depletion. Desmosomes become hyperadhesive during mouse embryonic development before embryo implantation; however, migration of the trophectoderm requires loss of hyperadhesion (Kimura et al. 2012) as does the remodeling that occurs during wound healing (Thomason et al. 2010). PKC-α is the predominant regulator of the switch between hyperadhesion and calcium dependence (Wallis et al. 2000). Desmosomes remain hyperadhesive in PKC-α null animals and re-epithelialization after wounding is delayed. In chronic human wounds PKC-α remains cytoplasmic and desmosomes do not become hyperadhesive (Thomason et al. 2012).

In addition to its role in converting mature desmosomes to a more dynamic form compatible with epithelial remodeling, PKC-α regulates the dynamics of desmosome assembly (Fig. 3). PKC inhibition decreases desmosome assembly at the leading edge in scratch wound assays (Roberts et al. 2011), and Dp translocation from the cytoplasm to the plasma membrane depends on PKC (Sheu et al. 1989; Bass-Zubek et al. 2008). Dp’s responsiveness to PKC is due in part to its association with the armadillo protein Pkp2, which serves as a scaffold for PKC-α. Data support a model whereby loss of Pkp2 results in failure of PKC to phosphorylate Dp and failure of Dp to incorporate into desmosomes owing to tight association with intermediate filaments (Bass-Zubek et al. 2008). A mutation in the Dp carboxyl terminus at S2849 prevents its phosphorylation and delays assembly into junctions. However, once incorporated, this phosphodeficient Dp mediates strong desmosome adhesion (Hobbs et al. 2011).

PKC-α is a calcium-dependent kinase and is thus sensitive to changes in intracellular calcium homeostasis. Supporting the importance of this relationship for desmosome assembly, the endoplasmic reticulum calcium pump Serca2, which is mutated in a skin disorder known as Darier’s disease, regulates intercellular adhesive strength through PKC-α (Hobbs et al. 2011). Serca2 deficient cells show reduced PKC-α and Dp movement to the membrane, but constitutively active PKC-α rescues this defect.

Desmosome–cytoskeleton interactions are important for regulating desmosome assembly state and turnover and, in turn, desmosomal components control cytoskeletal distribution and function. Desmosomes are well known for their role in anchoring keratin intermediate filaments to sites of cell adhesion, but they are also subject to regulation by keratins, which keep PKC-α-mediated Dp phosphorylation in check to stabilize desmosomes at the plasma membrane (Kroger et al. 2013). The actin cytoskeleton and associated contractile signaling also engages in a reciprocal functional relationship with desmosomes. Actin regulates desmosome dynamics during desmosomal plaque assembly and wound healing (Godsel et al. 2010; Roberts et al. 2011). In turn, desmosome molecules regulate contractile signaling through Pkp2, which recruits active RhoA at cell–cell interfaces to drive actin reorganization and actin-dependent desmosome assembly (Godsel et al. 2010). Dsg3 also dictates cytoskeletal organization and cell migration through regulation of the Rho GTPases Rac-1 and Cdc42 (Tsang et al. 2010, 2012a). Finally, desmosomes help remodel the microtubule cytoskeleton during epidermal stratification. Dp, together with the centrosomal protein ninein, facilitates redistribution of radially oriented microtubules to the cell cortex. Cortical microtubules in the suprabasal epidermis recruit myosin II to aid formation of the tight junction barrier (Lechler and Fuchs 2007; Sumigray and Lechler 2012). Microtubule-associated proteins such as Lis1, Nde1, and CLIP70 regulate desmosome stability and their loss leads to decreased expression of desmosomal compo-
nents (Sumigray et al. 2011; Sumigray and Lechler 2011). Thus, desmosomes engage the cytoskeleton in a more general way than previously recognized, contributing to cytoarchitectural remodeling during differentiation.

**PHARMACOLOGICAL APPROACHES TO REGULATING DESMOSOMAL EXPRESSION AND STABILITY**

Rescuing adhesive defects and improving outcomes for desmosomal diseases would be advantageous to human health. To that end, several pharmacologic strategies have been explored to regulate desmosome stability in epidermal cells. Treatment of organotypic epidermal models with retinoic acid results in normalization of desmosome appearance after a low dose of UVB exposure (Chouinard and Rouabhia 1999) but retinoic acid is more frequently reported to down-regulate expression of desmosomal components in human skin (Humphries et al. 1998; Wanner et al. 1999; Kim et al. 2011). A serine palmitoyltransferase inhibitor (ISP-I) increases the number of corneodesmosomes leading to a thicker stratum corneum and less transepidermal water loss (Mizukoshi et al. 2011).

Glucocorticoids are used together with immunosuppressive therapies to treat pemphigus (Frydman and Fairley 2011). Dsg3 and Dsc2 contain retinoic acid and glucocorticoid responsive elements in their promoters (Silos et al. 1996; Marsden et al. 1997), so use of these agents may alter desmosomal component transcription. In support of this, mice lacking the glucocorticoid receptor show reduced numbers of desmosomes (Bayo et al. 2008). A novel treatment option for pemphigus may also be emerging, as cross-linking of Dsg3 using a topically applied peptide on mice reduces skin blistering. The peptide stabilizes Dsg3 by blocking autoantibody-mediated interference of Dsg3 transinteraction, reduces p38/MAPK activation, and allows stabilization of keratins (Spindler et al. 2013). It is unknown whether a similar peptide-mediated cross-linking of Dsg1 would reduce blistering in pemphigus foliaceus. Other drugs that increase desmosomal protein expression and strengthen desmosomes may lead to reduced symptoms arising from desmosomal diseases, reduced epidermal damage after environmental exposure, and prevention of carcinogenesis. These include EGFR inhibitors, histone deacetylase inhibitors, cholinergic agonists, or tyrosine phosphatase inhibitors like sodium pervanadate (Nguyen et al. 2003; Lorch et al. 2004; Garrod et al. 2008; Simpson et al. 2010; Aktary and Pasdar 2012; Johnson et al. 2014).

**EMERGING AREAS IN DESMOSOME BIOLOGY: OUTLOOK FOR THE FUTURE**

Over the past decade we have come to appreciate desmosomes as both critical regulators of intercellular adhesive strength and modulators of intracellular signaling cascades (Green and Gaudry 2000; Thomason et al. 2010; Kowalczyk and Green 2013). At the same time, cell junctions have emerged as transducers of mechanical signals that affect stem cell maintenance, tissue morphogenesis, and differentiation. Whereas the mechanical importance of the desmosome-intermediate filament network is well accepted, the field of mechanotransduction has mainly focused on the role of actin-associated contacts. The adherens junction protein α-catenin undergoes conformational change in response to mechanical cues to affect recruitment of proteins such as vinculin and EPLIN. These changes affect junctional remodeling in response to shear in endothelial cells and establishment of barrier in simple epithelial cells (Twiss and de Rooij 2013). Desmosomal cadherins and plaque proteins may play similar roles in response to mechanical stresses experienced by skin and heart. Development of sensors that track mechanosensitive conformation changes in desmosome molecules will begin to shed light on the potential activity of desmosomes in mechanotransduction.

The critical role desmosomes play in establishing the epidermal barrier raises the possibility that their loss of function may activate pathways contributing to inflammation and allergy. Indeed, a new syndrome caused by homozygous mutations in Dsg1 was recently described with symptoms including severe dermatitis, multiple allergies and metabolic wasting (SAM syn-
drome). Dsg1 deficiency associated with increases in allergy-related cytokines strongly suggesting that allergy can result from desmosomal disruption (Samuelov et al. 2013). Further, mice deficient in envoplakin, periplakin, and the cell envelope protein involucrin show a reduction in the protease inhibitor serpin1b, delayed degradation of desmoglein 1 and corneodesmosin, and alterations in the T-cell population resembling atopic dermatitis (Sevilla et al. 2007). A variant of the protease inhibitor LEKT1 increases expression of the proallergic cytokine thymic stromal lymphopoietin (TSLP), a predisposing factor to atopic dermatitis (Descargues et al. 2006; Hovnanian 2013). Finally, there exists an inflammatory subtype of generalized peeling skin syndrome (PSS) in which patients show chronic exfoliation of the stratum corneum attributable to mutations in corneodesmosin (Oji et al. 2010). Corneodesmosin mutations also confer susceptibility to psoriasis indicating that intact desmosome-mediated epidermal barrier function is important for protection against the disease (Chang et al. 2003, 2006). The extent to which desmosomal disruption and changes in downstream signaling pathways drive atopy, inflammation, or psoriasis is unknown, but these emerging associations provide compelling basis for future work to directly link loss of desmosome function to these systemic and collectively common disorders.

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Desmosomes in Epidermal Health and Disease


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Desmosomes: Regulators of Cellular Signaling and Adhesion in Epidermal Health and Disease

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