CRITICAL REVIEWS IN ORAL BIOLOGY & MEDICINE

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*J Dent Res* 90(12):1367-1376, 2011

# Epithelial Integrins with Special Reference to Oral Epithelia

## ABSTRACT

Adhesion of epithelium to the extracellular matrix is crucial for the maintenance of systemic and oral health. In the oral cavity, teeth or artificial dental implants penetrate the soft tissue of the gingiva. In this interface, gingival soft tissue needs to be well attached *via* the epithelial seal to the tooth or implant surface to maintain health. After injury or wounding, epithelial tissue rapidly migrates to form the initial epithelial cover to restore the barrier against infection. These events are crucially dependent on deposition of extracellular matrix and proper activation and function of integrin receptors in the epithelial cells. Recent experimental evidence suggests that epithelial integrins also participate in the regulation of periodontal inflammation. In this review, we will discuss the structure and function of epithelial integrins and their extracellular ligands and elaborate on their potential role in disease and repair processes in the oral cavity.

**KEY WORDS:** wound healing, receptors, extracellular matrix (ECM), cell-matrix interactions, gingiva, keratinocyte(s).

DOI: 10.1177/0022034511402207

Received November 23, 2010; Last revision February 7, 2011; Accepted February 7, 2011

A supplemental appendix to this article is published electronically only at http://jdr.sagepub.com/supplemental.



## INTEGRINS

Integrins are cell adhesion receptors that bind to extracellular matrix ligands, such as fibronectin and collagens. An overview of integrins is presented in the Appendix. Briefly, all integrins are products of two separate genes encoding specific α and ß subunits (Fig. 1). Inside the cell, the cytoplasmic domains of integrins associate with cytoskeletal proteins (Fig. 2). Integrins can be activated by ligand binding or *via* intracellular processes (Fig. 2). Integrins mediate information from the extracellular matrix (ECM) into the cell in a two-way process that regulates gene expression, cell proliferation, and cell migration (Fig. 3).

## ADHESION MECHANISMS OF JUNCTIONAL EPITHELIUM TO TOOTH SURFACE

Junctional epithelium (JE) forms a non-keratinized thin structure that attaches the gingival soft tissue to tooth enamel or cementum (reviewed in Bosshardt and Lang, 2005). JE undergoes continuous renewal by active cell proliferation of basal epithelial cells (keratinocytes) both on the connective tissue side and against the hard tissue. Because of its unique location between hard and soft tissue, JE serves a crucial protective role against bacterial and physical insults. Intercellular junctions are relatively loose in JE that contains only a few desmosomes, adherens junctions, and gap junctions, thus allowing tissue exudate and inflammatory cells to penetrate toward the gingival sulcus (Bosshardt and Lang, 2005).

Unique to JE, it has a true basement membrane toward the connective tissue of gingiva (called the external basal lamina, EBL) and a simple ECM (called the internal basal lamina, IBL) against the enamel. The EBL contains the very same structures seen in typical basement membranes, namely, lamina lucida against the basal keratinocytes and lamina densa toward the connective tissue stroma. The IBL differs significantly from a typical basement membrane in terms of its protein composition (Table, A). All classic basement membrane zone proteins, including laminin 111, laminin 511, type IV and VII collagens, and perlecan, are absent from the IBL (Hormia *et al*., 1998). The main cell adhesion protein identified so far in the IBL is laminin 332 (previously called laminin 5), which is also present in the EBL (Hormia *et al*., 1998, 2001; Oksonen *et al*., 2001). Curiously, 2 proteins that are not commonly found in other epithelial basement membranes, namely, type VIII collagen and versican, have also been reported to be present at the JE-tooth interface (Salonen *et al*., 1991; Abiko *et al*., 2001). In addition, other proteins may also be present, such as tenascin-C (Ghannad *et al*., 2008). Likely more proteins will be found with emerging proteomics techniques.

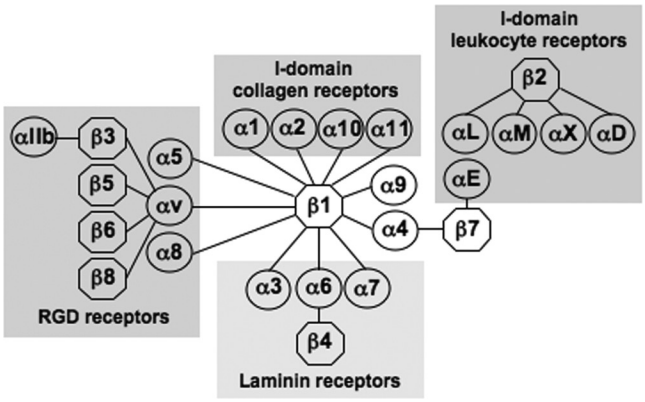


**Figure 1.** Schematic presentation of the integrin family. Modified from Hynes, 2002.

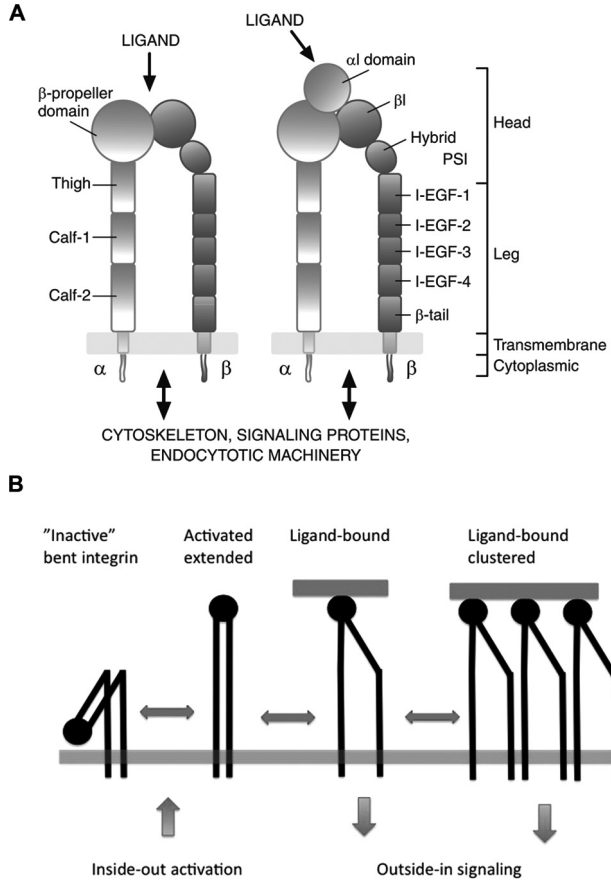


**Figure 2.** Basic domain structure of integrins **(A)** and integrin I-domain conformations **(B).** (A) The domain structure of an integrin. Nine out of 18 human integrin alpha subunits have an inserted domain (alphaI or alphaA domain) (on right) that is missing in the other 9 alpha subunits (on left). Otherwise the extracellular parts of all human integrins have identical domain structures. In the alphaI domain receptors, this domain forms the ligand-binding site. In the other integrins, ligands bind to the beta-propeller (alpha subunit)–betaI domain (beta subunit) interface. Both subunits have single transmembrane domains and short cytoplasmic domains (with the exception of the beta4 subunit, not shown in the Fig.). Cytoplasmic domains mediate the interaction of integrins with cytoskeletal proteins, signaling networks, and endocytotic machinery. I-EGF1-4, integrin epidermal growth factor-like domains 1-4; PSI/Hybrid, plexin-semaphorin-integrin domain/hybrid domain. (B) In an "inactive", "bent" conformation, the ligand-binding head domain of an integrin points toward plasma membrane. Intracellular signals can activate the integrins and force them to "stand up". The "extended" integrin binds to a ligand, which causes further changes in the conformation, *e.g.*, the separation of the leg parts and the intracellular domains. Multivalent ligands can cluster integrins, which also modifies signaling.

Basal keratinocytes adhere to the IBL *via* hemidesmosomes (reviewed in Bosshardt and Lang, 2005). At the most apical aspect of the JE, basal cells synthesizing both IBL and EBL are very close together, and it is unlikely that soluble mediators would be sufficiently different to regulate such dissimilar gene expression profiles. Although molecular cues from the mineralized matrix of the tooth may also play some role, it is more likely that lack of fibroblast influence (cross-talk) during the formation of IBL limits basal keratinocyte gene expression to a simpler variety. Consistent with this hypothesis is the fact that normal basement membranes are jointly produced by basal keratinocytes and fibroblasts, which have extensive cross-talk through paracrine-soluble mediators (Smola *et al*., 1998). Without the presence of fibroblasts, keratinocytes continue to express laminin 332, but fail to deposit laminin 111 and type IV collagen (Smola *et al*., 1998), mimicking the situation at the IBL zone. Recent investigations have demonstrated that, in murine JE, basal cells at the IBL express more than 10 times the laminin 332 transcript found in EBL or in oral epithelium (Kinumatsu *et al*., 2009). Laminin 332 expression is stimulated by several growth factors and cytokines, including TGFß1, tumor necrosis factor-α, keratinocyte growth factor, EGF, and interferon-γ (Kainulainen *et al*., 1998; Amano *et al*., 2004). Many of these factors are constitutively expressed at the JE and may, therefore, be responsible for the abundance of laminin 332 in the IBL (Li *et al*., 2005; Ghannad *et al*., 2008). The function of laminin 332 in the IBL may vary depending on the processing of the molecule (see Appendix). It may also regulate granulation tissue formation (see Appendix).

Expression of integrins in normal JE differs from that of basal cells in the intact oral gingival epithelium (Table, B). Interestingly, healthy JE appears to express integrins that are similar to the ones present in keratinocytes in the oral mucosa and skin during wound re-epithelialization, including expression of αvß6 integrin (see below). This suggests that JE cells are phenotypically unique and/or that they remain constantly in an activated state similar to wound healing (Table, B). In general, basal keratinocytes, including epithelial cells of the JE, interact with the C-terminal LG domains of the α3 chain of laminin 332 *via* α3ß1 and α6ß4 integrins (Fig. 4A; Aumailley *et al*., 2003; see below). Integrin α6ß4 is a crucial part of the hemidesmosome, where it binds to processed laminin 332 (reviewed in Litjens *et al*., 2006). This binding not only supports the firm adhesion of basal keratinocytes but also maintains cell proliferation (Murgia *et al*., 1998). Individuals with mutations in either α6 or ß4 integrins have junctional epidermolysis bullosa similar to patients with mutations in laminin 332 (Litjens *et al*., 2006),

but it is unclear if periodontal tissues are also affected in these patients. At the IBL, α6ß4 integrin co-localizes with laminin 332 (Hormia *et al*., 1992, 2001), suggesting that their interaction is the main mechanism holding the JE attached to the mineralized tissue. Intracellularly, α6ß4 integrin binds plectin to a complex that accumulates BP180 and BP230 (Hormia *et al*., 2001; Litjens *et al*., 2006). These interactions support the mechanical stability of hemidesmosomes.

During coronal migration of the DAT cells (see Appendix), hemidesmosomes are disassembled to allow for cell movement. Although the regulation of this process in JE is not fully understood, it is believed to start with phosphorylation of the ß4 integrin cytoplasmic domain, which leads to a disassociation between ß4 integrin and plectin (Litjens *et al*, 2006; Wilhelmsen *et al*., 2007). There are some indications that at least α5ß1 integrin and tenascin-C may also be present in JE (see Table). Thus, further research is needed to clarify the exact roles of α6ß4, α3ß1, and other integrins in keratinocyte migration in the JE and during periodontal pocket formation. Understanding how keratinocytes migrate on the IBL is also challenging, because the only "certified" ECM ligand consistently present at that location is laminin 332, whose proteolytic processing stage remains unknown.

## ADHESION OF PERI-IMPLANT EPITHELIUM

The dimension of the dento-gingival complex (distance from the gingival margin to bone) has been reported to be slightly greater for oral implants (2.85-3.80 mm) than the corresponding dimension of this complex around teeth (2.73-3.25 mm), regardless of whether the implants have been submerged (Buser *et al*., 1992; Abrahamsson *et al*., 1996, 1999; Berglundh and Lindhe, 1996; Cochran *et al*., 1997; Hermann *et al*., 2001; Fig. 5). The biological width around natural teeth has been reported to be about 2 mm, composed of 1 mm of epithelial attachment mediated by the JE and 1 mm of gingival connective tissue attachment (Gargiulo *et al*., 1961; Vacek *et al*., 1994). Many studies have reported that the peri-implant JE is about 2 mm long (Myshin and Wiens, 2005; Rompen *et al*., 2006; references above). Thus, the increase in the dimension of the dento-gingival complex around oral implants is largely due to the increase in the length of the peri-implant JE, suggesting that conventional implant surfaces cannot deter the formation of "long epithelial attachment" (Fig. 5). Many of these studies have demonstrated the presence of JE with hemidesmosomal attachments to the implant surface, and at the light-microscopic level, the epithelium appeared to be "attached" (see *e.g.,* Gould *et al*., 1984; reviewed in Rompen *et al*., 2006). More recent animal studies, however, challenge the presence of a true JE on dental implants (Ikeda *et al*., 2000, 2002; Fujiseki *et al*., 2003; Atsuta *et al*., 2005a,b). In a fairly recent study, peri-implant epithelium (PIE) appeared to "lean" on the implant, but was structurally very different from JE, displaying slower cell proliferation, weaker expression of JE differentiation marker cytokeratin 19, and no evidence of direct adhesion of the PIE on the implant surface (Fujiseki *et al*., 2003). Earlier studies have also shown slower proliferation of PIE (Inoue *et al*., 1997). Other studies indicate that only the bottom third of the PIE is actually attached to the implant (Ikeda

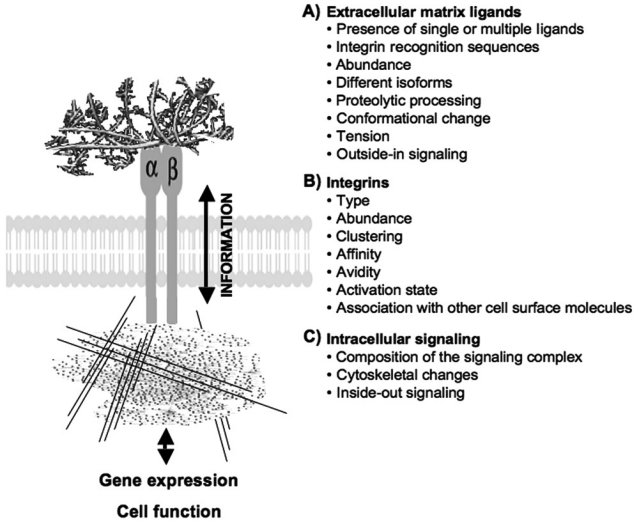


**Figure 3.** Summary of the key factors regulating integrin-mediated interactions and information exchange between the cell and extracellular matrix (ECM). Integrins mediate cell adhesion and migration on the ECM and function as two-way mediators of information between the ECM and cells. **(A)** While attaching the cells to the pericellular matrix, integrins also sense changes in the properties (*e.g.,* tension, proteolytic processing, conformational change) and composition of the ECM and relay this information outside-in to the cell. **(B)** The information exchange through integrins is modulated by and depends on several integrin-related factors, including integrin type, abundance, clustering, etc. **(C)** Interaction with the matrix triggers distinct signaling cascades and cytoskeletal changes allowing the cell to adapt its functions appropriately. Reciprocally, changes in the function of intracellular signaling networks or cytoskeleton modulate integrin activity that can then lead to appropriate changes in the cells' interactions with the ECM.

*et al*., 2000). Consistent with the latter paper, laminin 332 expression between PIE and the implant surface also appears to be limited to the lower part of the the PIE (Atsuta *et al*., 2005a,b; Fig. 5), but very little is known about the expression of integrins in the PIE. Suboptimal attachment of the PIE may contribute to the formation of inflammatory lesions and bone loss around the implants, which has become a common clinical problem (Roos-Jansåker *et al*., 2006; Máximo *et al*., 2008; Koldsland *et al*., 2010). It is possible that poor PIE adhesion allows for apical migration of plaque biofilm and could, therefore, directly explain inflammation and bone loss around bone-level dental implants. Future research should focus on improving epithelial attachment on implants and especially on different abutments, which mediate soft-tissue adhesion in 2-piece implant systems.

## FAILURE TO ACTIVATE INTEGRINS IS LINKED TO PERIODONTAL DISEASE

Kindlins (kindlin-1, -2, and -3) comprise a family of 3 related proteins that are involved in integrin activation inside cells (Larjava *et al*., 2008; Meves *et al*., 2009). Mutations in kindlin-1 and kindlin-3 are associated with human clinical syndromes (Larjava *et al*., 2008). Loss of kindlin-1 causes Kindler

**Table. (A)** Molecular Composition of the External (EBL) and Internal (IBL) Basal Lamina of the Junctional Epithelium; **(B)** Integrin Expression in the Junctional Epithelium (JE), Oral Keratinized Gingival Epithelium (GE), and Wound Epithelium of Keratinized Gingiva (WGE) (See text for references.)

| A. | Basal Lamina Component | EBL | IBL | B. | Integrin | JE | GE | WGE |
|---|---|---|---|---|---|---|---|---|
| | LM111 | √ | – | | α2ß1 | √ | √ | √ |
| | LM332 | √ | √ | | α3ß1 | √ | √ | √ |
| | LM511 | √ | – | | α5ß1 | √* | – | √ |
| | Type IV collagen | √ | – | | α9ß1 | ? | √ | √ |
| | Type VIII collagen | ? | √ | | α6ß4 | √ | √ | √ |
| | Perlecan | √ | – | | αvß1 | ? | – | √ |
| | Versican | ? | √ | | αvß6 | √ | – | √ |
| | Tenascin-C | √ | √* | | | | | |

√Molecule present; √*Variable expression (unpublished results); –Molecule not present; ?Not reported.

syndrome, which is a rare skin-blistering disorder with oral manifestations that include development of early-onset aggressive periodontitis (reviewed in Wiebe *et al*., 2008). In healthy individuals, kindlin-1 is localized in basal keratinocytes of oral epithelia, while it is absent in patients with the Kindler syndrome (Petricca *et al*., 2009). Functional studies using cultured keratinocytes have shown that kindlin-1 deficiency leads to reduced cell adhesion, migration, and proliferation due to deficient integrin activation (Herz *et al*., 2006; Lai-Cheong *et al*., 2008; Has *et al*., 2009; Petricca *et al*., 2009). Interestingly, analysis of histological data from a case report suggests that JE indeed fails to attach firmly to the tooth surface (Wiebe *et al*., 2008). Kindlin-1 binds to ß1 integrin in keratinocytes, and its deficiency does not affect hemidesmosome formation, suggesting that inter-hemidesmosomal ß1 integrin-mediated cell adhesion makes a significant contribution in the formation of firm adhesion of JE to tooth structure.

## REGULATION OF EPITHELIAL CELL PROLIFERATION AND INFLAMMATION *VIA* αvß6 INTEGRIN

Integrin αvß6 is an exclusively epithelial adhesion protein that is absent from most parts of normal healthy epidermis and oral mucosa (Breuss *et al*., 1993). However, αvß6 integrin is constitutively expressed in the JE and oral epithelium of the gingival papilla (Csiszar *et al*., 2007; Ghannad *et al*., 2008). *In vitro*, αvß6 integrin binds to the RGD-containing ECM ligands, including fibronectin, tenascin, vitronectin, and the latent TGFß1 (Huang *et al*., 1996; Koivisto *et al*., 1999; Munger *et al*., 1999). Expression of αvß6 integrin is induced during wound healing, in cancer, and in certain inflammatory conditions (Clark *et al*., 1996; Haapasalmi *et al*., 1996; Hamidi *et al*., 2000; Impola *et al*., 2004; Hahm *et al*., 2007). The function of αvß6 integrin in the progression of oral squamous cell carcinoma has been recently reviewed and will not be a subject of this review (Thomas *et al*., 2006). Interestingly, the major function of αvß6 integrin *in vivo* may not relate to cell adhesion *per se* but to its ability to activate latent TGFß1. The first evidence of this function came from findings showing that inactivation of the ß6 integrin gene results in mild inflammatory changes in the skin and lungs that are associated with altered TGFß1 signaling (Huang *et al*., 1996). TGFß1 belongs to a family of polypeptides that have multiple regulatory functions in tissue repair and the immune system (for reviews, see Chang *et al*., 2002 and Verrecchia and Mauviel, 2002). TGFß1 is synthesized as a latent precursor molecule containing latency-associated peptide (ß1-LAP) that associates with latent TGFß1-binding protein (LTBP1), a component of the ECM (Taipale *et al*., 1994). Activation of latent TGFß1 is a complex process that may involve proteolytic cleavage, conformational changes caused, *e.g.,* by transglutaminase, thrombospondin-1 (TSP-1), or αvß6 integrin. Fairly recent findings have shown that αvß6 integrin mediates TGFß1 activation by binding to the RGD sequence of the ß1-LAP of the TGFß1 protein complex that is fixed to the ECM by LTBP-1 (Annes *et al*., 2004). This binding is believed to generate a retractile force, which introduces a conformational change in the LAP and subsequent activation of TGFß1 (Annes *et al*., 2004).

TGFß1 inhibits epithelial cell proliferation *via* up-regulation of cyclin-dependent kinase inhibitors p15 and p21 (Kane *et al*., 1990; Glick *et al*., 1993; Robson *et al*., 1999). One of the most recognized functions of TGFß1, however, is in immunoregulation, where it can either act as a pro-inflammatory cytokine or induce an anti-inflammatory response (AIR), depending on the biological context and cell types (Wahl *et al*., 2004; Li *et al*., 2006). The TGFß1 AIR is evidenced by the fact that TGFß1 knockout animals die a few weeks after birth from massive infiltration of lymphocytes and macrophages in many organs (Shull *et al*., 1992; Kulkarni *et al*., 1993). TGFß1 mediates the AIR through its immunosuppressive action on T-cells and macrophages. Involvement of αvß6 integrin-mediated activation of TGFß1 in the regulation of lung and skin inflammation has been demonstrated in ß6 integrin-null and ß6/TSP-1 double-null animals whose phenotype resembles, in a milder form, that of TGFß1-null mice (Huang *et al*., 1996; Ludlow *et al*., 2005). Recent evidence indicates that integrin-mediated activation of TGFß1 plays a major role in the AIR *in vivo* (Yang *et al*., 2007). Thus, it has become evident that integrin-mediated activation of TGFß1 regulates the AIR in many tissues, including soft tissues of the oral cavity.

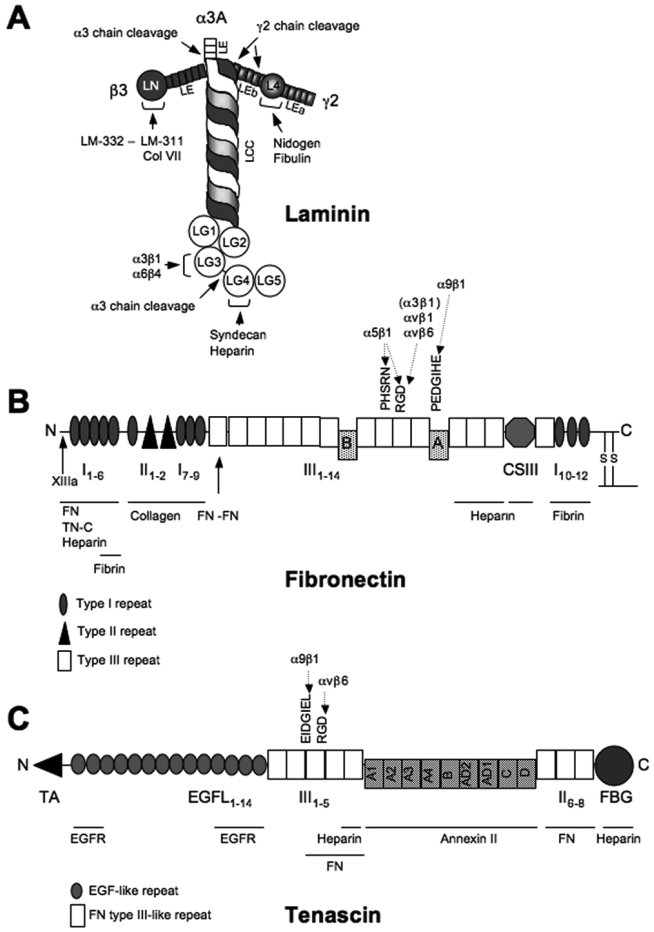


**Figure 4.** Structural and functional domains, major matrix-binding sites, and adhesion sites for epithelial integrins in laminin 332, fibronectin, and tenascin-C. Additional binding sites for non-epithelial integrins exist. **(A)** Laminin-332 is a T-shaped molecule consisting of 3 polypeptide chains, α3A (or long isoform α3B), ß3, and γ2. **(B)** Fibronectin protomer consists of 2 similar subunits linked in an antiparallel orientation by 2 disulphide bridges at their C-termini. It has 3 sites of alternative splicing: Type III repeats A and B can be independently included or excluded to form cellular fibronectin isoforms EDA and EDB, respectively. Splicing within the CSIII segment can produce several variations. **(C)** The N-termini of 3 tenascin-C monomers are joined *via* their TA domains to form a trimer. Two trimers are further linked *via* a disulfide bond to form a hexamer. Nine type III repeats (A-D) can be independently included or excluded to produce different isoforms.

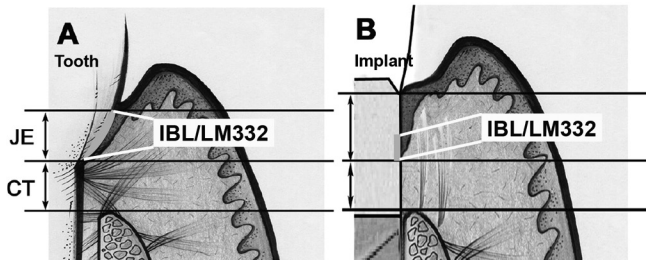


**Figure 5.** Comparison of epithelial adhesion to the natural tooth **(A)** and dental implant surface **(B).** Epithelium attaches to the implant by a longer junctional peri-implant epithelium (JE) as compared with the tooth. Internal basal lamina (IBL) containing laminin 332 (LM332) may be present only in the apical third of the implant-JE interface. CT, connective tissue.

As indicated above, αvß6 integrin is constitutively expressed in JE (Table, B) together with TGFß1 (Ghannad *et al*., 2008). No other αvß6 integrin ligands have been convincingly identified at the JE, although tenascin-C might be present (Table, A). Mice deficient in ß6 integrin develop all the classic signs of chronic periodontal disease, including inflammation, periodontal pocket formation, and bone loss (Ghannad *et al*., 2008). Thus, presence of αvß6 integrin in the JE plays an active protective role in periodontal tissues. Interestingly, expression of αvß6 integrin was markedly down-regulated in the pocket epithelium of chronic periodontitis patients (Ghannad *et al*., 2008). The current understanding of the role of αvß6 integrin in periodontal protection points to the AIR of TGFß1: The constitutive expression of αvß6 integrin in JE activates TGFß1, which controls inflammation at the site. During periodontal disease, increased proliferation of keratinocytes at the JE may also contribute to pocket formation, since reduced expression of αvß6 integrin would result in reduced TGFß1 activation and increased proliferation of JE cells. In fact, lack of TGFß-responsive cyclin-dependent kinase inhibitors in the JE has been shown to increase cell proliferation, suggesting that TGFß1 can play an important role in the regulation of JE proliferation (Watanabe *et al*., 2004). Consistent with the notion that TGFß1 is important in protecting the periodontium from inflammation, significantly increased levels of TGFß1 expression are found in non-active periodontal sites (Dutzan *et al*., 2009). Interestingly, mice deficient in the matricellular protein periostin also develop signs of periodontal disease (Rios *et al*., 2005). Periostin serves as a ligand for αvß3 and αvß5 integrins (Gillan *et al*., 2002). Periostin is strongly expressed in the periodontal ligament, but it is not clear whether periostin or αvß5 is expressed in the JE. Nevertheless, epithelial periostin can also regulate TGFß1 activation that could partially contribute to the immunoprotection of the periodontium (Sidhu *et al*., 2010). Thus, for periodontal health to be maintained, controlling inflammatory response may prove to be equally as important as the elimination of bacterial biofilm (Van Dyke and Serhan, 2003; Hasturk *et al*., 2006).

## ROLE OF EPITHELIAL CELL ADHESION MOLECULES DURING ORAL MUCOSAL WOUND HEALING

Few studies specifically explore the mechanisms of oral mucosal wound re-epithelialization. Therefore, much of the presented data draw from findings from skin wound healing and *in vitro* experiments, with an assumption that oral wounds heal largely in a similar manner.

After wounding occurs, epithelial cells come into contact with proteins from the underlying connective tissue at the wound edge, including type I collagen. In addition, they encounter the proteins present in the wound blood clot, consisting of polymerized fibrils

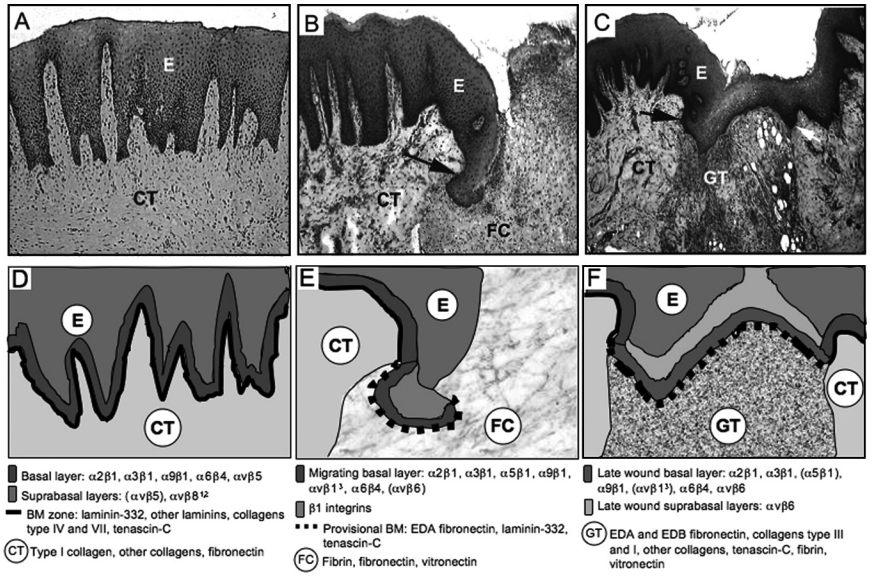


**Figure 6.** Structural organization (hematoxylin-eosin staining; **A-C**) and schematic presentation (**D-F**) of the expression of keratinocyte integrins and matrix molecules in healthy (A, D) and wounded (B, C, E, F) human gingival mucosa. Healthy epithelium (A, D), 3-day wound (early wound; B, E), and 7-day wound (migrating epithelial fronts have just joined; C, F). E, epithelium; CT, connective tissue, FC, fibrin clot; GT, granulation tissue; BM, basement membrane. Arrows mark the wound margin. [1]Expression shown in skin wounds, presence in oral epithelia unknown. [2]Expression has not been studied during re-epithelialization. [3]Induction of expression is based on indirect evidence from immunostaining experiments.

of plasma fibronectin that are cross-linked to fibrin (Figs. 4B, 6). This fibrin-fibronectin matrix acts as a scaffold for further accumulation of ECM molecules such as heparin, denatured collagen, and tenascin-C (Gailit and Clark, 1994; Pankov and Yamada, 2002; Figs. 4, 6). Wounding also induces the expression of novel matrix molecules underneath the migrating keratinocytes, such as the EDA fibronectin (extra domain A or EIIIA), tenascin-C, and the unprocessed laminin 332 (Ffrench-Constant *et al*., 1989; Larjava *et al*., 1993; Häkkinen *et al*., 2000; Singh *et al*., 2004; Figs. 4, 6). Therefore, in wounds, keratinocytes encounter an environment with a complicated composite matrix of novel substances. Of these molecules, especially EDA fibronectin and laminin 332 appear essential for keratinocyte migration and re-epithelialization during wound healing (Muro *et al*., 2003; Hartwig *et al*., 2007). Tenascin-C regulates fibronectin deposition in wounds but does not seem to play a critical role in wound re-epithelialization, at least in the skin, although its elimination interferes with corneal wound healing (Mackie and Tucker, 1999). Its increased expression in the subepithelial connective tissue in oral mucosal wounds, however, may be associated with significantly reduced scar formation in these wounds compared with skin (Wong *et al*., 2009).

Because wounding alters the composition of ECM around keratinocytes, they need to adjust their cell adhesion receptors to interact with it. The first major change in integrin expression happens shortly after wounding, when wound edge keratinocytes dissolve their hemidesmosomal connections with basement membrane, and the distribution of α6ß4 integrin becomes diffuse around the basal keratinocytes (Borradori and Sonnenberg, 1999). At the same time, the expression of α2ß1, α3ß1, and α9ß1 integrins increases (Cavani *et al*., 1993; Juhasz *et al*., 1993; Larjava *et al*., 1993; Häkkinen *et al*., 2000; Singh *et al*., 2004). Concurrently, wounding induces the expression of 3 new fibronectin receptors, namely, α5ß1, αvß1, and αvß6 integrins, in the wound keratinocytes (Cavani *et al*., 1993; Larjava *et al*., 1993; Haapasalmi *et al*., 1996; Fig. 6). The process of re-epithelialization is well protected by collaboration between these different integrins and other receptor systems (Fig. 6). To this end, many of the integrins expressed by wound keratinocytes can bind multiple ligands present in the wound matrix, and, conversely, the same ligand can be recognized by several different integrins. For example, wound keratinocytes may use α9ß1 and αvß6 integrins for tenascin-C binding, and laminin 332 is recognized by α2ß1, α3ß1, and α6ß4 integrins, whereas α5ß1, αvß1, and αvß6 integrins serve as receptors for both plasma and cellular EDA fibronectin (Carter *et al*., 1991; Prieto *et al*., 1993; Yokosaki *et al*., 1994; Johansson *et al*., 1997; Décline and Rousselle, 2001; Fig. 4). In addition, α9ß1 integrin can serve as a receptor for EDA fibronectin and regulate keratinocyte proliferation at the wound edge (Liao *et al*., 2002; Singh *et al*., 2009; Fig. 4). The overlapping functions of keratinocyte adhesion molecules help to explain why elimination of individual cell adhesion molecules often produces amazingly mild effects in animal wound-healing models. For example, cultured keratinocytes can adaptively use at least αvß6, αvß1, α5ß1, and α3ß1 integrins for fibronectin binding (Koivisto *et al*., 1999). However, it appears that ß1 integrins as a group are fundamental for wound re-epithelialization, since keratinocyte migration and re-epithelialization are severely compromised in mice with keratinocyte-specific knockout of the ß1 integrin subunit (Raghavan *et al*., 2000; Grose *et al*., 2002).

Since intermediate adhesiveness to matrix proteins favors cell motility, utilization of intermediate-strength integrin-matrix interactions in co-operation is required for re-epithelialization. This may be achieved by focalized denaturation of collagens, assembly of composite matrices with reduced adhesiveness, reducing the strength of high-affinity integrin binding, and robust expression of low-affinity integrins. For example, the high-affinity interaction of α2ß1 integrin with fibrillar collagens induces the expression of MMP-1 at the migrating epithelial front, resulting in focalized denaturation of the collagen matrix and dissociation of these high-affinity contacts (Saarialho-Kere *et al*., 1993; Pilcher *et al*., 1997). Notably, migration of human keratinocytes on type I collagen *in vitro* requires both α2ß1

integrin and MMP-1 (Pilcher *et al*., 1997). Denatured collagen may also indirectly influence keratinocyte migration through binding of fibronectin and growth factors (Davis *et al*., 2000).

Strong expression of αvß1 integrin, a low-affinity fibronectin receptor, may also facilitate keratinocyte migration by supporting cell attachment without decelerating the migration speed (Zhang *et al*., 1993; Koivisto *et al*., 1999). Additionally, it appears that the interplay between and among fibronectin, tenascin-C, and their integrin receptors regulates wound re-epithelialization, since binding of tenascin-C to fibronectin reduces the strength of the high-affinity α5ß1 integrin-fibronectin interaction to facilitate migration (Kim *et al*., 1992a; Hauzenberger *et al*., 1999; Ingham *et al*., 2004).

The role of α3ß1 integrin in re-epithelialization is complex, and its exact functions in re-epithelialization have not yet been conclusively established. Curiously, α3ß1 integrin has been reported to either mediate the migration of cultured keratinocytes or inhibit it (Kim *et al*., 1992b; Zhang and Kramer, 1996; Goldfinger *et al*., 1999; Décline and Rousselle, 2001; deHart *et al*., 2003). Similarly, *in vivo* re-epithelialization studies have yielded conflicting results. In two recent studies, re-epithelialization was either slightly accelerated or not negatively affected in skin wounds of mice with keratinocyte-targeted knockout of the α3 integrin subunit (Margadant *et al*., 2009; Mitchell *et al*., 2009). However, results of another recent study suggested that α3ß1 integrin facilitates re-epithelialization by modulating TGFß1-mediated responses in the wound (Reynolds *et al*., 2008). In addition, α3ß1 integrin can function as a trans-dominant inhibitor of other ß1 integrins, including α2ß1 and α5ß1 (Hodivala-Dilke *et al*., 1998), again reducing the strength of keratinocyte attachment during re-epithelialization. Interestingly, α6ß4 integrin facilitates re-epithelialization by supporting EGF signaling even when it is not bound to its ligand, laminin 332, and deletion of the signaling domain of the ß4 subunit causes decelerated wound re-epithelialization (Russell *et al*., 2003; Nikolopoulos *et al*., 2005). Further studies are needed for a more detailed understanding of the roles of the laminin receptors α3ß1 and α6ß4 integrins in wound re-epithelialization.

The re-epithelialization phase of oral mucosal wound healing comes to an end when the migrating epithelial fronts originating from the wound edges have joined and cover the wound surface. At this stage, the expression of ß1 integrins is down-regulated (Fig. 6), and α6ß4 integrin binding to the proteolytically cleaved laminin 332 is restored (Larjava *et al*., 1993; Goldfinger *et al*., 1999). As a consequence, hemidesmosomal adhesions provide nucleation sites for complete basement membrane restoration, allowing keratinocytes to resume their normal differentiation process (Jones *et al*., 1994; Litjens *et al*., 2006). In small oral mucosal wounds, the nucleation of the basement membrane occurs simultaneously in several places along the wound epithelium (Larjava *et al*., 1993).

During this phase of oral mucosal wound healing, αvß6 integrin expression is significantly up-regulated in the basal and several suprabasal keratinocyte layers, coinciding with the peak expression of biologically active TGFß1 (Haapasalmi *et al*., 1996; Yang *et al*., 1999; Häkkinen *et al*., 2000; Fig. 6). However, whether αvß6 integrin is involved in TGFß activation during wound healing, or whether it serves other functions, remains to be shown. Interestingly, αvß6 integrin seems to be dispensable during normal wound healing, but may play a significant role in chronic wounds and in wounds compromised by corticosteroids (Häkkinen *et al*., 2004; Xie *et al*., 2009).

## CONCLUDING REMARKS

Cell adhesion and integrins regulate many crucial functions of oral epithelial cells. Activation of ß1 integrins together with α6ß4 integrin-mediated laminin 332 binding regulates adhesion of JE cells to enamel. These mechanisms appear to be poorly developed in PIE. In addition, αvß6 integrin in JE may control periodontal inflammation *via* TGFß1 activation. Many integrins and matrix molecules collectively regulate re-epithelialization during wound healing. Overall, epithelial cells have been proven to function far beyond their traditional role in providing a protective barrier for connective tissues. Future research should be focused on identifying in more detail the cell adhesion molecules that are expressed in tooth and implant interfaces.

## ACKNOWLEDGMENTS

This study is supported by the following NIH grants: U01-DE018903, U01-HG004438, U01-HG004423, U01-HG004446, R01-DE014899, R01-DE0 9551, R01-DE12101, R03-DE021425, and P60-DE-13076, and by NIH contract HHSN268200782-096C. Other support was provided by the Danish NRF, Danish Pharmacists Fund, Egmont Foundation, March of Dimes, Augustinus Foundation, and Health Fund of the Danish Health Insurance Societies.

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