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Genomics & Gene Therapy International Journal
ISSN: 2642-1194

Orthodontic Forces Commanding Genes to Cue Teeth in Lines: A Meta Analysis

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Research Article

Volume 2 Issue 1

Received Date: April 02, 2018

Published Date: May 04, 2018

DOI: 10.23880/ggtij-16000106

Abstract

If orthodontic tooth movement is a drama, in the biological theater of PLD, genes are the directors, commands the rest of the cells of PDL in proper places and align in a single line.

Aims and objectives: The main aim of our study is to understand the generation and propagation of signaling cascades molecules and associated tissue remodeling in adjacent tissue response to applied mechanical loads from the central theme of orthodontic tooth movement

Materials and methods: We have searched those original articles, research work, and reviews that are used term genes, a role of genes in orthodontic tooth movement.

Data collection and analysis: Data was collected with a search on, EBSCO (2010-December); MEDKNOW (2013December); Ovid MEDLINE(R) (2016), SCOPUS, ELSEVIER, SAGE abstract and citation database.

The Results: Sum of 16 articles was completely meeting the inclusion criteria. Apart from which, none of the relevant articles were found by our reviewer and expertise. Most commonly discussed topics are Orthodontic Tooth Movement and ECM Remodeling, Pressure: Tension Related Effects, Cytokines in orthodontic tooth movement, RANK RANKL/OPG pathway, Role of growth factor, Colony-stimulating factors, and bone morphogenic factor.

Conclusion: Genes like SOX-9 gene, PTHrP and IHH, RANKL, M-CSF, and RANKL –OPG pathways mainly significant in avoiding ankylosis of tooth within and during orthodontic tooth movement. The supportive to these pathways are of IL-1 α, IL-6, IL-11, TNF- α,) BMP2, BMP7, (TGFβ) and FGF.

Keywords: Orthodontic; Osteoclastogenesis; Fibroblasts

Abbreviations: OTM: Orthodontic Tooth Movement; CGRP: Calcitonin Gene-Related Peptide; VEGF: Vascular Endothelial Growth Factor; IHH: Indian Hedge Hog; PTHrp: Parathyroid Hormone-Related Protein; TIMPs: Tissue Inhibitor of Matrix Metalloproteinases; MMPs: Matrix metalloproteinases; TGFβ: Transforming Growth Factor β; BMPS: Bone Morphogenetic Proteins; VEGF: Vascular Endothelial Growth Factor; PDL: Periodontal Ligament; TNF: Tumor Necrosis Factor; FGF: Fibroblast Growth Factor.

Introduction

Evolution initiates with the inheritance of genetic variations. The term genes can be defined as the basic physical and functional unit of heredity, composed of DNA; act as instructions to make molecules called proteins. Hence, if life is a drama, in the biological theater, genes are the directors, commanding the rest of the cell's biomolecules to their proper places and cueing their lines [1-5].

In humans, contain the same genes, but their expression depends on identity, shape, and function of a particular cell. Based on requirements genes vary in size from a few hundred DNA bases to more than 2 million bases. For example, Homeobox protein MSX 2 acts a molecular defense mechanism for preventing ossification in ligament fibroblasts and prevents ankylosis of the tooth [5-8].

During orthodontic treatment applied orthodontic force initiates various reactions in and around the teeth and its periodontium. It is crucial to know and understand a complete sequence of events that occurs and expression of genes in periodontium during orthodontic tooth movement [9-12].

The significance of presenting this review is, understanding of gene's involvement during orthodontic tooth movement is a very complex event, on the application of similar force in a different patient, gene expression will be different. Through this Meta-analysis, we would like to give a comprehensive knowledge of the changes in gene expression and its influence on orthodontic tooth movement.

Materials and Methods

We have searched those original articles, research work and reviews that are used term genes, a role of genes in orthodontic tooth movement: a qualitative research method has been used to scrutinize the meaning and characteristics and vital role in orthodontic tooth movement.

Based on available articles we have been framed the inclusive and exclusive criteria

Inclusion criteria:

Original, research work and systematic reviews were considered.

An article defining meaning and character role in orthodontic mechanism was included.

Articles published with animal experiments in relation to orthodontic tooth movement.

Exclusion criteria:

Articles were not included role of genes in tooth movement.

Studies dealing short communications and inefficient data.

Articles based online- studies exploring

Articles based short-term research

Articles based on supervision.

In order to perceive the accurate result, we have included that qualitative research article having Detail data.

Data Collection and Analysis

Data was collected with search onEBSCO (2010-December); MEDKNOW (2013December); Ovid MEDLINE(R) (2016), SCOPUS, ELSEVIER, SAGE abstract and citation database. The key words used were genes, role in orthodontic tooth movement, in the English language. To meet the inclusion criteria of obtaining articles, two reviewers were scrutinized independently, relevant article text, titles, and abstracts were reviewed. Primary research articles were analyzed based on obtaining data with Meta –summary (Meta-analysis). Secondary and abstract were modified into comprehensive, made a separate category.

Results

A total of 79 extracted articles was collected from the bibliographic database search, 39 full-text articles were reviewed, and 23 met inclusion criteria. From the remained article relevant data were extracted. Only 16 articles were completely meeting the inclusion criteria. Apart from which, none of the relevant articles were found by our reviewer and expertise.

Many of the articles have been proposed the following five features of mentoring:

Orthodontic Tooth Movement and ECM Remodeling,

Pressure: Tension Related Effects.

Cytokines in orthodontic tooth movement

RANK RANKL/OPG pathway
(5) The role of growth factor.
(6) Colony-stimulating factors
(7) bone morphogenic factor

Orthodontic Tooth Movement and Ecm Remodeling

The orthodontic tooth movement (OTM) induces biomechanical strain on periodontal, results into the displacement of ECM fluid in alveolar bone canaliculi, and inflammation-mediated nociceptive pain. Fluid displacement activates bone remodeling process, the nociceptive pain stimulates PDL neuronssecrete neuropeptides such as Substance P, calcitonin gene-related peptide (CGRP). These peptides induce the release of vascular endothelial growth factor (VEGF), essential for bone angiogenesis and in bone development [1-11].

The ECM is remodeling activates kinase- pathway resulting into a reorganization of the cytoskeleton in osteoblastic cells via synthesis of extracellular signal regulated kinase and intracellular proteins through gap junction.

Pressure: Tension Related Effects

On application of orthodontic forces, the periodontal ligament is stretched, bone apposition occurs on the tension side due to activation of extracellular signal regulated kinase pathway. Furthermore, local and systemic hematopoietic cells under the regulatory effect of Prostaglandin-2 (PGE 2) and COX 2 mRNA commands osetoclast cells for bone resorption on the compressed side [6-17].

Understanding the effect of orthodontic forces on teeth and bone is a very complex process, however, the university of honking has been simplified and suggested that the transcription factor SOX9 and parathyroid hormone-related protein (PTHrp) and Indian Hedgehog (IHH) protein plays a vital role directly in regulating the Type II collagen genes, and transmuting the applied force to bone and tooth during orthodontic tooth movement.

In a case of the functional appliance, PTHrP facilitate the growth plate of endochondral bone by signaling of chondrogenic transcription under the regulatory effect of SOX-9 and feedback control of Indian Hedgehog (IHH) genes. SOX-9 regulates the balanced conversion of chondrocytes into chondroblasts for the formation of endochondral bone formation; prevents proliferating chondrocytes into hypertrophic chondrocytes.

Indian Hedgehog (IHH) is protein has regulatory feedback control on PTHrP, SOX9. Hence, IHH protein controls chondrocyte differentiation, proliferation, and maturation, especially during endochondral ossification. Furthermore, in vitro studies done on the Regulatory effect of IHH suggests that IHH inhibits cementoblasts-mediated mineralization in vitro.

Secondly, growth modification process and tooth movement are under the control of Matrix metalloproteinases (MMPs) with their Tissue inhibitor of Matrix metalloproteinases (TIMPs), facilitating conversion of osteocytes into osteoblasts during growth modification.

Among the various types of MMPs, MMP-8 associated with the physiologic tooth eruption, MMP-13 associated with the conversion of osteocytes into osteoblasts during bone remodeling. Furthermore, most of in Vivo and intro studies have suggested that on an application of orthodontic and orthopedic forces transient increase of MMP-8, MMP-13 in both tension and compression side.

Cytokines in Orthodontic Tooth Movement

Cytokines are broad and loose category of small proteins act as immunomodulating agents involved in an autocrine, paracrine and endocrine signaling in low concentrations, which act on nearby target cells in cell-cell fashion communication, resulting in alteration of cell growth, proliferation, cell migration, differentiation, gene expression and cell-specific functions [6-20].

There are several types of pro- inflammatory cytokines (IL-1 β, Il-6, IL-8, Il-12, IL-13 TNF-alpha), anti-inflammatory cytokine IL-10 is seen in both compressed and tension zone. The secretionof IL1is a complex process associated with breakdown of stagnated RBC's(red blood corpuscle) in compressed area and triggered by various stimuli such as neurotransmitters, bacterial products, and mechanical forces.

The secreted pro-inflammatory cytokines directly stimulate osteoclast on the compressed side of PLD through the IL-1 receptor. During the process of IL1 a potent byproductTumor Necrosis Factor alpha (TNF α) molecule is responsible for a diverse range of signaling events within cells resulting in bone resorption. The studies on the mechanism of action of TNFα suggest that activated TNFα activates osteoclast progenitors to osteoclasts in the presence of macrophage colony-stimulating factor (M-CSF).

Rank Rankl/Opg Pathway

Osteoprotegerin (OPG) is a basic glycoprotein comprising of 401 amino acid residues arranged [7] structural domains. May be found in two form, i.e. 60 –KD as a monomer or 120kDa dimmer linked by a disulfide bond. However, in pertaining to humans, these proteins are present in cytokine receptors of tumor necrosis factor (TNF), and coded by TNFRSF11B genes [10-17].

OPG is a key regulator of inflammation, and cell differentiation by entangling with RANKL which is a transcription factor for immune-related genes. OPG controls the production of osteoclast by inhibiting differentiation osteoclast precursors, thus it plays a vital role in bone remodeling.

The mechanisms of bone remodeling are still not fully explained, but on an application of orthodontic force alteration in the local area to fulfill the normal wear and tear by the release of cytokines, or growth factors. RANKL is the only cytokine that plays vital role in bone metabolism as it regulates the development, maintenance, and activation of osteoclasts.

RANKL is composed of chondrocytes, activated T lymphocytes, TCD4+, TCD8+, and CD4 CD8 thymocytes. The calciotropic factors activate RANKL on which it stimulates bone resorption of formation hormones (parathyroid hormone (PTH), PTHrP, vitamin D3, interleukin-1 (IL-1), IL-11, IL-17, TNF-alpha, prostaglandin E2 (PGE2) and CD40L).

Role of Growth Factor

Transforming growth factor β (TGFβ) possess N-terminal signal peptide of 20-30 amino acids secreted from cells like fibroblasts and osteoblasts. TGFβ composed of 390, and 412 amino acid and encoded with large protein precursors. Most of the studies have shown that there are three types of TGFβ, TGFβ1, TGFβ2, and TGFβ3. On application of orthodontic forces, secretion of the latent form of TGFβ factor in ECM.

The matured TGF-β is dimerizing to a 25 kDa protein with a various conserved structural pattern such as TGF-β has nine cysteine residues with a disulfide bond [1-18].

TGFβ attracts monocytes, fibroblast and stimulates angiogenesis in vitro, resulting in cell growth, differentiation, and apoptosis, as well as in developmental processes and bone remodeling. TGFβ present mainly in platelet and bone, hence combining with RANKL and M-CSF facilitates the osteoclast differentiation in PDL cells.

Colony-Stimulating Factors

These are the glycoprotein binds to blood stem cell receptors in the form of granulocytes (G-CSF), macrophages (M-CSF), or to both cell types (GM-CSF), critically involved in bone remodeling (osteoclast formation and thereby during tooth movement). Furthermore, they Stimulate fibroblasts with epidermal growth factor, PDGF, FGF, and IL-1 induce M-CSF expression by these cells; M-CSF is the most potent in stimulating bone-marrow cells to produce osteoclasts, followed by GM-CSF, IL-3, and G-CSF [10-20].

Bone Morphogenetic Proteins (BMPS)

These are a group of growth factors known as metabologens, which can induce the formation of bone and cartilage. BMPs is now considered to constitute a group of pivotal morphogenetic signals, orchestrating tissue architecture throughout the body. The important functioning of BMP signals in physiology is emphasized by the multitude of roles for dysregulated BMP signaling in pathological processes. The cancerous disease often involves misregulation of the BMP signaling system [20-26].

In orthodontic tooth movements, helps in up-regulating multifunction factor related to TGF- β, critically play role in bone formation by osteoblastic differentiation. There were more 20 BMPS in which BMP-2, BMP-6, BMP-7 and BMP-9seem to have the most predominant osteogenic activity in the tension zone.

Discussion

Bone is a mineralized dynamic tissue with plastic in nature in which orthodontic forces are dissipated and remold into the desired shape. This inherent property of the bone cell to react to a mechanical stimulus in both extracellular and intracellular, initiate and propagate signaling cascades molecules critically involved in bone remodeling [1-27].

Most of the articles in our study explains that upon application of orthodontic force initiates mechanosensing, transduction, and cellular response such as in vasculature, induce release of vascular endothelial growth factor (VEGF), essential for bone angiogenesis and extracellular matrix remodeling in the periodontal ligament (PDL), gingiva, and alveolar bone, remodeling facilitated by proliferation, differentiation, and apoptosis of local periodontal cells, bone cell precursors, and leukocyte migration from the microvascular compartment.

Potent response to applied orthodontic force (continuous/ intermittent) accumulated in the DNA of periodontal ligament (PDL) and alveolar bone cells, initiate osteoclastogenesis through downregulation of OPG and upregulation of RNKL using a prostaglandin E 2 (PGE2) and interleukin (IL) -1 β synthesis [29-31].

Various researchers have been reported in detail that regulation of RNKL and OPG differ in compression and tension zone. The process of formation of osteoclastogenesis regulated through M-CSF and RANKL signaling by PDL cells on the compression side appears in the first week of orthodontic force. However, OPG and RNKL, Tumor necrosis factor (TNF) appear within 24 hours in compression side with signs of acute as well as chronic inflammation, and Tumor necrosis factor TNF-α is another proinflammatory cytokine that involved in bone resorption [31,32].

In our study, maximum referred articles have been published that TNF- α is activated by monocytes and macrophages that are directly or indirectly initiate osteoclastogenesis by binding to a receptor on osteoclast precursors through upregulating of RANKL, MCSF, pathways on compression side and RNKL, OPG pathways tension side. Furthermore, most of the studies have reported that PDL fibroblasts secrete higher levels of TNF- α at the PDL compression side than at the tension side.

Few in vitro study articles have been reported that on an application of continuous orthodontic force, initiates osteoblastic autocrine mechanism. Increase amount of IL-1 α, IL-6, IL-11, TNF- α and receptors for IL-1, IL-6 and IL-8, indicating that the response is mailed through osteoblastic cells. However, in absence of IL-1 α and/or TNF-α signaling results in impaired tooth movement [32-35].

Increased amount of osteoblast cell indicating that the synthesis of Bone morphogenetic proteins like (a growth factor) BMP2, BMP7. BMP2 initiates cementoblast differentiation along with the elevation of Osteopontin. Osteopontin (OPN) complex protein synthesized from fibroblasts, osteoblasts, osteocytes, odontoblasts, in the compression side of PDL [32-37].

Most of the articles have been reported about growth factors, transforming growth factor β (TGFβ) with its types and functions, and also another factor like fibroblast growth factor (FGF) and insulin-like growth factor (IGF). TGFβ controls BMP's production and stimulates bone formation under regulatory pathways RANKL and M-CSF. The functions of fibroblast growth factor (FGF) are responsible for their synthesis and are released only when there are disruptions of the plasma membrane facilitate uptake and release of large signaling molecules bone remodeling during orthodontic tooth movement.

Conclusion

Understanding of the gene's role during orthodontic tooth movement is a very complex procedure. In which Osteocytes, osteoblasts, PL fibroblasts, osteoclasts, chondrocytes and immune cells are the principal cell types responsible for producing a number of cytokines, growth factors, and transcription factors and other regulatory molecules which modulate cell proliferation, differentiation, gene expression and cell functions. Genes like SOX-9 gene, PTHrP and IHH, RANKL, M-CSF, and RANKL –OPG pathways mainly significant in avoiding ankylosis of tooth within and during orthodontic tooth movement. The supportive to these pathways are of IL-1 α, IL-6, IL-11, TNF- α,) BMP2, BMP7, (TGFβ) and FGF.

Acknowledgement

I would like to thank our young and dynamic chairman Mr. Gaurav Tiwari sir, for his constant support and encouragement to write this article.

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