British Journal of Medicine & Medical Research
9(10): 1-8, 2015, Article no.BJMMR.19544
ISSN: 2231-0614

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Integrins and Reorganization of Osteoclast Cytoskeleton under Orthodontic Force

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Authors' contributions

This work was carried out in collaboration among all authors. Authors JF and YX contributed equally and majorly to the draft. Authors LX and ZW helped with figures in this paper. Authors DB, XH and QG assisted in literature reviewing and amendment. All co-authors approved this final edition.

Article Information

DOI: 10.9734/BJMMR/2015/19544
Editor(s):
(1) Hai Ming Wong, The University of Hong Kong, 2/F, Prince Philip Dental Hospital, Hong Kong.
Reviewers:
(1) Angelo Troedhan, Faculty of Dentistry, Health Science University, Vientiane, Laos.
(2) Anonymous, USA.
(3) Deepak Kadeli, Department of Internal Medicine, BLDE University, India.
Complete Peer review History: http://sciencedomain.org/review-history/10227

Mini-review Article

Received 15th June 2015
Accepted 1st July 2015
Published 17th July 2015

ABSTRACT

Integrins are mechanoreceptors and mediate mechanotransduction by transferring forces into focal adhesions. Osteoclastogenesis starts with adhesion to the bone matrix, leading to cytoskeleton reorganization that is important for osteoclast polarization and migration. However, there are several signaling pathways mediating this process, and integrins have been shown to be important signaling molecules participating osteoclastogenesis. Particularly, integrins have played an important role in both force transduction and osteoclastogenesis. This paper reviewed the findings on the relationship between integrins and reorganization of osteoclast cytoskeleton under orthodontic force.

Keywords: Orthodontic force; integrin; osteoclastogenesis; cytoskeleton.

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1. INTRODUCTION

Orthodontic forces induce cell differentiation, cell repair, and cell migration, resulting in alveolar bone remodeling [1,2]. Upon mechanical stimuli such as orthodontic force, cells dynamically adapt to force by modifying their behavior and remodeling their microenvironment. They would exert actomyosin contractility and cytoskeleton-dependent force in response to matrix stiffness cues. This adaptation is favored by integrin activation switch [3]. The integrin signaling regulates a variety of cell functions, including bone resorption, platelet aggregation, leukocyte homing and activation, tumor cell growth and metastases, cell survival and apoptosis, and cellular responses to mechanical stress [4]. Integrins work as mechanoreceptors that mediate mechanotransduction by transferring forces to focal adhesions. These adhesion proteins are sensitive to tension and activate intracellular signals in response to force.

Osteoclasts are multinucleated, terminally differentiated cells derived from macrophage lineage [5], and osteoclastogenesis is a sophisticated process. There are several stages such as commitment, differentiation, multinucleation, and activation of immature osteoclasts [6]. This procedure is controlled by proliferation and homing of the progenitors to bone, followed by their differentiation and fusion to form multinucleated cells [6]. Besides, osteoclast differentiation is regulated by a variety of systemic hormones and locally secreted cytokines and self-produced cytokines [6]. The myeloid and B lymphoid transcription factor PU.1, macrophage colony-stimulating factor (M-CSF or CSF-1), c-fos, p50/p52 subunits of NF-kB, RANK, and its soluble receptor, osteoprotegerin (OPG), were shown to be essential for osteoclast differentiation [7-10]. Osteoclasts are dynamic and versatile cells [11], whose function is regulated at many levels including migration to and between the resorption site, polarization of the mature osteoclasts during the resorption process, and the assembly of a podosome based sealing zone [12]. Importantly, osteoclasts start to act with adhesion to the bone matrix, leading to cytoskeletal reorganization that is important for the migration of these cells and their polarization. Osteoclasts exhibit two different actin cytoskeleton organizations: on non-mineralized substrates they form canonical podosomes, but on mineralized substrates they form a sealing zone [13] enriched in peculiar adhesions [14].

2. ORTHODONTIC FORCE AND OSTEOCLAST FORMATION

Skeletal bone mass and architecture are susceptible to various mechanical stimuli. The balance between osteoblasts and osteoclasts plays a significant role in the adaptation of bone to mechanical stimuli [15,16]. Bone resorption occurs with osteoclasts, which create lacunae that will be filled by osteoblast cells later. Osteoclasts, which differentiate from hematopoietic stem cells for controlling bone resorption [17], could be induced by mechanical loading [18]. During orthodontic treatment, compression force leads to disarrangement of tissues and deformation of blood vessels surrounding teeth, which results in hypoxic conditions and changes cellular metabolism. The mechanism of orthodontic tooth movement, as explained by in vivo-models regarding bone remodeling by mechanical stimuli, suggest that orthodontic forces stimulate mechanosensitive ion channels and receptors in the cell membrane [19], then up-regulate important cellular mediators related to bone resorption like protein kinase C, prostaglandin E2, cyclooxygenase 2 et al. [20-22]. A previous study demonstrated changes in RANK, RANKL, and osteoprotegerin (OPG) during orthodontic treatment [23], where RANKL stimulation and OPG inhibition support osteoclastogenesis [24]. Thus, the process of alveolar bone resorption occurs on the compression side [25] and exhibits the activation of osteoclast [26]. With mechanical stimulation, osteoclast formation is mediated by several factors including TNF-α, M-CSF, RANKL, cytokines et al. [27-30]. Osteoclast function for bone resorption is activated with its migration to the resorption site, adhesion to mineralized bone matrix, polarization and then the development of a ruffled border and a sealing zone, followed by the secretion of acids and lysosomal enzymes to dissolve organic matter and inorganic matter, which in general is a result of cytoskeletal reorganization in osteoclasts.

3. INTEGRINS MEDIATE MECHANO-TRANSDUCTION THROUGH FOCAL ADHESION

Integrins are heterodimeric transmembrane protein complexes that are fundamental to mechanically linking the extracellular matrix to the cytoskeleton, and particularly to actin filaments [31]. The process is known as mechanotransduction, referring to cell-matrix

interactions transducing the mechanical stimuli to biochemical down- stream responses [32]. There is an active promotion of equilibrium by biological systems, which is mechanical homeostasis [33]. Integrins act as the sensors in mechanical homeostasis [33]. They are among the most abundant cell surface receptors and are expressed in all cell types apart from erythrocytes; they constitute the principal adhesion receptors for the extracellular matrix (ECM) [4]. Integrin is considered of major importance for the formation of an elaborate meshwork of fibronectin fibrils and for the extracellular matrix deposition and remodeling [4].

Integrins consist of a α and β subunit, which each have a large ectodomain, a single transmembrane domain and a generally short cytoplasmic tail. Eighteen α subunits and eight βsubunits can assemble in 24 different combinations that have overlapping substrate specificity and cell-type-specific expression patterns [34]. Integrin-mediated adhesions play a central role in transducing effects of forces to regulate cell functions by transmitting forces between the extracellular matrix and the actin cytoskeleton [35]. Focal adhesions are clusters of integrin trans membrane receptors that couple the ECM to the actin cytoskeleton [36]. Focal adhesions sense and respond to variations in force transmission along proteins. This chain of protein-protein interactions links actin filaments, actin binding proteins (ABPs), integrins and the extracellular matrix successively so as to adapt cell-matrix adhesion to the composition and mechanical properties of the extracellular matrix. ABPs do not convey the force passively but control the elongation of actin filaments and the activation of integrins, thus modulate transmission efficiency [37,38].

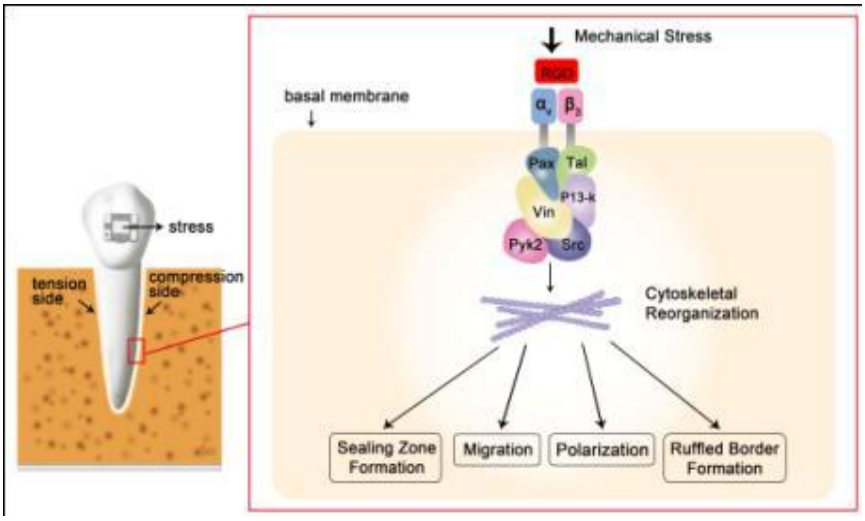
Generally, there are three mechanochemical steps of how integrins respond to force [39]. Integrins first bind to extracellular matrix molecules to become activated. Second, these forces transmit to the cell interior where they are converted into biochemical signals (i.e., mechanotransduction). Lastly, integrins link to the cytoskeleton to transmit the forces throughout the cell and reinforce their adhesions to resist the force. They can transmit bi-directional signals across the plasma membrane [40]. Inside-out activating signal from some cell surface receptors bound with soluble agonists triggers integrins conformational change leading to high affinity for extracellular ligands. Then binding of ligands to integrins results in outside-in signaling, leading to formation of focal adhesion complex at the integrin cytoplasmic tail and activation of downstream signal pathways. Inhibiting or changing these components leads to altered sensing of stiffness or stress and strain through the ECM [33].

4. INTEGRIN'S POTENTIAL ROLE IN CYTOSKELETAL REORGANIZATION OF OSTEOCLASTS

Recognition of ECM components by osteoclasts is an important step in initiating osteoclast function. Integrins, as a superfamily of heterodimeric transmembrane receptors, mediate cell-to-matrix and cell-to-cell interactions [41]. Osteoclasts are signaled by bone matrix proteins via integrins like integrin αvβ3 which is the most abundant one in osteoclasts [42] and the interaction of integrins with ECM proteins influenced on osteoclasts' adhesion to the bone surface [43]. Upon ligand binding, integrins usually undergo receptor clustering, leading to the formation of focal adhesion contacts, where these receptors are linked to intracellular cytoskeletal complexes and bundles of actin filaments [44]. Macromolecules in extracellular matrix proteins (ECM) contribute to the bio-mechanical properties of bone, among which fibronectin (FN), vitronectin (VN), and osteopontin (OPN) are more abundant ones called Arg-Gly-Asp (RGD) containing glycoproteins [45]. In fact, several studies have demonstrated that integrins mediate cell adhesion to VN, FN, or collagen [46], which was reported to affect cell spreading and actin rearrangement in osteoclasts [47]. The presence of the RGD sequence in osteopontin [48], a bone matrix protein produced by osteoblasts and osteoclasts, suggests the attachment at the sealing zone may be mediated by integrins. Integrins is likely to alter the cell's adhesion, transfer outside stimulation, thereby incent cytoskeleton reorganization and then promote bone-resorption.

It has long been recognized that the short cytoplasmic domains of the α and β-integrin subunits can recruit a variety of cytoskeletal and signaling molecules [49]. Podosomes play a key role in the bone-resorptive activity of osteoclasts. Integrin, as an important component, is essential for osteoclasts to reorganize their cytoskeleton [50,51]. Integrin αvβ3 is crucial in the regulation of two processes required for effective osteoclastic bone resorption: cell migration and maintenance of the sealing zone. αvβ3 transmits

bone matrix-derived signals and ultimately activate intracellular events. Research interests have been focused on identifying the hierarchy of the αvβ3-regulated cascade of signaling and structural proteins required for this cytoskeletal organization [52]. Upon occupancy by its RGD ligand, αvβ3 activates a signaling complex consisting of Pax, Tal, Vin, Src, Pyk2, P13-k et al, which permits the cell to form sealing zone, ruffled border and proceed migration and polarization [53]. Schematic illustration of the recruitment of these signaling molecules to αvβ3 integrins in resting and activated osteoclasts is shown in Fig. 1. However, the exact relationship between these proteins and αvβ3 subunits is still not firmly established. Deletion of the β3 subunit, which express the central role of αvβ3 in organizing the osteoclast cytoskeleton in mice, leads to progressive osteopetrosis in the β3-/- mice [50]. But they retain some bone resorptive capacity which indicates compensation perhaps by another integrin(s) [52].



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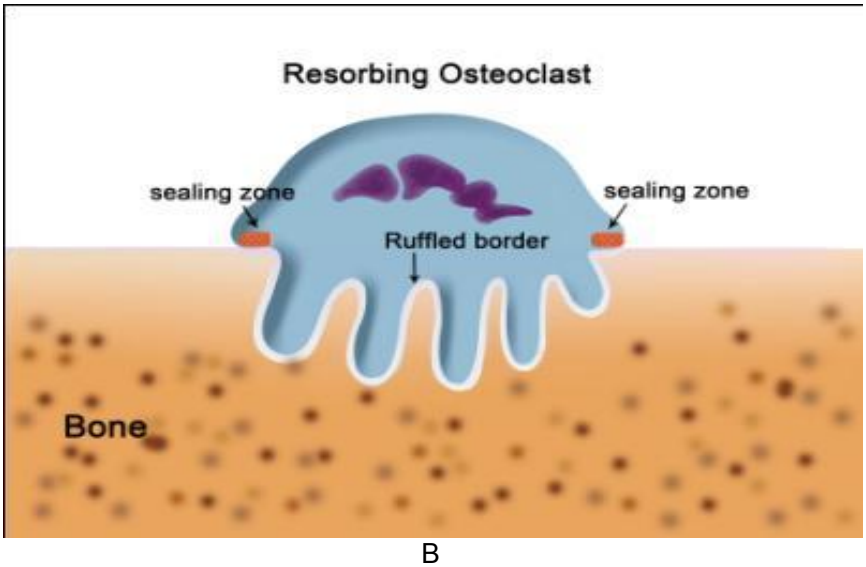

B

Fig. 1. (A) The αvβ3 signaling is activated under orthodontic force, thus leading to skeletal reorganization of osteoclasts through a downstream complex on the compression side. (B) Skeletal reorganization is essential for osteoclasts to form sealing zone and ruffled border, following which the osteoclasts will migrate and polarize and become functional bone-resorbing osteoclast

5. DISCUSSION

Cells employ an adaptive cellular stiffening response in an effort to resist increased tensile strain through integrins under mechanical stresses [54]. Applying orthodontic force would result in orthodontic teeth movement. In the tensional force site, osteoclastogenesis is prominent; while in the pressure stress site, osteoclastogenesis is dominant [55]. It is known that orthodontic forces have effects on both cellular activities and vascular changes. On the compression side, periodontal ligament vessels occlude and hypoxia is induced. Hypoxia signaling pathways have profound effects on bone development and homeostasis [56]. However, it is still unclear how bone cells at different sites detect mechanical loading and how site-specific mechanotransduction affects bone homeostasis [57]. Osteocytes are known to regulate bone resorption in response to changes in mechanical stimuli. IL-1b increases osteocyte-modulated osteoclastogenesis, and that mechanical loading of osteocytes may abolish IL-1b-induced osteoclastogenesis [58]. As previously reviewed, integrins have been involved in mechanical force transduction. They are one kind of mechanosensitive proteins, which mediate cell-to-matrix and cell-to-cell interactions. OCs may recognize the motif RGD in bone matrix components, then initiates skeletal reorganization that is the start of osteoclast polarization and migration. αvβ3 integrin has been elaborated to play a key role in this process. But other integrin (s) may also be contributory. Tension has been shown to promote recruitment of cytoskeletal proteins that strengthen the integrin–actin connection [54], while the potential role of compression on integrin induced osteoclastogenesis remains unknown. Evidence is still insufficient to demonstrate how integrins signaling participate in bone remolding under orthodontic force. Whether integrins are involved in osteoclastogenesis in orthodontic tooth movement needs further exploring.

6. CONCLUSION

Orthodontic forces induce osteoclastogenesis on the compression side, which is fundamental for tooth movement. As critical morphological change, cytoskeleton reorganization of osteoclast is the initiation of further polarization and foundation of normal function. Integrins have been related to this process and may have a part in osteoclast cytoskeleton reorganization. Integrins sense mechanical force, leading to mechanotransduction and cell responses. Whether integrins can induce osteoclast cytoskeleton reorganization or osteoclasto-genesis under orthodontic stress is not fully understood, and neither is the complete and concrete molecular mechanism behind these processed. Further research is still needed.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

Our work is under the support of National Natural Science Foundation of China (NSFC grant no.81371172 to Dr. Han Xianglong and NSFC grants no. 11172190 to Dr. Ding Bai).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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