Plakins, a Versatile Family of Cytolinkers: Roles in Skin Integrity and in Human Diseases

Jamal-Eddine Bouameur[1,2], Bertrand Favre[1] and Luca Borradori[1]

The plakin family consists of giant proteins involved in the cross-linking and organization of the cytoskeleton and adhesion complexes. They further modulate several fundamental biological processes, such as cell adhesion, migration, and polarization or signaling pathways. Inherited and acquired defects of plakins in humans and in animal models potentially lead to dramatic manifestations in the skin, striated muscles, and/or nervous system. These observations unequivocally demonstrate the key role of plakins in the maintenance of tissue integrity. Here we review the characteristics of the mammalian plakin members BPAG1 (bullous pemphigoid antigen 1), desmoplakin, plectin, envoplakin, epiplakin, MACF1 (microtubule-actin cross-linking factor 1), and periplakin, highlighting their role in skin homeostasis and diseases.

Journal of Investigative Dermatology (2014) **134,** 885–894; doi:10.1038/jid.2013.498; published online 19 December 2013

INTRODUCTION

The plakins are a family of cytolinkers characterized by a multimodular structure that enables them to function as versatile cross-linkers of the cytoskeleton. They connect the microfilament, microtubule (MT), and intermediate filament (IF) systems with each other and with junctional complexes in organelle and plasma membranes, thereby contributing to cell shape and polarity. They also act as scaffolds and adaptors for signaling proteins that modulate cytoskeletal dynamics or cell migration, differentiation, and stress responses. First identified as important structural elements in the epidermis, they were subsequently found to exert other complex functions in a variety of tissues, including striated muscles and the central nervous system. Their analogs fulfill equivalent functions in zebrafish and in invertebrate organisms, such as *Caenorhabditis elegans* or *Drosophila melanogaster* (previously reviewed in (Roper *et al.*, 2002; Jefferson *et al.*, 2004; Sonnenberg and Liem, 2007; Boyer *et al.*, 2010; Suozzi *et al.*, 2012).

Mammalian plakins share a similar structural organization and comprise seven members: bullous pemphigoid antigen 1 (BPAG1), desmoplakin, envoplakin, epiplakin, microtubule-actin cross-linking factor 1 (MACF1), periplakin, and plectin (Figure 1) (Choi *et al.*, 2002; Jefferson *et al.*, 2007; Choi and Weis, 2011; Ortega *et al.*, 2011). The existence of developmentally regulated and tissue-specific splice variants of some plakins further increases the diversity and versatility of these proteins (Table 1; Figure 1; Leung *et al.*, 2001; Rezniczek *et al.*, 2003; Lin *et al.*, 2005; Jefferson *et al.*, 2006; Cabral *et al.*, 2010).

PLAKINS IN THE EPIDERMIS

Epithelial BPAG1 (BPAG1e, also called BP230) constitutes the epithelium-specific isoform of BPAG1 and is localized in basal keratinocytes in hemidesmosomes, junctional adhesion complexes that mediate dermo-epidermal cohesion (Sawamura *et al.*, 1991; Leung *et al.*, 2001); reviewed in (Borradori and Sonnenberg, 1999; Litjens *et al.*, 2006). Via its N-terminal domains, BPAG1e interacts with the hemidesmosomal transmembrane proteins α6β4 integrin and BP180 (also called BPAG2 or type XVII collagen; Hopkinson and Jones, 2000; Koster *et al.*, 2003). Its C-terminal tail specifically binds to the epidermis-specific IF network formed by the keratins 5 and 14 (K5, K14) and thereby connects the cytokeratin network of basal keratinocytes to the extracellular matrix (Figure 1; Guo *et al.*, 1995; Fontao *et al.*, 2003).

Plectin, similarly to BPAG1e, connects the K5/K14 network to hemidesmosomes (Gache *et al.*, 1996; Nikolic *et al.*, 1996). However, three plectin isoforms are expressed in the epidermis: plectins 1, 1a, and 1c. They exclusively differ from each other in their N extremities, which confer different tethering properties (Rezniczek *et al.*, 2003; Wilhelmsen *et al.*, 2005; Rezniczek *et al.*, 2007; reviewed in Wiche and Winter, 2011). Plectin 1a seems to be the major variant in hemidesmosomes (Walko *et al.*, 2011). However, plectin 1c is also able to localize either in or close to hemidesmosomes (Litjens *et al.*, 2003; Walko *et al.*, 2011). In contrast to BPAG1e, the IF-binding region of plectin is more versatile and binds to several types of IF proteins, such as epidermal keratins, simple epithelial keratins, the muscle-specific IF protein desmin, and IF proteins expressed in the central nervous system (Figure 1; Foisner *et al.*, 1988; Nikolic *et al.*, 1996; Reipert *et al.*, 1999; Favre *et al.*, 2011).

Desmoplakin is an obligate component of desmosomes, which are highly specialized complexes that ensure cell–cell adhesion and serve as anchorage sites for the keratin network.

[1]*Departments of Dermatology and Clinical Research, Inselspital, Bern University Hospital, and University of Bern, Bern, Switzerland and* [2]*Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland*

Correspondence: Bertrand Favre, Department of Dermatology, Inselspital, Bern University Hospital, Freiburgstrasse, Bern 3010, Switzerland.
E-mail: Bertrand.Favre@insel.ch

Received 10 July 2013; revised 16 October 2013; accepted 25 October 2013; published online 19 December 2013

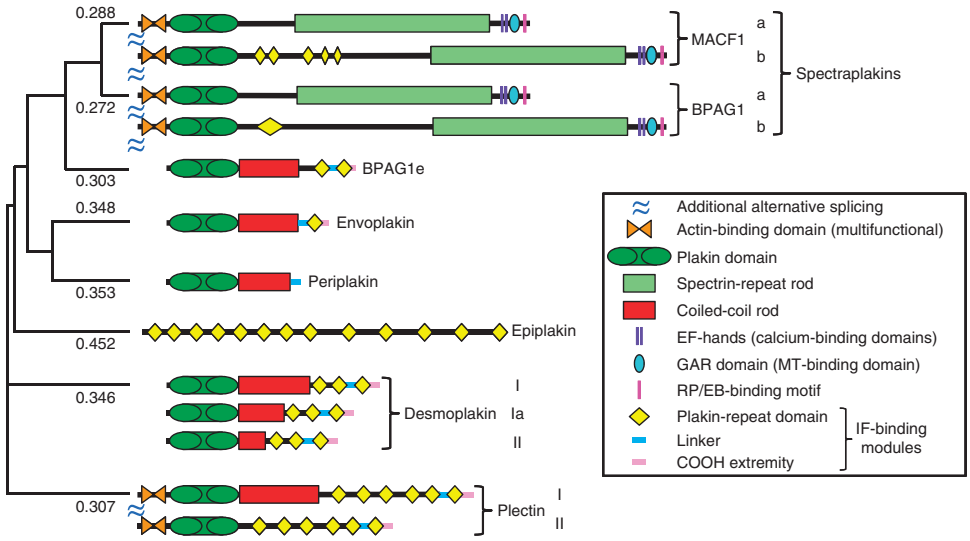

Figure 1. The mammalian plakin family. The members and structural organization of the plakin family are depicted. Plakins are arranged in a phylogenetic tree (with distances) based on their protein sequences. Plakins can be divided into two groups according to their structures and binding partners. The first group encompasses the epithelial isoform of bullous pemphigoid antigen 1 (BPAG1; BPAG1e), desmoplakin, envoplakin, periplakin, and plectin and bears a central coiled-coil rod (CC-ROD) domain, which mediates their homodimerization or oligomerization, and a variable number of plakin-repeat domains and connecting segments in their C tails that give plakins the ability to interact with intermediate filaments (IFs) with various affinities and specificities. The second group consists of the neuronal and muscular variants of BPAG1 (BPAG1a and BPAG1b, respectively) and all microtubule-actin cross-linking factor 1 (MACF1) isoforms. This group carries additional spectrin repeats forming a rod-like domain in their middle parts. They are also called spectraplakins. GAR, growth arrest specific 2-related; MT, microtubule.

Table 1. Spectraplakin family members, associated diseases, and distribution

			Human diseases		
Plakins	**Tissue distribution**	**Major localization and binding partners**	**Genetic**	**Autoimmune**	**Mouse models**
BPAG1a and BPAG1b	Broad (nervous system, striated muscles)	Microtubules, microfilaments	Lethal form of dysautonomia, psychomotor retardation	Not known	Sensory and motor neuron abnormalities, myopathy
BPAG1e	Epidermis and other stratified epithelia	Hemidesmosomes, intermediate filaments	EBS	Bullous pemphigoid, paraneoplastic pemphigus	EBS-like phenotype
Plectin	Broad (skin, muscles, nervous system, gastrointestinal tract)	Hemidesmosomes, muscle Z-disks, intermediate filaments, microfilaments, microtubules	EBS, pyloric atresia, myopathy (cerebral atrophy, ophthalmoplegia)	Paraneoplastic pemphigus, bullous pemphigoid	EBS-like phenotype, myopathy, pyloric atresia, CNS manifestations
Desmoplakin	Broad (stratified epithelia, heart)	Desmosomes, intercalated discs, intermediate filaments	Palmoplantar keratoderma, woolly hair, cardiomyopathy lethal acantholytic epidermolysis bullosa	Paraneoplastic pemphigus	Early lethality (extraembryonic tissue defects, cardiac and epidermal defects, intestinal abnormalities)
Envoplakin	Epidermis and other stratified epithelia	Cornified envelope, intermediate filaments	Not known	Paraneoplastic pemphigus	Abnormalities of the cornified cell envelope
Periplakin	Epidermis and other stratified epithelia	Cornified envelope, intermediate filaments	Not known	Paraneoplastic pemphigus	No obvious phenotype
Epiplakin	Epidermis and other stratified epithelia	Cornified envelope, intermediate filaments	Not known	Blistering diseases	Accelerated wound healing
MACF1	Broad	Microtubules, microfilaments	Not known	Not known	Developmental defects at gastrulation stage

Abbreviations: BPGA1, bullous pemphigoid antigen 1; CNS, central nervous system; EBS, epidermolysis bullosa simplex; MACF1, microtubule-actin cross-linking factor 1.

The desmosomes comprise desmogleins and desmocollins, transmembrane glycoproteins of the cadherin family, as well as plakoglobin and plakophilins, members of the armadillo protein family. By means of linear and lateral interactions, they link the IF cytoskeleton to the cell membrane via desmoplakin (Smith and Fuchs, 1998; reviewed in Nekrasova and Green, 2013). Desmosomes' stability is affected by the IF network. In fact, some K5 and K14 keratin mutations in humans lead to a reduction in the expression of desmosomal components (Liovic *et al.*, 2009; Wagner *et al.*, 2012), whereas mouse keratinocytes lacking keratins showed destabilized desmosomes and reduced intercellular adhesion (Kroger *et al.*, 2013). However, the exact mechanisms underlying these observations remain unclear (Hobbs *et al.*, 2011; Kroger *et al.*, 2013).

Periplakin and envoplakin are highly abundant in the granular cell layer of the epidermis and are subject to protein cross-linking mediated by transglutaminases (Ruhrberg *et al.*, 1996, 1997; Aho, 2004; reviewed in Kalinin *et al.*, 2002). These two proteins can form heterodimers and provide a scaffold onto which the cornified cell envelope can be formed (DiColandrea *et al.*, 2000). They are associated with the plasma membrane and desmosomes via the interaction of the N terminus of periplakin with kazrin (Groot *et al.*, 2004).

The spectraplakin MACF1, also named ACF7, is expressed in the epidermis and particularly in hair follicles (Karakesisoglou *et al.*, 2000). Despite the similar structural organization of MACF1a and MACF1b to BPAG1a and BPAG1b, their function and expression are different (Guo *et al.*, 1995; Leung *et al.*, 2001; Chen *et al.*, 2006).

PLAKIN-ASSOCIATED FUNCTIONS

Lessons from mouse models and genetic diseases

The key role of BPAG1e in the maintenance of epidermis integrity was first disclosed by gene-targeting experiments. Null-mutant mice for the BPAG1-encoding gene dystonin (DST) showed discrete signs of skin blistering as a result of impaired attachment of keratin filaments to hemidesmosomes. Unexpectedly, these mice also developed severe neurodegeneration with dystonia, ataxia, and myopathy (Guo *et al.*, 1995). This phenotype originates from the concomitant inactivation of the other isoforms of BPAG1: a and b (Leung *et al.*, 2001), which were found to be essential for the maintenance of the cytoarchitecture of neurons and skeletal muscles, respectively (Brown *et al.*, 1995; Yang *et al.*, 1996; Dalpe *et al.*, 1998, 1999; De Repentigny *et al.*, 2011). Evidence for an implication of BPAG1 in human inherited diseases was found only a decade later. Disruption of *DST* due to a 6;15 translocation, resulting in the loss of BPAG1a and BPAG1b, was first described in a child suffering from encephalopathy and severe motor and mental retardation (Giorda *et al.*, 2004). Subsequently, a *DST* mutation was found to cause a lethal form of dysautonomia with progressive limb contractures and psychomotor retardation (Edvardson *et al.*, 2012). Recently, the first cases of autosomal recessive epidermolysis bullosa simplex (EBS), due to a homozygous nonsense mutation in *DST* specifically affecting BPAG1e, were described, providing the unequivocal proof for the critical role of BPAG1e in the tethering of the epidermal K5/K14 keratin network to hemidesmosomes and in the maintenance of the integrity of the basal cell layer (Groves *et al.*, 2010; Liu *et al.*, 2012).

Mutations of the human plectin gene (*PLEC*) also result in EBS but not exclusively, as plectin is ubiquitously expressed in mammalian tissues. Muscular dystrophy, pyloric atresia, as well as central nervous system manifestations, including cerebral atrophy and myasthenic syndrome, have also been linked to *PLEC* mutations (Gache *et al.*, 1996; McLean *et al.*, 1996; Smith *et al.*, 1996; Banwell *et al.*, 1999; Schroder *et al.*, 2002; Charlesworth *et al.*, 2003; Pfendner and Uitto, 2005; McMillan *et al.*, 2007; Bolling *et al.*, 2010a; reviewed in Winter and Wiche, 2013). Loss of the full-length plectin isoforms often leads to EBS in association with late-onset muscular dystrophy. In contrast, when mutations affect both the full-length and rodless plectins (Table 1), the resulting phenotypes are more severe, with EBS and pyloric atresia causing early postnatal death (Charlesworth *et al.*, 2003; Natsuga *et al.*, 2010a, b; Charlesworth *et al.*, 2013). The observation that both BPAG1e and plectin defects lead to cytoskeletal disorganization and increased cell fragility in EBS clearly proves the importance of hemidesmosomes as keratin IF–anchoring sites important for skin resilience. In analogy to what is observed in humans with inherited plectin defects, inactivation of the plectin gene in mice leads to skin blistering and myopathy with necrotic muscle fibers, streaming of Z-discs, focal rupture of the sarcolemma, and accumulation of mitochondria (Andrä *et al.*, 1997; Konieczny *et al.*, 2008). Isoform-specific knockout mice have further disclosed other unexpected functions of plectin, such as for the motility of immune cells or for conduction velocity in motor nerves (Winter and Wiche, 2013). The conclusions, derived from knockout mouse models, that the various plectin variants exert important tissue-specific functions are further substantiated by some clinical observations. For example, a mutation affecting the muscle-specific plectin 1f isoform causes isolated limb-girdle muscular dystrophy (Gundesli *et al.*, 2010). Furthermore, a dominant missense mutation, which was found to lead to the selective proteolysis of the hemidesmosomal plectin 1a isoform in a mouse model, causes the so-called Ogna variant of EBS that only affects the skin (Koss-Harnes *et al.*, 2002; Walko *et al.*, 2011).

Mutations in the desmoplakin gene (*DSP*) have been linked to devastating inherited diseases that variably affect the skin, hair, nails, and teeth, as well as the heart (Table 1) (Carvajal-Huerta, 1998; Chalabreysse *et al.*, 2011; Boule *et al.*, 2012; reviewed in Lai Cheong *et al.*, 2005). Specifically, palmoplantar keratoderma, woolly hair, and cardiomyopathy have been described with both recessive and dominant mutations (Armstrong *et al.*, 1999; Norgett *et al.*, 2000). Severe phenotypes with early postnatal death and acantholytic epidermolysis bullosa have been observed in cases of complete loss of desmoplakin or with homozygous truncations of its C-terminal tail encompassing the IF-binding domain (Figure 1; Table 1; Jonkman *et al.*, 2005; Bolling *et al.*, 2010b). In the affected skin, the connection of the keratin network to desmosomes is variably lost. Similar deleterious

consequences may be observed in cases of genetic defects of other desmosomal components, as well as of keratins 1 and 10, an observation implying functional synergy of these molecules (reviewed in Lai Cheong *et al.*, 2005; Simpson *et al.*, 2011; Petrof *et al.*, 2012). In cardiomyocytes, desmoplakin defects critically impair the tethering of the desmin–IF network and its attachment to the intercalated disc junctions, resulting in sarcomeric disorganization and loss of tissue integrity (Kartenbeck *et al.*, 1983; Meng *et al.*, 1997; Lapouge *et al.*, 2006). These alterations contribute to the development of right-sided or left-sided dilated arrythmogenic cardiomyopathies and sudden death. Although desmoplakin-null mutant mice show early embryonic lethality before E6.5, with defects of the extra-embryonic tissue (Gallicano *et al.*, 1998), chimeric *morulae* expressing desmoplakin in extraembryonic tissues do not survive beyond E9.5. In the latter case, defects of the developing epidermis, neuroepithelium, and heart are observed with perturbation of desmosome assembly and loss of the IF–cell membrane attachment (Gallicano *et al.*, 2001). Epidermis-specific desmoplakin knockout mice die early after birth owing to intercellular epidermal separation and defective epidermal sheet formation. Desmosomes seem morphologically normal but completely lack IF attachments (Vasioukhin *et al.*, 2001). Together, these findings confirm the key role of desmoplakin for the assembly of functional desmosomes, the maintenance of cytoskeletal architecture, and stable intercellular adhesion.

Other plakins, such as envoplakin, periplakin, and epiplakin, appear to have less critical functions in the skin. Nevertheless, they regulate terminal differentiation or wound healing, as inferred from various knockout animal studies (Maatta *et al.*, 2001; Goto *et al.*, 2006; Spazierer *et al.*, 2006; Sevilla *et al.*, 2007).

PLAKINS IN AUTOIMMUNE DISEASES

BPAG1e was first identified as the target autoantigen in the most frequent autoimmune subepidermal blistering disease of the skin—bullous pemphigoid (Stanley *et al.*, 1988; Sawamura *et al.*, 1991). Affected patients are typically elderly and have an increased risk to concomitantly suffer from neurological diseases, such as dementia, Parkinson disease, epilepsy, and multiple sclerosis (reviewed in Di Zenzo *et al.*, 2012). These observations raise the intriguing question of the involvement of the neuronal variants of BPAG1a as additional autoantigens and their contribution to these neurological manifestations. Despite the intracellular location of BPAG1, some evidence suggests that autoantibodies to BPAG1e participate in tissue damage (Hall *et al.*, 1993). For instance, in a passive transfer animal model, injection of antibodies to BPAG1e was reported to induce subepidermal blistering (Kiss *et al.*, 2005).

Autoantibodies to plectin, epiplakin, and desmoplakin have also been detected in few cases of autoimmune blistering diseases and of severe drug eruptions, but their effects remain to be established (Table 1; Fujiwara *et al.*, 1996; Ohnishi *et al.*, 2000; Fujiwara *et al.*, 2001; Laffitte *et al.*, 2005).

Finally, there is a rare but devastating autoimmune multiorgan syndrome, paraneoplastic pemphigus, in which an autoantibody response to several plakins is a striking finding. This disease is characterized by severe mucocutaneous lesions in association with underlying malignancy. Patients' autoantibodies almost systematically recognize periplakin and envoplakin and often also desmoplakin, plectin, and BPAG1e (Table 1) (Anhalt *et al.*, 1990; Borradori *et al.*, 1998; Mahoney *et al.*, 1998; Nguyen *et al.*, 2001). Autoantibodies react with unique and shared epitopes within their C tails, including the common linker domain involved in IF binding (Figure 1; Table 1; Mahoney *et al.*, 1998). The development of an autoimmune response to plakins is thought to occur secondarily after initial tissue damage. Although autoantibodies to desmogleins and the broad-spectrum protease inhibitor A2ML1 may be involved as initial triggers for damage, the mechanisms responsible for the distinct reactivity with several plakins remain unclear (Schepens *et al.*, 2010; Saleh *et al.*, 2012; Numata *et al.*, 2013).

PLAKINS REGULATE CYTOSKELETON SHAPE AND DYNAMICS

Plakins critically orchestrate the organization of various cytoskeletal networks and their linkage to the plasma and nuclear membranes, as well as to various organelles (Table 1; Figure 2; Koster *et al.*, 2003; Lin *et al.*, 2005; Wilhelmsen *et al.*, 2005; Wu *et al.*, 2008; Ryan *et al.*, 2012b). Besides cross-linking MTs and microfilaments, spectraplakins (see Figures 1 and 2 and Table 1) are involved in MT dynamics and stabilization (Yang *et al.*, 1999; Karakesisoglou *et al.*, 2000; Kodama *et al.*, 2003; Slep *et al.*, 2005; Drabek *et al.*, 2006; Gupta *et al.*, 2010; Ryan *et al.*, 2012a), as well as in the vesicular transport (Figure 2; Guo *et al.*, 1995; Yang *et al.*, 1999; Liu *et al.*, 2003; Kakinuma *et al.*, 2004; Liu *et al.*, 2007; Wu *et al.*, 2008; Burgo *et al.*, 2012).

Specifically, plectin binds to microfilaments and modulates their rearrangement in response to various stimuli, leading to the activation of Rho, Rac, and Cdc42 pathways (Andrä *et al.*, 1998; Rezniczek *et al.*, 2003). Plectin also regulates in a complex manner the vimentin network assembly and disassembly (Spurny *et al.*, 2008). Similar effects are observed with different IF types, indicating a regulatory role of plectin in precursor formation and dynamics of various IF networks, which may also apply to desmoplakin and BPAG1e (Osmanagic-Myers *et al.*, 2006; Tian *et al.*, 2006; Konieczny *et al.*, 2008; Burgstaller *et al.*, 2010). By attaching the IFs to organelles and plasma membrane sites, plectin contributes to the positioning and stabilization of the nucleus, centrosomes, and mitochondria (Rezniczek *et al.*, 2003; Wilhelmsen *et al.*, 2005; Winter *et al.*, 2008; Niwa *et al.*, 2009; reviewed in Wiche and Winter, 2011). The plectin 1c isoform cross-links MTs to IFs (Svitkina *et al.*, 1996; Valencia *et al.*, 2013). Binding of plectin to MTs seems to occur directly via its actin-binding domain (Valencia *et al.*, 2013). Plectin-knockout keratinocytes exhibit more stable MTs and defects of the mitotic spindle during cell division, indicating that plectin 1c acts as an MT destabilizer via its interaction with microtubule-associated proteins (Valencia *et al.*, 2013).

Although it does not directly interact with MTs and microfilaments, desmoplakin affects their tethering and organization. In fact, desmoplakin loss leads to MT aggregation

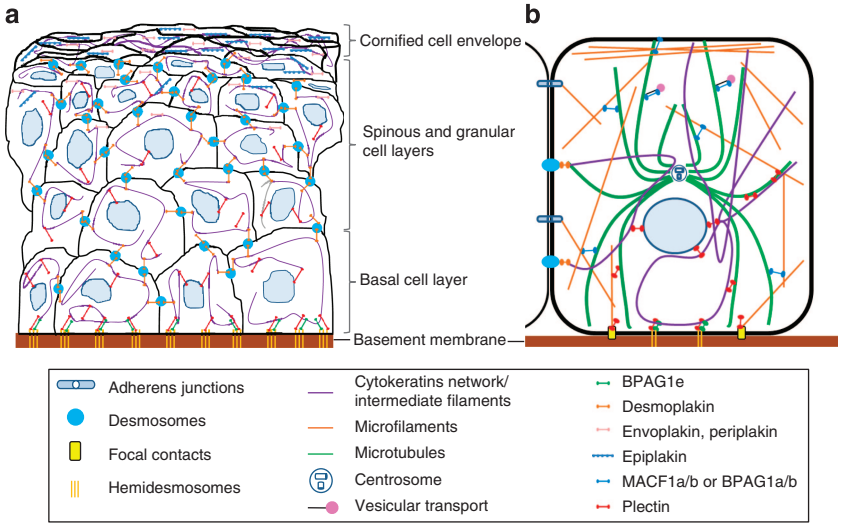

Figure 2. Schematic representation of spectraplakin localization. (**a**) In the epidermis, (**b**) in a virtual cell. Plectin and bullous pemphigoid antigen 1e (BPAG1e) anchor intermediate filaments (IFs) to hemidesmosomes, junctional adhesion complexes promoting strong cell-substrate cohesion in squamous epithelia. Desmoplakin attaches the IF network to desmosomes, cell–cell adhesion complexes. Some plectin variants are also present in focal contacts and at the nucleus surface, recruiting IFs to the perinuclear region. Plectin cross-links microfilament or microtubules (MTs) with IFs. In analogy to desmoplakin, envoplakin, periplakin, and epiplakin attach keratins to the cell membrane in the epidermis. Spectraplakins attach microfilaments to MTs. They are also involved in vesicular transport, such as in neuronal cells. MACF1, microtubule-actin cross-linking factor 1.

(Lechler and Fuchs, 2007; Sumigray *et al.*, 2011) and to an aberrant microfilament reorganization in the epidermis (Vasioukhin *et al.*, 2001). These effects reflect the role of desmosomes in the modulation of the cytoskeleton (Waschke *et al.*, 2006; reviewed in Green *et al.*, 2010). In intestinal epithelium, desmoplakin is important for the control of the size and shape of actin-rich microvilli (Sumigray and Lechler, 2012).

Epiplakin silencing causes IF disruption in keratinocytes (Jang *et al.*, 2005). Gene-targeting studies have revealed the role of epiplakin in lateral bundling of keratins in migrating keratinocytes during wound healing (Ishikawa *et al.*, 2010).

PLAKINS' EFFECTS ON CELL MIGRATION AND POLARIZATION

BPAG1e was shown to regulate cell polarity and migration through the integrin-β4 subunit–mediated modulation of Rac1 and cofilin activities. The latter are required for microfilament-dependent formation of lamellipodia (Hamill *et al.*, 2009). Interestingly, human keratinocytes, carrying homozygous nonsense mutations in the *DST* gene, exhibited reduced adhesion but increased spreading and migration, as well as abnormal protein levels of keratin 14, integrins β1, and β4 (Michael *et al.*, 2013). These alterations were not mimicked by the knockdown of BPAG1e expression in normal keratinocytes, suggesting that either the complete absence of BPAG1e or the expression of a truncated protein is responsible for this phenotype.

The effects of plectin on migration and polarization depend on the cell types and are most likely variant-specific. Ablation of plectin results in the acceleration of migration of keratinocytes or pancreatic cancer cells, whereas fibroblast or lymphocyte migration is reduced (Andrä *et al.*, 1998; Abrahamsberg *et al.*, 2005; Osmanagic-Myers *et al.*, 2006; Yu *et al.*, 2012). In fact, cells slowed down by plectin ablation do not form hemidesmosomes. On the other hand, plectin loss in cells able to form hemidesmosomes significantly increases their migration potential as their adhesion is reduced. Moreover, plectin-deficient keratinocytes show loss of directionality in migration and cell shape changes (Valencia *et al.*, 2013).

Finally, the spectraplakin MACF1 participates in the polarization of stem cells in the epidermis by interacting with the + tip of MTs and their associated proteins (Wu *et al.*, 2011). In the absence of MACF1, loss of MT–microfilament cross-linking activity leads to a stabilization of the focal contacts and thereby reduces cell migration of hair follicle stem cells (Wu *et al.*, 2008, 2011). Neuronal migration also depends on MACF1 (Goryunov *et al.*, 2010).

PLAKINS AND CELL SIGNALING

Phosphorylation sites have been identified in all plakins (Hornbeck *et al.*, 2012). They are particularly abundant in the C-terminal region of desmoplakin, plectin, and spectraplakins. Nevertheless, only a few plakin phosphorylation pathways have been identified so far. Phosphorylation events are thought to be important for the dynamic regulation of the association of plakins with their binding partners in processes, such as cell mitosis, migration, and differentiation.

In the C-terminal region of plectin, a cell cycle–dependent phosphorylation of a threonine by Cdk1 is implicated in the dissociation of plectin from the cytoskeleton (Skalli *et al.*, 1992; Foisner *et al.*, 1996; Malecz *et al.*, 1996). It was recently found that phosphorylation of a serine residue in plectin C extremity by protein kinase A or the mitogen-activated kinase-interacting kinase 2 weakens its interaction with IFs

(Bouameur *et al.*, 2013). This serine residue is highly conserved across species and is also found in desmoplakin. In the latter, its phosphorylation modulates its binding to IFs and its incorporation into desmosomes (Stappenbeck *et al.*, 1994; Fontao *et al.*, 2003; Godsel *et al.*, 2005; Hobbs and Green, 2012). The interaction of plectin with vimentin is also affected by the nitrosylation state of its plakin-repeat domains (Spurny *et al.*, 2007). In analogy to what was observed with α-actinin, phosphomimetic substitution of a tyrosine residue in the actin-binding domain of plectin inhibits its interaction with microfilaments (Izaguirre *et al.*, 2001; Burgstaller *et al.*, 2010). MACF1–MT interaction is inhibited by a glycogen synthase kinase 3β–mediated polyphosphorylation of glycine-serine-arginine motifs in MACF1 (Wu *et al.*, 2011). BPAG1a, BPAG1b, desmoplakin, and plectin also bear such motifs, suggesting similar regulatory mechanisms.

Plakins are not only substrates for post-translational modifications but they also modulate several signaling pathways. Plectin directly or indirectly interacts with several kinases and signaling molecules. Specifically, plectin associates with and modulates the activities of the nonreceptor tyrosine kinase Fer, energy-controlling AMP-activated protein kinase, the protein kinase C receptor RACK1, and β-dystroglycan (Lunter and Wiche, 2002; Osmanagic-Myers and Wiche, 2004; Gregor *et al.*, 2006; Osmanagic-Myers *et al.*, 2006; Rezniczek *et al.*, 2007; Takawira *et al.*, 2011). Thus, plectin affects a variety of processes, such as control of cell adhesion, regulation of protein kinase C signaling, or cellular stress responses. Plectin is not only involved in the activation of extracellular signal–regulated kinases 1/2 (ERK1/2) after β-dystroglycan-mediated mechanical stress but also in its basal activity in distinct squamous carcinoma–derived cell lines (Takawira *et al.*, 2011; Katada *et al.*, 2012). In contrast, plectin inactivation in keratinocytes increases basal ERK1/2 activity, suggesting that it has opposite effects depending on the isoforms and the cellular context (Osmanagic-Myers *et al.*, 2006).

PLAKINS AS CANCER MARKERS

On the basis of their role in cell signaling, coordination of the cytoskeletal networks, cell adhesion, and migration, the available evidence pointing to a role of plakins in cancer development and as tumor markers is not unexpected. For example, the expression level of desmoplakin is reduced in metastatic oropharyngeal tumors (Depondt *et al.*, 1999; Papagerakis *et al.*, 2004, 2009). In analogy to other desmosomal proteins that are downregulated in invasive cancers, plectin and epiplakin are upregulated in pancreatic ductal adenocarcinoma or precursor lesions (Kelly *et al.*, 2008; Yoshida *et al.*, 2008). Plectin is also more expressed in a colon carcinoma cell line (SW480), in which its deletion by small interfering RNA reduced migration, invasion, and adhesion of these tumor cells (McInroy and Maatta, 2011). Finally, plectin is also more abundant in head and neck squamous cell carcinoma cells where its expression level inversely correlates with survival rate. Knockdown of plectin suppresses proliferation, migration, and invasion of tumor cells (Katada *et al.*, 2012). Together, these observations position plakins not only as useful severity markers but also as potential therapeutic targets.

CONCLUSION

In the past two decades, our understanding of the plakin protein family has significantly evolved. These proteins are not mere structural cytoskeletal elements, but they act as dynamic regulators of numerous cellular processes. Congenital defects of plakins lead to devastating diseases affecting particularly organs exposed to mechanical stress, such as the skin and muscles, as well as to more complex and subtle phenotypes, such as encephalopathy, autonomic neuropathy, and myasthenic syndrome. These clinical manifestations reflect the function of plakins as scaffolds for a variety of cytoskeletal elements and signaling molecules. Abnormal expression of plakins also represents a characteristic of different cancers. It is anticipated that future studies will unravel novel insights into the biological roles of these giant multidomain proteins in a variety of processes ranging from tissue morphogenesis and homeostasis to tissue regeneration.

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

We are greatly indebted to many investigators who supported our studies over the years by sharing ideas and providing support and working tools, namely Professor K.J. Green (Chicago, USA), H. Herrmann (Heidelberg, Germany), I. Leigh (Dundee, UK), R.K. Liem (New York, USA), T. Magin (Leipzig, Germany), A. Sonnenberg (Amsterdam, The Netherlands), and G. Wiche (Vienna, Austria). The work has been supported by a grant from the Swiss National Foundation for Scientific Research (3100A0-121966 to L.B.).

REFERENCES

Abrahamsberg C, Fuchs P, Osmanagic-Myers S *et al.* (2005) Targeted ablation of plectin isoform 1 uncovers role of cytolinker proteins in leukocyte recruitment. *Proc Natl Acad Sci USA* 102:18449–54

Aho S (2004) Many faces of periplakin: domain-specific antibodies detect the protein throughout the epidermis, explaining the multiple protein-protein interactions. *Cell Tissue Res* 316:87–97

Andrä K, Lassmann H, Bittner R *et al.* (1997) Targeted inactivation of plectin reveals essential function in maintaining the integrity of skin, muscle, and heart cytoarchitecture. *Genes Dev* 11:3143–56

Andrä K, Nikolic B, Stocher M *et al.* (1998) Not just scaffolding: plectin regulates actin dynamics in cultured cells. *Genes Dev* 12: 3442–51

Anhalt GJ, Kim SC, Stanley JR *et al.* (1990) Paraneoplastic pemphigus. An autoimmune mucocutaneous disease associated with neoplasia. *N Engl J Med* 323:1729–35

Armstrong DK, McKenna KE, Purkis PE *et al.* (1999) Haploinsufficiency of desmoplakin causes a striate subtype of palmoplantar keratoderma. *Hum Mol Genet* 8:143–8

Banwell BL, Russel J, Fukudome T *et al.* (1999) Myopathy, myasthenic syndrome, and epidermolysis bullosa simplex due to plectin deficiency. *J Neuropathol Exp Neurol* 58:832–46

Bolling MC, Pas HH, de Visser M *et al.* (2010a) PLEC1 mutations underlie adult-onset dilated cardiomyopathy in epidermolysis bullosa simplex with muscular dystrophy. *J Invest Dermatol* 130:1178–81

Bolling MC, Veenstra MJ, Jonkman MF *et al.* (2010b) 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

Borradori L, Sonnenberg A (1999) Structure and function of hemidesmosomes: more than simple adhesion complexes. *J Invest Dermatol* 112:411–8

Borradori L, Trueb RM, Jaunin F *et al.* (1998) Autoantibodies from a patient with paraneoplastic pemphigus bind periplakin, a novel member of the plakin family. *J Invest Dermatol* 111:338–40

Bouameur JE, Schneider Y, Begre N *et al.* (2013) Phosphorylation of serine 4642 in the C-terminus of plectin by MNK2 and PKA modulates its interaction with intermediate filaments. *J Cell Sci* 126:4195–207

Boule S, Fressart V, Laux D *et al.* (2012) Expanding the phenotype associated with a desmoplakin dominant mutation: Carvajal/Naxos syndrome associated with leukonychia and oligodontia. *Int J Cardiol* 161:50–2

Boyer JG, Bernstein MA, Boudreau-Lariviere C (2010) Plakins in striated muscle. *Muscle Nerve* 41:299–308

Brown A, Bernier G, Mathieu M *et al.* (1995) The mouse dystonia musculorum gene is a neural isoform of bullous pemphigoid antigen 1. *Nat Genet* 10:301–6

Burgo A, Proux-Gillardeaux V, Sotirakis E *et al.* (2012) A molecular network for the transport of the TI-VAMP/VAMP7 vesicles from cell center to periphery. *Dev Cell* 23:166–80

Burgstaller G, Gregor M, Winter L *et al.* (2010) Keeping the vimentin network under control: cell-matrix adhesion-associated plectin 1f affects cell shape and polarity of fibroblasts. *Mol Biol Cell* 21:3362–75

Cabral RM, Wan H, Cole CL *et al.* (2010) Identification and characterization of DSPIa, a novel isoform of human desmoplakin. *Cell Tissue Res* 341:121–9

Carvajal-Huerta L (1998) Epidermolytic palmoplantar keratoderma with woolly hair and dilated cardiomyopathy. *J Am Acad Dermatol* 39:418–21

Chalabreysse L, Senni F, Bruyere P *et al.* (2011) A new hypo/oligodontia syndrome: Carvajal/Naxos syndrome secondary to desmoplakin-dominant mutations. *J Dent Res* 90:58–64

Charlesworth A, Chiaverini C, Chevrant-Breton J *et al.* (2013) Epidermolysis bullosa simplex with PLEC mutations: new phenotypes and new mutations. *Br J Dermatol* 168:808–14

Charlesworth A, Gagnoux-Palacios L, Bonduelle M *et al.* (2003) Identification of a lethal form of epidermolysis bullosa simplex associated with a homozygous genetic mutation in plectin. *J Invest Dermatol* 121: 1344–8

Chen HJ, Lin CM, Lin CS *et al.* (2006) The role of microtubule actin cross-linking factor 1 (MACF1) in the Wnt signaling pathway. *Genes Dev* 20:1933–45

Choi HJ, Park-Snyder S, Pascoe LT *et al.* (2002) Structures of two intermediate filament-binding fragments of desmoplakin reveal a unique repeat motif structure. *Nat Struct Biol* 9:612–20

Choi HJ, Weis WI (2011) Crystal structure of a rigid four-spectrin-repeat fragment of the human desmoplakin plakin domain. *J Mol Biol* 409: 800–12

Dalpe G, Leclerc N, Vallee A *et al.* (1998) Dystonin is essential for maintaining neuronal cytoskeleton organization. *Mol Cell Neurosci* 10:243–57

Dalpe G, Mathieu M, Comtois A *et al.* (1999) Dystonin-deficient mice exhibit an intrinsic muscle weakness and an instability of skeletal muscle cytoarchitecture. *Dev Biol* 210:367–80

De Repentigny Y, Ferrier A, Ryan SD *et al.* (2011) Motor unit abnormalities in Dystonia musculorum mice. *PLoS One* 6:e21093

Depondt J, Shabana AH, Florescu-Zorila S *et al.* (1999) Down-regulation of desmosomal molecules in oral and pharyngeal squamous cell carcinomas as a marker for tumour growth and distant metastasis. *Eur J Oral Sci* 107:183–93

Di Zenzo G, Della Torre R, Zambruno G *et al.* (2012) Bullous pemphigoid: from the clinic to the bench. *Clin Dermatol* 30:3–16

DiColandrea T, Karashima T, Maatta A *et al.* (2000) Subcellular distribution of envoplakin and periplakin: insights into their role as precursors of the epidermal cornified envelope. *J Cell Biol* 151:573–86

Drabek K, van Ham M, Stepanova T *et al.* (2006) Role of CLASP2 in microtubule stabilization and the regulation of persistent motility. *Curr Biol* 16:2259–64

Edvardson S, Cinnamon Y, Jalas C *et al.* (2012) Hereditary sensory autonomic neuropathy caused by a mutation in dystonin. *Ann Neurol* 71:569–72

Favre B, Schneider Y, Lingasamy P *et al.* (2011) Plectin interacts with the rod domain of type III intermediate filament proteins desmin and vimentin. *Eur J Cell Biol* 90:390–400

Foisner R, Leichtfried FE, Herrmann H *et al.* (1988) Cytoskeleton-associated plectin: in situ localization, *in vitro* reconstitution, and binding to immobilized intermediate filament proteins. *J Cell Biol* 106:723–33

Foisner R, Malecz N, Dressel N *et al.* (1996) M-phase-specific phosphorylation and structural rearrangement of the cytoplasmic cross-linking protein plectin involve p34cdc2 kinase. *Mol Biol Cell* 7:273–88

Fontao L, Favre B, Riou S *et al.* (2003) Interaction of the bullous pemphigoid antigen 1 (BP230) and desmoplakin with intermediate filaments is mediated by distinct sequences within their COOH terminus. *Mol Biol Cell* 14:1978–92

Fujiwara S, Kohno K, Iwamatsu A *et al.* (1996) Identification of a 450-kDa human epidermal autoantigen as a new member of the plectin family. *J Invest Dermatol* 106:1125–30

Fujiwara S, Takeo N, Otani Y *et al.* (2001) Epiplakin, a novel member of the Plakin family originally identified as a 450-kDa human epidermal autoantigen. Structure and tissue localization. *J Biol Chem* 276:13340–7

Gache Y, Chavanas S, Lacour JP *et al.* (1996) Defective expression of plectin/HD1 in epidermolysis bullosa simplex with muscular dystrophy. *J Clin Invest* 97:2289–98

Gallicano GI, Bauer C, Fuchs E (2001) Rescuing desmoplakin function in extra-embryonic ectoderm reveals the importance of this protein in embryonic heart, neuroepithelium, skin and vasculature. *Development* 128:929–41

Gallicano GI, Kouklis P, Bauer C *et al.* (1998) Desmoplakin is required early in development for assembly of desmosomes and cytoskeletal linkage. *J Cell Biol* 143:2009–22

Giorda R, Cerritello A, Bonaglia MC *et al.* (2004) Selective disruption of muscle and brain-specific BPAG1 isoforms in a girl with a 6;15 translocation, cognitive and motor delay, and tracheo-oesophageal atresia. *J Med Genet* 41:e71

Godsel LM, Hsieh SN, Amargo EV *et al.* (2005) Desmoplakin assembly dynamics in four dimensions: multiple phases differentially regulated by intermediate filaments and actin. *J Cell Biol* 171:1045–59

Goryunov D, He CZ, Lin CS *et al.* (2010) Nervous-tissue-specific elimination of microtubule-actin crosslinking factor 1a results in multiple developmental defects in the mouse brain. *Mol Cell Neurosci* 44:1–14

Goto M, Sumiyoshi H, Sakai T *et al.* (2006) Elimination of epiplakin by gene targeting results in acceleration of keratinocyte migration in mice. *Mol Cell Biol* 26:548–58

Green KJ, Getsios S, Troyanovsky S *et al.* (2010) Intercellular junction assembly, dynamics, and homeostasis. *Cold Spring Harb Perspect Biol* 2:a000125

Gregor M, Zeold A, Oehler S *et al.* (2006) Plectin scaffolds recruit energy-controlling AMP-activated protein kinase (AMPK) in differentiated myofibres. *J Cell Sci* 119:1864–75

Groot KR, Sevilla LM, Nishi K *et al.* (2004) Kazrin, a novel periplakin-interacting protein associated with desmosomes and the keratinocyte plasma membrane. *J Cell Biol* 166:653–9

Groves RW, Liu L, Dopping-Hepenstal PJ *et al.* (2010) A homozygous nonsense mutation within the dystonin gene coding for the coiled-coil domain of the epithelial isoform of BPAG1 underlies a new subtype of autosomal recessive epidermolysis bullosa simplex. *J Invest Dermatol* 130:1551–7

Gundesli H, Talim B, Korkusuz P *et al.* (2010) Mutation in exon 1f of PLEC, leading to disruption of plectin isoform 1f, causes autosomal-recessive limb-girdle muscular dystrophy. *Am J Hum Genet* 87:834–41

Guo L, Degenstein L, Dowling J *et al.* (1995) Gene targeting of BPAG1: abnormalities in mechanical strength and cell migration in stratified epithelia and neurologic degeneration. *Cell* 81:233–43

Gupta T, Marlow FL, Ferriola D *et al.* (2010) Microtubule actin crosslinking factor 1 regulates the Balbiani body and animal-vegetal polarity of the zebrafish oocyte. *PLoS Genet* 6:e1001073

Hall RP 3rd, Murray JC, McCord MM *et al.* (1993) Rabbits immunized with a peptide encoded for by the 230-kD bullous pemphigoid antigen cDNA develop an enhanced inflammatory response to UVB irradiation: a potential animal model for bullous pemphigoid. *J Invest Dermatol* 101:9–14

Hamill KJ, Hopkinson SB, DeBiase P *et al.* (2009) BPAG1e maintains keratinocyte polarity through beta4 integrin-mediated modulation of Rac1 and cofilin activities. *Mol Biol Cell* 20:2954–62

Hobbs RP, Amargo EV, Somasundaram A *et al.* (2011) The calcium ATPase SERCA2 regulates desmoplakin dynamics and intercellular adhesive strength through modulation of PKCα signaling. *FASEB J* 25: 990–1001

Hobbs RP, Green KJ (2012) Desmoplakin regulates desmosome hyperadhesion. *J Invest Dermatol* 132:482–5

Hopkinson SB, Jones JC (2000) The N terminus of the transmembrane protein BP180 interacts with the N-terminal domain of BP230, thereby mediating keratin cytoskeleton anchorage to the cell surface at the site of the hemidesmosome. *Mol Biol Cell* 11:277–86

Hornbeck PV, Kornhauser JM, Tkachev S *et al.* (2012) PhosphoSitePlus: a comprehensive resource for investigating the structure and function of experimentally determined post-translational modifications in man and mouse. *Nucleic Acids Res* 40:D261–70

Ishikawa K, Sumiyoshi H, Matsuo N *et al.* (2010) Epiplakin accelerates the lateral organization of keratin filaments during wound healing. *J Dermatol Sci* 60:95–104

Izaguirre G, Aguirre L, Hu YP *et al.* (2001) The cytoskeletal/non-muscle isoform of alpha-actinin is phosphorylated on its actin-binding domain by the focal adhesion kinase. *J Biol Chem* 276:28676–85

Jang SI, Kalinin A, Takahashi K *et al.* (2005) Characterization of human epiplakin: RNAi-mediated epiplakin depletion leads to the disruption of keratin and vimentin IF networks. *J Cell Sci* 118:781–93

Jefferson JJ, Ciatto C, Shapiro L *et al.* (2007) Structural analysis of the plakin domain of bullous pemphigoid antigen1 (BPAG1) suggests that plakins are members of the spectrin superfamily. *J Mol Biol* 366:244–57

Jefferson JJ, Leung CL, Liem RK (2004) Plakins: goliaths that link cell junctions and the cytoskeleton. *Nat Rev Mol Cell Biol* 5:542–53

Jefferson JJ, Leung CL, Liem RK (2006) Dissecting the sequence specific functions of alternative N-terminal isoforms of mouse bullous pemphigoid antigen 1. *Exp Cell Res* 312:2712–25

Jonkman MF, Pasmooij AM, Pasmans SG *et al.* (2005) Loss of desmoplakin tail causes lethal acantholytic epidermolysis bullosa. *Am J Hum Genet* 77:653–60

Kakinuma T, Ichikawa H, Tsukada Y *et al.* (2004) Interaction between p230 and MACF1 is associated with transport of a glycosyl phosphatidyl inositol-anchored protein from the Golgi to the cell periphery. *Exp Cell Res* 298:388–98

Kalinin AE, Kajava AV, Steinert PM (2002) Epithelial barrier function: assembly and structural features of the cornified cell envelope. *Bioessays* 24: 789–800

Karakesisoglou I, Yang Y, Fuchs E (2000) An epidermal plakin that integrates actin and microtubule networks at cellular junctions. *J Cell Biol* 149: 195–208

Kartenbeck J, Franke WW, Moser JG *et al.* (1983) Specific attachment of desmin filaments to desmosomal plaques in cardiac myocytes. *EMBO J* 2:735–42

Katada K, Tomonaga T, Satoh M *et al.* (2012) Plectin promotes migration and invasion of cancer cells and is a novel prognostic marker for head and neck squamous cell carcinoma. *J Proteomics* 75:1803–15

Kelly KA, Bardeesy N, Anbazhagan R *et al.* (2008) Targeted nanoparticles for imaging incipient pancreatic ductal adenocarcinoma. *PLoS Med* 5:e85

Kiss M, Husz S, Janossy T *et al.* (2005) Experimental bullous pemphigoid generated in mice with an antigenic epitope of the human hemidesmosomal protein BP230. *J Autoimmun* 24:1–10

Kodama A, Karakesisoglou I, Wong E *et al.* (2003) ACF7: an essential integrator of microtubule dynamics. *Cell* 115:343–54

Konieczny P, Fuchs P, Reipert S *et al.* (2008) Myofiber integrity depends on desmin network targeting to Z-disks and costameres *via* distinct plectin isoforms. *J Cell Biol* 181:667–81

Koss-Harnes D, Hoyheim B, Anton-Lamprecht I *et al.* (2002) A site-specific plectin mutation causes dominant epidermolysis bullosa simplex Ogna: two identical *de novo* mutations. *J Invest Dermatol* 118:87–93

Koster J, Geerts D, Favre B *et al.* (2003) Analysis of the interactions between BP180, BP230, plectin and the integrin alpha6beta4 important for hemidesmosome assembly. *J Cell Sci* 116:387–99

Kroger C, Loschke F, Schwarz N *et al.* (2013) Keratins control intercellular adhesion involving PKC-alpha-mediated desmoplakin phosphorylation. *J Cell Biol* 201:681–92

Laffitte E, Burkhard PR, Fontao L *et al.* (2005) Bullous pemphigoid antigen 1 isoforms: potential new target autoantigens in multiple sclerosis? *Br J Dermatol* 152:537–40

Lai Cheong JE, Wessagowit V, McGrath JA (2005) Molecular abnormalities of the desmosomal protein desmoplakin in human disease. *Clin Exp Dermatol* 30:261–6

Lapouge K, Fontao L, Champliaud MF *et al.* (2006) New insights into the molecular basis of desmoplakin- and desmin-related cardiomyopathies. *J Cell Sci* 119:4974–85

Lechler T, Fuchs E (2007) Desmoplakin: an unexpected regulator of microtubule organization in the epidermis. *J Cell Biol* 176:147–54

Leung CL, Zheng M, Prater SM *et al.* (2001) The BPAG1 locus: Alternative splicing produces multiple isoforms with distinct cytoskeletal linker domains, including predominant isoforms in neurons and muscles. *J Cell Biol* 154:691–7

Lin CM, Chen HJ, Leung CL *et al.* (2005) Microtubule actin crosslinking factor 1b: a novel plakin that localizes to the Golgi complex. *J Cell Sci* 118:3727–38

Liovic M, D'Alessandro M, Tomic-Canic M *et al.* (2009) Severe keratin 5 and 14 mutations induce down-regulation of junction proteins in keratinocytes. *Exp Cell Res* 315:2995–3003

Litjens SH, de Pereda JM, Sonnenberg A (2006) Current insights into the formation and breakdown of hemidesmosomes. *Trends Cell Biol* 16:376–83

Litjens SH, Koster J, Kuikman I *et al.* (2003) Specificity of binding of the plectin actin-binding domain to beta4 integrin. *Mol Biol Cell* 14:4039–50

Liu JJ, Ding J, Kowal AS *et al.* (2003) BPAG1n4 is essential for retrograde axonal transport in sensory neurons. *J Cell Biol* 163:223–9

Liu JJ, Ding J, Wu C *et al.* (2007) Retrolinkin, a membrane protein, plays an important role in retrograde axonal transport. *Proc Natl Acad Sci USA* 104:2223–8

Liu L, Dopping-Hepenstal PJ, Lovell PA *et al.* (2012) Autosomal recessive epidermolysis bullosa simplex due to loss of BPAG1-e expression. *J Invest Dermatol* 132:742–4

Lunter PC, Wiche G (2002) Direct binding of plectin to Fer kinase and negative regulation of its catalytic activity. *Biochem Biophys Res Commun* 296:904–10

Maatta A, DiColandrea T, Groot K *et al.* (2001) Gene targeting of envoplakin, a cytoskeletal linker protein and precursor of the epidermal cornified envelope. *Mol Cell Biol* 21:7047–53

Mahoney MG, Aho S, Uitto J *et al.* (1998) The members of the plakin family of proteins recognized by paraneoplastic pemphigus antibodies include periplakin. *J Invest Dermatol* 111:308–13

Malecz N, Foisner R, Stadler C *et al.* (1996) Identification of plectin as a substrate of p34cdc2 kinase and mapping of a single phosphorylation site. *J Biol Chem* 271:8203–8

McInroy L, Maatta A (2011) Plectin regulates invasiveness of SW480 colon carcinoma cells and is targeted to podosome-like adhesions in an isoform-specific manner. *Exp Cell Res* 317:2468–78

McLean WH, Pulkkinen L, Smith FJ *et al.* (1996) Loss of plectin causes epidermolysis bullosa with muscular dystrophy: cDNA cloning and genomic organization. *Genes Dev* 10:1724–35

McMillan JR, Akiyama M, Rouan F *et al.* (2007) Plectin defects in epidermolysis bullosa simplex with muscular dystrophy. *Muscle Nerve* 35:24–35

Meng JJ, Bornslaeger EA, Green KJ *et al.* (1997) Two-hybrid analysis reveals fundamental differences in direct interactions between desmoplakin and cell type-specific intermediate filaments. *J Biol Chem* 272: 21495–503

Michael M, Begum R, Fong K *et al.* (2013) BPAG1-e restricts keratinocyte migration through control of adhesion stability. *J Invest Dermatol*; e-pub ahead of print 17 October 2013, doi:10.1038/jid.2013.382

Natsuga K, Nishie W, Akiyama M *et al.* (2010a) Plectin expression patterns determine two distinct subtypes of epidermolysis bullosa simplex. *Hum Mutat* 31:308–16

Natsuga K, Nishie W, Shinkuma S *et al.* (2010b) Plectin deficiency leads to both muscular dystrophy and pyloric atresia in epidermolysis bullosa simplex. *Hum Mutat* 31:E1687–98

Nekrasova O, Green KJ (2013) Desmosome assembly and dynamics. *Trends Cell Biol* 23:537–46

Nguyen VT, Ndoye A, Bassler KD *et al.* (2001) Classification, clinical manifestations, and immunopathological mechanisms of the epithelial variant of paraneoplastic autoimmune multiorgan syndrome: a reappraisal of paraneoplastic pemphigus. *Arch Dermatol* 137:193–206

Nikolic B, Mac Nulty E, Mir B *et al.* (1996) Basic amino acid residue cluster within nuclear targeting sequence motif is essential for cytoplasmic plectin-vimentin network junctions. *J Cell Biol* 134:1455–67

Niwa T, Saito H, Imajoh-ohmi S *et al.* (2009) BRCA2 interacts with the cytoskeletal linker protein plectin to form a complex controlling centrosome localization. *Cancer Sci* 100:2115–25

Norgett EE, Hatsell SJ, Carvajal-Huerta L *et al.* (2000) Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum Mol Genet* 9:2761–6

Numata S, Teye K, Tsuruta D *et al.* (2013) Anti-alpha-2-macroglobulin-like-1 autoantibodies are detected frequently and may be pathogenic in paraneoplastic pemphigus. *J Invest Dermatol* 133:1785–93

Ohnishi Y, Tajima S, Ishibashi A *et al.* (2000) A vesicular bullous pemphigoid with an autoantibody against plectin. *Br J Dermatol* 142:813–5

Ortega E, Buey RM, Sonnenberg A *et al.* (2011) The structure of the plakin domain of plectin reveals a non-canonical SH3 domain interacting with its fourth spectrin repeat. *J Biol Chem* 286:12429–38

Osmanagic-Myers S, Gregor M, Walko G *et al.* (2006) Plectin-controlled keratin cytoarchitecture affects MAP kinases involved in cellular stress response and migration. *J Cell Biol* 174:557–68

Osmanagic-Myers S, Wiche G (2004) Plectin-RACK1 (receptor for activated C kinase 1) scaffolding: a novel mechanism to regulate protein kinase C activity. *J Biol Chem* 279:18701–10

Papagerakis S, Shabana AH, Depondt J *et al.* (2004) Altered plakoglobin expression at mRNA and protein levels correlates with clinical outcome in patients with oropharynx squamous carcinomas. *Hum Pathol* 35:75–85

Papagerakis S, Shabana AH, Pollock BH *et al.* (2009) Altered desmoplakin expression at transcriptional and protein levels provides prognostic information in human oropharyngeal cancer. *Hum Pathol* 40:1320–9

Petrof G, Mellerio JE, McGrath JA (2012) Desmosomal genodermatoses. *Br J Dermatol* 166:36–45

Pfendner E, Uitto J (2005) Plectin gene mutations can cause epidermolysis bullosa with pyloric atresia. *J Invest Dermatol* 124:111–5

Reipert S, Steinbock F, Fischer I *et al.* (1999) Association of mitochondria with plectin and desmin intermediate filaments in striated muscle. *Exp Cell Res* 252:479–91

Rezniczek GA, Abrahamsberg C, Fuchs P *et al.* (2003) Plectin 5′-transcript diversity: short alternative sequences determine stability of gene products, initiation of translation and subcellular localization of isoforms. *Hum Mol Genet* 12:3181–94

Rezniczek GA, Konieczny P, Nikolic B *et al.* (2007) Plectin 1f scaffolding at the sarcolemma of dystrophic (mdx) muscle fibers through multiple interactions with beta-dystroglycan. *J Cell Biol* 176:965–77

Roper K, Gregory SL, Brown NH (2002) The ''spectraplakins'': cytoskeletal giants with characteristics of both spectrin and plakin families. *J Cell Sci* 115:4215–25

Ruhrberg C, Hajibagheri MA, Parry DA *et al.* (1997) Periplakin, a novel component of cornified envelopes and desmosomes that belongs to the plakin family and forms complexes with envoplakin. *J Cell Biol* 139:1835–49

Ruhrberg C, Hajibagheri MA, Simon M *et al.* (1996) Envoplakin, a novel precursor of the cornified envelope that has homology to desmoplakin. *J Cell Biol* 134:715–29

Ryan SD, Bhanot K, Ferrier A *et al.* (2012a) Microtubule stability, Golgi organization, and transport flux require dystonin-a2-MAP1B interaction. *J Cell Biol* 196:727–42

Ryan SD, Ferrier A, Sato T *et al.* (2012b) Neuronal dystonin isoform 2 is a mediator of endoplasmic reticulum structure and function. *Mol Biol Cell* 23:553–66

Saleh MA, Ishii K, Yamagami J *et al.* (2012) Pathogenic anti-desmoglein 3 mAbs cloned from a paraneoplastic pemphigus patient by phage display. *J Invest Dermatol* 132:1141–8

Sawamura D, Li K, Chu ML *et al.* (1991) Human bullous pemphigoid antigen (BPAG1). Amino acid sequences deduced from cloned cDNAs predict biologically important peptide segments and protein domains. *J Biol Chem* 266:17784–90

Schepens I, Jaunin F, Begre N *et al.* (2010) The protease inhibitor alpha-2-macroglobulin-like-1 is the p170 antigen recognized by paraneoplastic pemphigus autoantibodies in human. *PLoS One* 5:e12250

Schroder R, Kunz WS, Rouan F *et al.* (2002) Disorganization of the desmin cytoskeleton and mitochondrial dysfunction in plectin-related epidermolysis bullosa simplex with muscular dystrophy. *J Neuropathol Exp Neurol* 61:520–30

Sevilla LM, Nachat R, Groot KR *et al.* (2007) Mice deficient in involucrin, envoplakin, and periplakin have a defective epidermal barrier. *J Cell Biol* 179:1599–612

Simpson CL, Patel DM, Green KJ (2011) Deconstructing the skin: cytoarchitectural determinants of epidermal morphogenesis. *Nat Rev Mol Cell Biol* 12:565–80

Skalli O, Chou YH, Goldman RD (1992) Cell cycle-dependent changes in the organization of an intermediate filament-associated protein: correlation with phosphorylation by p34cdc2. *Proc Natl Acad Sci USA* 89: 11959–63

Slep KC, Rogers SL, Elliott SL *et al.* (2005) Structural determinants for EB1-mediated recruitment of APC and spectraplakins to the microtubule plus end. *J Cell Biol* 168:587–98

Smith EA, Fuchs E (1998) Defining the interactions between intermediate filaments and desmosomes. *J Cell Biol* 141:1229–41

Smith FJ, Eady RA, Leigh IM *et al.* (1996) Plectin deficiency results in muscular dystrophy with epidermolysis bullosa. *Nat Genet* 13:450–7

Sonnenberg A, Liem RK (2007) Plakins in development and disease. *Exp Cell Res* 313:2189–203

Spazierer D, Fuchs P, Reipert S *et al.* (2006) Epiplakin is dispensable for skin barrier function and for integrity of keratin network cytoarchitecture in simple and stratified epithelia. *Mol Cell Biol* 26:559–68

Spurny R, Abdoulrahman K, Janda L *et al.* (2007) Oxidation and nitrosylation of cysteines proximal to the intermediate filament (IF)-binding site of plectin: effects on structure and vimentin binding and involvement in IF collapse. *J Biol Chem* 282:8175–87

Spurny R, Gregor M, Castanon MJ *et al.* (2008) Plectin deficiency affects precursor formation and dynamics of vimentin networks. *Exp Cell Res* 314:3570–80

Stanley JR, Tanaka T, Mueller S *et al.* (1988) Isolation of complementary DNA for bullous pemphigoid antigen by use of patients' autoantibodies. *J Clin Invest* 82:1864–70

Stappenbeck TS, Lamb JA, Corcoran CM *et al.* (1994) Phosphorylation of the desmoplakin COOH terminus negatively regulates its interaction with keratin intermediate filament networks. *J Biol Chem* 269:29351–4

Sumigray KD, Chen H, Lechler T (2011) Lis1 is essential for cortical microtubule organization and desmosome stability in the epidermis. *J Cell Biol* 194:631–42

Sumigray KD, Lechler T (2012) Desmoplakin controls microvilli length but not cell adhesion or keratin organization in the intestinal epithelium. *Mol Biol Cell* 23:792–9

Suozzi KC, Wu X, Fuchs E (2012) Spectraplakins: master orchestrators of cytoskeletal dynamics. *J Cell Biol* 197:465–75

Svitkina TM, Verkhovsky AB, Borisy GG (1996) Plectin sidearms mediate interaction of intermediate filaments with microtubules and other components of the cytoskeleton. *J Cell Biol* 135:991–1007

Takawira D, Budinger GR, Hopkinson SB *et al.* (2011) A dystroglycan/plectin scaffold mediates mechanical pathway bifurcation in lung epithelial cells. *J Biol Chem* 286:6301–10

Tian R, Gregor M, Wiche G *et al.* (2006) Plectin regulates the organization of glial fibrillary acidic protein in Alexander disease. *Am J Pathol* 168: 888–97

Valencia RG, Walko G, Janda L *et al.* (2013) Intermediate filament-associated cytolinker plectin 1c destabilizes microtubules in keratinocytes. *Mol Biol Cell* 24:768–84

Vasioukhin V, Bowers E, Bauer C *et al.* (2001) Desmoplakin is essential in epidermal sheet formation. *Nat Cell Biol* 3:1076–85

Wagner M, Hintner H, Bauer JW *et al.* (2012) Gene expression analysis of an epidermolysis bullosa simplex Dowling-Meara cell line by subtractive hybridization: recapitulation of cellular differentiation, migration and wound healing. *Exp Dermatol* 21:111–7

Walko G, Vukasinovic N, Gross K *et al.* (2011) Targeted proteolysis of plectin isoform 1a accounts for hemidesmosome dysfunction in mice mimicking the dominant skin blistering disease EBS-Ogna. *PLoS Genet* 7:e1002396

Waschke J, Spindler V, Bruggeman P *et al.* (2006) Inhibition of Rho A activity causes pemphigus skin blistering. *J Cell Biol* 175:721–7

Wiche G, Winter L (2011) Plectin isoforms as organizers of intermediate filament cytoarchitecture. *Bioarchitecture* 1:14–20

Wilhelmsen K, Litjens SH, Kuikman I *et al.* (2005) Nesprin-3, a novel outer nuclear membrane protein, associates with the cytoskeletal linker protein plectin. *J Cell Biol* 171:799–810

Winter L, Abrahamsberg C, Wiche G (2008) Plectin isoform 1b mediates mitochondrion-intermediate filament network linkage and controls organelle shape. *J Cell Biol* 181:903–11

Winter L, Wiche G (2013) The many faces of plectin and plectinopathies: pathology and mechanisms. *Acta Neuropathol* 125:77–93

Wu X, Kodama A, Fuchs E (2008) ACF7 regulates cytoskeletal-focal adhesion dynamics and migration and has ATPase activity. *Cell* 135:137–48

Wu X, Shen QT, Oristian DS *et al.* (2011) Skin stem cells orchestrate directional migration by regulating microtubule-ACF7 connections through GSK3beta. *Cell* 144:341–52

Yang Y, Bauer C, Strasser G *et al.* (1999) Integrators of the cytoskeleton that stabilize microtubules. *Cell* 98:229–38

Yang Y, Dowling J, Yu QC *et al.* (1996) An essential cytoskeletal linker protein connecting actin microfilaments to intermediate filaments. *Cell* 86:655–65

Yoshida T, Shiraki N, Baba H *et al.* (2008) Expression patterns of epiplakin1 in pancreas, pancreatic cancer and regenerating pancreas. *Genes Cells* 13:667–78

Yu PT, Babicky M, Jaquish D *et al.* (2012) The RON-receptor regulates pancreatic cancer cell migration through phosphorylation-dependent breakdown of the hemidesmosome. *Int J Cancer* 131:1744–54