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Review Article

Role of Interleukin-1 Beta in Orthodontics

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ABSTRACT

The core of orthodontic treatment philosophy was to move the teeth through the bone to a favourable position thereby obtaining an aesthetically and functionally stable occlusion. The mechanical force was the therapeutic tool used by an orthodontist during orthodontic treatment. An efficient orthodontic tooth movement can be accomplished with the appropriate use of mechanics and adequate knowledge about the biological response. Interleukin-1beta, a member of cytokine family was one among the various molecules that got activated and released in response to the applied mechanical force in tissues and cells surrounding the tooth structure and plays a key role in initiating an aseptic inflammatory response which was not only a prerequisite for bone remodelling and tooth movement but also had an effect on other associated phenomenon such as pain and resorption during orthodontic tooth movement. This paper contains a brief description on the significance of Interleuin-1beta in orthodontics and an attempt had been made to understand the cross talk between the pathways leading to bone remodelling, pain, tooth movement, and root resorption as they all have inflammation as a common thread.

Key Words: IL-1beta, Inflammation, OTM, EARR, pain, bone remodelling.

INTRODUCTION

The transduction ofmechanical stimuli from an orthodontic appliance to the cells in periodontal tissue triggers a biological response that facilitates the remodelling of alveolar bone and periodontal ligament (PDL) resulting in orthodontic tooth movement (OTM). This biological response is an inflammatory reaction but it does not represent a pathological condition hence it is considered as an aseptic inflammation. The findings of DAMP system by Chen and Nunez [1] further supported the concept of aseptic inflammation. Orthodontic force induced inflammatory mediators have been identified and these were listed out by Yamaguchi and Garlet. [2]

Cytokines are one among them and it grabbed its attention in the field of orthodontics due to its many characteristics features. Interleukin - 1 beta (IL-1 beta) is an extensively studied cytokine expressed in gingival crevicular fluid (GCF) in orthodontic literature. It is a potent pro inflammatory and bone resorptive marker. The aim of this review is to give an insight about Interleukin -1 beta and its role in orthodontic tooth movement and its associated phenomenon.

History and background

Cytokines-Interleukins:

Cytokines are pleiotropic, they can be redundant, they synergize and antagonize each other, create cascade effect by stimulating the production of other

cytokines. They have influence over the expression of cytokine receptors. Cytokines can be groupedinto interleukins (IL), tumour necrosis factors (TNF), chemokines, interferons (IFN), and growth factors. Cytokines involved in a variety of immune and inflammatory activities. Depending on their action the cytokines may be pro inflammatory (increase the inflammatory response), anti-inflammatory (decreases the inflammatory response), Macrophage activating cytokines, B cell activating cytokines, T cell activating cytokines, Eosinophil and/ or mast cell activating cytokines, inhibition of virus replication. Interleukins that are associated with bone remodelling include IL-1 alpha, IL-1 beta,IL-2, IL-3, IL-4, IL-6, IL-8, IL-13. [3] Among these, IL-1 beta is the earliest marker identified for bone resorption. [4] It is one of the seven molecules (IL-1 alpha, IL-1 beta, IL-18, IL-33, IL-36 alpha, IL-36 beta, and IL-36 gamma) with agonist activity within the IL-1 family ligands which constitutes in addition to the seven the molecules, three receptor antagonists (IL-1Ra, IL-36Ra, and IL-38), an anti-inflammatory cytokine (IL-37) and there are eleven molecules included in the IL-1R family. [5]

Discovery of IL-1 beta:

The discovery of IL-1 betabegan in 1948 when Paul Beeson reported in his investigation on fever, the release of an endotoxin-free protein material known as endogenous pyrogen from a rabbit. [6] After Forty years this material was further explored by Patrick Murphy and Barry Wood. [7] Bodel et al [8] in 1977 found in their study that this material was not pre-formed but it was released by human peripheral blood following *de novo* synthesis. Later in 1980 Bodel et al [9] found this material which came to be known as IL-1beta in human white blood cells, as well as Hodgkin's and lymphoma cells.

Location, Synthesis, activation and signalling mechanism:

It is located on chromosome 2 between IL-1alpha and IL1-Rn, 40 to 110kb from IL-1alpha. The synthesis and activation of IL-1 beta are regulated by various mechanisms. The expression of IL-1 beta in the cytoplasm is brought about by inflammatory signals and it is not constitutively expressed. [10] It is expressed in pro-form and it is converted into an active form by caspase-1, a type of cysteine protease while caspase -1 gets activated by inflammasome, a large cytoplasmic multiprotein complex.

Interleukin 1 beta in orthodontics

Interleukin 1 beta and pain:

It was well established in the literature about the effect of Cytokines in pain. [11] Orthodontic pain commonly accompanies OTM in almost all the treatment stages of orthodontic treatment. Orthodontic pain is inflammatory in nature resulted from the force induced vascular occlusion in the periodontium. The response includes the interaction of vascular, cellular and chemical events. [12] Interleukin-1beta one of the chemical mediators released during tooth movement encourages secretion of pain producing substance and they have a key role in activating or sensitizing nociceptors in the periodontium around teeth and orthodontic pain is mediated by these nociceptive fibres in the periodontium. [13-16] The nociceptive stimuli picked up by the nerve fibres in periodontium are transmitted to Central nervous system (CNS) via three-order neurons namely, trigeminal ganglia, the trigeminal nucleus caudalis and the ventroposterior nucleus. [12] As pain and immune system are interrelated it often becomes difficult to say whether the reduction in production of pro inflammatory cytokines reduce the pain or blocking nociception results in the lesser formation of proinflammatory cytokines. [17] Stimulation of inflammation mediators results in the release of neuropeptides which in turn

enhance the inflammatory reaction by again stimulating the inflammatory factors which triggerthe release of more neuropeptides thus creating a vicious cycle. Neurogenic inflammation is an inflammatory reaction enhanced by the neuropeptides. The expression of neuropeptides in periodontium and dental pulp during orthodontic tooth movement indicates its role in neurogenic pain during orthodontic treatment. [18,19] studies have found that the immune and nervous system are linked by cytokines and they may play a role in pain and hyperalgesia. Among these cytokines, IL-1 activates or sensitise the nociceptor fibres by directly or indirectly by a complex signalling cascade. [20-23] Studies have been carried out to find out the correlation between the levels of interleukin – 1 beta in GCF and pain experienced during orthodontic treatment. [15,24-26] In spite of the increased number ofresearch in the field of pain utilizing orthodontic tooth movement as a model to explore the complex mechanisms of neuronal involvement, missing links still exist in the pathway of pain during orthodontic tooth movement.

Levels of Interleukin 1 beta in oral fluids and tooth movement/force or stress applied:

During the lastdecades, various studies have been extensively done to understand the changes in the periodontium assocoatd with OTM. The recent advance in cellular and molecular biology played a way to investigate the role of different PDL cells in bone remodelling during orthodontic tooth movement. [27-30] Studying the mediators in oral fluid (both saliva /GCF) will help us to understand the changes taking place in the periodontium as these mediators reflect the microenvironment where the force being transferred, in addition, it supports us in assessing and improving the orthodontic tooth movement. [31] As a result of force application, an adequate amount of IL-1 beta produced in the periodontal ligament diffuse into the GCF and studies have identified IL-1 beta has a biomarker of orthodontic tooth movement. [32,33]

Among the variousregulatory proteins detected in gingival crevicular fluid, cytokines is a protein of interest as they play an important role in cell signalling and bone remodelling. [34-36] Various clinical studies have been carried out to study the up and down regulation of these cytokines from GCF and its role in orthodontic tooth movement. [25,37,38]

Since IL-1 beta is produced under mechanical stress, studies have been done to discover the relationship between force application (intensity, duration) and production of IL-1beta in GCF. Production of IL-1 beta reaches its peak levels differently in different studies (24 hr/ 4hr/8hr/3 days/7days/21 days/2 months/ 3 months/6months). [15,24,32,37,39-43] Influence of Type and amount of force on the expression levels of IL-1 beta had also been considered by certain authors. Lee et al [44] studied and compared the influence of continuous and interrupted force on the expression levels of IL-1 beta. They stated that for continuous force the level reached its peak at 24hr while for interrupted force it reaches after the first activation of the appliance. While Luppanapornlarp et al [15] compared 150g and 50g force and evaluated the levels of IL-1beta and pain in response to these force. He concluded in his study that there is a rise in the level of IL-1 beta expression and pain in higher force while 50g of force could produce similar tooth movement with less pain. Certain studies did not concentrate on the peak value but they correlated the fluctuated levels of IL-1 beta: IL-1 RA ratio (activity index) with the velocity of tooth movement when various stresses applied to the teeth. [40,45-47] Being an inexpensive and non-invasive method, whole saliva samples can be considered as an alternative to GCF for analysing markers that reflects the periodontal environment [48] and the mediators can be detected as they are washed out into saliva from the gingivalcrevice. Noor Saadi and Ghaib [49] in their study estimated IL-1 beta in saliva and

find an association between the force applied and IL-1 beta during tooth movement. Luppanapornlarp and Iida [50] in their review stated that the most of the studies reporting the association between IL-1beta or receptors in GCF with tooth movement or pain or force are arriving at a conclusion that there is an instant release of IL-1 beta in 1 hr which reaches its peak at 24 hr on application of force thus supports the concept that inflammation plays a vital role during orthodontic tooth movement.

Interleukin-1 beta and root resorption:

The process of resorption was defined using various terminology namely apical root resorption (ARR), external apical root resorption (EARR), orthodontically induced root resorption (OIRR), orthodontically induced inflammatory root resorption (OIIRR) and others. [51-55] Recently the new term orthodontitis is being introduced to define this process. [56] Based on the radiographic findings orthodontitis can be divided into two groups as instrumental orthodontitis and instrumental – detrimental orthodontitis. [57]

The inflammation process which is an important feature of tooth movement is also an important component behind root resorption process. Even though the cellular process underlying tooth movement and root resorption is thought to be similar evidence based data related to the molecular basis of root resorption is comparatively less at this point.Yamaguchi and Garlet [2] considered the possibility of this similar inflammatory mechanism to be operated as a constructive one mediating the tooth movement and as destructive one that ends up in root resorption. He further added that there exists an unclarity about the driving factor which dictates constructive or destructive inflammation. Studies have reported the role of inflammatory mediators and chemokines in root resorption process. [58-60] Diercke et al [61] reported in his study the role IL-1 beta and a compressive force in inducing the production of RANKL in cementoblasts suggesting that particular cell type on activation could dictate root resorption in the apex area. For a long time, it has been suggested to use lighter force to overcome root resorption. Laterregime of force application was related to root resorption and studies have been conducted and recommended to use an intermittent type of force as it causes less severe root resorption than the continuous type of force. [62] Root resorption is affected by both patient and treatment related factors. Studies done by Harris et al [63] and Al-Qawasami et al [64] can be considered as a milestone in relating genetics and root resorption. In 2003 Al-Qawasami et al [64] is the first one to report the association of EARR and IL-1betapolymorphism therebyemphasizing the role of IL-1 beta gene polymorphism in external apical root resorption. They have also suggested to screen orthodontic patients for IL-1beta genotype and to identify those who carry 2 copies of allele 1 of IL-1beta by analysing the DNA which might help to identify people who are at risk of developing root resorption before orthodontic treatment. Following this, various others studies [65-70] replicated the probable association of IL-1 beta gene polymorphism with root resorption and also explored other gene polymorphism such as vitamin D receptor. [71] Gülden et al [72] in his retrospective study found that IL-1 beta gene polymorphism does not predispose external apical root resorption. While another study [66] found that not only variation in IL-1 beta but also variation in IL-1RN are responsible for post orthodontic external apical root resorption. Hope further research in future will resolve the debate over the role of IL-1 beta gene variation and other biological agents like interleukins, RANK and RANKL, prostaglandins and OPG in predisposing external apical root resorption. Iglesias-Linares and Hartsfield [73] suggested that root resorption results not from a single pathway or factor but by the interaction of several pathways at the level of cell fusion/activation, clastic cell adhesion, and mineralized tissue reparative capabilities

Interleukin-1 beta and alveolar bone remodelling:

The osseous response that permits tooth movement in orthodontics results from functional load overlaid by the static load to produce a dynamic load. [74] The bone remodelling process during OTM is a result of effective interaction between osteoclasts, osteoblasts, osteocytes and PDL cells. When the mechanical load is applied during OTM the PDL mediated immune response induces the inflammatory response results in bone remodelling that involves many regulators. Cytokines are one among them. Cytokines possess not only osteoclastogenic activity but also anti osteoclastogenic properties and there by maintains the bone homeostasis. IL-1beta is a potent initiator of osteoclast differentiation. [75]

During initial stages of orthodontic tooth movement, IL-1beta is produced in the compression side of periodontal space and it has a direct effect on bone resorption. [76]

IL-1beta produced in response to orthodontic force stimulates osteoclastogenesis. [33,37] By induction of TNF-α and upregulation of RANKL &MMPs, IL1beta participate in several stages of osteoclastogeeneis and determines the bone remodelling process. [75,77,78] The role of these factors in orthodontic tooth movement is well co-ordinated. [79] This phenomenon was confirmed in a mice model in which the administration of exogenous IL-1beta receptor antagonist results in not only a reduction in a number of osteoclasts but also the rate of tooth movement. [80] The inter-connection between the immune and skeletal system, the basis of osteoimmunology can be well explained using OTM model. Understanding this complex interaction in the orthodontic field is in its early stage and in future, works in this area will give us more in depth knowledge about osteoimmunology and tooth movement.

CONCLUSION

The production and activation of Interleukin 1 beta are certain during orthodontic tooth movement as the underlying biological response is inflammatory in nature. Even though earlier attempts have been made to understand the influence of intensity of force on the expression level of IL-1 beta, the recent focus of research is on the effect of a regime of force application. IL-1 beta not only have an effect on bone remodelling and tooth movement but also on the various other associated phenomenons such as pain, root resorption. There might be a cross talk between the pathways leading to bone remodelling, pain, tooth movement, and root resorption as they all have inflammation as a common thread. Current researches on biological response during tooth movement are focusing on a panel of associated or relevant biomarkers or genes instead of one. From this review it is obvious that when designing such a panel, IL-1 beta will definitely finda place in it.

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