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ORIGINAL ARTICLE

Comparative Evaluation of the Efficacy of Human Periostin and Enamel Matrix Derivative (Emdogain®) on Proliferation and Migration of Periodontal Ligament Fibroblasts

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ABSTRACT

Objective: To explore the proliferative and wound-healing potential of Periostin and Emdogain® on periodontal fibroblasts. **Material and Methods:** Human PDL (hPDL) fibroblasts were cultured and treated with two biological agents, Emdogain® and Periostin. The Dulbecco's Modified Eagle Medium (DMEM) served as the control. The cytotoxic effects of Emdogain® and Periostin were analyzed using the Clonogenic assay. Cell viability was estimated using the CCK-8 assay. Further, the migratory potential of the hPDL fibroblasts was assessed using the scratch migration assay. **Results:** The results showed that 1/1000 dilution of Emdogain® and 1/10 dilution of Periostin had the highest cell survival fraction ($p<0.05$). In the CCK-8 assay, Emdogain® displayed maximum cell viability compared to Periostin ($p=0.000$) and control ($p=0.006$). The PDL fibroblasts' migratory rate corresponded to the experimental agents' wound-healing potential. Emdogain® presented with earlier wound closure compared to Periostin ($p=0.002$) and control ($p=0.000$). **Conclusion:** Thus, based on the results of this study, Periostin may be a viable biologic agent for promoting periodontal regeneration.

Keywords: Periostin; Guided Tissue Regeneration, Periodontal; Wound Healing; Periodontal Ligament.

Introduction

Periodontitis is a chronic inflammatory disease that results from multiple factors, which leads to the gradual destruction of the tooth-supportive structures and eventually results in tooth loss. Periodontal therapy aims to remove local factors and inflammatory components using mechanical debridement techniques, which can be non-surgical and surgical [1]. These interventions decrease clinical inflammation, halt the progression of the disease, and promote the regeneration of the destroyed periodontal tissues [2]. The efficacy and predictability of regenerative materials, such as bone substitutes, collagen-based guided barrier membranes, and surgical therapy, exhibit varied outcomes [3]. Biomimetic agents like Enamel matrix derivative (EMD) and other biological factors have been widely employed to promote hard and soft tissue regeneration [4]. Emdogain® contains 90% amelogenins, which play a crucial role in the development of supporting structures and the overall tooth development process [5]. It also induces favorable effects in restoring bone defects and promotes wound healing, resulting in soft tissue regeneration. Earlier studies have reported that Emdogain® induced PDL fibroblast proliferation and migration, total protein synthesis, bone mineralization, and a significant focus on utilizing biological proteins to stimulate tissue regeneration [5,6]. Despite the potential benefits of Emdogain®, there is research in the literature that highlights its limits. Lab-based investigations have demonstrated that though Emdogain® significantly promotes the initial proliferation of osteoprogenitor and cementoblast progenitor cells, it hampers the final differentiation of cells, resulting in inadequate development and impeding the creation of fully mature cells [6]. In addition, the gel-like nature of Emdogain® was found to be insufficient in maintaining the necessary space to develop new bone [7].

Furthermore, it has been demonstrated to possess osteoconductive qualities instead of osteoinductive properties [8]. Emdogain® has been utilized for periodontal regeneration procedures. However, the results have been inconsistent [9]. These limitations of Emdogain® have spurred considerable research interest in exploring native biomolecules that could regulate periodontal healing and regeneration. Periostin is a 90 kDa substance secreted by the extracellular matrix (ECM) protein. It is a member of the fasciclin family and is found in collagen-rich connective tissues such as the periosteum, endocardial cushions, cardiac valves, and PDL [10]. Periostin, an extracellular matrix protein, maintains bone homeostasis, which is essential for maintaining the integrity of the periodontal ligament and the nearby alveolar bone [11].

Undifferentiated osteoblasts synthesize Periostin, contributing to a cellular differentiation mechanism that facilitates bone repair [12]. Additionally, it stimulates the migration of fibroblasts and osteoblasts to sites that need to be repaired, thus enabling the regeneration of periodontal tissue by increasing cellular activity. Based on Periostin's functional and biological importance in the tissue repair process, an in vitro study was planned to investigate the effect of two extracellular protein derivatives, Emdogain® and Periostin, on tissue healing and the influence of these proteins on periodontal regeneration. The null hypothesis tested were: (1) there are no differences in the clonogenic capacity of hPDL, cells after treatment with Emdogain® and Periostin, (2) there were no differences in the viability of hPDL cells after treatment with Emdogain® and Periostin (3) there were no differences in the migratory rate of hPDL cells after treatment with Emdogain® and Periostin.

Materials and Methods

Ethical Clearance

Human periodontal ligament (hPDL) fibroblasts were utilized to investigate the effectiveness of Periostin and/or Emdogain® as regenerative biologic agents. This study commenced after obtaining approval from the Institutional Ethics Committee and Review Board.

Procedures

The hPDL cells were obtained from patients undergoing extraction for orthodontic reasons or impacted third molar tooth. The teeth were extracted atraumatically and rinsed twice with phosphate-buffered saline (PBS) to eliminate debris and residual blood remnants. Periodontal ligament (PDL) tissues attached only to the mid-third of the root surface were carefully scraped off using a #15 scalpel blade following aseptic protocols. The cell culture procedure was adapted from the work conducted by Chung et al. [13]. In brief, hPDL cells were cultured in Dulbecco's modified Eagle's medium (DMEM) with 10% FBS, antibiotics, antifungal, and glutamine at 37°C in a 5% CO_2 atmosphere. Cells were grown to 70% confluence in T-75 flasks, rinsed with phosphate buffer saline, and detached using a trypsin, glucose, and citrate-saline solution. Media was replaced every three days, and cells were used for experiments during passages 5 to 8, routinely sub-cultured to maintain 60-70% confluence.

The cultured cells were then allocated into three groups based on the biological agents used in this study. Group I: Dulbecco's modified Eagle's medium (Gibco, Life Technologies Corporation, Grand Island, NY, USA), which served as a positive control. Group II: Emdogain® (Emdogain®, Straumann AG Basel, Switzerland) - 20µg/ml of Emdogain® was used in the present study based on previous literature [14]. Group III: Recombinant human Periostin™ (Bio-techne brand, R&D systems, USA) -50ng/ml. The concentration used was based on the results of earlier research [15].

Clonogenic (Colony Forming) Assay

This experiment investigated the effect of Emdogain® and Periostin on the cell survival capability of human PDL fibroblast cells. The methodology was described previously by Franken et al. in 2006 [16] with minimal modifications. In brief, approximately 200 exponentially developing hPDL cells were seeded on 60-mm Petri dishes (Nest Biotechnology Co., Ltd., USA) and cultured overnight for adhesion. Following this process, the hPDL cells were treated with Emdogain® and Periostin at various dilutions of 1/10, 1/100, and 1/1000 for 15 minutes. After incubation, the media containing Emdogain® and Periostin were aspirated under thorough aseptic conditions, and the cultures were rinsed with growth media to eliminate the biological agents.

Additionally, the cultures were replenished with 5 mL of growth medium and again incubated at 37 °C in a 5% CO_2 incubator for 12 days to ensure colony formation. Then, the media was discarded, and the cell cultures were rinsed with sterile PBS. The colonies were stained with 0.1% (w/v) crystal violet in absolute methanol. The Petri dishes were rinsed and air-dried to remove excess stains. This experiment was conducted in triplicate. The surviving fraction was calculated by manually counting blue-stained colonies. A group of 50 cells was considered one viable colony after an incubation period of 21 days.

The Cell Counting Kit-8 (CCK-8) Assay

The hPDL cell viability after the use of EMD® and Periostin™ at specific time intervals (0hr, 48hr, 96hr) was quantified using the colorimetric CCK-8 kit assay. The present methodology was adapted from previous work conducted by Cai et al. [17]. It involved seeding around 1000 hPDL cells in a 96-well (corning® 96 well plates, Merck KGaA, Darmstadt, Germany) and incubating them at 37°C with 5% CO_2 for 24 hours. Based on the clonogenic assay results, a 1:1000 dilution of EMD® and a 1:10 dilution of Periostin™ provided maximum viable cells. Hence, the specified dilutions were utilized for the further parameters. Then, the culture medium was replaced with 1:1000 Emdogain® and 1:10 Periostin diluted with culture fluid. The experiments were triplicate, and the co-incubation time depended on the experimental agent's efficacy. Each well with cells

received 10 microliters of CCK-8 reagent and was cultured for 1 to 4 hours in an incubator under standard conditions. The formazan-stained cells were quantified using a cell plate reader to measure absorbance at 450 nm after incubation.

Scratch Migration Assay

This assay estimates the cell migratory rate, which is similarly observed during wound healing. Cells from the tissue culture flask were detached using 0.25% Trypsin-EDTA solution. A 15 mL conical tube was used to pellet the cells by centrifugation. The supernatant was aspirated, and cells were resuspended in culture media. In a 6-well plate, the appropriate number of cells was plated for 100% confluence in 24 hours. Amidst a sterile environment, a 200 µl pipette tip was used to tighten the top of the tissue culture plate, and a vertical wound was made down through the cell monolayer (scratch made was ~2mm). The media was carefully aspirated, and cell debris was removed. A sufficient quantity of culture medium was steadily added with the desired amount of sample to the wall of the well so that it covers the bottom and leaves no more cells. The first photograph was taken after the wound was created and examined. The tissue culture was then placed at the appropriate temperature, typically 37°C, and a CO_2 concentration of 5% in the environment to mimic a cell's natural environment. Every 24 hours, the plate was removed from the vacuum and placed in an inverted microscope to take pictures to check for wound closure. The distance from one side of the wound to the other was measured using the ruler in the Image J software to verify the imaging results. The wound closure over time was analyzed using a bar graph [18]. The groups were tested with experimental agents, i.e., 1:1000 Emdogain® and 1:10 Periostin.

Statistical Analysis

The data was analyzed using the statistical software SPSS 26.0 (IBM Corp., Armonk, NY, USA) with a significance threshold set at $p<0.05$. Descriptive statistics were used to analyze the average and variability of each group. The data's normality was evaluated using the Shapiro-Wilk test. Inferential statistics were used to determine the group differences by one-way ANOVA, followed by a Bonferroni post hoc test. Intergroup comparisons were conducted using repeated measures ANOVA and a Bonferroni post hoc test. Comparison between the Emdogain® and Periostin group was done using an independent t-test.

Results

The present study examined different dilutions (1:10,1:100, 1:1000) of Emdogain® and Periostin to understand their potential for periodontal regeneration. Results from the clonogenic assay indicated that the highest survival fraction of the PDL cells occurred at 1:1000 dilution of Emdogain® and 1:10 dilution of Periostin ($p<0.001$) (Table 1). Intergroup analysis between the 1:1000 dilution of Emdogain® and Periostin resulted in a significant difference, with the highest cell viability observed at the 1:1000 dilution of Emdogain® ($p=0.0001$). However, no significant alterations were seen for the 1:10 and 1:100 dilutions for either Emdogain® or Periostin ($p=0.42$ and $p=0.18$) (Table 1). Based on the results obtained from the colometric CCK-8 assay used to estimate cell viability with 1:10 Periostin and 1:1000 Emdogain® dilutions at specific time intervals (0 hr, 48 hr, 96 hr), no significant difference was observed between the experimental groups at the initial 0 hour time point. At 48 and 96 hrs, Emdogain® (group II) demonstrated substantially higher levels of cell viability compared to Periostin and the control group ($p=0.0001$). However, a considerable decline in cell viability was noted in the Periostin group compared to the control ($p=0.0001$). Intergroup comparison between the experimental groups at the

specified time points indicated that Emdogain® (group II) showed the highest cell viability, followed by the control group (p=0.0001), with the Periostin group displaying lower viability (p=0.001) (Table 2).

Table 1. Comparative assessment of the surviving fraction of PDL cells formed in each experimental group at different dilutions of Emdogain® and Periostin.

Variables	Mean and Standard Deviation	p-value+#
Experimental Groups with Different Dilutions		
Control	8.00 ± 1.0	0.001*
Emdogain® 1:10	19 ± 1.0	
Emdogain®1:100	16.33 ± 1.528	
Emdogain®:1000	28.00 ± 1.0	
Periostin 1:10	18 ± 2.0	0.001*
Periostin 1:100	14.33 ± 1.52	
Periostin 1:1000	16 ± 1.0	
Intergroup Comparison within Experimental Groups	Concentration	p-value++
Emdogain®	1:10	0.42
Periostin		
Emdogain®	1:100	0.18
Periostin		
Emdogain®	1:1000	0.0001*
Periostin		

+ANOVA test; #Bonferroni Post hoc Test; ++Independent 't' test; *Statistically Significant.

Table 2. Comparison of cell viability between and within the groups using CCK-8 assay at different time intervals.

Variables	Groups	Mean	p-value
Between the groups using the CCK-8 assay at different time intervals			
0-hour	Control	100.00	0
0-hour	Emdogain®	100.00	
0-hour	Periostin	100.00	
48 hours	Control	116.7080333	0.0001*
48 hours	Emdogain®	133.5410667	
48 hours	Periostin	75.4615333	
96 hours	Control	129.5886333	0.0001*
96 hours	Emdogain®	149.2368333	
96 hours	Periostin	104.4258833	
Within the groups using the CCK-8 assay at different time intervals			
Control	0-hour	100.000000	0.0001*
Control	48 hours	116.708033	
Control	96 hours	129.588633	
Emdogain®	0-hour	100.000000	0.0001*
Emdogain®	48 hours	133.541067	
Emdogain®	96 hours	149.236833	
Periostin	0-hour	100.0000000	0.0001*
Periostin	48 hours	75.4615333	
Periostin	96 hours	104.4258833	

+ANOVA test; #Bonferroni Post hoc Test; *Statistically Significant.

According to the scratch assay analysis, the migratory rate of the PDL cells at the stipulated time points (24, 48, and 72 hours) following the application of Emdogain® and Periostin is illustrated in Table 3. At 48 hr, significant effects were noticed between control (group I), Emdogain® (group II), and Periostin (group III), in which Emdogain® displayed maximum migration of cells (p= 0.0001), followed by Periostin (p=0.002) and the control group (Table 3). Intergroup comparison at the definite time intervals revealed significant differences, in which the Emdogain® group demonstrated a higher migratory rate (p=0.001) than other groups. Subsequently,

at the 72 hr time interval, all the experimental groups (I, II, and III) showed complete migration of the PDL cells across the induced injury, resulting in complete wound closure (Table 3).

Table 3. Comparison of migration rate between and within the groups using scratch migration assay at different time intervals.

Variables	Groups	Mean	p-value
Between the groups using the scratch migration assay at different time intervals			
24 hours	Control	50.02	0.36
24 hours	Emdogain®	53.728667	
24 hours	Periostin	51.729733	
48 hours	Control	84.7066667	0.0001*
48 hours	Emdogain®	100.0000000	
48 hours	Periostin	91.8697000	
72 hours	Control	100.0	0
72 hours	Emdogain®	100.0	
72 hours	Periostin	100.0	
Within the groups using the scratch migration assay at different time intervals.			
Control	24 hours	50.0200	0.0001*
Control	48 hours	84.7067	
Control	72 hours	100.0000	
Emdogain®	24 hours	53.7286	0.0001*
Emdogain®	48 hours	100.0	
Emdogain®	72 hours	100.0	
Periostin	24 hours	51.7297	0.0001*
Periostin	48 hours	91.86970	
Periostin	72 hours	100.0	

+ANOVA test; #Bonferroni Post hoc Test; . *Statistically Significant.

Discussion

The primary objective of periodontal regeneration is to restore or regenerate the lost periodontal structures, i.e., alveolar bone, cementum, and the periodontal ligament. Biological agents have been employed to regulate and enhance natural processes within the affected site, promoting tissue regeneration [19]. The present study explored the influence of two regenerative biomaterials, Periostin and Emdogain®, on the migratory and proliferative abilities of periodontal ligament fibroblast cells, which play a crucial role in wound healing, which subsequently results in periodontal regeneration. The hypotheses of this study were rejected, as Emdogain® outperformed Periostin across all tested parameters. In the present study, the prolonged survival fraction rate of the hPDL cells after using various dilutions of Emdogain® and Periostin was highest at a 1:1000 dilution of Emdogain® and a 1:10 dilution of Periostin. Emdogain® supports the wound-healing process in the gingival and periodontal tissues. A literature review by Fraser et al. [19] on periodontal wound healing and tissue regeneration has summarized that Emdogain® portrays a strong positive biological effect on the proliferative capacity of PDL fibroblast cells [19]. It enhances tissue healing by forming protein aggregates, creating a unique environment for cell-matrix interaction, further leading to the proliferation of PDL fibroblasts [20].

In a related manner, Periostin, a part of the matricellular protein family, is an adhesion-related protein secreted by cells of the periosteum and periodontal ligament. It plays a key role in regulating various biological processes and influences PDL cell proliferation and migration by employing multiple signaling pathways [21]. The studies referenced above support the biological effectiveness of Emdogain® and Periostin on cellular processes of PDL fibroblast cells, consistent with the current study's findings. Another observation from the CCK-8 assay indicated that Periostin decreased PDL cell viability at the 48 and 96-hour time points compared to the control (DMEM). This decrease may be attributed to the diminishing effect of the 1:10 dilution of Periostin

on PDL cell viability over the mentioned period. In a research conducted by Molina et al. [21], investigating the effect of Periostin on human PDL cell migration and proliferation, the authors observed an increase in cell proliferation and migration only within the first 18 hours. Wound healing is a multifaceted process that includes cell migration, cell attachment to extracellular matrix components, and cell proliferation.

Additionally, growth factors play crucial roles in regulating these processes. Emdogain® exhibits several properties akin to growth factors. The mechanism of action of Emdogain® seems to involve an interaction between the amelogenin aggregate of Emdogain® and the periodontal ligament cells within the matrix [22]. In this study, an essential *in vitro* wound healing test (scratch assay) showed that Emdogain® achieved complete wound closure within 48 hours following the induced injury. In contrast, Periostin required slightly more than 48 hours to close the artificially created scratch. The findings align with an *in vitro* wound healing model in which Emdogain® was used on human periodontal ligament fibroblasts. The authors observed that cells populated the space, leading to prompt healing of the wound [14].

In contrast, Wu et al. [23] conducted an *in vitro* investigation to assess the impact of Periostin on human periodontal ligament cells. The researchers observed a substantial enhancement in wound closure in 24 hours and concluded that Periostin could accelerate the movement, multiplication, and specialization of human periodontal ligament cells [23]. At 72 hours of the wound healing assay, it was observed that all the experimental groups showed complete closure of the wound area. This indicates that both Emdogain® and Periostin had beneficial effects during the early stage of the injury.

In vitro and *in vivo* studies have shown that both Emdogain® and amelogenins promote the proliferation of various mesenchymal cell types, including fibroblasts, cementoblasts, osteoblasts, and stem cells. Migration of suitable cells to the target area is the initial and crucial step for effective tissue healing and regeneration. The data also suggests that Emdogain® may include extra mitogenic factors, like transforming growth factor-β and bone morphogenetic-like growth factors, which boost fibroblastic proliferation and aid in periodontal regeneration [6,22]. Periostin may serve as a critical regulator in periodontal tissue development. By promoting collagen fibrillogenesis and supporting the migration of fibroblasts and osteoblasts, Periostin likely plays a role in regenerating the periodontal ligament (PDL) and alveolar bone after periodontal surgery [24].

To our knowledge, no previous studies have directly compared the impact of both Emdogain® and Periostin on the proliferation and migration of hPDL fibroblasts. Further long-term clinical studies comparing Emdogain® and Periostin are necessary to understand the effect of these biological agents in wound healing and periodontal regeneration.

Conclusion

The results from this study indicate that, *in vitro*, Emdogain® promoted cell migration and proliferation, facilitating enhanced wound closure, while Periostin supported cell migration and proliferation, however, to a lesser extent than Emdogain®. The stimulatory actions of Emdogain® on periodontal ligament stem cells, which stimulate periodontal tissue regeneration, have been extensively reported in the literature and make it a popular commercial product in clinical periodontal therapy. Limitations of this study include the varying response of the PDL fibroblasts to Emdogain® and Periostin. This may be due to the variability and heterogeneity within the PDL fibroblast cultures, as they were procured from different individuals [25]. Secondly, *in vitro*, wounding of cell cultures across different studies may lead to varying degrees of wound closure depending on the cell type and culture media used. However, research has shown that Periostin may beneficially affect the cells of the

periodontal ligament. It can still be considered for clinical use because it maintains tissue integrity and maturity, modulating periodontal ligament hemostasis.

Authors' Contributions

SM	https://orcid.org/0009-0000-8011-7636	Formal Analysis, Investigation, and Writing - Original Draft.
JMV	https://orcid.org/0000-0002-8503-5039	Conceptualization, Methodology, Writing - Review and Editing, and Project Administration.
SPK	https://orcid.org/0000-0002-4158-3893	Methodology and Investigation.

All authors declare that they contributed to the critical review of intellectual content and approval of the final version to be published.

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None.

Conflict of Interest

The authors declare no conflicts of interest.

Data Availability

The data used to support the findings of this study can be made available upon request to the corresponding author.

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