

Brief insight into the Homeostasis of the Periodontal Ligament

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ABSTRACT:

The periodontal ligament is a dynamic, vascular and complex connective tissue component of the periodontium. The Periodontal ligament is formative, nutritive, sensory and protective in function. The periodontal ligament width is usually about 0.25mm. This tissue is characterized by rapid turnover and a high remodelling capacity, which give it adaptability, maintaining a constant width despite being exposed to rapidly changing physical forces such as mastication, speech and orthodontic tooth movement. The cells of the PDL, form, maintain and repair not only the ligament itself, but also the adjacent alveolar bone. There are various cellular, biochemical, genetic and mechanical factors that play a role in maintaining the periodontal ligament space. This review discusses the importance of maintaining the periodontal ligament space and the various factors that play a role in regulating the periodontal ligament homeostasis, with emphasis more on the biochemical factors regulating the periodontal homeostasis.

Key words: Periodontal ligament, homeostasis, maintenance, periodontal ligament space.

INTRODUCTION

The periodontal ligament (PDL) is a complex, vascular, and highly cellular soft connective tissue that attaches the tooth roots to the inner wall of the alveolar bone.¹ The PDL consists of a fibrous stroma in a gel of ground substance containing cells, blood vessels and nerves.² The PDL can be subdivided into three regions: 1. A bone-related region, rich in cells and blood vessels. 2. A cementum-related region, characterized by dense, well-ordered collagen bundles. 3. A middle zone containing fewer cells and thinner collagen fibrils.³

The healthy PDL contains several discrete cell populations including fibroblasts, endothelial cells, epithelial cell rests of Malassez, sensory cells, osteogenic and osteoclastic cells and cementoblasts.¹ The predominant cell type is the fibroblast.¹ Type I collagen accounts for approximately 80% of the total collagen

content. It is the major component of the principal fibers. Elastin fibres, oxytalan and eluanin exist within the ligament.³

The PDL provides a soft tissue casing to protect nerves and vessels from injury by mechanical forces, it serves as an attachment of teeth to bone, maintains the gingival tissue in proper relation to teeth and resists impact of occlusal forces.⁴

Normal periodontal ligament Space

In humans, the PDL has an average width of 0.25 mm (0.15-0.38mm). Its width varies according to the functional state of tissue⁵. Radiographically, it appears as a thin radiolucent line surrounding the roots of the teeth.⁶

Maintaining the Periodontal Ligament Space

Health in the periodontium is the result and sum of an ongoing dynamics characterized by both anabolic and catabolic activities⁷. This normalcy or balance is important in maintaining the normal periodontal ligament space. This tissue is characterized by rapid turnover and a high remodelling capacity, which give it adaptability, maintaining a constant width despite being exposed to rapidly changing physical forces such as mastication, speech and orthodontic tooth movement.^{5,8}

The remarkably precise maintenance of periodontal ligament width in spite of these force levels or the restoration of the ligament space after surgical ablation indicates the existence of highly effective regulatory systems for “measuring” tissue domains and for initiating localized matrix resorption and synthesis.¹

The cells of the PDL, form, maintain and repair not only the ligament itself, but also the adjacent alveolar bone.⁵ The neurosensory system within the PDL have important proprioceptive function and may play a part in the control of masticatory movements. Therefore, it is important to maintain the periodontal ligament space.

Factors that play a role in PDL homeostasis

Various factors play a role in regulating the periodontal ligament homeostasis. Conceivably, these factors may modulate the osteogenic activity of periodontal ligament cell populations and contribute to the preservation of periodontal ligament width.¹ They may be described as cellular, biochemical, mechanical or genetic factors (Table 1). Since, influence of mechanical forces on the periodontal ligament is an area vastly explored and studied, this review concentrates to a greater level on the other factors controlling Periodontal ligament space maintenance, mainly the biochemical factors.

Cellular factors

1. Mesenchymal Stem Cells

This small population of progenitor cells remain within the periodontal ligament throughout life and are responsible for tissue homeostasis.⁹ Their presence maintains the periodontal ligament space as they have the potential to differentiate into cells that can regenerate tissue as well as into cells that have resorptive functions.

2. Epithelial cell rests

Epithelial cells rests seem to have possible roles in maintenance of the periodontal ligament¹⁰ and differentiation of cementoblasts. They inhibit osteogenesis in the periodontal space.¹¹ Malassez epithelium could be involved, at least in part, in maintaining the periodontal space width. It might prevent alveolar bone compartments from migrating into the cementum surface.¹¹

However, since the epithelial rests of Malassez are embedded in the periodontal ligament, consequently making it difficult to isolate and/or manipulate Malassez epithelium both in vitro and in vivo, no firm evidence has been obtained to support their functional role.^{12,13}

It has been shown that reformation of the periodontal ligament does occur without the re-

appearance of rests of Malassez,¹² suggesting that these cells do not play a critical role in maintaining the normal width of the ligament and in cementum formation and do not prevent ankylosis and root resorption.

Also, the Malassez epithelium is predominantly localized on the coronal side of the periodontal ligament, but much less on the apical side. Therefore, other mechanisms must contribute to maintaining the width of the periodontal space in the apical regions. It is possible that cementum might also contain putative molecules that regulate the periodontal space width along with the epithelial rests of Malassez.¹¹

3. Fibroblast

Periodontal ligament fibroblasts, the chief cells of the periodontal ligament are needed to maintain the normal width of the PDL by preventing the encroachment of bone and cementum into the PDL space.¹⁴

These cells have two lineages- the fibroblastic and osteoblastic lineage.¹⁵ The fibroblastic lineage has functions of preventing mineralisation and maintain the periodontal ligament space, by upregulating Nitrous Oxide and osteocalcin expression, and increased prostaglandin expression. Osteoblastic lineage cells show more of alkaline phosphatase activity with a tendency for bone formation and are found along the ligament region lining the alveolar bone.¹⁵

Sometimes localized ankylotic areas can be removed and the integrity of the ligament restored when periodontal ligament fibroblasts or their progenitors are allowed to gain access to the root and repopulate the area.¹⁵

Expression of desmoplakin in the Periodontal Ligament Fibroblasts has been considered to protect gap junctions in these cells against cell transformation caused by cell contraction, which may relate to tooth movement and repair of periodontal tissues.¹⁶ Given the adaptive role of the

periodontium, the presence of these specific cytoskeletal molecules suggests a central role of periodontal ligament Fibroblasts in the maintenance of periodontal tissue homeostasis and in tooth movement.¹⁷

It has been shown that heat killing of these cells induces ankylosis,¹⁸ and also in vitro studies have shown that periodontal ligament cells can inhibit mineralised bone nodule formation by rat bone stromal cells.¹⁹

Biochemical factors

1. Osteocalcin

Osteocalcin is one of the most abundant noncollagenous proteins of bone matrix. It binds to Osteopontin that interacts with osteoclasts and acts as a negative regulator of mineralisation.

2. Bone sialoprotein

Immunostaining of periodontal ligament cells for bone sialoprotein, a marker of differentiated osteoblasts and cementoblasts, shows no staining reaction in periodontal ligament cells.²⁰ The absence of this late marker of osteoblast differentiation in repopulating periodontal ligament demonstrates that, while a significant portion of periodontal ligament cells may have osteogenic characteristics, these cells are blocked from differentiating into osteoblasts.

3. Glycosaminoglycans

Periodontal ligament contains predominantly dermatan sulfate while cementum and alveolar bone contains mostly chondroitin sulfate.²¹ A role for glycosylaminoglycans in maintaining the unmineralized state of the periodontal ligament is suggested. Control of expression of specific proteoglycan species on a spatially restricted basis is presumably central to this role.²¹

4. Osteonectin

A collagen binding protein is frequently associated with tissues with high rates of collagen

turnover, and it is critical in the control of tissue collagen content and is necessary for PDL homeostasis.²²

5. Nitrous Oxide (NO)

It has been demonstrated that administration of exogenous NO inhibits proliferation and promotes expression of specific markers of the osteoblastic phenotype in primary cultured PDL cells.²³ PDL cells may produce NO by many types of mechanical stress²⁴. The increase in level of nitrous oxide may be the indirect effect of IL-1 activation as a result of altered occlusal stimuli.²⁴ This mediator may play an important regulatory role for blood vessel expansion and as a mediator of mechanical stress, maintaining the integrity of periodontal tissues under physiological conditions²⁵

6. Osteoprotegrin (OPG)

It is a decoy receptor of RANKL. PDL cells secrete more OPG (3-4 times) than RANKL on the cemental surface, thus preventing cemental resorption²⁶. IL-1 β & TGF- β 1 stimulate OPG expression in PDL fibroblasts²⁶

7. Prostaglandins

Prostaglandins, which are also produced by periodontal ligament cells, can inhibit mineralized bone nodule formation and prevent mineralization by periodontal ligament cells in vitro¹⁹

8. Transforming growth factor (TGF) β

Isoforms synthesized by periodontal ligament cells can induce mitogenic effects but can also dose-dependently down-regulate osteoblastic differentiation of periodontal ligament cells²⁷

9. IL-1 β

It is an important regulator of PDL cell functions and directs these cells to participate actively in an immune response during infections, at the expense of their normal osteoblast-like functions. The altered PDL cell phenotype and functions are transient; these cells reacquire their original characteristics following removal of IL-1 β . Taken together, these

findings suggest that proinflammatory cytokines control the homeostasis of the PDL, a function that may be pivotal to the integrity of the PDL as well as to the host immune response²⁸

10. Growth Factors

EGF and NGF play important roles in maintaining the PDL by having an influence on the epithelial cell rests²⁹

11. Periostin

Originally termed osteoblast-specific factor-2 (Osf-2), this protein was renamed "periostin," based on its localization in the periosteum and PDL. Periostin maintains the integrity of the PDL during occlusal function and inflammation.³⁰ It was observed to be preferentially expressed in the periosteum and periodontal ligament, indicating its tissue specificity and a potential role in maintenance of tissue structure³¹

12. S100A4

It is a calcium binding protein, which was reported as an extracellular inhibitor of mineralization and may be one of the factors responsible for keeping PDL space free of mineralization³²

Genetic factors

1. Runx2/Osf2

PDL has a mechanism for regulating PDL width and maintaining periodontal homeostasis that is resistant to the strong osteogenic stimulation by BMP by means of suppression of the transcriptional activity of Runx2/Osf2, since the transcription factor is necessary for calcification of bone^{33,34}

2. Msx2

The transcription factor Msx2 has recently been suggested as a molecular defense mechanism that prevents mineralization in the PDL,³⁵ but the nature of the specific molecular regulators on the surface of the PDL fibroblasts that "sense" the matrix status and control collagen turnover has remained elusive.

3. Twist gene

It is a basic helix loop helix protein, which regulates early osteogenesis. It is constitutively expressed higher in osteoblast like cells of PDL. It is a negative regulator of osteoblastic differentiation in PDL cells, thus inhibiting mineralisation.³⁶

4. RGD-CAP

It is a collagen-associated protein containing the RGD (arginine-glycine-aspartic acid) sequence, named RGD-CAP.³⁷ RGD-CAP has a negative function on osteogenesis.³⁷

Studies have shown that RGD-CAP contributes to the maintenance of elasticity of periodontal ligament by inhibiting mineralisation³⁷. Possible mechanisms include inhibition of downregulation of the type I collagen mRNA level, reduction of bone sialoprotein mRNA level, suppression of ALP activity³⁷, and also it is thought that RGD-CAP adhesive functions contribute to maintenance or regeneration of PDL architecture, induced by TGFbeta in response to mechanical stimuli³⁹

5. PLAP-1

Periodontal ligament-associated protein-1 (PLAP-1)/asporin is a recently identified novel member of the small leucine-rich repeat proteoglycan family⁴⁰. PLAP-1/asporin is expressed specifically and predominantly in the periodontal ligament and that it negatively regulates the mineralization of PDL cells.⁴⁰

Endogenous PLAP-1/asporin may prevent the PDL from undergoing osteogenic and cementogenic processes probably by inhibiting BMP-2 functions to maintain PDL homeostasis in vivo⁴⁰. This may be the molecular mechanism by which the PDL prevents the onset of ossification despite having osteoblastic potential^{40,41}

Mechanical Factors

The effect of mechanical forces on the periodontal ligament homeostasis is a topic of vast research, and it is detrimental role in the

maintenance of the ligament space is proved beyond doubt.

General trend after application of physical forces to teeth is preservation of the width of the periodontal ligament, a remarkable process involving precisely controlled osteogenic resorption and deposition at specific sites in the tissues.⁸

Masticatory function can accelerate the resolution of ankylotic areas and restoration of normal periodontal ligament width.⁸ It is the mechanical forces exerted on the ligament that induce production of other biochemical factors like IL-1, TGF-B, NO that prevent the mineralisation of periodontal ligament, and maintain normal homeostasis.

Alterations in PDL space

Decreased functional loads have a tendency to decrease the width of the periodontal ligament. The width of the PL tends to decrease with age. The loss of normal occlusal function leads to atrophic changes in the PDL, such as narrowing of the periodontal space, disorientation of collagen fibers, and vascular constriction.^{42,43} Due to persistent trauma from occlusion, there can be funnel-shaped widening of the crestal portion of the periodontal ligament with resorption of the adjacent bone.⁴⁴ Widening of the periodontal ligament space is observed in patients with systemic sclerosis who do not have plaque or calculus.⁴⁵ In hyperparathyroidism there is loss of lamina dura and widening of ligament space⁴⁶

Conclusion

The periodontal ligament is a structure of complex functions, it is important for preserving the tooth and its integrity within socket. Disruption of the homeostasis of the PDL space jeopardises the existence of the tooth. Understanding the factors that regulate the homeostasis and studies performed in relation to this aspect would benefit the dental fraternity immensely with regards to future periodontal therapeutic interventions.

Abbreviations

PDL	- Periodontal Ligament
NO	- Nitrous oxide
OPG	- Osteoprotegrin
RANKL	- Receptor activator of nuclear factor kappa-B ligand
TGF	- Transforming Growth Factor
EGF	- Epidermal Growth Factor
NGF	- Nerve Growth Factor
Osf-2	- Osteoblast specific factor
RGD-CAP	- Collagen-associated protein containing the RGD sequence
PLAP	- Periodontal Ligament Associated protein

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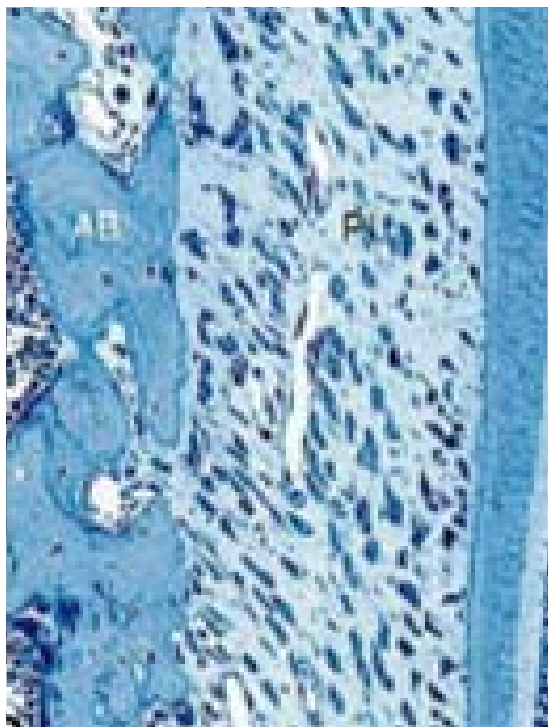


Figure 1: Periodontal Ligament(PL) space spanning between alveolar bone (AB) and cementum(Adapted from McCulloch CA, Lekic P, McKee MD Role of physical forces in regulating the form and function of the periodontal ligament Periodontol 2000;24:56-72)



Figure 2: Widening of periodontal ligament space in systemic sclerosis with respect to mandibular molars(Adapted from Auluck A Widening Of Periodontal Ligament Space And Mandibular Resorption In Patients With Systemic Sclerosis Dentomaxillofac Radiol 2007;36(7): 441-442)

TABLE 1: FACTORS REGULATING PERIODONTAL LIGAMENT HOMEOSTASIS

Cellular Factors	Biochemical Factors	Genetic Factors	Mechanical Factors
<ul style="list-style-type: none"> ● Mesenchymal stem cells ● Epithelial cell rests ● Fibroblasts 	<ul style="list-style-type: none"> ● Osteocalcin ● Bone sialoprotein ● Glycosaminoglycans ● Osteonectin ● Nitrous oxide ● Osteoprotegrin ● Prostaglandins ● Cytokines ● Growth Factors ● Periostin ● S100A4 ● RGD-CAP ● Asporin 	<ul style="list-style-type: none"> ● Runx2 ● Msx2 ● Twist gene 	