

DOI: <https://doi.org/10.56936/18290825-2026.20v.2-50>**mRNA-BASED REGENERATION OF PERIODONTAL LIGAMENT FIBROBLASTS: A TRANSLATIONAL PILOT STUDY****JALALUDDIN M.¹, CALIAPEROUMAL S.K.², JAYANTI I.³, PATIL M.³,
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ABSTRACT

Introduction: Periodontitis causes irreversible loss of supporting apparatus of the tooth, i.e., periodontal ligament. Although there has been promise in the growth factor therapies with recombinant proteins, including Fibroblast growth factor-2 (FGF-2) and the biological half-lives of these proteins, recombinant proteins have high costs, instability, and limited usability. Nucleoside-modified messenger RNA (mRNA) technology provides a new therapeutic modality approach with the use of host cell machinery to endogenously produce therapeutic proteins and, possibly, provide sustained bioactivity.

Material and Methods: Healthy premolars were used as sources of primary human periodontal ligament fibroblasts (n=10). The cells were separated into 3 conditions, which are Negative Control (untransfection), Positive Control (treated with recombinant human fibroblast growth factor-2 [rhFGF-2]) and Test Group (transfected with lipid nanoparticle-mRNA-FGF2). The proliferation of the cells was measured spectrometrically using Cell counting Kit-8 after 24, 48 and 72 hours. The migration capacity was measured based on a scratch wound healing assay. The expression of osteogenic and fibroblastic genes (COL1A1, POSTN, RUNX2) was determined by Reverse transcription quantitative polymerase chain reaction.

Results: mRNA-FGF2 showed a much higher proliferation at 72 hours than rhFGF-2 (Optical Density: 1.42 ± 0.11 vs. 1.15 ± 0.09 , $p < 0.01$), indicating longer protein synthesis. The highest percentage of wound close up at 24 hours was found in mRNA group ($88.4\% \pm 4.2$) when compared with the protein group ($76.1\% \pm 5.5$; $p < 0.05$). In addition, POSTN (Periostin) increased by 4.5-fold when mRNA was transfected compared to controls.

Conclusion: Intracellular exposure to lipid nanoparticle-encapsulated mRNA coding FGF-2 enhances better proliferation and migration in human periodontal ligament fibroblasts when compared to the exogenous application of proteins. In this pilot study, it is proposed that mRNA technology is a viable, powerful platform to next-generation periodontal regenerative therapies.

KEYWORDS: mRNA therapy; Periodontal regeneration; Fibroblast Growth Factor-2; Tissue engineering; Periodontal ligament fibroblasts

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INTRODUCTION

Periodontitis is a chronic inflammatory condition that is known by the progressive loss of the bone that supports the tooth such as the alveolar bone, the cementum and periodontal ligament (PDL) [Pihlstrom BL et al., 2005]. It is a significant disease in the adult world population and one of the leading causes of tooth loss [Eke PI et al., 2015]. Periodontal therapy is not only aimed at the prevention of inflammation but the restoration of the lost attachment apparatus. The existing regenerative techniques e.g. Guided tissue regeneration and application of Enamel matrix derivatives have been shown to be clinically effective yet have not been predictable in cases of advanced defects [Cortellini P, Tonetti MS, 2015].

In order to improve regenerative predictability, the use of bioactive molecules namely growth factors has also been widely studied. Basic Fibroblast growth factor is also referred to as Fibroblast growth factor-2 (FGF-2) which is a powerful mitogen inducing angiogenesis and mesenchymal cell growth [Murakami S, 2011]. The effectiveness of recombinant human FGF-2 (rhFGF-2) in the regeneration of the periodontal tissues has been demonstrated in clinical trials and this has resulted in its commercial acceptance in some markets [Kitamura M et al., 2011]. Nonetheless, the protein-based therapies are subject to severe translational challenges. The recombinant proteins tend to have short biological half-lives because of fast degradation by enzymes and clearance in the body [Lee K et al., 2011]. As a result, keeping a therapeutic level on the defect site commonly demands supraphysiological doses, which casts doubts on the aspect of expense and off-target side effects [Carrion B, Putnam AJ, 2013].

Coupled with the SARS-CoV-2 vaccinations, messenger RNA (mRNA) therapeutics have become a new frontier in regenerative medicine, as nucleoside-modified mRNA (mRNA) has become a groundbreaking platform [Sahin U et al., 2014]. In comparison to DNA-based gene therapies, which allow entry into the nucleus and introduce a threat of insertional mutagenesis, mRNA acts inside the cytoplasm and is inherently transient and safe [Pardi N et al., 2018]. The delivery of chemically modified mRNA through lipid nanoparticles (LNPs) is considered the host cell acting as a bio-reactor, where protein therapeutic is generated on a

prolonged basis [Kowalski PS et al., 2019].

The latest experiments in the orthopedic researches have used the mRNA encoding Bone Morphogenetic Protein-2 (BMP-2) to regenerate bone successfully in rat models, with better results than the recombinant protein delivery [Zhang W et al., 2019]. Nonetheless, the use of this technology in the context of soft tissue regeneration of the periodontal complex has not been studied extensively. A significant research gap exists on the response of periodontal ligament fibroblasts, which are the important effector cells that are involved in periodontal regeneration to intracellular mRNA therapeutic treatment versus extracellular protein stimuli.

Thus, this translational pilot study was intended to design and synthesize LNP-encapsulated nucleoside-modified mRNA that encodes FGF-2 (LNP-mRNA-FGF-2) and test its biological actions on human periodontal ligament fibroblasts. We theorized that, mRNA-mediated delivery would lead to longer-term cellular increase, increased migration, and improved periodontal ligament-specific marker expression as compared to traditional recombinant protein therapy.

MATERIALS AND METHODS

Design and Ethics of the research: In this *in vitro* research, a parallel-group design was used to compare three experimental conditions, which are Negative control (NC), recombinant human FGF-2 (Positive control) (rhFGF-2), and LNP-encapsulated nucleoside-modified mRNA that encodes FGF-2 (Test Group).

Isolation and Culture of human periodontal ligament fibroblasts (hPDLFs): The tissue of periodontal ligament was collected on healthy premolars (n=10) that were removed due to orthodontic indicators in systemic healthy donors aged between 18 and 25 years. Phosphate-buffered saline (PBS) was used to wash the teeth with sterile. The periodontal ligament tissue was scraped at the mid-third area of the root surface to eliminate any possible contamination with the gingival fibroblasts or apical pulp tissue. The explants were minced and cultured in Dulbecco modified eagle medium, which was supplemented with 10 percent Fetal bovine serum and 1 percent penicillin/streptomycin at 37°C in a humid environment of 5 percent CO₂. All experi-

ments were done on cells of passages 3 to 5 in order to achieve phenotypic stability.

Production of Nucleoside-Modified mRNA: The human FGF-2 coding sequence was cloned in a plasmid vector with 5' and 3' untranslated regions and poly(A) tail template and expressed in vitro by transcription with RNA polymerase from the T7 bacteriophage. In order to inhibit innate immune activation Uridine-5'-triphosphate (UTP) was substituted entirely with N1-methylpseudouridine-5'-triphosphate in transcription. A Vaccinia Capping System was used to cap the synthesized mRNA.

Lipid Nanoparticle (LNP) Encapsulation: The altered mRNA was enclosed in lipid nanoparticles with the help of a microfluidic mixing device. The lipid phase was composed of an ionizable phosphatidylcholine cationic lipid, cholesterol and polyethylene glycol (Peg) lipids in ethanol. The mRNA was in citrate buffer (pH 4.0) in the aqueous phase. At the flow rate ratio of 3:1 (aqueous:lipid), the phases were mixed. The lipid nanoparticles that resulted were centrifugally filtered against PBS and dialyzed. A RiboGreen assay was used to determine that encapsulation efficiency was greater than 90%.

Experimental Grouping: The human periodontal ligament fibroblasts were placed in either a 6-well plate or 96-well plate based on the test and left to dry.

1. Negative Control (NC): Cells incubated with PBS/empty lipid nanoparticles.

2. Positive Control (rhFGF-2): Cells exposed to a recombinant protein of human FGF-2 in concentration 10 ng/mL (added daily to the cell to simulate normal procedure).

3. Test Group (mRNA-FGF2): Cells were transfected with LNP-encapsulated nucleoside-modified mRNA that encodes FGF-2 (1 µg mRNA per well) at once at the baseline.

Cell Proliferation Assay: The Cell Counting Kit-8 was used to evaluate the cell proliferation. The seeding density of the cells was 3 x 10³ cells/well in the 96-well plates. Kit-8 reagent was brought at 24, 48, and 72 hours after the treatment and then the plates were incubated at 2 hours. A microplate reader was used to achieve absorbance at 450nm.

Scratch Wound Healing Assay: In order to test cell migration, human periodontal ligament fibroblasts were cultured to confluence in 6-wells.

A uniform scratch was made at the middle of the monolayer with sterile 200 µL tip of the pipette. The debriefing was conducted through PBS washing. At 0, 12 and 24 hours, an inverted phase-contrast microscope was used to capture images. ImageJ software was used to measure the wound area, and a percentage of wound closure calculated.

Gene Expression Analysis: RNA was isolated off the cells at 72 hours by the use of TRIzol reagent and cDNA generated by the help of a High-Capacity cDNA Reverse Transcription Kit. Reverse transcription quantitative polymerase chain reaction (**RT-qPCR**) was conducted to correct the expression of Collagen Type I Alpha 1, Periostin and Runt-related transcription factor 2. Glyceraldehyde-3-phosphate dehydrogenase was used as the housekeeping gene. Relative gene expression was determined through Delta-delta Ct method (also known as the 2^{-ΔΔCt} method). The method was devised by Kenneth Livak and Thomas Schmittgen in 2001 [Livak K, Schmittgen T, 2001]

Statistical Analysis: Each experiment was conducted 3 times and in triplicate and independently repeated. The data is shown in the form of mean and Standard Deviation (SD). One-way Analysis of Variance (ANOVA) was used to analyze the statistical differences followed by the Tukey post hoc test that compares multiple differences. Significance of p-value was set at below 0.05.

RESULTS

Sustained Cell Proliferation via mRNA Transfection: The proliferation rates of human periodontal ligament fibroblasts were monitored over a 72-hour period (Table 1). At the 24-hour time point, the Positive Control (rhFGF-2) group exhibited the highest proliferation rate, significantly higher than the Negative Control (p < 0.05), while the Test Group

TABLE I.

Cell Proliferation Assessment (OD Values at 450 nm)			
Groups	Observation Time		
	24 h	48 h	72h
Negative Control	0.45±0.03	0.58±0.05	0.67±0.06
Positive control	0.78±0.06*	1.05±0.08*	1.15±0.09*
Test group	0.69±0.05	1.10±0.07*	1.42±0.11 ^{^†}

NOTES: (*) - p<0.05 vs. Negative Control, (^) - p<0.01 vs. Negative Control, (†) - p < 0.01 vs. Positive control

TABLE 2.

Wound Closure Percentage in Scratch Assay			
Groups	Observation Time		
	0h	12h	24h
Negative Control	0	15.2 ± 3.1	32.5 ± 4.8
Positive control	0	48.5 ± 5.2*	76.1 ± 5.5*
Test group	0	55.3 ± 4.9*	88.4 ± 4.2 ^{^†}

NOTES: (*) - $p < 0.05$ vs. Negative Control, (^) - $p < 0.001$ vs. Negative Control, (†) - $p < 0.05$ vs. Positive control

showed a slight lag, likely due to the time required for intracellular translation of the protein. However, by 48 hours, the mRNA group equalized with the protein group. Notably, at 72 hours, the mRNA that encodes FGF-2 (mRNA-FGF2) group demonstrated a statistically superior proliferation rate compared to the recombinant human FGF-2 group ($p < 0.01$). This trend indicates that a single transfection of mRNA provided a more sustained mitogenic effect than the exogenous protein application.

Enhanced Migration Capability: The migratory potential of human periodontal ligament fibroblasts is critical for defect repopulation. The scratch assay revealed that both treatment groups significantly accelerated wound closure compared to the control (Table 2). The mRNA-FGF2 group displayed the most rapid closure rates. At 24 hours, the mRNA group achieved near-complete closure (88.4%), which was significantly higher than the recombinant human FGF-2 group (76.1%) and the control (32.5%).

Gene Expression Profile: Reverse transcription quantitative polymerase chain reaction (RT-qPCR) analysis at 72 hours assessed the differentiation state of the cells (table 3). The mRNA-FGF2 group induced a robust upregulation of Periostin, a marker specific to periodontal ligament integrity and function, showing a 4.5-fold increase over the control. Collagen type I alpha 1 expression was significantly elevated in both treatment groups, indicating active extracellular matrix production.

TABLE 3.

Relative Gene Expression (Fold Change vs. Negative Control)				
Gene	Negative Control	Positive control	Test group	p-value*
COL1A1	1.0 ± 0.1	3.2 ± 0.4	3.8 ± 0.5	> 0.05 (ns)
POSTN	1.0 ± 0.2	2.8 ± 0.3	4.5 ± 0.6	< 0.01
RUNX2	1.0 ± 0.1	1.5 ± 0.2	1.8 ± 0.3	> 0.05 (ns)

NOTES: (*) - mRNA vs Protein, COL1A1 - Collagen Type I Alpha 1, RUNX2 - Runt-related transcription factor 2

Interestingly, runt-related transcription factor 2, an osteogenic marker, showed only mild elevation in the mRNA group, suggesting that the treatment primarily favored fibroblastic/ligamentous differentiation rather than mineralization at this time point, which is desirable for preventing ankylosis.

DISCUSSION

The pilot study is one of the initial attempts in the research of the use of chemically modified mRNA technology in the regeneration of periodontal ligament. The findings confirm the hypothesis of FGF-2 LNP-encapsulated mRNA successfully transfection of the human periodontal ligament fibroblasts with the subsequent biological activity i.e. proliferation and migration, comparable to or better than that of conventional recombinant protein therapy.

The main conclusion of the present research is the proliferative ability that was sustained in the mRNA group. Although there was a peak of proliferation in the recombinant human FGF-2 group, the rate flattened by 72 hours. Conversely, the mRNA group kept speeding up. This is in line with the recent report of tissue engineering that intracellular growth factor production represents physiological secretion more closely than bolus protein delivery [Balmayor ER, 2022]. Recombinant proteins on cultures are prone to quick degradation and denaturation [Chen FM et al., 2010]. The cells produced new FGF-2 protein constantly throughout the duration of the experiment by providing the instruction manual (mRNA), not the end product, thus keeping the receptors saturated and other downstream signaling pathways like MAPK/ERK alive [Takayama S et al., 1997].

The observed mRNA group improvement in migration is clinically significant (Table 2). The success of the attachment in Guided tissue regeneration procedures is dependent on the race of slow-migrating periodontal ligament cells and prompt migrating epithelial cells [Melcher AH, 1976]. The capacity of mRNA-FGF2 to trigger speedy wound healing (88.4% at 24h) indicates that this modality might generate a competitive edge of periodontal ligament fibroblasts in vivo. This fact supports the works of Khorsand et al., who observed the increase in macrophage and stem cell recruitment in the bone defects upon mRNA-BMP2 administra-

tion [Khorsand B et al., 2017].

In terms of gene expression, Periostin is a multicellular protein that is essential to the periodontal ligament integrity and reacting to mechanical loading [Rios H et al., 2008]. The much greater upregulation of POSTN in the mRNA group relative to the protein group is an indication that the endogenous production of FGF-2 can cause stronger feedback loops to be activated in relation to the organization of the matrix. In addition, runt-related transcription factor 2 expression is controlled, too much osteogenic differentiation of periodontal ligament cells may result in ankylosis (fusion of root to bone) [Bosshardt DD, 2008]. The results indicate that the mRNA therapy preserves fibroblastic phenotype that is necessary in soft tissue binding, and this is a problem frequently referred to in growth factor treatments [Bartold P et al., 2016].

The success of this study was determined by the use of pseudouridine modification and LNP delivery. Indeed, early mRNA therapeutic approaches were crippled by excessive immunogenicity, in which exogenous RNA was recognized as viral and induced interferon signaling that aborted translation [Karikó K et al., 2005]. When we applied the N1-methylpseudouridine modification (Same technology used in COVID-19 vaccines) to the transfected cells, we did not see any traces of cytotoxicity or growth arrest, which supported the biocompatibility of this platform in dental applications [Badiyan Z, Evans T, 2021].

This pilot study has limitations even though these are good results. Being an in vitro monolayer study, it is not able to capture the intricate immune

and microbial environment of the periodontal pocket. The efficacy of transfection in the 2D culture can vary at the 3D fibrin clot or scaffold setting [Elangovan S et al., 2015]. Also the length of the production time of a single dose of mRNA has to be characterized through a longer time span to make judgments on whether there is need to dope more than once although the limited lifespan of mRNA is thought to be a safety benefit over DNA vectors [Weng Y et al., 2020].

Further studies ought to be aimed at packing these mRNA-LNPs into scaffold materials, including collagen sponges or hydrogels, to be tested in in vivo periodontal defect models. These studies will help to decide whether the enhanced cellular reactions in this case result into real functional repair of cementum and periodontal ligament.

CONCLUSION

This paper shows that LNP-contained nucleoside-modified mRNA which encodes FGF-2 is effective in enhancing the proliferation and migration of human periodontal ligament fibroblasts. The mRNA platform demonstrated a maintained bioactive effect that was better than recombinant protein administration, which was probably as a result of sustained intracellular protein production. Moreover, the level of Periostin was also greatly increased by mRNA transfection, which suggests a high prospect of the restoration of functional periodontal ligament tissue. These results indicate that a broad range of mRNA therapeutics has a promising future as an alternative to existing protein-based regenerative therapy in periodontology.

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