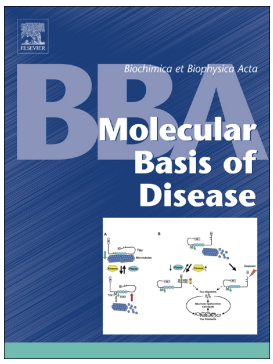
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The biological basis of treating jaw discrepancies: An interplay of mechanical forces and skeletal configuration

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INVITED REVIEW

The biological basis of treating jaw discrepancies: An interplay of mechanical forces and skeletal configuration

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ABSTRACT

Jaw discrepancies and malrelations affect a large proportion of the general population and their treatment is of utmost significance for individuals' health and quality of life. The aim of their therapy is the modification of aberrant jaw development mainly by targeting the growth potential of the mandibular condyle through its cartilage, and the architectural shape of alveolar bone through a suture type of structure, the periodontal ligament. This targeted treatment is achieved via external mechanical force application by using a wide variety of intraoral and extraoral appliances. Condylar cartilage and sutures exhibit a remarkable plasticity due to the mechano-responsiveness of the chondrocytes and the multipotent mesenchymal cells of the sutures. The tissues respond biologically and adapt to mechanical force application by a variety of signaling pathways and a final interplay between the proliferative activity and the differentiation status of the cells involved. These targeted therapeutic functional alterations within temporo-mandibular joint ultimately result in the enhancement or restriction of mandibular growth, while within the periodontal ligament lead to bone remodeling and change of its architectural structure. Depending on the form of the malrelation presented, the above treatment approaches, in conjunction or separately, lead to the total correction of jaw discrepancies and the achievement of facial harmony and function. Overall, the treatment of craniofacial and jaw anomalies can be seen as an interplay of mechanical forces and adaptations occurring within temporo-mandibular joint and alveolar bone. The aim of the present review is to present up-to-date knowledge on the mechano-biology behind jaw growth modification and alveolar bone

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remodeling. Furthermore, future molecular targeted therapeutic strategies are discussed aiming at the improvement of mechanically-driven chondrogenesis and osteogenesis.

KEYWORDS

Mechano-transduction, malocclusion, orthopedics, orthodontics, mandibular condyle, periodontal ligament

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1. INTRODUCTION

Jaw malrelations and discrepancies refer to a broad spectrum of oral disorders characterized by maxillo-mandibular discrepancies and alveolar bone and teeth irregularities. A large portion of the general population, ranging between 50% and 75% presents with some type of malrelation referred as malocclusion [1] while jaw discrepancies affect almost 28% of the population [2]. The severity of malocclusion may vary from simple deviations within the alveolar bone and the aligned teeth to serious dentofacial anomalies and craniofacial deformities. Several studies have highlighted the significant role that malocclusion possesses in oral health as well as in the quality of life [3, 4, 5]. Particularly, it is reported that oral health in general [6], masticatory function [7], vulnerability to dental trauma [8] and social and emotional welfare [9, 10, 11] may be affected to a varying extent depending on the severity of the existed discrepancies. Moreover, the treatment of these cranio-dentofacial problems has been proved to ameliorate oral function and oral health related quality of life [6, 12, 13, 14], whereas patients with jaw deformities who remain untreated seem to be adversely affected psychologically and physically [15, 16]. On the other hand, lack of treatment of these traits could lead from severe deviations in normal facial growth and appearance to speech difficulties, mastication problems, traumatic injuries of prominent teeth and periodontal problems.

Craniofacial deformities and jaw discrepancies often require a multidisciplinary approach by a team of specialists encompassing dentofacial orthopedists/orthodontists, dental and oral surgeons, craniofacial and plastic

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surgeons. The surgical interventions are required for the correction of severe deformities in patients with syndromes [17, 18, 19] and clefts [20, 21] as well as in older patients with jaw discrepancies that remained untreated beyond completion of craniofacial growth [22, 23, 24]. This is the reason why jaw deformities are more easily addressed in an early stage, during the development of the maxilla and the mandible through growth modification of the jaws. A large number of treatment modalities and mechano-therapies have been implemented in order to normalize aberrant mandibular growth and treat jaw discrepancies [25]. In the era of molecular medicine and dentistry, efforts have also been made to discover and apply treatment strategies that are based on gene interventions and are targeted to mechano-sensitive molecules [26, 27]. Herein, we focus on the biological response of facial bones and more specifically maxilla and mandible, to mechano-therapies applied in the course of treating jaw discrepancies and malrelations, the cellular events and the molecular signaling mechanisms involved. Unraveling of these molecular responses will offer novel routes for targeted treatment strategies aiming at the best possible tackling of the problems.

2.1 MECHANICAL STIMULI AS MODULATORS IN JAW GROWTH MODIFICATION

It has long been recognized that mechanical forces and the surrounding muscular environment affect and regulate skeletal growth, maintenance and homeostasis [28, 29, 30, 31]. It has also been demonstrated that the growth pattern and the configuration of cartilaginous tissue and bone are tightly controlled by mechanical forces exerted on human skull and face [32, 33, 34]. The craniofacial

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complex as a whole as well as the osseous formation in the facial sutures are strongly influenced by mechanical loading [35, 36, 37]. Notably, studies regarding the evolution of the human skull have revealed that the shift towards a softer diet results in changes in the craniofacial shape and a reduction in the cranial size in modern humans [38]. Moreover, it has been documented that changes in dietary habits result in alterations in the skeletal configuration of the mandible due to different loads applied during mastication and changes in the muscular function [39].

The fact that a great proportion of jaw discrepancies are attributed to anomalies in mandibular size and position, has led clinicians to focus on mandibular growth modification at the cartilaginous area of the condyles [40]. A wide spectrum of appliances targeting manipulate condylar growth is prescribed to growing patients for the treatment of mandibular retrognathism [41, 42], mandibular prognathism [43] and abnormal vertical growth pattern of the jaws [44, 45].

Mandibular condylar cartilage consists of an articular part which functions within temporo-mandibular joint (TMJ) and a part which is characterized as secondary cartilage [46, 47]. Although condylar cartilage differs from the primary growth cartilages of the limbs and cranial synchondroses, it is considered to be a principal site during mandibular development, where growth and ossification are dictated by mechanical stimuli, such as alterations in mandibular position [47, 48, 49]. It has been shown that the chondrocytes within the condylar cartilage respond and adapt to mechanical forces exerted on the mandibular condyle, by shifting their differentiation status [50, 51].

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Unequivocal evidence supports that functional appliances which change mandibular posture result in alterations in the loading conditions within TMJ and influence the proliferative activity of the condylar chondrocytes as well as their maturation [52, 53]. The intra-oral devices which are designed to translocate the mandible to a forward position result in an unloading of the condyle, mainly in its posterior and posterior-superior regions, and in the application of tensile forces in the posterior fibres of the articular disc. Animal studies have shown that the protrusive appliances stimulate proliferation in the chondroblastic zone of the condylar cartilage and induce the growth potential of the condyle [53, 54, 55]. Cellular changes and adaptive remodeling have also been observed in the area of the glenoid fossa which articulates with the condyle within TMJ [53, 56]. In clinical practice, the aforementioned mechano-therapy is prescribed in patients with retrognathic and under-developed mandible, aiming at promoting mandibular growth and normalizing its relationship with the maxilla [57, 58, 59]. Conversely, experiments in primates [60] and in rats [61, 62] have demonstrated that the application of forces constraining the forward movement and development of the mandible produce a restraining effect on the condylar growth. Specifically, appliances attached to the chin transmit higher levels of compressive forces to the area of the mandibular condyle, which in turn reduce the proliferative activity of the chondrocytes thus leading to a restriction of the overall mandibular growth [63]. Such treatment has been implemented in growing patients with dentofacial anomalies characterized by mandibular prognathism [64].

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In agreement with the above studies, *in vivo* experiments that examined mandibular condyle specimens upon alterations in the functional loading revealed that soft diet results in a higher proliferative activity of the condylar chondrocytes, whereas hard diet and heavier mastication forces induce their maturation [65, 66, 67, 68, 69]. Moreover, it was reported that changes in loading conditions not only stimulate differentiation in condylar chondrocytes, but also alter gene expression in the underlying osteoblasts of the subchondral area [70].

2.2 MECHANO-TRANSDUCTION IN MANDIBULAR CONDYLE DURING GROWTH MODIFICATION

The unloading of the mandibular condyle and the application of tensile forces stimulate proliferation of the chondrocytes and enhance mandibular growth, whilst increased functional loading seems to restrict growth potential of the condyle. *In vitro* experiments unveiled that the application of compressive forces to condylar chondrocytes accelerates their differentiation and subsequent maturation, which in turn down-regulates their proliferative activity and the overall growth of the cartilage [71, 72, 73].

According to the process of mechano-transduction [74, 75], the mechanical forces applied to the mandibular condylar chondrocytes are transformed into intra-cellular molecular signals and trigger morphologic and phenotypic changes [76]. Various mechano-sensitive structures have been found to act as mechano-receptors on mandibular condylar chondrocytes, including G proteins [77] and integrins [77, 78, 79]. Furthermore, it has been shown that the presence of primary cilia on

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chondrocytes is of utmost importance for cartilage growth as well as for the transduction of mechanical cues into intra-cellular signaling cascades [80, 81]. Polycystin-1 (PC-1) is a protein localized on plasma membranes and on primary cilia structures and by interacting with its counterpart polycystin-2 (PC-2) regulate Ca^{2+} levels and possess a pivotal role in mechano-sensation on various tissues [82, 83, 84]. PC-1 and PC-2, encoded by *polycystic kidney disease 1* (*Pkd1*) and *2* (*Pkd2*), respectively, are present in bone cells and in chondrocytes and as mechano-responsive proteins mediate mechanically-induced alterations in cell proliferation and differentiation [85, 86, 87]. The expression of *Pkd1* is considered to be essential for the development and function of chondrocyte precursors within cranial sutures and synchondroses [88], as well as for the responsiveness of osteochondroprogenitor cell populations during the application of expansive forces on the midpalatal suture [86]. Additionally, it has been reported that PC-1 regulates osteogenesis through up-regulation of runt-related transcription factor-2 (RUNX2) [89].

The application of mechanical forces of different nature, i.e. compression or stretching, triggers various signaling cascades within chondrocytes which potentiate transcription factors that, in turn, activate or silence genes mastering the cell cycle and chondrocyte phenotypic expression [74]. Specifically, SOX9 and RUNX2 are crucial transcription factors which dictate the multistep pathways of chondrogenesis and osteogenesis [90, 91]. *Sox9* is expressed during early chondrogenesis by proliferative chondrocytes, but it is down-regulated during chondrocyte maturation [92, 93]. SOX9 activates the expression of collagen II [94] and aggrecan [95], which

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are basic components of the extracellular matrix secreted by the initially differentiated chondrocytes (Figure 1). Inversely, RUNX2 mediates late chondrogenesis phenomena and is detected on mature hypertrophic chondrocytes [96, 97].

Both SOX9 and RUNX2 transcription factors have been recognized as downstream targets of signaling cascades activated upon transmission of mechanical signals on mandibular chondrocytes [71]. *In vitro* experiments investigating the short-term effect of compressive forces on the differentiation of mandibular chondrocytes revealed changes in SOX9 and RUNX2 levels, which supports the hypothesis that compression enhances and accelerates the process of chondrogenesis [71]. Similar experiments demonstrated that the application of hydrostatic pressure for 2 hours to primary chondrocytes isolated from rat condyles, stimulated their proliferative activity through potentiation of a signaling axis involving integrins α2, α5 and β1, focal adhesion kinase (FAK), extracellular signal-related kinase 1/2 (ERK1/2) and phosphatidylinositol-3-kinase (PI3K) [78] (Figure 1). However, a recent study showed that the application of long-term hydrostatic pressure to chondrocytes induces changes in SOX9 and RUNX2 protein levels which reflect a phenotypic shift of the chondrocytes towards terminal differentiation and hypertrophy. Furthermore, changes in the aforementioned proteins corresponded to alterations in the mRNA levels of *Pkd1* and *Pkd2*, indicating another potential transduction pathway involving these molecules during compression of chondrocytes [98] (Figure 1).

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In vivo experiments demonstrated that mandibular advancement in rats resulted in an increase in *sox9* expression which was consistent with the apposition of new bone [53]. The application of hyperpropulsive forces in the rat mandible has also led to a stronger expression of *runx2* in the hypertrophic layer, further pointing to RUNX2 transcription factor as a key regulator during the terminal stages of chondrocyte differentiation and the transition towards endochondral ossification in the mandibular condyle [99]. Additionally, in a study exploring the effects of food hardness on condylar cartilage, a decline in *sox9* expression was detected in the hard-diet group, probably because of the increased loading conditions transmitted to the mandibular condyle. In contrast, the expression of *vascular endothelial growth factor* (*vegf*) and *fibroblast growth factor receptor-3* (*fgfr-3*), which are markers of chondrocyte maturation, were elevated in the hypertrophic and early hypertrophic zones, respectively [67] (Figure 1). Another set of experiments revealed that increased functional loading in the TMJ induces the expression of activator protein-1 (AP-1) and RUNX2 transcription factors, through activation of the c-Jun N-terminal kinase (JNK) and ERK mitogen-activated protein kinases (MAPKs) signal transduction pathways [68, 69] (Figure 1).

Indian hedgehog (IHH), a protein which belongs to the family of vertebrate Hedgehog morphogens, is highly mechano-sensitive and modulates important events during endochondral growth occurring at growth plates and at mandibular condylar cartilage [100, 101, 102, 103]. IHH is detected in the proliferative zone of the mandibular condyle and regulates/induces the proliferation of chondroblasts [104]. However, another study reported that *Ihh* is expressed by prehypertrophic

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chondrocytes in the mandibular condylar cartilage [105]. IHH triggers the release of parathyroid hormone-related peptide (PTHrP) from the perichondrium and together constitute a regulatory feedback loop which orchestrates the rate of chondrocyte proliferation and maturation [102, 106]. *In vitro* and *in vivo* experiments revealed that IHH-PTHrP loop is another signaling cascade which participates in mechanically-induced alterations on the condylar cartilage [71, 104, 107] (Figure 1). Experiments in rats demonstrated that mandibular advancement resulted in an up-regulation in the expression of *Ihh*, which corresponded to an increase in the proliferative activity of mesenchymal cells [104]. A similar study revealed an increase in PTHrP levels as well, which in turn stimulated the differentiation of mesenchymal cell population into chondroblasts and down-regulated the rate of their maturation, subsequently leading to a further proliferative activity and an overall increase in condylar growth [107] (Figure 1).

Collectively, mechanical forces influence condylar growth and allow for jaw modification. Patients with skeletal discrepancies between maxilla and mandible can be treated with proper coordination in jaw function, achieved with the prescription of functional appliances. Condylar chondrocytes respond to the mechanical cues initiated by alterations in the loading conditions within TMJ and subsequently regulate the development of mandibular cartilage via changes in their differentiation and proliferation. The mechano-transduction events taking place in the condylar cartilage during application of orthopedic forces are modulated by multiple signaling cascades. It should be noted that aberrant mechano-signaling is involved in cartilage degeneration [108] as well as in the pathophysiology of various cartilaginous and

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osseous disorders [109, 110, 111, 112, 113, 114], further supporting the pivotal role of proper coordination between function and mechano-sensation process for cartilage and bone development and maintenance. Future studies are expected to investigate potential pharmacological interventions targeting mechano-sensing key molecules of chondrogenesis, in order to obtain optimal and long-lasting results during growth modification with orthopedic appliances [115].

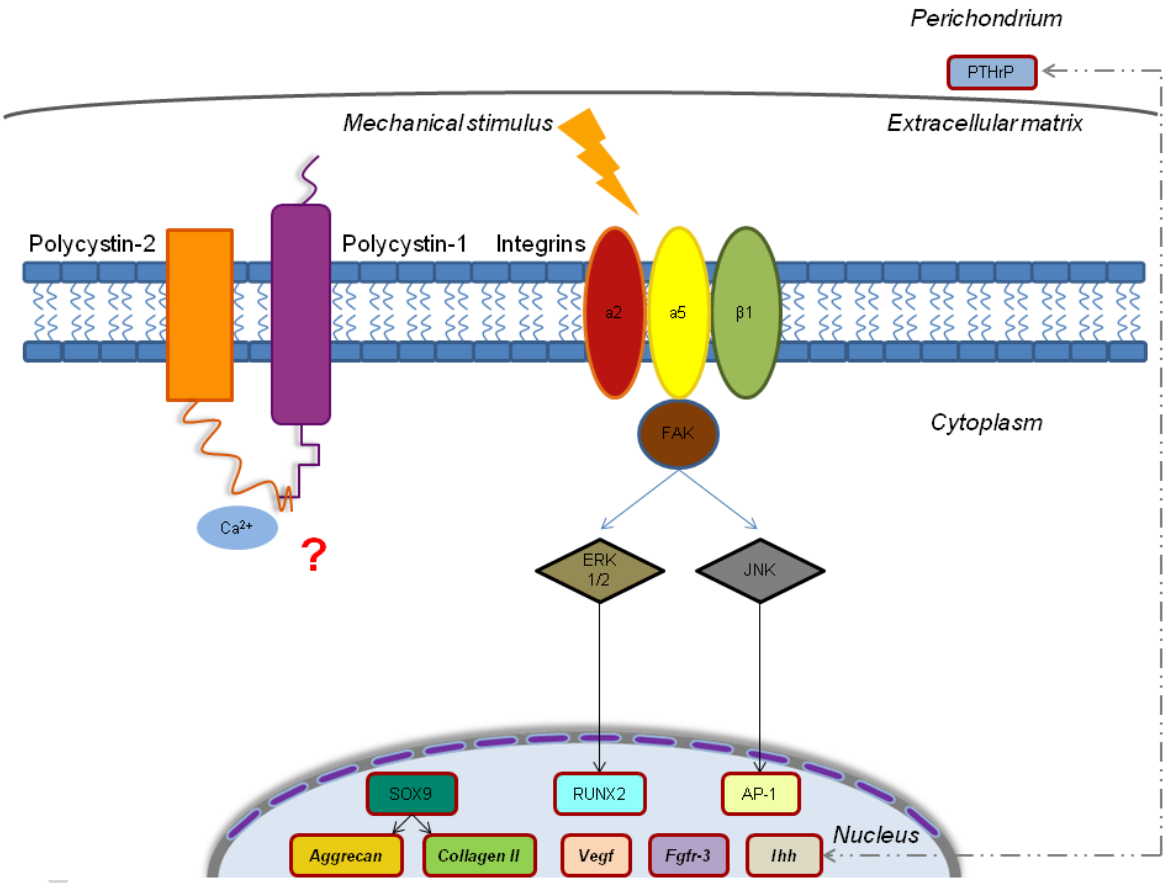


Figure 1. Illustration of the mechano-transduction pathways controlling growth modification in mandibular condyle.

(a) Increased functional loading of the mandibular condylar cartilage is sensed by the the complex Intregrin-FAK, which triggers the ERK1/2 and JNK MAPKs pathways that,

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in turn, activate the transcription factors AP-1 and RUNX2, promoting chondrocyte maturation and transition from chondrogenesis to osteogenesis. (b) Increased functional loading also increases the expression of *vegf* and *fgfr-3*, which are markers of chondrocyte hypertrophy. (c) The unloading of the mandibular condyle increases SOX9 levels in the proliferative chondrocytes, which promotes the expression of *aggrecan* and *collagen II*, basic components of the extracellular matrix of the condylar cartilage. (d) The application of tensile forces to the mandibular condyle activates the IHH-PTHrP feedback loop, resulting in enhanced chondrocyte proliferative activity by up-regulating the expression of *ihh* and increasing the levels of PTHrP secreted by the perichondrium. (e) The mechano-sensitive complex of PC-1 and PC-2 regulates Ca^{2+} concentration and mediates mechanically-induced alterations in chondrocyte proliferation and differentiation. The downstream signaling pathway remains to be elucidated. Abbreviations: FAK, focal adhesion kinase; ERK1/2, extracellular signal-related kinase 1/2; JNK, c-Jun N-terminal kinase; MAPKs, mitogen-activated protein kinases; AP-1, activator protein-1; RUNX2, runt-related transcription factor-2; *vegf*, vascular endothelial growth factor; *fgfr-3*, fibroblast growth factor receptor-3; SOX9, SRY box 9 transcription factor; IHH, Indian hedgehog; PTHrP, parathyroid hormone-related peptide; PC-1, polycystin-1; PC-2, polycystin-2.

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3. ALVEOLAR BONE ARHITECTURAL CHANGES BY MECHANO-TRANSDUCTION EVENTS WITHIN THE PERIODONTAL LIGAMENT

In clinical practice, the prescription of functional appliances to patients aims at eliciting skeletal effects for the proper correction of jaw discrepancies. The long-term stability of growth changes in the mandible has long been a controversial issue between researchers supporting a true modification in mandibular configuration upon functional treatment [116, 117, 118], and others suggesting a return in the initial growth pattern of the craniofacial structures after the active treatment period [58, 119]. Moreover, net skeletal growth is hardly obtained due to the fact that most of the functional appliances are tooth-borne, thus transmitting forces to the teeth and leading to teeth movements and ultimately structural changes to the surrounding alveolar bone [120, 121]. It seems that growth modification constitutes a part of the total correction of jaw malrelations, and alveolar bone remodeling within jaw bone is required to compensate for the rest of it [120]. Additionally, some patients present with malocclusion problems which may have been developed due to genetic teeth anomalies, such as supernumerary and missing teeth, transpositions and other discrepancies [122, 123].

The application of orthodontic forces to the teeth results in their movement through remodeling processes occurring in both periodontal ligament (PDL) and surrounding alveolar bone [124, 125]. Various theories have been proposed to explain how teeth and periodontal tissues respond to mechanical forces [126, 127] and many theoretical and experimental models have been suggested to unravel the biological basis of orthodontic movement [128, 129, 130]. Nevertheless, most

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theories seem to converge that PDL carries the critical role in the mechano-biology of alveolar bone remodeling. The PDL is a connective tissue consisting of collagen-rich extracellular matrix and cell populations including fibroblasts, cementoblasts, osteoblasts and undifferentiated mesenchymal cells. Cells within the PDL have properties of pre-osteoblasts exhibiting alkaline phosphatase (ALP) activity and expressing osteocalcin [131, 132, 133], and constitute a source for stem cells [134].

It should be noted that experiments investigating the role of cellular senescence in human PDL fibroblasts upon replicative exhaustion or ionizing radiation, reported a decline in the expression levels of osteoblastic differentiation markers, *RUNX2 and ALP*, together with an acquisition of a catabolic phenotype [131]. PDL fibroblasts respond to the exerted mechanical forces either through fluid flow within the PDL [135] or via extracellular matrix deformation [136], which in turn leads to alterations in the cytoskeleton through cell-matrix interactions [125, 137]. It has been reported that integrins [138, 139], FAK [138, 139, 140] and Rab and Rho GTP-binding proteins [141, 142, 143] are fundamental mechano-receptors in PDL fibroblasts (Figure 2). Moreover, the presence of the mechano-sensing polycystins PC-1 and PC-2 has also been detected in PDL fibroblasts [144] (Figure 2). Interestingly, a recent study revealed that the expression of *Pkd1* is crucial for the transmission of the mechanical signals to PDL during orthodontic tooth movements [145].

Following the application of external mechanical forces, areas of unloading and increased loading are distributed within the PDL space [146]. Depending on the nature of the stimuli, signaling cascades are potentiated within the PDL fibroblasts

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regulating the activity of transcription factors hence expression of cognate genes, which in turn determine either the acquisition of the osteoblast phenotype or the secretion of proteins that induce the osteoclast differentiation and activation [141, 147, 148, 149]. MAPKs signaling cascades have been recognized as important mediators in the series of mechano-transduction events occurring during force transmission to PDL fibroblasts [150, 151, 152, 153] (Figure 2). Activation of ERK MAPK pathway has been observed during mechanical loading of PDL fibroblasts [154, 155]. Furthermore, other studies confirmed that p38 and JNK MAPK pathway [156] as well as p42/44 and p38 cascade [157] mediate the mechanically-induced secretion of matrix metalloproteinases (MMPs) by PDL fibroblasts (Figure 2).

In vitro experiments investigating the effect of mechanical stretching on PDL fibroblasts revealed stimulation in their proliferation [158], augmented levels of AP-1 transcription factor [153, 159] and up-regulation of *runx2* expression [160], alterations mediated through activation of MAPKs signaling axes [151, 160, 161] (Figure 2). Similar experiments also demonstrated a PC-1-mediated activation of calcineurin/nuclear factor of activated T-cells (NFAT) pathway, which most likely further regulates the expression of its downstream target, *runx2* [144] (Figure 2). Moreover, a recent study demonstrated that tensile forces exerted on PDL fibroblast cultures potentiate the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling cascade via PC-1 and induce the expression of *runx2* [162] (Figure 2). Additionally, it was reported that cyclic stretching of human PDL fibroblasts leads to RhoK-mediated activation of p38, ERK and JNK MAPKs pathways ultimately regulating the expression of c-*fos*. Furthermore, stretching was found to

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up-regulate the expression of *ALP*, a gene marker of early osteoblastic differentiation [152] (Figure 2). In the same study, it was demonstrated that senescent PDL fibroblasts present with similar mechano-responsiveness regarding the activation of the aforementioned signaling cascades. They also responded with an increase in the expression levels of *c-fos* and *ALP*, although the levels of *ALP*, were significantly lower when compared to young PDL fibroblasts which were not subjected to mechanical stimulation [152]. The Connexin 43-ERK1/2 cascade has also been implicated in mediating the up-regulation of genes assigned to osteogenesis pathways and the suppression of osteoclastogenic factors upon application of cyclic tensile forces to human PDL fibroblasts [163] (Figure 2). It should be reported that experiments comparing the effects of cyclic and static stretching on human PDL fibroblasts demonstrated similar molecular response and kinetics to both types of mechanical stimulation. However, dynamic stretching resulted in activation of MAPKs signaling cascades which lasted for a longer period of time and elicited a stronger increase in the expression levels of *c-fos* and *c-jun* genes [151].

Conversely, the application of compressive forces to PDL fibroblasts reduces their proliferative activity and triggers signaling cascades related to osteoclastogenesis [147, 164]. Specifically, it has been shown that upon compression of PDL fibroblasts, the integrin-FAK cascade is activated and results in an increase in the levels of prostaglandin E_2 (PGE_2) [139, 140], and up-regulates the expression of the osteoclastogenic receptor activator of nuclear factor-kB ligand (RANKL), tumor necrosis factor-α (TNF-α) and macrophage colony stimulating factor (M-CSF) [138] (Figure 2). Another study demonstrated FAK- and nitric oxide (NO)-mediated

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activation of β-catenin axis via stimulation of PI3K/Act pathway [140] (Figure 2). Moreover, the osteoclastogenic effects of the compressive forces are further supported by experiments reporting an increase in the expression of *RANKL* [138, 165, 166, 167] and a decrease in the expression of *osteoprotegerin* (*OPG*) [138]. NO signaling also seems to play a significant role in the response of PDL fibroblasts to the application of mechanical forces, since both *in vitro* [168, 169] and *in vivo* [170, 171] experiments revealed an increase in its production during application of mechanical loading to PDL fibroblasts, by means of either compressive or tensile forces.

Overall, during treatment PDL fibroblasts seem to serve as the basic mediators that fine tune alveolar bone remodeling through the processes of bone formation and resorption, by acquiring an osteoblast-like phenotype and by regulating osteoclast activation, respectively. Following treatment, the reformed alveolar bone structure functions in the newly established equilibrium of forces, reorganization of the fibers within the PDL occurs and the treatment result is stabilized minimizing relapse and other adversities [172].

The molecular mechanisms underpinning orthodontic tooth movement need to be further investigated so that innovative interventions in the sub-tissue level can be applied in the future [26]. Treatment modalities involving the infusion of pharmacological agents within the PDL, aiming to interfere with the aforementioned molecular mechanisms, could be implemented in order to accelerate treatment by facilitating alveolar bone remodeling, obtaining more stable treatment results and achieving optimum control of the applied mechanical forces [26, 27].

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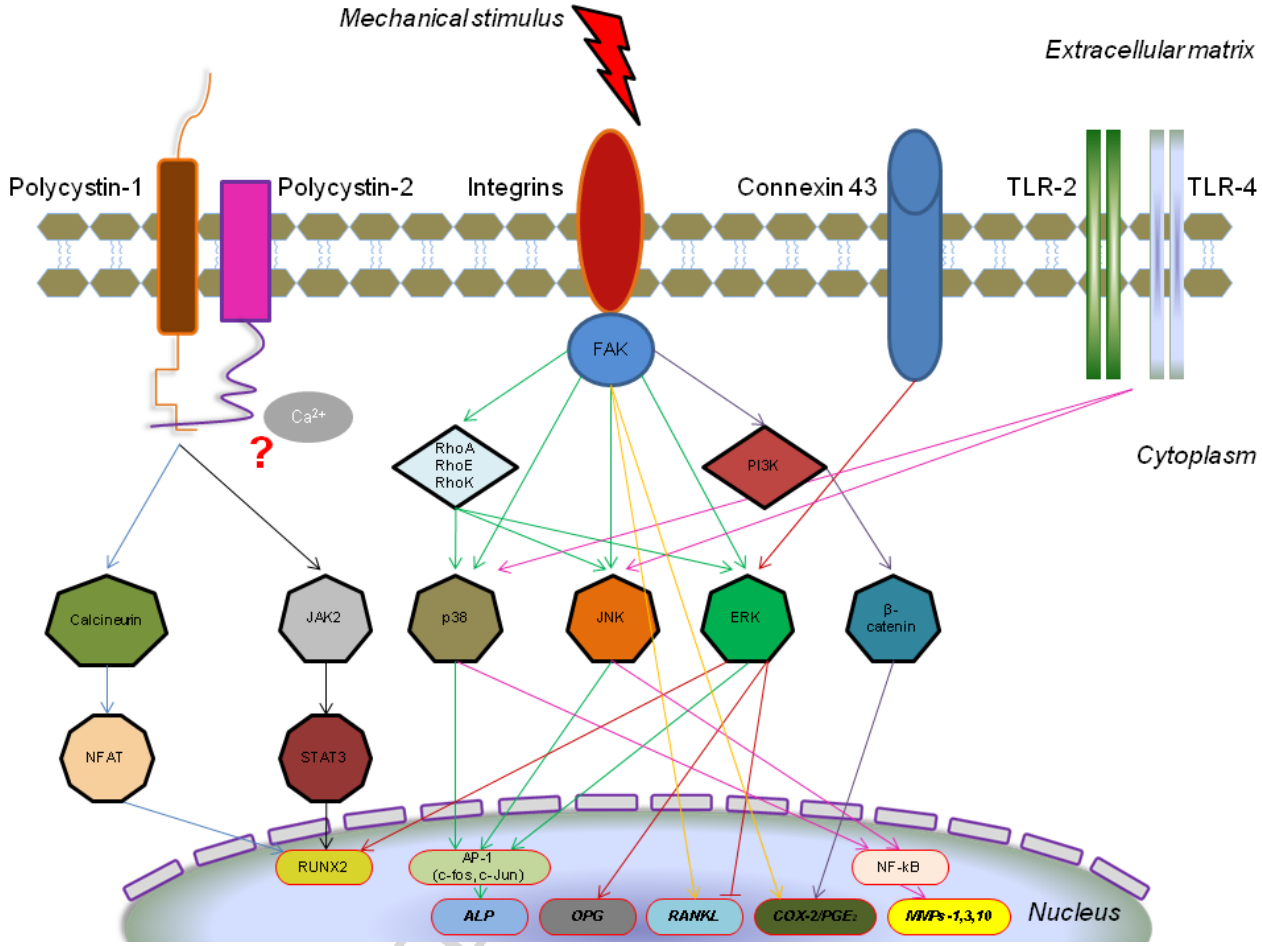


Figure 2. Illustration of the major signaling pathways involved in mechano-transduction events within the periodontal ligament, a suture-like tissue.

(a) Mechanical stimulation of PDL fibroblasts is sensed by TLR-2 and TLR-4, which activate p38 and JNK MAPKs signaling. Further downstream NF-kB is activated which induces the expression of *MMPs-1,3,10*. (b) Integrin-FAK complex responds to mechanical stretching of PDL fibroblasts by stimulating Rab and Rho GTPases and potentiating p38, JNK and ERK MAPKs signaling pathways, which lead to activation of AP-1 that, in turn, up-regulates the expression of *ALP*. (c) Mechanical stretching of PDL fibroblasts activates Connexin 43–ERK cascade which activates RUNX2, up-regulates the expression of *OPG* and suppresses the expression of *RANKL*. (d) PC-1 is

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triggered upon application of tensile forces to PDL fibroblasts and activates RUNX2 through potentiation of both calcineurin/NFAT and JAK2/STAT3 signaling axes. (e) The complex of PC-1 with PC-2 responds to mechanical stimuli and regulates Ca^{2+} levels within PDL fibroblasts. The downstream signaling pathway and the exact role of PC-2 remain to be elucidated. (f) Application of compressive forces to PDL fibroblasts stimulates Integrin-FAK complex, which subsequently up-regulates the expression of *RANKL* and PGE_2. (g) Compressive forces sensed by Integrin-FAK complex lead to potentiation of PI3K pathway which, in turn, activates β-catenin and induces PGE_2 expression. Abbreviations: PDL, periodontal ligament; TLR-2,4, toll-like receptor-2,4; JNK, c-Jun N-terminal kinase; MAPKs, mitogen-activated protein kinases; NF-kB, nuclear factor-kappaB; *MMPs-1,3,10*, matrix metalloproteinases-1,3,10; FAK, focal adhesion kinase; ERK, extracellular signal-regulated kinase; AP-1, activator protein-1; *ALP*, alkaline phosphatase; RUNX2, runt-related transcription factor-2; *OPG*, osteoprotegerin; *RANKL*, receptor activator of nuclear factor-kB ligand; PC-1, polycystin-1; NFAT, nuclear factor of activated T-cells; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; PC-2, polycystin-2; PGE_2, prostaglandin E_2; PI3K, phosphatidylinositol-3-kinase.

4. CONCLUSIONS – OUTLOOK AND CLINICAL PERSPECTIVES

Treatment of craniofacial anomalies and malocclusion comprises an interplay among external forces, condylar cartilage and paradental tissues. The application of functional mechano-therapies together with external mechanical forces initiate a cascade of biochemical events which determine the differentiation and proliferation

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of chondrocytes and PDL fibroblasts, respectively, ultimately regulating the processes of chonrogenesis and bone remodeling in craniofacial structures. Alterations in loading conditions within TMJ result in restriction or enhancement of condylar growth, depending on the nature of mechanical stimuli. Similarly, altered loading within PDL provokes molecular changes within fibroblasts which exert anabolic or catabolic effects to the adjacent alveolar bone altering its shape. Hitherto, only some of the molecular mechanisms mediating the aforementioned interventions have been clarified. Further insight into the signaling events and recognition of possible cross-talks between them, will possibly pave the way to pharmacological interventions targeting pivotal molecules participating in the cascades that govern chondrogenesis and bone remodeling for optimum therapeutic outcomes. It should also be noted that as with shear-stress models developed for the study of various vascular pathophysiologies [173], the mechanobiology behind alveolar bone remodeling after external force application offers an excellent *in vivo* model that could be implemented in the field of Orthopedics, in order to improve our understanding of the regulatory effects of mechanical forces in bone homeostasis, remodeling and regeneration. In the new era of biomedicine, molecularly-based cranio-dento-facial orthopedic strategies are expected to ameliorate the quality and effectiveness of treatment that patients are provided with.

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Highlights

- Jaw orthopedics involve mandibular growth modification and changes in alveolar bone
- Mechanically-driven chondrogenesis of the condyle is mediated by multiple signaling
- Orthodontic forces initiate cascades in PDL fibroblasts leading to bone remodeling
- Treating jaw anomalies requires interplay between forces and skeletal adaptations
- Molecular strategies may optimize chondrogenesis and osteogenesis mechano-treatment

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