



Review Article

Role of integrins in wound repair and its periodontal implications

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ABSTRACT

Wound healing in human periodontium is a complex process which involves both cell-cell and cell-matrix interactions. Integrins play a major role in regulation of these cell-cell, cell-matrix interaction. Wound healing involves two major events i.e. re-epithelialization and connective tissue repair. In this concise review, we will discuss the role of integrins in these major events as well as their implications in periodontal wound repair. Integrins are differentially expressed in both of these major events. In re-epithelialization, keratinocytes express novel integrins receptors $\alpha v \beta 1$, $\alpha 5 \beta 1$ and $\alpha v \beta 6$ which are not expressed in normal healthy epithelium. Re-epithelialization also involves interaction of integrins with TGF- β and fibronectin. Similarly, in connective tissue repair, the activation of fibroblast as well as the expression of integrins $\alpha 5 \beta 1$ and $\alpha 3 \beta 1$ is upregulated. In healthy periodontium, integrin $\alpha v \beta 6$ is normally expressed in junctional epithelium which is generally expressed only at wound sites in other parts of the body. The epithelialization at implant surface has not been yet fully explored with respect to interactions among integrins and other extra-cellular matrix molecules.

1. Introduction

Wound healing in human periodontium is a complex process that restores tissue integrity and involves coordinated functions and interactions of different cell types, extracellular matrix, cytokines and certain growth factors.¹ Periodontal wound healing is of great significance in the treatment of periodontal diseases involving non-surgical and surgical procedures.¹ Interactions between cell and extracellular matrix in periodontal wound healing is controlled by certain cell surface receptors including integrins and other ECM molecules.²

Integrins are heterodimeric transmembrane glycoproteins receptors formed by non covalently associated α and β subunits and are critical in a number of physiologic and pathologic process including cell differentiation and proliferation in wound healing, cell-cell adhesion, attachment and signal transduction between cell and extracellular matrix.^{3,4} Integrins belong to family of cellular adhesion molecules (CAM) and function as cell surface receptors for specific ligands.⁵ Adequate ligand binding to both α and β heterodimers is followed by specific cell-extracellular matrix interactions.⁵ In mammals, integrin receptor family comprises of 8β and 18α subunits, the combination of which results in 24 distinct integrins having specificity for different ligands.^{5,6}

Integrins are expressed by various cell types including epithelial cells, fibroblasts, osteocytes, endothelial cells, leukocytes and platelets.⁵

Human epithelial cells express 7 distinct type of integrins $\alpha 2 \beta 1$, $\alpha 3 \beta 1$, $\alpha 5 \beta 1$, $\alpha 9 \beta 1$, $\alpha 6 \beta 4$, $\alpha v \beta 1$, $\alpha v \beta 6$.² However, due to unique structural morphology, $\alpha 9 \beta 1$ and $\alpha v \beta 1$ are not reported in junctional epithelium.² Interestingly, $\alpha v \beta 6$ is absent from most parts of normal healthy epidermis, oral mucosa and is only expressed in junctional epithelium and oral epithelium of gingival papilla.^{7,8}

Integrins play a key role in wound repair involving epithelial and connective tissue repair through their function in cell adhesion as bi-directional, allosteric signaling machines.^{6,9,10}

2. Epithelial wound healing

2.1. Epithelial integrins and their ligands in wound healing

Certain proteins and glycoproteins act as ligands for epithelial integrins in wound healing. Collagen is seen to be the optimum ligand for $\alpha 2 \beta 1$ whereas tenascin binding is also highly expressed in migrating keratinocytes.¹¹ $\alpha 3 \beta 1$ is the receptor capable of binding multiple ligands, however in wound healing, binding of $\alpha 3 \beta 1$ to laminin 332 (previously called laminin -5) plays a significant role in promotion of migrating pattern of keratinocytes.^{2,11} Laminin 332 is highly expressed by migrating keratinocytes and is also seen to be an adequate ligand for $\alpha 6 \beta 4$ integrin acting as a nucleator of basement membrane

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organization.^{11,12} Integrin $\alpha 5\beta 1$ is of particular significance in wound healing and is key receptor exclusively for serum fibronectin and fibronectin EIII/A.^{11,13} $\alpha 5\beta 1$ and $\alpha \nu\beta 5$ are vitronectin receptor and attach to RGD cell attachment sequence of the protein.¹⁴ Integrin $\alpha \nu\beta 6$ is not normally found in healthy epithelium, but appears in wound healing and binds to transforming growth factor $\beta 1$ (TGF $\beta 1$) through its latency-activated peptide that contains an Arg-Gly-Asp (RGD) peptide sequence.^{2,9,11} Integrin $\alpha \nu\beta 1$, not normally found in healthy epithelium has affinity to attach to fibronectin EIII/A which is believed to be involved in cell interactions with molecules present in the initial clot.^{9,11}

2.2. Integrins interactions with extracellular matrix in re-epithelialization

Wound healing involves series of controlled events followed by formation of provisional extracellular matrix, which is mainly composed of fibrin, fibronectin, vitronectin, and migration of epithelial cells from edges of wound.¹ Keratinocytes express novel matrix integrin receptors $\alpha \nu\beta 1$, $\alpha 5\beta 1$ and $\alpha \nu\beta 6$ to migrate and adhere to wound matrix proteins that resting keratinocytes in healthy epithelium do not encounter.^{10,15} Expression of other $\beta 1$ integrins is also upregulated during migration of keratinocytes to wound matrix and is critical in proper re-epithelialization.⁹ Integrin $\alpha 2\beta 1$, besides of having crucial role in binding to collagen type I, III and V also induces the expression of MMP1 in keratinocytes, cleave the exposed collagen matrix, and thus facilitate the migration of wound keratinocytes by focalized denaturation of collagen matrix.^{9,10} In addition, $\alpha 2\beta 1$ integrin is seen to further facilitate keratinocytes migration by binding to its ligand laminin-332 Y2 chain.¹⁶

Integrin $\alpha 3\beta 1$ is seen to have a complex role in re-epithelialization including the regulation of TGF- $\beta 1$ mediated responses.^{17,18} $\alpha 3\beta 1$ integrin regulates Smad7, which is an inhibitor of TGF- $\beta 1$ mediated signaling. Smad 7 inhibits TGF- $\beta 1$ mediated signaling by binding to TGF- $\beta 1$ receptor by its transient translocation from nucleus to cytoplasm.¹⁷ Thus, $\alpha 3\beta 1$ integrins may present another mechanism for keratinocytes motility by reducing the attachment of keratinocytes during re-epithelialization.¹⁷ Integrin $\alpha 3\beta 1$ association with urokinase type plasminogen activator receptor mediates focalized activation of plasmin and plasmin mediated digestion of LM-332 which is crucial for keratinocyte invasion to fibrin clot during wound healing.^{2,12,13} TGF- $\beta 1$ role is crucial in re-epithelialization.^{17,19} $\alpha 3\beta 1$ in epidermis is seen to regulate angiogenesis by controlling the mitogen-regulated protein 3 (MRP3) but its role in oral mucosa is not yet clear.¹⁸

In migrating epithelial cells $\alpha 9\beta 1$ integrins are highly expressed during early wound repair, considered to be crucial for keratinocyte proliferation at wound edge and are crucial in cell migration through nitric oxide synthase activity which is regulated by Src tyrosinase.^{2,10,20,21} Activation of $\alpha 9\beta 1$ integrins upon specific ligation further activates Src tyrosine kinase by phosphorylation of p130Cas and activation of Rac-1.²⁰ Inhibition of Src Tyrosine kinase results in decreased cell migration activity.²⁰ $\alpha 9\beta 1$ signaling introduces a novel mechanism for cell migration in which $\alpha 9$ cytoplasmic domain is seen as crucial for coordinated interactions.²⁰

Integrin $\alpha 6\beta 4$, ligand for laminin 332, is crucial in formation and stabilization of junctional adhesion complexes called hemidesmosomes and is important in signalling pathways.^{9,11} The extracellular domain of integrin $\alpha 6\beta 4$ interacts with laminin-5 and is important in linking the basal keratinocytes to the basement membrane.² Integrin $\alpha 6\beta 4$ is necessary for epidermal growth factor (EGF) induced keratinocyte migration which is associated by activation of integrin associated tyrosine kinase Fyn and increased phosphorylation of the $\beta 4$ integrin cytoplasmic domain.²² Epidermal growth factor promotes disruption of hemidesmosomes, thus increasing cell motility.^{22,23} Integrin $\alpha 6\beta 4$ plays key role in reforming basement membrane by binding to proteolytically cleaved $\alpha 3$ subunit of laminin 332, relocating back from wound edge keratinocytes.^{2,22}

2.3. Fibronectin receptor integrins and re-epithelialization

Fibronectin acts as an adhesive molecule which plays a key role in binding to integrins as well as other extracellular components including collagen, fibrin, proteoglycans etc.²⁴

$\alpha \nu\beta 1$, $\alpha 5\beta 1$ and $\alpha \nu\beta 6$ are three fibronectin receptor that binds to RGD sequence of fibronectin, serving as key role in wound healing. These integrins are expressed by keratinocytes after coming in contact with fibronectin-rich provisional matrix.² $\alpha 5\beta 1$ expression in keratinocytes occur during early stages of wound healing and promotes keratinocytes adhesion and motility. $\alpha 5\beta 1$ interacts with fibronectin through Ganglioside GM3 and GT1b interactions in which Ganglioside GM3 promotes and GT1b inhibits interaction with fibronectin.²⁵ $\alpha 5\beta 1$ integrins promotes cell proliferation and limits cell differentiation of non migratory keratinocytes by their interaction with EIIIA(EDA) fibronectin.^{2,13} Integrin $\alpha 5\beta 1$ binding to fibronectin seems to induce Epidermal Growth Factor Receptor (EGFR) signaling directly or indirectly which is localized into migrating tip of wound edge, thus serving as key player in both migration and proliferation of keratinocytes during wound repair.^{2,10}

Integrin $\alpha \nu\beta 1$, a low affinity fibronectin receptor, is highly expressed by basal epithelial cells against the fibrin clot and at the wound edges and may facilitate keratinocyte migration on the underlying fibronectin EDA by supporting cell attachment without decelerating the migration.² TGF- $\beta 1$ interaction with $\alpha \nu\beta 1$ integrin may help to accumulate and focalize inactive TGF- $\beta 1$ which are activated later by proteolytic cleavage, however TGF- $\beta 1$ remain inactivated after TGF- $\beta 1$ - $\alpha \nu\beta 1$ integrin interaction.²⁶

2.4. Integrin $\alpha \nu\beta 6$ and transforming growth factor β in re-epithelialization

Integrin $\alpha \nu\beta 6$ in wound healing, binds to fibronectin and tenascin and is highly expressed in basal and suprabasal keratinocyte layers after the epithelial sheet formation.^{11,21} Integrin $\alpha \nu\beta 6$ locally activates Transforming growth factor β (TGF- β) by conformational changes independent from any proteolytic activity.^{23,27} TGF- $\beta 1$ - $\beta 3$ are active in wound healing, TGF- $\beta 1$ induces recruitment of inflammatory cells, including macrophages, initiation of granulation tissue formation.^{2,23,27} TGF- $\beta 1$ and $\beta 3$ colocalize with integrin $\alpha \nu\beta 6$ in 7 day old gingival wounds.¹⁹ Integrin $\alpha \nu\beta 6$ activates latent TGF- $\beta 1$, which is synthesized as latent precursor molecule containing latency-associated peptide ($\beta 1$ -LAP) and latent TGF $\beta 1$ -binding protein (LTBP1).^{2,26} TGF- $\beta 1$ activation can be both integrin dependent and integrin independent, however $\alpha \nu\beta 6$ integrin mediates TGF $\beta 1$ activation by binding to RGD sequence of $\beta 1$ -LAP of the TGF $\beta 1$ protein complex that is fixed to ECM by LTBP1.²⁷

TGF $\beta 1$ inhibits epithelial cell proliferation via up regulation of cyclin dependent kinase inhibitors p15 and p21 and promotes keratinocyte migration by switching the cells from a differentiative to regenerative phenotype.^{19,23} TGF $\beta 1$ is seen to have major function in regulation of inflammation by inducing anti-inflammatory (AIR) response through its immunosuppression action on T-cells and macrophages.^{19,26} TGF $\beta 1$ overexpression has also been associated with profound wounds, causing excessive ECM accumulation and scar formation, which supports importance of controlling of TGF $\beta 1$ activity in successful wound healing.¹⁹ TGF- $\beta 3$ is seen to have anti-fibrogenic action, hence its prolonged activation by $\alpha \nu\beta 6$ integrin mediated interaction may be important in protection of gingiva from scar formation.¹⁹

3. Connective tissue repair

Epithelial wound healing is followed by connective tissue repair and plays an important role in restoring function of tissue.^{1,15}

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