Invited review article

Hemidesmosomes and focal contact proteins: Functions and cross-talk in keratinocytes, bullous diseases and wound healing

Daisuke Tsuruta\textsuperscript{a,b,c,*}, Takashi Hashimoto\textsuperscript{a,b}, Kevin J. Hamill\textsuperscript{d}, Jonathan C.R. Jones\textsuperscript{d}

\textsuperscript{a}Department of Dermatology, Kurume University School of Medicine, Japan
\textsuperscript{b}Kurume University Institute of Cutaneous Cell Biology, Japan
\textsuperscript{c}Department of Dermatology, Osaka City University Graduate School of Medicine, Japan
\textsuperscript{d}Department of Cell and Molecular Biology, Northwestern University the Feinberg School of Medicine, United States

1. Introduction

Keratinocytes in the basal layer of the epidermis adhere to the connective tissue via interaction with extracellular matrix proteins organized into a sheet-like structure termed the basement membrane zone (BMZ). Keratinocyte-extracellular matrix adhesion...

\textsuperscript{*} Corresponding author at: Department of Dermatology, Kurume University School of Medicine, 67 Asahimachi, Kurume, Fukuoka 830-0011, Japan. Tel.: +81 942 31 7571; fax: +81 942 34 2620.
E-mail address: tsuruta_daisuke@med.kurume-u.ac.jp (D. Tsuruta).

© 2011 Japanese Society for Investigative Dermatology. Published by Elsevier Ireland Ltd. All rights reserved.

doi:10.1016/j.jdermsci.2011.01.005
matrix interactions along the BMZ regulate a variety of cell behaviors, including proliferation, adhesion, differentiation, migration and apoptosis [1].

In intact skin, the adherence of keratinocytes to the BMZ is mediated by cell-matrix junctions termed hemidesmosomes, which also tether the keratin cytoskeleton to the cell surface [2]. Adhesion mediated by hemidesmosomes is considered stable and robust [3-5]. Ultrastructural examination of intact skin reveals hemidesmosomes dispersed all along the BMZ. Each has a tripartite electron dense cytoplasmic plaque to which tonofibrils adhere [5]. In contrast, keratinocytes in culture fail to assemble bona fide hemidesmosomes. Rather, hemidesmosome-enriched protein complexes, which one group has termed stable anchoring complexes (SACs), are found along the substrate-attached surface of keratinocytes maintained in culture [4]. SACs lack the ultrastructural features of hemidesmosomes found in tissues and possess immature plaques, at best. Moreover, SACs are not static, but exhibit dynamic properties during migration and chemical/antibody treatment as we detail below [2].

When grown in culture on glass or plastic, keratinocytes assemble matrix adhesion devices termed focal contacts [3]. Focal contacts differ from the hemidesmosomes of intact skin by being associated with the actin cytoskeleton. In vitro, focal contacts appear dynamic and move rapidly in the plane of the membrane [6]. Moreover, focal contacts are considered to function as hubs that direct numerous inside-out and outside-in signals [7]. Whether keratinocytes assemble focal contacts in skin tissue and whether focal contact proteins are involved in the adherence of keratinocytes to the BMZ is debatable. Indeed, certain focal contacts proteins, such as α3β1 and α2β1 integrin, are not associated with BMZ in intact skin but are found concentrated at sites of cell–cell contact [3].

In this review, we briefly describe the molecular components, function, dynamics and cross-talk of hemidesmosomes and focal contacts. We also detail the pathological significance of the proteins of both hemidesmosomes and focal contacts in relation to genetic and autoimmune blistering disease of the skin. We focus a large section of this review on a discussion of some recent novel, albeit controversial, data that hemidesmosomal components regulate the directed migration of keratinocytes while focal contact proteins in skin cells may actually retard keratinocyte motility.

2. The molecular composition of hemidesmosomes and focal contacts in keratinocytes

The core of each hemidesmosome consists of four single-span-transmembrane proteins, namely the 180 kDa-bullous pemphigoid antigen (BP180, type XVII collagen, BPAG2), the two subunits of the α6β4 integrin and a tetraspanin protein termed CD151 [8]. Both BP180 and α6β4 integrin interact with laminin-332 in the BMZ [9]. The α6β4 integrin associates with the keratin cytoskeleton, rather than actin, making this heterodimer unique among the integrin family [5]. This interaction is facilitated by the long 1000 amino acid cytoplasmic tail of the β4 integrin subunit which not only binds BP180 but also the 230 kDa bullous pemphigoid antigen (BP230 or BPAG1e) and plectin. The latter two proteins are plakin family members that mediate the indirect linkage of keratin to α6β4 integrin [5] (Fig. 1).

Focal contacts are complex molecular adhesion sites and each contains many more proteins than have so far been identified in the hemidesmosome. The focal contacts of cultured keratinocytes are no exception and contain numerous actin-binding proteins, including paxillin, vinculin, talin and actinin isoforms, via which they associate with actin [10]. A number of distinct integrin heterodimers including α2β1, α3β1 and α5β1 have been identified within each focal contact and these exhibit interactions with various matrix ligands including fibronectin, collagen and laminins [11]. Molecules involved in signaling, such as focal adhesion kinase and integrin-linked kinase, are also found in focal contacts [12].

3. The functions of hemidesmosomes and focal contacts in keratinocytes

Evidence for the adhesive function of hemidesmosomes comes from studies of several skin diseases where loss of hemidesmosomes results in dysadhesion of the epidermis and the development of blisters between the keratinocyte layers of the skin and the dermis [13]. In cultured skin cells, loss of hemidesmosome proteins does not dramatically impact adhesion of the cells to tissue culture surfaces. Rather, such loss inhibits several signaling pathways that are mediated by α6β4 integrin [14]. These data have led to the conclusion that the integrin component of the hemidesmosome is involved in signaling [14]. However, in all likelihood, α6β4 integrin primarily signals when outside the confines of the hemidesmosome.

There is considerable evidence that focal contacts in cultured cells, including keratinocytes, are involved in inside-out and outside-in signaling. For example, in keratinocytes, the mitogen-activated protein (MAP) kinase pathway is activated following ligation of α3β1 integrin by laminin-332 [15]. In addition, it has been reported that laminin-332-α3β1 integrin interaction induces activation of cdc42 and its effector the serine threonine kinase PAK1, thereby enhancing cell motility [16]. Laminin-332-α3β1 integrin mediated signaling may also activate the FAK/Src/Rac1 pathway and the formation of lamellipodia [17]. In addition to these outside-in signaling pathways, α3β1 integrin, through the activity of a protein termed T-lymphoma invasion and metastasis 1 (Tiam1), regulates assembly of laminin-332 matrix in an inside-out signaling mechanism [18,19].

4. The dynamics of cell-extracellular matrix attachment devices in keratinocytes

Focal contacts in both stationary and actively migrating cells are known to be highly dynamic. In brief, in cultured cells focal
contacts begin life as focal complexes at the cell surface, enlarge, and move primarily towards the cell center, although some also exhibit perimembranous movement [6]. In migrating cells, focal contacts at the trailing edge of the cell disassemble in a microtubule-dependent manner [20].

Hemidesmosomes in tissues are considered stable adhesion devices. However, in cultured keratinocytes, hemidesmosome protein-rich complexes or SACs show considerable dynamics in the plane of the membrane [2,21]. These dynamics have been reported to be dependent on the actin cytoskeleton and laminin-332-mediated clustering of α6β4 integrin heterodimers [2,21]. Moreover, fluorescent recovery after photobleaching (FRAP) studies suggest that β4 integrin protein can exchange rapidly between cell surface clusters and a cytoplasmic or membrane pool of protein [2].

In keratinocytes in vitro, the dynamics of focal contacts and hemidesmosome-rich protein complexes are tightly co-regulated during the closure of scratch wounds created in confluent monolayer cultures (Fig. 2) [22]. Both focal contact and hemidesmosome proteins are dispersed along the leading edge of cells populating a wound in vitro. Intriguingly, hemidesmosome protein complexes appear between or just behind actinin proteins in the advancing lamellipodia of motile skin cells [22]. In addition, inhibition of hemidesmosome proteins or their knockdown results in enhanced focal contact dynamics while blocking the inhibition of hemidesmosome proteins or specific mutations in β4 integrin at sites where it interacts with BP180 [13,24,25].

JB patients present with mutations in any of the genes encoding the three subunits of laminin-332, BP180, or α6β4 integrin [13]. In the case of JEB, the most severe phenotype (termed JEB-Herlitz) result from loss of expression mutations in laminin α3, β3 or γ2, while the other forms (JEB-Other) occur either as a result of missense mutations in the laminin subunits (JEB non-Herlitz), or missense/loss of expression mutations in BP180 (JEB non-Herlitz), or missense/loss of expression of α6β4 integrin (JEB with pyloric atresia) [13,23]. In addition, a rare form of JEB, pretibial EB with hereditary nephritis, is known to be caused by CD151 gene mutations [26].

Identifying specific phenotype/genotype correlations can be of great value to expanding our understanding of how matrix adhesion proteins interact and how they function. A good example

![Fig. 2. Still images for the dynamics of hemidesmosomal proteins and focal contact proteins in live migrating keratinocytes.](image-url)

5. Skin diseases involving hemidesmosomes and focal contacts of cell-extracellular matrix adhesion (the diseases described here are summarized in Table 1 and shown in Fig. 3)

5.1. Inherited disorders affecting hemidesmosome or focal contact protein components

The involvement of hemidesmosome and focal adhesion proteins in human disease has been the subject of a number of excellent recent reviews. Thus, we will provide only a general overview of the literature.

Loss of function mutations affecting matrix adhesion components have been identified as pathogenic in a family of skin fragility and blistering disorders termed, collectively, epidermolysis bullosa (EB) [13,23]. Classification of the EB family of disorders has recently been rationalized and we will use this new classification [23]. Specifically, the EB disorders are broken down into four main classifications based upon ultrastructural examination of the blistering site: intraepidermal (EB simplex, EBS, Fig. 3a), junctional (JEB), dermolytic (dystrophic EB, DEB) and mixed (Kindler syndrome, Fig. 3b) [23]. Patients are further separated into minor EB subtypes based on clinical presentation and mode of inheritance.

In general, the phenotypic classification of patients provides an indication of the mutated gene and the type of mutation. Thus, basal EBS is associated with mutations in the basal keratinocyte keratins (K5 and K14), with mutations in those proteins (plectin or BP230) which mediate keratin association with hemidesmosomes or with specific mutations in β4 integrin at sites where it interacts with BP180 [13,24,25].

Patients with JEB may present with mutations in any of the genes encoding the three subunits of laminin-332, BP180, or α6β4 integrin [13]. In the case of JEB, the most severe phenotype (termed JEB-Herlitz) results from loss of expression mutations in laminin α3, β3 or γ2, while the other forms (JEB-Other) occur either as a result of missense mutations in laminin subunits (JEB non-Herlitz), or missense/loss of expression mutations in BP180 (JEB non-Herlitz), or missense/loss of expression of α6β4 integrin (JEB with pyloric atresia) [13,23]. In addition, a rare form of JEB, pretibial EB with hereditary nephritis, is known to be caused by CD151 gene mutations [26].

Using specific phenotype/genotype correlations can be of great value to expanding our understanding of how matrix adhesion proteins interact and how they function. A good example

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Diseases whose pathogenesis involves hemidesmosomal or focal contact components</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inherit bullous diseases</td>
</tr>
<tr>
<td>Hemidesmosome-related</td>
<td>Epidermolysis bullosa (EB)</td>
</tr>
<tr>
<td></td>
<td>(EB) hereditaria</td>
</tr>
<tr>
<td></td>
<td>EB simplex (EBS)</td>
</tr>
<tr>
<td></td>
<td>Weber-Cockayne</td>
</tr>
<tr>
<td></td>
<td>Koebner</td>
</tr>
<tr>
<td></td>
<td>Dowling-Meara</td>
</tr>
<tr>
<td></td>
<td>Pretibial</td>
</tr>
<tr>
<td></td>
<td>EBS with muscular dystrophy</td>
</tr>
<tr>
<td></td>
<td>Junctional EB (JEB)</td>
</tr>
<tr>
<td></td>
<td>Herlitz type</td>
</tr>
<tr>
<td></td>
<td>JEB with pyloric atresia</td>
</tr>
<tr>
<td></td>
<td>Non-Herlitz type</td>
</tr>
<tr>
<td></td>
<td>Dystrophic EB (DEB)</td>
</tr>
<tr>
<td></td>
<td>Dominant DEB</td>
</tr>
<tr>
<td></td>
<td>Recessive DEB</td>
</tr>
<tr>
<td>Focal contact-related</td>
<td>Kindler syndrome</td>
</tr>
</tbody>
</table>
of this is a rare disorder termed laryngo-onycho-cutaneous syndrome (LOC) which presents with non-healing cutaneous erosions and chronic overproduction of granulation tissue without apparent skin fragility [27]. Mutational analyses have revealed that LOC syndrome results from mutations in the first exon of the laminin α3a transcript implicating this region in the regulation of the granulation tissue response [27].

Mutations in every known component of the hemidesmosome have now been identified in human genetic disorders. In contrast, the only focal contact protein in which mutations resulting in a genodermatosis have been identified is kindlin-1, named after Kindler syndrome in which mutations in the gene were identified [28]. Similar to those afflicted with EBS, Kindler syndrome patients present with neonatal blistering [28]. Kindlin-1 protein possesses a central region containing an unusual arrangement of a pleckstrin homology (PH) domain flanked by two regions of homology to the four-point-one, ezrin, radixin, moesin (FERM) domain [29]. Both PH and FERM domains have been identified as being involved in membrane binding [30]. Kindlin-1 colocalizes with vinculin at focal contacts and interacts with the actin cytoskeleton via migfilin and filamin A [31]. Kindlin-1 therefore appears to play a critical role in the maintenance of the actin-extracellular matrix attachment [29]. The lack of identification of pathogenic mutations in other focal contact genes is likely a reflection of the developmental requirement for core focal contact components.

5.2. Autoimmune disorders affect keratinocyte-extracellular matrix adhesion

To date autoimmune disorders targeting focal contact proteins have not been identified. In contrast, a number of autoimmune disorders where circulating autoantibodies target hemidesmosome components have been described. The prototypical example is bullous pemphigoid (BP), which is characterized by subepidermal blisters with inflammatory infiltrate (Fig. 3c) [32]. Typically, there is a linear deposit of IgG at the BMZ and presence of circulating antibodies to BP230 and BP180. The role of anti-BP1G antibody in bullae formation in BP has been considered to be cell-mediated cytolysis induced by the activation of complements, the migration of neutrophils and the effects of neutrophil elastases [32,33]. However, this model has been questioned since Iwata et al.

have presented evidence that pathogenic autoantibodies against BP180 decrease the strength of adhesion of keratinocyte to matrix in the absence of complement and neutrophils [34]. Indeed, other mechanisms of pathogenesis of BP autoantibodies have been proposed. Several authors have suggested that BP autoantibodies may induce cellular signaling events that result in keratinocyte dysadhesion [35,36]. In addition, Kitajima et al. has provided some evidence that internalization of BP180 in basal keratinocytes occurs in affected skin samples of BP patients [37].

Autoantibodies in a variant of BP, termed mucous membrane pemphigoid (MMP), also target hemidesmosome proteins. Approximately 95% of MMP patients produce antibodies directed against BP180, while 5% of patients produce autoantibodies against laminin-332. MMP patients present with blistering, erosive and scarring lesions of mucous membranes [38].

6. Focal contact and hemidesmosome proteins in wound healing of the skin

Wound healing is a complex but regulated series of events that results in restoration of skin integrity. Re-epithelization is a part of the overall wound healing mechanism and is initiated by the dissociation of keratinocytes from the BMZ at the undamaged wound margins [39]. Dissociation involves hemidesmosome disassembly and matrix remodeling. By evading the constraints of the BMZ, keratinocytes move directionally over the provisional matrix in the wound bed and reestablish an intact epithelial sheet [40]. Upon wound coverage, the BMZ is reassembled and hemidesmosomes are reformed [41].

As part of the process that leads to hemidesmosome disassembly, the γ2 subunit of laminin-332 is enzymatically cleaved by members of the metalloprotease (MMP) family, including membrane-type 1 (MT1)-MMP, MMP-2, MMP-3, MMP-12, MMP-13, MMP-19, and MMP-20 [9]. In addition, the astacin family member, bone morphogenic protein (BMP)-1, and its related enzyme, mammalian tolloid (mTLD), also have been reported to cleave both the γ2 subunit of laminin-332, but the precise functional consequences of this cleavage are unknown [42]. In contrast, MT1-MMP and MMP-2 cleavage of the laminin γ2 subunit results in the production of 100-, 85-, 27-, and 25-kDa protein fragments [9]. Of these, the 27-kDa fragment is found in circulating blood in cancer patients and has been reported to
stimulate the epidermal growth factor receptor and, hence, cell migration [43]. In addition, epidermal growth factor mediated phosphorylation of \( \beta_4 \) integrin cytoplasmic tail induces hemidesmosome disassembly [44]. Serine phosphorylation disrupts \( \beta_4 \) integrin-plectin association and likely destabilizes the hemidesmosome [44]. Phosphorylation of other hemidesmosomal components may also play a role in inducing hemidesmosome disassembly. Finally, endocytotic uptake of hemidesmosomes has also been observed and likely contributes to the dissociation of stable adhesion of keratinocytes to the BMZ at the wound margin [45].

Focal adhesion proteins are involved in directed migration, the process via which keratinocytes move over the wound bed, by mediating movement of cells over the extracellular matrix components, including fibronectin, fibrogenin and collagen in the wound bed [46]. Thus, it is not surprising that receptors of the latter molecules, such as \( \alpha_5\beta_1 \), \( \alpha_2\beta_1 \) and \( \alpha_3\beta_1 \) integrin and several syndecans, are involved in regulating keratinocyte motility [47].

Laminin-332 is also present towards the leading front of the migrating sheet of keratinocytes that populate a wound bed [48]. Laminin-332, containing a full length \( \alpha_3 \) subunit is initially deposited along the edge of the migrating keratinocytes and is believed to support directed migration [49]. Subsequently, laminin-332 undergoes enzymatic processing such that the \( \alpha_3 \) laminin subunit is cleaved within its G domain. These include the serine protease, plasmin, BMP-1 and mTLD [42,49]. Following cleavage, laminin-332 supports the assembly of hemidesmosomes and thereby stabilizes the interaction of keratinocytes with the wound bed [49].

Until recently, integrin \( \alpha_3\beta_1 \) association with laminin-332 at the site of focal contacts was considered to enhance keratinocyte migration whereas integrin \( \alpha_6\beta_4 \) integrin association with laminin-332 was thought to retard keratinocyte motility by stabilizing attachment to the extracellular matrix [50]. However, both these viewpoints have been questioned recently. First, the Sonnenberg lab has presented that \( \alpha_3\beta_1 \) integrin, rather than supporting migration, inhibits the motility of keratinocytes [51]. These workers generated mice exhibiting an epidermal targeted \( \alpha_3 \) integrin knockout. Wound closure in the knockout mice migrate faster than their wild type counterparts and exhibit enhanced directional migration. To confirm that this unexpected phenotype is because of the absence of \( \alpha_3 \) integrin, the \( \alpha_3 \) integrin subunit was re-expressed in the knockout skin cells. The rescued cells show slower migration in an in vitro scratch wound. How can this study be reconciled with the literature implicating \( \alpha_3 \) integrin in supporting migration on laminin-332 matrices? Primarily, data in support of the later conclusion comes from the use of an \( \alpha_3 \) integrin monoclonal antibody, P1B5. This antibody inhibits cell adhesion to laminin-332 and migration on laminin-332 extracellular matrix. We suspect that P1B5 may not only block \( \alpha_3\beta_1 \) integrin adhesion to ligand but also, by clustering \( \alpha_3\beta_1 \) integrin, may trigger signaling that inhibits the activity of a motility receptor. The notion that \( \alpha_3\beta_1 \) integrin crosstalks and inhibits the activation state of other integrin receptors has been suggested by others [52,53].

There is also emerging data that \( \alpha_6\beta_4 \) integrin and its associated proteins play essential roles in the mechanisms that positively regulate keratinocyte migratory behavior [14,54–56]. Specifically, in motile epithelial cells populating a wound in vitro, both \( \alpha_6\beta_4 \) integrin and its matrix ligand laminin-332 are found towards the leading edge of their extending lamellipodium [14,48]. In addition, in migrating cells \( \alpha_6\beta_4 \) integrin shows actin-dependent dynamics at the site of the nascent lamellipodium as determined by FRAP [14]. Moreover, we and others have demonstrated that \( \alpha_6\beta_4 \) integrin through activation of Rac, regulates keratinocyte front-rear polarity and directed migration [54,57]. Taken together, these data suggest that \( \alpha_6\beta_4 \) integrin is an important part of the steering machinery of keratinocytes.

\( \alpha_6\beta_4 \) integrin is not the only hemidesmosomal component involved in regulating keratinocyte motile behavior. Specifically, BP230, which mediates the interaction of \( \alpha_6\beta_4 \) integrin in hemidesmosomes with the keratin cytoskeleton in stationary cells, regulates Rac/\( \alpha_6\beta_4 \) integrin association in motile keratinocytes and is found along the advancing lamellipodia of migrating cells [14]. Furthermore, BP230 deficiency results in a loss of front-rear polarity and inhibits directed migration of skin cells in vitro and inhibits wound closure in vivo [14,58].

How does Rac regulate skin cell motility? As in other cell systems, in skin keratinocytes Rac1 signals to the actin severing protein coflin [54,59–61]. By severing actin filaments, coflin increases the number of free actin barbed ends while simultaneously increasing the depolymerization rate of older actin filaments, thereby increasing the local pool of free actin monomers [54,60]. Polymerization of actin at the free ends of the freshly severed actin filaments extends the membrane of the lamellipodium [54,60]. This would suggest that loss of Rac activation induced by \( \beta_4 \) integrin or BP230 deficiency would perturb lamellipodial formation and/or stability. Indeed, keratinocytes lacking either \( \beta_4 \) integrin or BP230 exhibit abnormal lamellipodial number and lack front-rear polarity [14,56].

Coflin phosphorylation is regulated by phosphatases, slingshot (SSH) or chronophin (CIN) [62,63]. Keratinocytes express all members of the SSH family and CIN [56]. However, expression of phosphatase-dead versions of all three SSH proteins, but not dominant inactive CIN, results in phosphorylation/inactivation of coflin, changes in actin cytoskeleton organization, loss of cell polarity and assembly of aberrant arrays of laminin-332 in human keratinocytes [56]. SSH activity is regulated by 14-3-3 protein binding, and intriguingly, 14-3-3/\( \alpha_6\beta_4 \) integrin protein interaction is required for keratinocyte migration. This raises the intriguing possibility that 14-3-3 proteins function as molecular switches, regulating Rac1 mediated keratinocyte migration patterns. In support of this hypothesis, inhibition of Rac1 results in an increase in 14-3-3 protein association with SSH and a concomitant loss of 14-3-3 protein interaction with \( \alpha_6\beta_4 \) integrin [55,56]. Moreover, using amino or carboxy terminal domains of 14-3-3\( \gamma \), it has been demonstrated that in keratinocytes, 14-3-3\( \gamma \)/R heterodimers bind SSH1 in the absence of Rac1 signaling [55]. This interaction leads to an inhibition of SSH1 activity, as measured by an increase in phosphorylated coflin levels. Overexpression of the carboxy terminal domain of 14-3-3\( \gamma \) acts as a dominant negative and inhibits the interaction between 14-3-3\( \gamma \) and SSH1, providing evidence that 14-3-3\( \gamma \)/R heterodimers function as key regulators of SSH1 activity in keratinocytes [55]. Taken together, these results indicate that \( \alpha_6\beta_4 \) integrin signaling via Rac1, 14-3-3 proteins and SSH family members regulates coflin activation, cell polarity and matrix assembly, leading to specific epidermal cell migration behavior.

Based on the above published data, we propose a working model that provides an overview of how \( \alpha_6\beta_4 \) integrin and the BP antigens may regulate keratinocyte motility (Fig. 4). \( \alpha_6\beta_4 \) integrin heterodimers move into the assembling lamellipodium (Fig. 4). They interact with ligand (laminin-332) in the matrix, recruit the BP antigens, and associate (indirectly) with the cytoskeleton (Fig. 4). We suggest that in the lamellipodium and along its base, \( \alpha_6\beta_4 \) integrin and the BP antigens interact with actin (Fig. 4). The latter is consistent with reports of an association of actin with \( \alpha_6\beta_4 \) integrin in actively migrating cancer cells [64]. It should be noted that \( \alpha_6\beta_4 \) integrin at the site of the lamellipodium is unlikely to interact with the keratin cytoskeleton since intermediate filaments are extremely sparse within the lamellipodium [65].
Moreover, keratin bundles in keratinocytes are found in the cytoplasm inside the circular arrays of actin that occur at the base of the lamellipodium [86] (unpublished observations).

The formation of α6β4 integrin/BP antigen/actin cytoskeleton/laminin-protein complexes stabilizes the lamellipodium required for cell movement. In addition, by recruiting the BP antigens, α6β4 integrin activates Rac and subsequently coflin. As mentioned above, the consequence of coflin activation is the further extension of the lamellipodial surface and directed migration. As the cell moves forward the tethered integrin stays in place. This whole process is then repeated.

7. Conclusions

Two major inherited bullous diseases, epidermolysis bullosa and Kindler syndrome, have taught us much about the structure and functions of both focal contact and hemidesmosome proteins. Molecular genetic and live cell imaging analyses have elucidated new functions for the latter in both migration and adhesion. The dogma that hemidesmosome proteins are exclusively involved in stable adhesion while focal contacts are primarily involved in migration is being questioned. Novel signal pathways regulated by hemidesmosome protein complexes in migrating cells have recently been uncovered. It is to be hoped that this new knowledge may lead eventually to therapies that enhance wound closure. Numerous question, however, remain. Why are there unaffected areas of the skin in inherited blistering skin diseases, such as EB and Kindler syndrome? Is this due to compensation by other adhesion systems? Will identification of such compensatory areas of the skin in inherited blistering skin diseases, such as EB, lead eventually to therapies that enhance wound closure. Numerous question, however, remain. Why are there unaffected areas of the skin in inherited blistering skin diseases, such as EB and Kindler syndrome? Is this due to compensation by other adhesion systems? Will identification of such compensatory areas of the skin in inherited blistering skin diseases, such as EB, lead eventually to therapies that enhance wound closure.

Conflict of interest

The authors have no conflict of interest to declare.

Acknowledgements

Grant support: The work was supported in part by a grant from the National Institutes of Health (RO1 AR054184) to JCRJ. We are grateful to Drs. Toshiyuki Ozawa, Sho Hiroyasu, Hiromi Kobayashi, Masamitsu Ishii (Osaka City University), Dr. Yasuo Kitajima (Gifu University) and Yumi Aoyama (Okayama University) for their helpful discussion during the preparation of this article.

Funding source: The work was supported in part by a grant from the National Institutes of Health (RO1 AR054184) to JCRJ.

References


