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# THE CURRENT ROLE OF PERIODONTAL LIGAMENT STEM CELLS IN DENTAL IMPLANTOLOGY.


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**ABSTRACT** In the present times, partial dentures are replaced by implants, which hold the ideal for replacing missing dentition. For implants to be successful, such as enough bone height and width is very crucial. Before placement of the implant, local bone defects and bone unsatisfactory patterns necessitate bone reconstruction. Besides that, localized bone loss across the implant fixture represents the clinical challenge, especially within the case of gingival recession, which requires in addition surgical interventions. However, problems nonetheless exist with these implants as they lack periodontal tissue, due to the fact any infection around them may cause serious bone loss than does the inflammation around the natural enamel with PDL. In addition, these implants are ankylosed and do not have the same mobility as the natural teeth. These troubles can be resolved, if implant with PDL will be developed that is performed through Ligaplants, that is nothing but aggregate of the PDL cells with implant biomaterial. In this review, we summarize and explore the preceding trials and literature which aimed at forming periodontal tissues round dental implants.

**KEYWORDS :** Periodontal ligament stem cells, Dental Implant, Regeneration

## INTRODUCTION:

Periodontal disease involves the chronic inflammation of tooth supporting periodontal tissues. As the disease progresses, it manifests destruction of periodontal tissues and eventual tooth loss. The regeneration of lost periodontal tissue has been one of the most important subjects in periodontal research. Since their discovery, periodontal ligament stem cells (PDLSCs), have been transplanted into periodontal bony defects to examine their regenerative potential. Periodontal defects were successfully regenerated using PDLSC sheets, which were fabricated by cell sheet engineering in animal models, and for which clinical human trials are underway. [1,2]

If the disease is not properly treated, and disease progression is not arrested, the tooth may require extraction. Therefore, the regeneration of periodontal tissues has been an important and dynamic field of periodontal research. It has been demonstrated that the periodontal ligament (PDL) – a thin connective tissue that bridges tooth and bone – plays a key role in periodontal tissue regeneration by being a source of cells having regenerative potential for periodontal tissues [3, 4, 5, 6]. A unique PDL cell population has been identified that exhibits mesenchymal stem cell (MSC)-like characteristics. Named periodontal ligament stem cells (PDLSCs) in 2004 [7], PDLSCs demonstrated the capacity to differentiate into three mesenchymal lineages of cells in vitro; osteoblasts, adipocytes, and chondrocytes [7, 8, 9]. In addition to its MSC-like characteristics, PDLSCs were found to differentiate into cementoblasts and form cementum-PDL like structures upon transplantation in vivo [7, 10]. Additionally, PDLSCs exhibited the marker expression of pericytes, a mesenchymal-like cell type localized around blood vessels. This finding is in keeping with the classical concept that stem/progenitor cells are located in the perivascular niche in PDL [11]. Thus, PDLSCs are now thought to be putative adult stem cells in PDL.

Dental implants made of titanium and its alloys show high long-term survival and success rates [12]. Though, implant failure exists that has been mainly attributed to inflammatory processes of the peri-implant tissues [13], mostly due to accumulation of plaque around the mucosal margins of the implants [14]. These processes include peri-implant mucositis and peri-implantitis being the two main disease entities. Whereas peri-implant mucositis is defined as inflammation in the mucosa at an implant with no signs of loss of supporting bone, peri-implantitis combines inflammation in the mucosa and respective bone loss past normal biological remodeling [15]. It was reported that the prevalence of periimplantmucositis is 43% whereas 22% of the implants show peri-implantitis [16]. Nevertheless, these numbers should be handled with care due to different case definitions, diagnostic methods, as well as different thresholds for probing depth, and bone loss [17]. To expand the utility of PDLSC sheet, some studies haveattempted to construct periodontal tissues around titanium implants with the goal of facilitating the prevention of peri-implantitis.

In this mini review, we summarize the literature regarding cell-based periodontal regeneration using PDLSCs, as well as previous trials aimed at forming periodontal tissues around dental implants. Moreover, the recent findings in cementogenesis are reviewed from the perspective of the formation of further stable periodontal attachment structure on dental implant.

**Challenges in current implantology**

Localized bone loss around osseointegrated implants represent a clinical challenge.[18] Excessive stress that accumulate at the crestal region of the implants leads to bone loss at this region.[19] This concentration of stresses at the crestal region is mainly attributed to the lack of the periodontal ligament, which is essential for distributing the forces throughout the length of the root. Periodontal ligament additionally dissipates these forces through the compression and redistribution of its fluid elements, as well as through its fiber system and hence provides shock absorption and cushioning effect to the teeth in response to these forces.[20] Furthermore, the periodontal ligament has a sensitive proprioceptive mechanism and is therefore capable of detecting and responding to a wide range of forces applied to the teeth. When these forces are transmitted through the periodontal ligament, they result in the remodeling of the alveolar bone to allow tooth movements (as seen in orthodontics) or in the widening of the periodontal ligament space leading to an increase in tooth mobility in response to excessive forces (e.g., occlusal trauma).[21]

The osseointegrated dental implants on the other hand, physiologically differ from natural teeth as they lack periodontal ligament support and hence when loaded mechanically, evoke a peculiar sensation, which has been termed as osseoperception. Hence the osseointegrated implants not only become a part of the body but also of the mind and this mental acceptance named as osseoperception[10] has been described as a kinesthetic oral perception, which is derived from temporomandibular joint, cutaneous, muscle, mucosal and periosteal mechanoreceptors that provides mechanosensory information on oral kinesthetic sensibility in relation to jaw function and contacts of artificial teeth, in the absence of a functional periodontal mechanoreceptive input.[21,22]

Furthermore, the passive threshold level of implants determined by the application of an external stimulus has been found to be 50 times higher than that of natural teeth;[13] which means that patients with osseointegrated implants will subjectively feel tangible sensation only when a force greater than that required to evoke sensation in natural teeth is applied. Hence, one of the reasons for the diminished ability of dental implants to adapt to occlusal trauma can be attributed to this lack of periodontal proprioceptive mechanism, which results in microfractures of the crestal bone and ultimately leads to bone loss. Moreover, connecting teeth to osseointegrated implants presents a biomechanical challenge due to the differential support and mobility provided by the implant and the tooth and consequently have also shown a higher rate of failures and complications.[14] However, when tooth-implant supported restorations would be fabricated using support from periodontio-integrated implants higher success rates can be expected due to similar resilience of tissues supporting teeth and implants. Furthermore, considering the use of osseointegrated implants in growing patients and the influence of maxillary and mandibular skeletal and dental growth on the stability of these implants, it is recommended to wait for the completion of dental and skeletal growth[15] since, the osseointegrated implants behave as an ankylosed element and don't follow the growth and evolution of the jawbones and certainly not of the alveolar process and hence, may disturb a normal development of the jawbones, leading to unesthetic situations, especially in the anterior region (e.g., resulting in "regeneration" infraocclusion or labioversion).[16]

Nonetheless, with the provision of peri-implant tissue remodeling offered by the periodontio-integrated implants it would not only be possible to successfully place implants in patients undergoing craniofacial/skeletal growth process, but also to move them orthodontically.[23] It has been seen that peri-implant infections progress faster than the infections around natural teeth. Lindhe et al.[24] demonstrated larger inflammatory cell infiltrate and destruction around implants, which extended more apically when compared with a corresponding lesion in the gingival tissue around natural teeth. In addition, the tissues around implants are more susceptible to plaque-associated infections that spread into the alveolar bone, primarily due to the lack of a periodontal ligament, making them more prone to bone loss. Periodontal ligament by virtue of its rich vascular supply is a reservoir of defense cells and undifferentiated mesenchymal cells; hence, the presence of the periodontal ligament around implants would not only provide better defensive capacity, but also enhance repair and regeneration of bone defects in their vicinity.[25,26,27,28]

**Current research:**

A recent review pointed out that surgical treatment of periimplantitisshould be considered in cases of evident bone lossand pocket formation of larger than 5mm [26,27]. Chemical,mechanical, and/or laser decontamination of the affectedimplant surfaces is of high importance for a successful treatment[29]. Especially, the combination of mechanical and chemical removal of the biofilm has been recommended[30]. Even so, there is limited evidence that the periimplantbone level may be arrested. At the moment, theeffectiveness of treating peri-implantitis via different nonregenerativetechniques seems to be limited whereas a regenerativeapproach is considered to be the treatment of choice[10]. Nevertheless, mostly due to a lack of evidence, this isdiscussed controversially [31]. Schwarz et al., using GBRtechniques including collagen membranes, bovine, andequine bone material as well as recombinant human bonemorphogenic protein 2 (rhBMP-2), came to the conclusionthat predictable results in order to obtain complete defectclosure could not be obtained [16]. Other authors could notdetect significant differences between the surgical protocolswhen using GBR techniques as well [12, 32].

Extensive research and several experiments have been carried out to develop periodontal ligament around an implant, i.e., for the creation of a bio-root, which would provide ideal conditions for the implant-supported treatments in future.[33] Nyman et al.[34] suggested that the cells of the periodontal ligament possess the ability to reestablish connective tissue attachment. Nunez et al.[35] have further validated the regenerative potential of periodontal ligament-derived cells in a proof of principle study. Several in vivo experiments have demonstrated the formation of cementum-like tissue with an intervening periodontal ligament, when the dental implants were placed in proximity to tooth roots.[25,28,31,36] The mechanism of this phenomenon appeared to be due to the migration of cementoblast and periodontal ligament fibroblast precursor cells towards dental implants due to contact or proximity of the tooth-related cell populations to those implants.[5]

Although partial regeneration of the periodontium consisting of cementum, periodontal ligament and alveolar bone, was possible, application of such methods in patients seemed impossible due to technical and physical factors.[37] Yet, the potential for the clinical implementation of customized periodontal biomimetic hybrid scaffolds for engineering human tooth-ligament interfaces has been demonstrated by Park et al.[38] There is indeed a growing body of evidence validating the significant potential of the in vivo formation of ligamentous attachments to the biomaterials. Takata et al.,[39] in an animal study examined whether connective tissue attachment could occur on implant materials by repopulating periodontal ligament derived cells and found that while new connective tissue attachment occurred on bioactive materials such as bioglass and hydroxyapatite, little or no cementum deposition was seen on bioinert materials such as titanium alloy and partially stabilized zirconium, i.e., the formation of new connective tissue attachment was influenced by bioactivity of the materials. Choi,[40] placed implants with the cultured autologous periodontal ligament cells in the mandibles of the dogs and histologically revealed that after 3 months of healing, a layer of cementum-like tissue with inserting collagen fibers had been achieved on some implant surfaces, demonstrating that cultured periodontal ligament cells can form tissue resembling a true periodontal ligament around implants. In 2005, researchers also explored the formation of periodontal tissues around titanium implants using a novel dentin chamber model, which demonstrated newly formed periodontal ligament, alveolar bone and root cementum, filling the space between the implant and the wall of the chamber. This study displayed a remarkable capacity for new periodontal tissue formation at a site where no such tissues ever existed.[35]

In a yet another study, implantation of titanium fixture with porous hollow root-form poly (DL-Lactide-co-Glycolide) scaffold seeded with autogenous bone marrow-derived mesenchymal stem cells in goats exhibited periodontium-like tissue with newly formed bone both at 10 days and after 1 month, substantiating that undifferentiated mesenchymal stem cells were capable of differentiating to provide the three critical tissues required for periodontal tissue regeneration: Cementum, bone and periodontal ligament around the titanium implants.[37] The cellular seeding methodology utilizing bioreactors to culture and maintain the "stemness" of these cells during the in vitro culture period before transplantation has allowed for a spatial distribution of cells over the surfaces of the prototype implant devices to eventually form the ligamentous constructs.[5] However, it was a scientific breakthrough when Gault et al.[41] demonstrated for the first time the tissue engineering of the periodontal ligament and cementum-like structures on oral implants in humans, to promote the formation of implant-ligament biological interfaces or ligaplants capable of true, functional loading.

One of the interesting facts in the Gault research-work was that periodontal ligament fibroblasts could be harvested from hopeless teeth of mature individuals and cultured in bioreactors to preserve their state of differentiation. Out of the eight implants inserted, one implant was still in place and functioning even after 5 years and even exhibited substantial bone regeneration in the adjacent bone defect 2 years after implantation. This implies that future clinical use of ligaplants might also be able to avoid bone grafting, its expense, inconvenience and discomfort to the patient.[38] Lately, Kano et al.[42] have suggested that implants surrounded by periodontal ligament-like tissue could be developed, when immediately after the extraction, tooth-shaped hydroxyl-apatite coated titanium implants were placed into the tooth socket where some periodontal ligament still remained; maintenance of original periodontal tissue domains most likely being the cause of prevention of osseointegration of the implants.[41]

## Cell sheet based periodontal regeneration

MSCs are the most widely investigated cell type for cell-based treatmentbecause of their characteristics such as multi-differentiation capacity, immunomodulation, anti-apoptosis, angiogenesis, and cellrecruitment [14]. Besides these MSC characteristics, PDLSCs possess aunique potential to form cementum, and this characteristic of PDLSCs hasstimulated many researchers to examine periodontal regeneration bytransplantation of PDLSCs. We have made significant contributions tothis research field in periodontology, by demonstrating the regenerationof periodontal tissues after transplantation of a "PDLSC sheet" preparedusing cell sheet engineering in various animal models since 2005 [15,16]. Cell sheet engineering is a unique tissue engineering method toobtain cells in a sheet format, which allows collection of the cell sheetwithout destruction of extracellular matrix components secreted fromcells. We have previously reported on human clinical studies using PDLcell sheet transplantation for periodontal regeneration in Japan and somecases have been published [17].

The understanding that transplantation of PDLSCs induces regenerationof periodontal tissues, is gaining wide acceptance and review papershave summarized the results of PDLSC transplantation studies [18,19, 20]. PDLSC transplantation is now considered one of the promisingregenerative approaches for periodontal tissues.While the initial results using PDLSC sheets for periodontal regenerationappear promising, a new trial is underway to extend the applicabilityof this powerful tool to develop periodontal tissues on the surface oftitanium implants. It is a novel tissue engineering approach to formperiodontal tissue-bearing implants.Dental titanium implants directly integrate with the bone and lack several important functional structures associated with a natural tooth, such as cementum and PDL. These attachment structures, normallyassociated with teeth, could function collectively as a buffering structureagainst the forces of mastication to help protect the implant from traumaticmechanical load. Moreover, the direct interface between oralepithelium and titanium implant presents higher risks of bacterial invasionand consequential inflammatory peri-implant mucositis and periimplantitis. Recent studies showed that peri-implantitis is considered amajor and growing problem in dentistry [21]. Since the PDL function as areservoir of immune cells, the formation of a cementum-PDL structurearound dental implants could help protect the implant-bone interfacefrom oral bacterial challenge. To overcome the above-mentioned shortcomings of dental implants,successful formation of periodontal tissues has recently been demonstratedon titanium implants after transplantation of PDLSC sheets in ratsand dogs [13].

## Periodontal tissue formation around implants and cementogenesis

As mentioned earlier, the possibility of periodontal tissue formationaround titanium implants has been suggested. However, there is someroom for improvements in the methodology. Detachment of collagen fibersfrom the titanium surface and the parallel orientation of PDLcollagen fibers relative to the titanium surface have been observed inanimal studies. Thus, it is important to improve the implant/PDL interfacein the interest of stability of the PDL-implant association, and therobust formation of cementum on the implant surface may be the key toimproving the construction of periodontal tissues around implants.[34,37]

Since the induction of cementum formation on the dental implant isvital to the construction of the PDL-implant, it is essential to have anunderstanding of the mechanisms of cementogenesis. Unfortunately, theavailable information regarding the induction of cementum formation islimited. Previously, the essential cellular signals for cementum formationduring tooth root formation have been examined in genetically-targetedmice. Among the various molecules tested, Wnt was the most prominentsignaling molecule that showed phenotypic changes in root cementum. Lim et al. have reported thick cementum formation in mice upon deletionof Wntsignaling, specifically in odontoblasts and osteoblasts [37].

Furthermore, Kim et al. [43] have demonstrated that mice with stabilized Wntsignaling, specifically in dental mesenchymal cells, exhibit thickcementum [38]. Additionally, Nemoto et al. have reported that Hertwig'sepithelial root sheath and epithelial cell rests of Malassez, important regulators of cementogenesis and homeostasis, produced Wnt3a [39].These results strongly suggested that Wntsignaling facilitates the formation ofcementum in vivo.The research group led by Sommerman et al. have demonstrated thatacellularcementum formation is sensitive to local inorganic phosphate(Pi)/inorganic pyrophosphate (PPi) concentration in their series of studies using knockout mice, including the deletion of progressiveankylosis gene (Ank) [44], tissue non-specific alkaline phosphatase(TN-ALP) [41], ectonucleotidepyrophosphatase/phosphodiesterase 1(ENNP1) [41], and integrin binding sialoprotein [42]. All of these moleculescontrol the concentrations of Pi and PPi. Pi has an important rolein mineralization through hydroxyapatite crystal growth, while PPicompetitively inhibits hydroxyapatite precipitation. Thus, the localPi/PPi level controls the mineralization of hard tissues. Acellularcementum formation was increased in a higher Pi/PPi environment andthis increment was observed specifically in cementum. Their resultsdemonstrated that the higher Pi/PPi ratio may be an induction signal ofcementum formation and suggested the possibility of artificial formationof cementum through controlling the local level of Pi/PPi.[45]

**Future research and current pitfalls:**

Construction of periodontal tissues around implants may be beneficialfor the improved longevity of dental implants, because the PDL contributesphysiological protective functions including immune surveillanceand buffering of large occlusal forces. However, several questionsremain unanswered relative to the current status of implants with associatedperiodontal tissues. Although a cementum-PDL structure has beenformed on an implant surface, it is unclear to what extent it worksfunctionally. Buffering of mechanical force by a PDL is advantageous forthe reduction of occlusal force applied to an implant; however, theattachment strength at the interface between cementum and implant is asyet unknown. Moreover, another question is whether titanium is the bestmaterial for a functional tooth substitute. Historically, titanium has beenthe implant material of choice, because its unique characteristics allowfor a rigid connection to bone. However, when it comes to selecting animplant material around which to construct periodontal tissues, titaniummay not always be the best choice. Therefore, the selection of a suitablematerial for the PDL-implant is remains to be determined and is importanttopic for future research.

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