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

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Abstract

The outer most layer of the skin, the epidermis, is attached to the dermis via a sheet of extracellular matrix proteins termed the basement membrane zone (BMZ). In the intact skin, adhesion of the keratinocytes in the basal layer of the epidermis to the BMZ is facilitated primarily by hemidesmosomes which associate with the keratin cytoskeleton. Cultured keratinocytes do not assemble bona fide hemidesmosomes although hemidesmosome protein clusters (stable anchoring contacts) are found along the substrate-attached surface of the cells and towards the leading edge of keratinocytes repopulating scratch wounds. Actin cytoskeleton-associated matrix adhesion devices termed focal contacts are not thought to play an important role in the adhesion of keratinocytes to the BMZ in intact skin but are prominent in cultured keratinocytes where they are believed to regulate cell migration. We review the molecular components, functions, dynamics and cross-talk of hemidesmosomes and focal contacts in keratinocytes. In addition, we briefly describe what is known about their role in autoimmune and genetic blistering diseases of the skin. We also discuss recent publications which indicate, contrary to expectation, that certain focal contact proteins retard keratinocyte migration while hemidesmosomal proteins regulate directed keratinocyte motility during wound healing.

Keywords

Matrix adhesion; Focal adhesion; Focal complex; Bullous pemphigoid; Epidermolysis bullosa; Wound repair

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Conflict of interest

The authors have no conflict of interest to declare.

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 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 actively 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 α3 integrin component of the focal contacts of keratinocytes stabilizes hemidesmosome protein complexes in the plane of the membrane. Furthermore, both the dynamics of focal contacts and hemidesmosome proteins complexes and their interplay is energy and myosin dependent [22].

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].

JEB 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), 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 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-BPIgG 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 β4 integrin cytoplasmic tale induces hemidesmosome disassembly [44]. Serine phosphorylation disrupts β4 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 hemidesmosome 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, fibrinogen and collagen in the

wound bed [46]. Thus, it is not surprising that receptors of the latter molecules, such as α5β1, α2β1 and α3β1 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 α3 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 α3 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 α3β1 association with laminin-332 at the site of focal contacts was considered to enhance keratinocyte migration whereas integrin α6β4 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 α3β1 integrin, rather than supporting migration, inhibits the motility of keratinocytes [51]. These workers generated mice exhibiting an epidermal targeted α3 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 α3 integrin, the α3 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 α3 integrin in supporting migration on laminin-332 matrices? Primarily, data in support of the later conclusion comes from the use of an α3 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 α3β1 integrin adhesion to ligand but also, by clustering α3β1 integrin, may trigger signaling that inhibits the activity of a motility receptor. The notion that α3β1 integrin crosstalks and inhibits the activation state of other integrin receptors has been suggested by others [52,53].

There is also emerging data that α6β4 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 α6β4 integrin and its matrix ligand laminin-332 are found towards the leading edge of their extending lamellipodium [14,48]. In addition, in migrating cells α6β4 integrin shows actin-dependent dynamics at the site of the nascent lamellipodium as determined by FRAP [14]. Moreover, we and others have demonstrated that α6β4 integrin through activation of Rac, regulates keratinocyte front-rear polarity and directed migration [54,57]. Taken together, these data suggest that α6β4 integrin is an important part of the steering machinery of keratinocytes.

α6β4 integrin is not the only hemidesmosomal component involved in regulating keratinocyte motile behavior. Specifically, BP230, which mediates the interaction of α6β4 integrin in hemidesmosomes with the keratin cytoskeleton in stationary cells, regulates Rac/α6β4 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 cofilin [54,59–61]. By severing actin filaments, cofilin 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 β4 integrin or BP230 deficiency would perturb lamellipodial formation and/or stability. Indeed, keratinocytes lacking either β4 integrin or BP230 exhibit abnormal lamellipodial numbers and lack front-rear polarity [14,56].

Cofilin phospholyration 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 cofilin, 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/α6β4 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 α6β4 integrin [55,56]. Moreover, using amino or carboxy terminal domains of 14-3-3ζ, it has been demonstrated that in keratinocytes, 14-3-3ζ/τ 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 cofilin levels. Overexpression of the carboxy terminal domain of 14-3-3ζ acts as a dominant negative and inhibits the interaction between 14-3-3τ and SSH1, providing evidence that 14-3-3ζ/τ heterodimers function as key regulators of SSH1 activity in keratinocytes [55]. Taken together, these results indicate that α6β4 integrin signaling via Rac1, 14-3-3 proteins and SSH family members regulates cofilin 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 α6β4 integrin and the BP antigens may regulate keratinocyte motility (Fig. 4). α6β4 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, α6β4 integrin and the BP antigens interact with actin (Fig. 4). The latter is consistent with reports of an association of actin with α6β4 integrin in actively migrating cancer cells [64]. It should be noted that α6β4 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 [66] (unpublished observations).

The formation of α6β4 integrin/BP antigen/actin cytoskeleton/matrix complexes stabilizes the lamellipodium required for cell movement. In addition, by recruiting the BP antigens, α6β4 integrin activates Rac and subsequently cofilin. As mentioned above, the consequence of cofilin 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 mechanisms lead to new treatments for these devastating diseases? How precisely are the dynamics of hemidesmosome protein complexes and focal contacts coordinated? Is laminin-332 a key player in the latter since laminin-332 is a ligand for integrins of both the focal contact and hemidesmosome. What are the mechanisms that regulate the deposition of patterns of laminin-332 by moving skin cells and do these patterns determine motility behavior? By what molecular mechanism does α3 integrin retard skin cell motility? Finally, mechanisms regulating hemidesmosome disassembly have been identified [44]. However, we still do not understand the molecular mechanisms that control the switch that changes hemidesmosome protein function from being a “driver” of motility to being a mediator of stable attachment to the BMZ. Uncovering this mechanism will be an important avenue of research to pursue in the future.

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Biography

Daisuke Tsuruta received the MD degree from Osaka City University Medical School, Osaka, Japan in 1992. He researched on the interaction between Langerhans cells and dendritic epidermal T cells in contact hypersensitivity and received the PhD degree from Osaka City University Graduate School of Medicine in 1999. He worked as a postdoctoral research fellow in the Department of Cell and Molecular Biology, Northwestern University, Chicago in 2000–2003 supervised by Prof. Jonathan Jones. After coming back to Japan, he appointed as an assistant professor in Osaka City University Graduate School in 2003–2010 with Prof. Masamitsu Ishii. His research interests include dynamics of matrix adhesions in normal, wound, and diseased keratinocytes and the role of matrix adhesions in hair cycle. He is currently working as an associate professor in the Department of Dermatology, Kurume University School of Medicine and Kurume University Institute of Cutaneous Cell Biology, Kurume, Fukuoka, Japan.

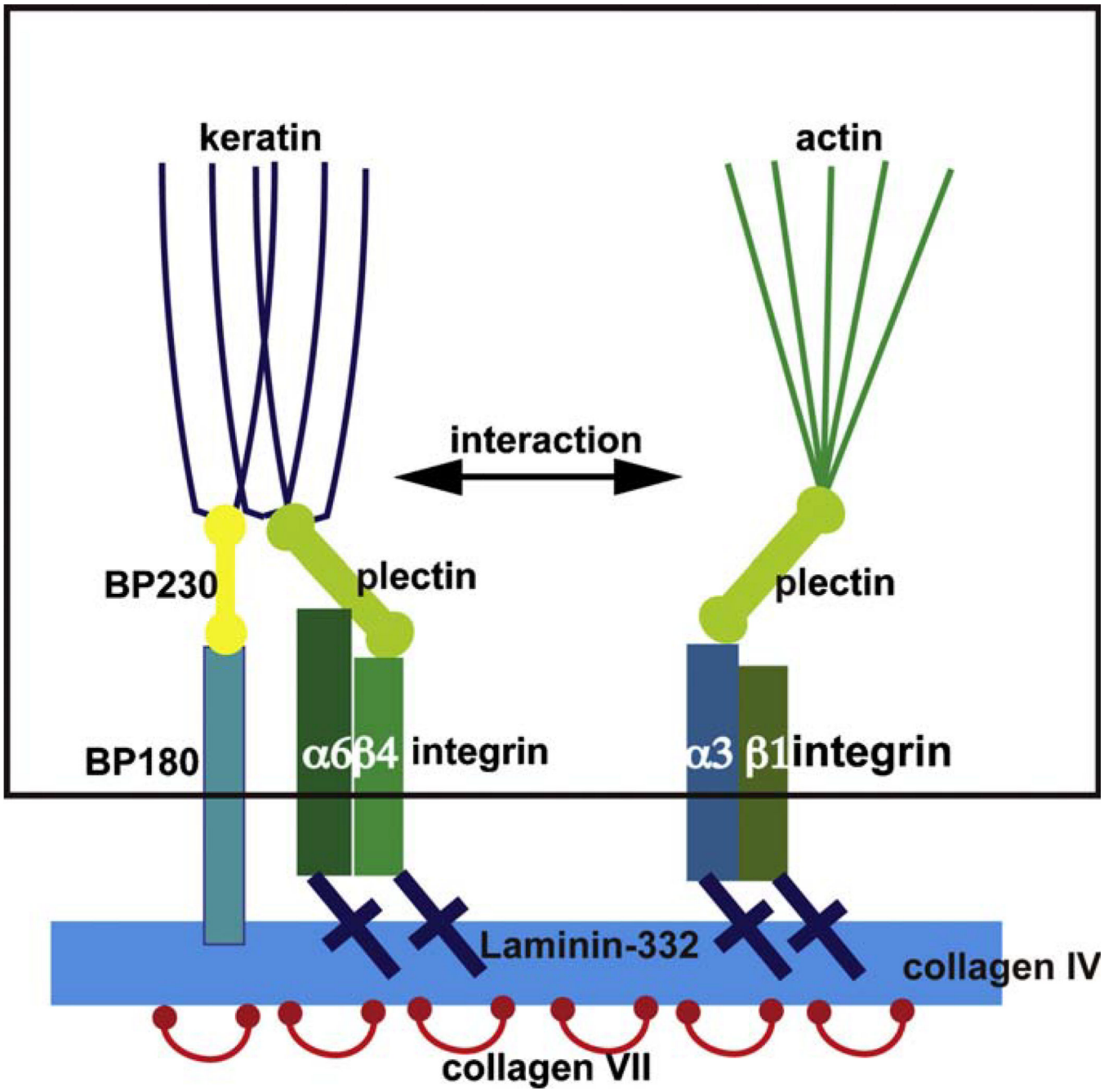

Fig. 1.
Molecular composition of hemidesmosomes and focal contacts in keratinocytes.

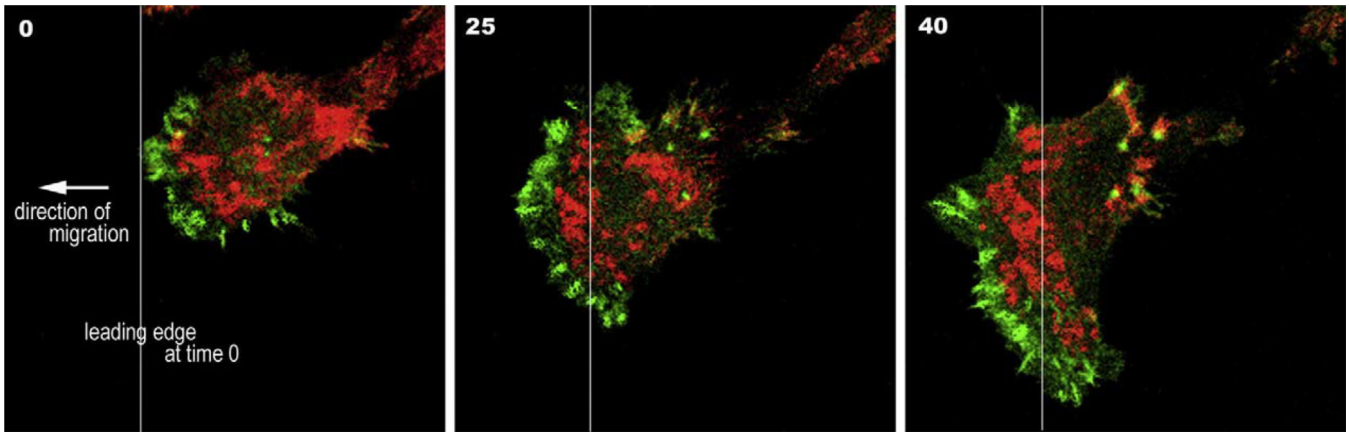

Fig. 2.

Still images for the dynamics of hemidesmosomal proteins and focal contact proteins in live migrating keratinocytes.

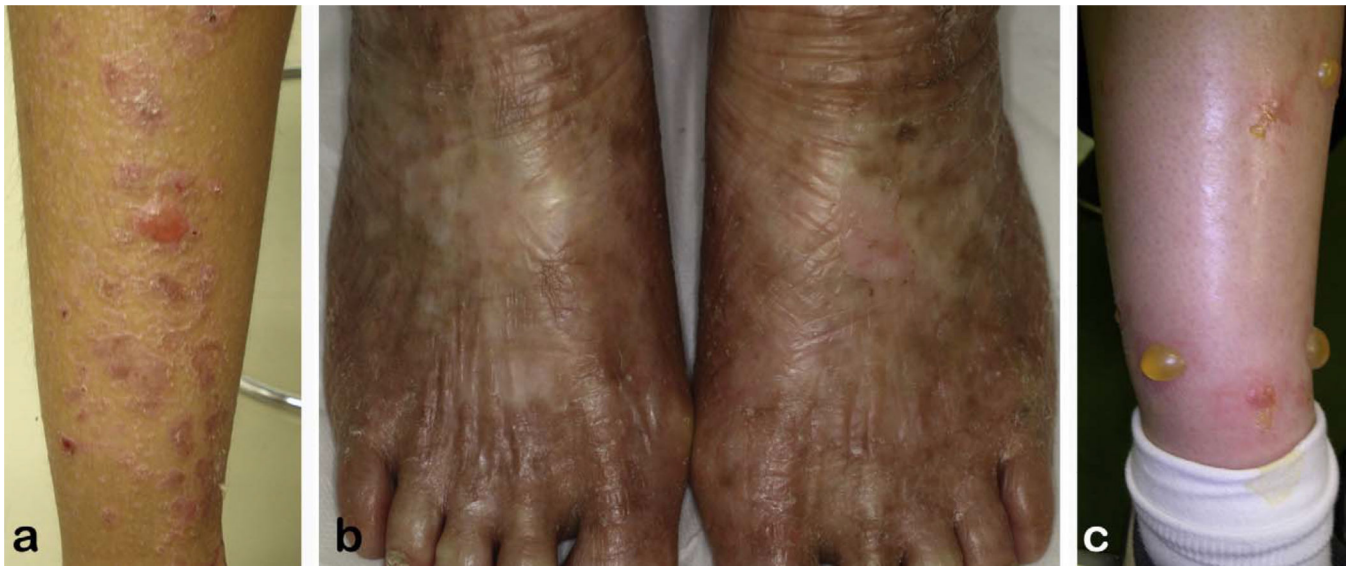

Fig. 3.
Clinical photos for epidermolysis bullosa simplex (a), Kindler syndrome (b), and bullous pemphigoid (c).

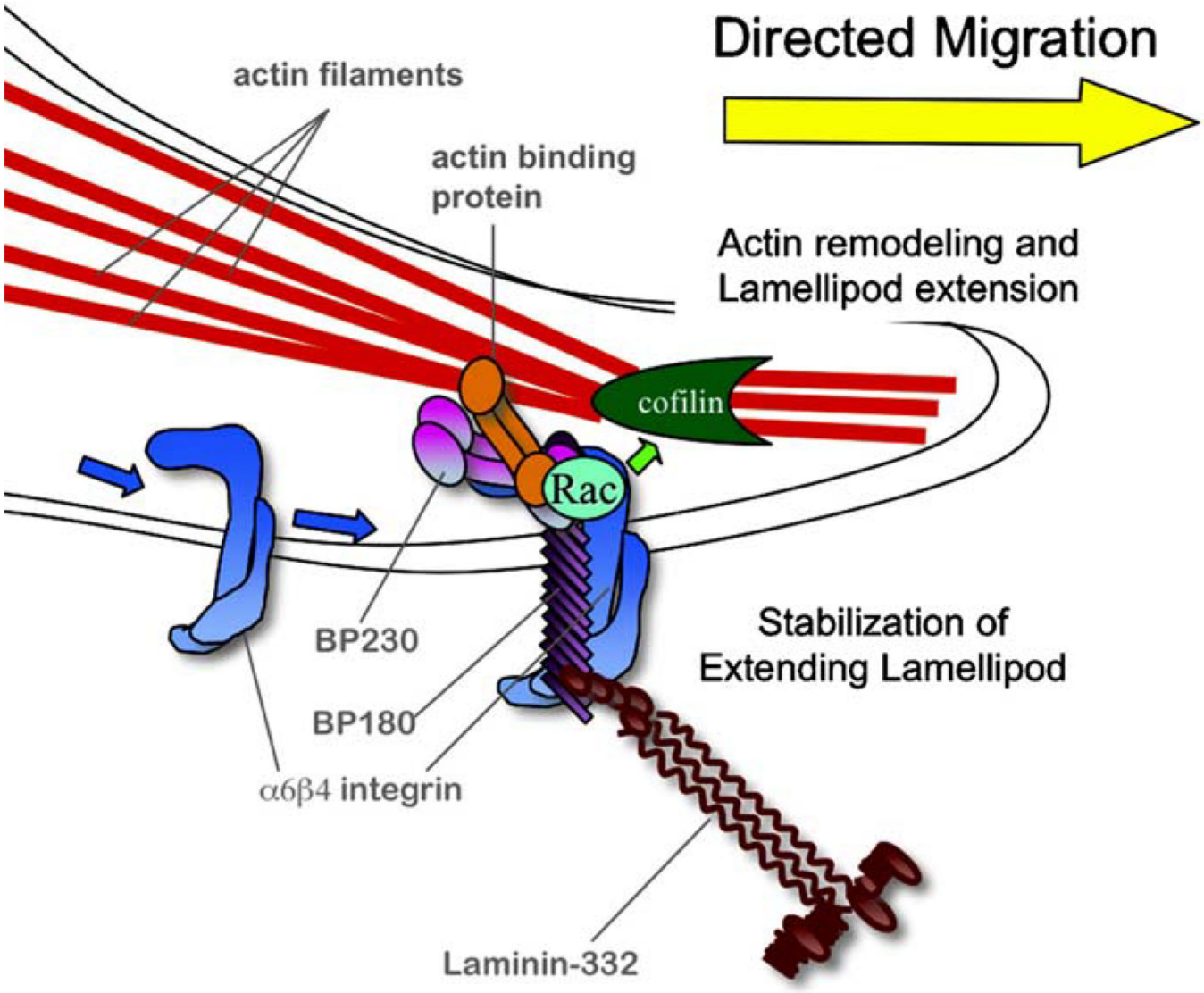

Fig. 4.
Model for the role of hemidesmosome protein complexes in migration.

Table 1

Diseases whose pathogenesis involves hemidesmosomal or focal contact components.

	Inherit bullous diseases	Autoimmune bullous diseases
Hemidesmosome-related	Epidermolysis bullosa (EB) hereditaria	Bullous pemphigoid
	EB simplex (EBS)	Acquired EB
	Weber-Cockayne	Anti-laminin γ1 pemphigoid
	Koebner	Linear IgA bullous dermatosis
	Dowling-Meara	mucous membrane pemphigoid (MMP)
	Pretibial	
	EBS with muscular dystrophy	
	Junctional EB (JEB)	
	Herlitz type	
	JEB with pyloric atresia	
	Non-Herlitz type	
	Dystrophic EB (DEB)	
	Dominant DEB	
	Recessive DEB	
Focal contact-related	Kindler syndrome	None