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Semiorthotopic Model for Stem Cell-Based Pulp Regeneration: Foundation for Preclinical Research

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ABSTRACT

Background: Advances in biotechnology and tissue engineering have laid the foundation for the development of new strategies in regenerative endodontics. In recent years, the regeneration of dental tissues, particularly the restoration of the dental pulp, has emerged as a dynamic and promising field of research.

Objectives: Several preclinical and experimental models are used to investigate the mechanisms of dental pulp regeneration and to evaluate the efficacy of newly developed bioengineered materials. In the present study, we describe a method for constructing a bioengineered tooth-slice model and assess the performance of its incorporated material using a semiorthotopic experimental design.

Methods: For the preparation of tooth slices, four mandibular incisor teeth (n = 4) from sheep were used. Following longitudinal sectioning, two-thirds of the pulp tissue were amputated, and the remaining canal space was filled with mesenchymal stromal cells derived from human exfoliated deciduous teeth (SHED) loaded onto microcarriers (CultiSpher®) and embedded within a fibrinogen–thrombin gel. The resulting bioengineered construct was implanted subcutaneously in the dorsal region of rats. Histological evaluation of the bioengineered material's effect was performed at 7 and 28 days.

Results: The bioengineered material introduced into the tooth slice, in conjunction with the remaining pulp tissue, promoted the formation of pulp-like and dentin-like structures.

Conclusions: The development of a bioengineering algorithm represents a multistage, technologically demanding process that requires the iterative optimization of cellular, scaffold, and matrix components to achieve a functional synergistic effect. The present study demonstrated the distinct odontogenic and regenerative potential of the formulated bioengineered material, providing a robust basis for subsequent preclinical validation and translational application in regenerative endodontics.

Keywords: Regenerative endodontics; semiorthotopic model; tooth-slice model.

BACKGROUND

Following carious or traumatic injury, the ensuing inflammatory process within the dental pulp frequently progresses to necrosis. In devital teeth, the loss of pulpal vitality results in the disruption of trophic regulation, proprioceptive function, and innate immune defense. Consequently, dehydration of the hard dental tissues occurs, resulting in a significant reduction in their mechanical integrity and overall structural resilience. Loss of pulpal vitality not only compromises tissue homeostasis but also predisposes teeth to structural failure. In Japan, 32% of tooth extractions and in Sweden, 58% are attributed to root or crown fractures.[1,2] Within this context, stem cell–based and bioengineered approaches have gained increasing attention, aiming to restore the vitality and the corresponding physiological functions of the pulp. Over the past decade, tooth slices have been increasingly employed as experimental models for studying dental tissue regeneration under both in vitro and in vivo conditions. The Tooth Slice Model of dental pulp tissue engineering, established by Cordeiro et al. (2008),[3] was conceptually derived from the earlier Tooth Slice Organ Culture Model introduced by Sloan and Smith (1999),[4] which provided one of the first three-dimensional organotypic systems for investigating pulp–dentin interactions. In most studies employing the tooth-slice model in combination with bioengineered materials, implantation is performed extraorally, most commonly in animal models within the subcutaneous tissue of the dorsal region or other anatomical sites.

Currently, experiments utilizing tooth slices are considered an effective platform for elucidating both the behavior of transplanted stem cells and the biological effects of other components incorporated into bioengineered complexes.[5,6] The interpretation of such results contributes to the optimization of bioengineering combinations and scaffold designs.[5,6] Accordingly, the tooth-slice model was selected in our study as the most appropriate approach for evaluating the efficacy of the proposed bioengineered material within a semi-orthotopic experimental framework.

The tooth-slice model developed in this study consisted of a sheep tooth slice combined with mesenchymal stromal cells derived from human exfoliated deciduous teeth (SHED), which were seeded onto gelatin-based microcarriers (CultiSpher®) and embedded within a fibrinogen–thrombin gel. Each component of the bioengineering algorithm designed for pulp regeneration was intended to act synergistically. The tooth fragment served as a unidirectional mechanical barrier, protecting the bioengineered material from mechanical injury and preventing its diffusion into the surrounding tissues.

Studies have confirmed that among the broad spectrum of stem cells derived from various tissues, mesenchymal stem cells (MSCs) represent the most promising source for regenerating the pulp–dentin complex. MSCs constitute a heterogeneous subpopulation of progenitor stromal cells

characterized by high proliferative capacity and potent regenerative ability. They can be isolated from multiple human and animal tissues, including bone marrow, epidermal and muscle tissue, liver, placenta, amniotic fluid, umbilical cord blood, menstrual blood, adipose tissue, and dental pulp, among others. In addition to promoting the regeneration of damaged tissues, mesenchymal stem cells (MSCs) modulate inflammatory responses by suppressing the expression of pro-inflammatory cytokines and enhancing the production of anti-inflammatory mediators. Moreover, MSCs exhibit potent immunomodulatory properties, inhibiting the activity of T cells and natural killer (NK) cells, while regulating the function of dendritic cells.[5,6] In the present study, mesenchymal stromal cells derived from the dental pulp of human exfoliated deciduous teeth (SHED) were selected due to their remarkable proliferative capacity and strong regenerative potential within the dentin–pulp complex.[7-9] Previous studies have demonstrated that dental pulp–derived stem cells (PSCs) express a broad range of neurogenic markers, including c-fos, γ-enolase, nestin, βIII-tubulin, A2B5, musashi 1, neurofilament heavy and light chains, microtubule-associated protein 2, glial fibrillary acidic protein, and oligodendrocyte-associated CNPase, confirming their intrinsic neurotropic and neuroregenerative properties.[10] In addition, SHED display embryonic marker expression, reflecting an immature and highly plastic phenotype.[11] Their non-invasive and ethically acceptable acquisition from naturally exfoliated teeth makes SHED a promising and clinically feasible source of mesenchymal stromal cells for regenerative endodontic applications.

The use of microcarriers in bioengineering provides several significant advantages, including an expanded surface area for cell attachment, which facilitates the formation of dense, viable cell populations while preserving their proliferative capacity. Microcarriers are particularly advantageous for anchorage-dependent cell types, such as SHED, as they enable uniform cell distribution across their surface and create a more favorable microenvironment compared to traditional two-dimensional cultures. Notably, the microporous architecture of CultiSpher® microcarriers enhances oxygen and nutrient exchange, further supporting cell viability and metabolic activity.[12,13]

With advances in biotechnology and regenerative medicine, the range of materials available for bioengineering applications has expanded considerably.[14] Among the broad spectrum of extracellular matrix–associated biomaterials with odontogenic potential, fibrinogen–thrombin gel was selected for this study. Compared with synthetic polymeric matrices, the principal advantage of fibrin gel lies in its controllable rate of biodegradation, which closely corresponds to the phases of tissue regeneration. As a natural plasma-derived fraction, the fibrinogen–thrombin gel exhibits pronounced angiogenic activity and sequentially releases bioactive peptides and cytokines (PDGF, VEGF, TGF-β) that stimulate angiogenesis, cellular proliferation, and extracellular matrix regeneration.[15,16] The regenerative potential of the fibrinogen–thrombin gel arises from a combination of intrinsic properties, including superior biocompatibility, tunable biodegradation kinetics, inherent hemostatic activity, and a robust capacity to support cellular adhesion, migration, and differentiation.[17,18]

Considering the biological properties of SHED, CultiSpher®, and fibrinogen–thrombin gel, these components can be integrated within a tooth-slice model to assess their synergistic potential in promoting pulp–dentin tissue regeneration.

METHODS

Isolation of mesenchymal stromal cells from human exfoliated deciduous teeth (SHED)

The exfoliated deciduous teeth were collected from healthy donors aged 5–9 years at the Apolon Urushadze Dental Clinic of Tbilisi State Medical University and the UNIDENT Dental Clinic, Training and Research Center. The study protocol was approved by the Biomedical Research Ethics Committee of Tbilisi State Medical University (Session No. N6-2022/99). Tissue processing, cultivation, proliferation, and phenotypic characterization were performed according to the protocol previously described by T. Jikia et al. (2025).[19]

Briefly, after pulp extraction, the tissues were immersed in 70% ethanol for 30 seconds and subsequently rinsed twice with Dulbecco's phosphate-buffered saline (DPBS) containing gentamicin (0.05 mg/mL). The pulp tissues were then minced into 1–2 mm fragments using a #20 surgical scalpel, and the explants were evenly distributed in two 35 mm Petri dishes pre-coated with CELLstart™ (Thermo Fisher Scientific, USA). After securing the explants, 1 mL of culture medium was added to each dish, consisting of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 15% fetal bovine serum (FBS), 2 mL of GlutaMAX™, and an antibiotic–antimycotic (AA) solution. The cultures were maintained at 37°C in a humidified incubator with 5% CO_2, and the medium was replaced every four days until the cells reached 70-80% confluence. Cell viability during subculture was evaluated using the Trypan Blue exclusion assay. To confirm their identity, the mesenchymal stromal cells derived from the dental pulp of exfoliated deciduous teeth were assessed by flow cytometry.

Loading of CultiSpher® microcarriers with SHED

0.06 g of rehydrated CultiSpher and SHED (7.0 × 10^6) were placed in a 24-well Companion Plate (Falcon; Corning Life Sciences) and incubated at 37°C with 5% CO2 and 90% humidity. Dulbecco's modified Eagle's medium containing 10% fetal bovine serum (Millipore Sigma), 50 U/mL penicillin, and 0.05 mg/mL streptomycin was used as the cell culture medium.

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SHED were co-cultured with CultiSpher for seven days, and the culture medium was changed every three days. After culture, the CultiSpher was loaded with mesenchymal stromal cells and then freeze-dried using a lyophilizer (Heto Power Dry PL6000 Freeze Dryer; Sjia Lab, Shenzhen, China).

Preparation of the fibrinogen–thrombin gel

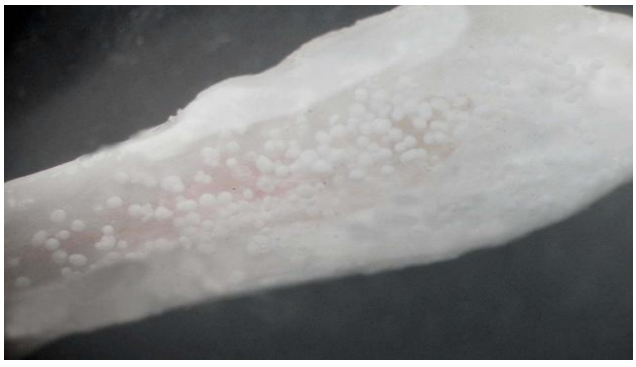
To construct the fibrinogen gel, we used the protocol of Yuan et al. (2011),[20] with modifications. Our modification was described previously.[21] The original solution of fibrinogen (Fibrinogen- CAS 9001-32-5. Sigma-Aldrich, USA) with a concentration of 33 mg/mL was placed in 20 mM HEPES buffer in 0.9% saline and slowly mixed for three hours at 37°C. Next, 0.1 g of rehydrated CultiSpher, which was loaded with freeze-dried SHED, was placed into the fibrinogen gel. Then, the fibrinogen solution together with CultiSpher was poured into aliquots of 1 mL and stored at -20°C until use.

Thrombin solution (Thrombin – CAS 9002-04-4. Sigma-Aldrich, USA) was prepared by adding 18 mL of 0.9% saline and 2 mL of sterile deionized water to 500 U of thrombin. The solution was then filtered through a 0.2-µm filter, aliquoted into 250 µL portions, and stored at -80°C until use.

Semi-Orthotopic transplantation of the tooth slice loaded with bioengineered material

Four mandibular incisors (n = 4) were obtained from 2-year-old sheep designated for utilization. Each tooth was sectioned longitudinally under continuous water irrigation using a turbine handpiece equipped with a fissure bur. Approximately two-thirds of the pulp tissue was removed, and the root canal cavity was filled with a bioengineered composite consisting of mesenchymal stromal cells derived from human exfoliated deciduous teeth (SHED) seeded onto microcarriers, which were subsequently mixed with fibrinogen solution and combined with thrombin gel to induce polymerization (Fig.1).

FIGURE 1. Placement of SHED-loaded CultiSpher® microcarriers combined with fibrinogen–thrombin gel within the canal lumen of the tooth slice

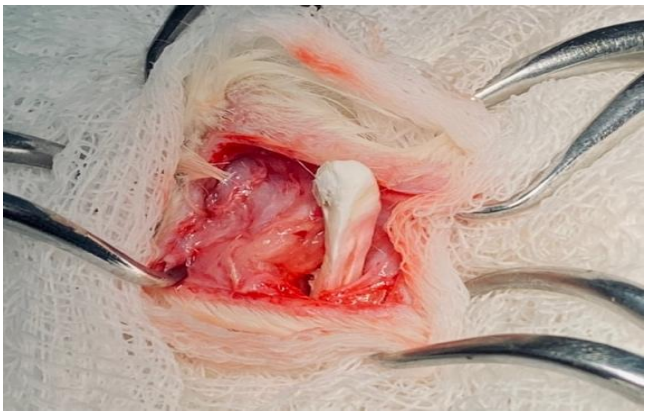


The prepared slices were incubated at 37°C for 10 minutes before transplantation.

Semi-orthotopic transplantation was performed in laboratory rats. Two rats were purchased from the vivarium of Tbilisi State Medical University (Tbilisi, Georgia). Animals were housed 5 per cage under 12/12 h day/night cycles and provided with a pelleted rodent diet and water ad libitum. All experimental procedures were performed in accordance with the EU Directive 2010/63/EU for animal experiments and the guidelines of the Animal Care.

Under general anesthesia induced by intraperitoneal administration of ketamine (100 mg/kg) and xylazine (7 mg/kg), a 2-cm incision was made in the dorsal region. The underlying muscles were bluntly dissected to form a subcutaneous pocket, into which the slice was inserted. The surgical wound was closed in layers with interrupted sutures (Fig.2).

FIGURE 2. A bioengineered construct is implanted in the dorsal subcutaneous region of the rat



Animals were maintained under standard vivarium conditions with unrestricted access to food and water. Specimens were retrieved at postoperative days 7 and 28.

At each time point, the animals were anesthetized with an intraperitoneal dose of sodium thiopental. The implantation site was palpated to locate the tooth slice, and a 2-cm incision was made over the dorsal region. The slice was carefully dissected free from the surrounding tissues and extracted. The wound was closed in layers, and the animal was returned to standard housing conditions.

Histological processing and staining

For histopathological evaluation, retrieved specimens were fixed in 10% neutral-buffered formalin, decalcified for three weeks, embedded in paraffin, and sectioned at a thickness of 3 µm using a rotary microtome. Sections were stained with

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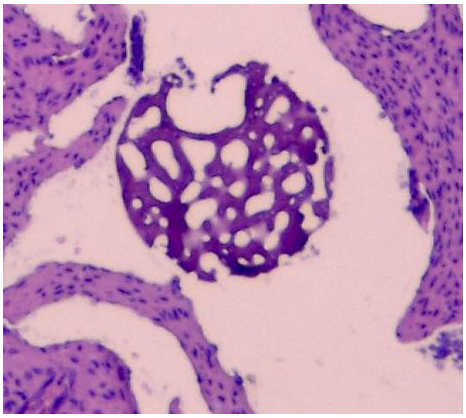
hematoxylin and eosin (H&E) according to a standard histological protocol.

RESULTS

The study demonstrated that incorporating fibrinogen–thrombin gel with SHED-loaded CultiSpher microcarriers within the tooth-slice construct enabled the evaluation of stem cell proliferative and differentiation potential in a semi-orthotopic rat model. This experimental design also allowed detailed observation of angiogenic activity and the formation of dentin-like matrix within the implanted slices.

A distinct host response to the implanted microcarriers was observed during the first week. CultiSpher® microcarriers exhibited minimal structural degradation and retained their original morphology at this stage. A localized inflammatory infiltrate was present around the implantation site, composed mainly of lymphocytes, macrophages, and neutrophils. Concurrently, mesenchymal stem cells were identified on the surface of the microcarriers and appeared to migrate progressively into the surrounding tissue (Fig.3).

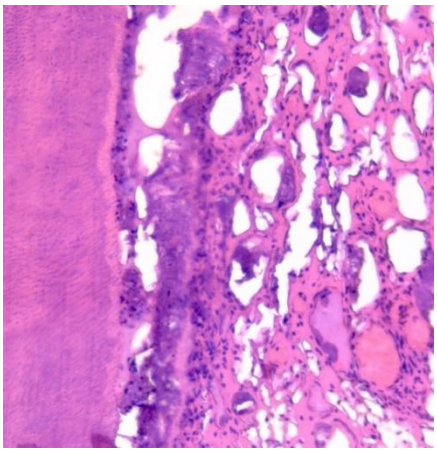
FIGURE 3. The biodegradation process of the Cultispher® microcarrier, accompanied by mesenchymal stem cell migration (SHED), was observed after 7 days. Stained with H&E. Magnification ×200



At four weeks post-transplantation, histological evaluation of the implanted tooth slices demonstrated the formation of dentin-like tissue, characterized by areas of mineralized matrix interspersed with fibrous connective tissue and small blood vessels. Within the canal region, odontoblast-like cells were evident, oriented along and migrating toward the dentinal wall. The organization of the regenerated tissue and the presence of early mineral deposition indicated the onset of reparative dentinogenesis (Fig.4).

Overall, subcutaneously transplanted teeth slices containing the bioengineered material facilitated extracellular matrix deposition and promoted the development of pulp- and dentin-like tissues. The composite comprising fibrinogen–thrombin gel and lyophilized CultiSpher® microcarriers loaded with mesenchymal stromal cells derived from human exfoliated deciduous teeth (SHED) exhibited evidence of early vascularization and mineralized matrix formation in vivo. These findings underscore the effectiveness of microcarriers as localized vehicles for stem cell delivery and confirm their regenerative potential in promoting pulp–dentin complex formation within the in vivo environment.

FIGURE 4. Formation of dentin-like and connective tissue within the tooth slice, with migration of odontoblast-like cells toward the canal wall. Observation period: 28 days. Stained with H&E. Magnification ×400



DISCUSSION

The present study demonstrated that microcarriers loaded with human exfoliated deciduous teeth (SHED), in combination with fibrinogen–thrombin gel, created a supportive microenvironment conducive to the proliferation and differentiation of transplanted stem cells, thereby facilitating pulp-like tissue regeneration and angiogenesis. During the preparation of the slices, the material exhibited a high degree of adaptability to the canal walls. The biodegradation of the implanted material within the tooth slices was likely accompanied by its gradual replacement with newly formed, regenerative pulp-like tissue, indicating dynamic remodeling and integration between the bioengineered scaffold and host tissues.

It is likely that, within the bioengineering algorithm developed in this study, the CultiSpher® microcarriers also served as a three-dimensional extracellular matrix, providing structural and biochemical support for the proliferation, differentiation, and regenerative activity of transplanted stem cells. Mesenchymal stromal cells derived from human exfoliated deciduous teeth (SHED) adhering to the porous

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surface of the microcarriers gradually migrated toward the dentinal walls of the tooth fragment, where they differentiated into odontoblast-like cells. Notably, the CultiSpher microcarriers appeared to act not only as vehicles for mesenchymal stem cell delivery but also as an autonomous extracellular matrix–like system that reinforced the fibrin–thrombin gel, collectively enhancing the integrity and regenerative performance of the bioengineered algorithm.

In the present bioengineered material, an essential component was the combined lyophilization of microcarriers and mesenchymal stromal cells, designed to mitigate the antigenicity of allogeneic cell populations in vivo. This approach aimed to enhance biocompatibility and minimize potential immune responses following transplantation. Post-rehydration analysis demonstrated that the viability of lyophilized stromal cells remained at approximately 75%, confirming the preservation of their metabolic activity and regenerative competence. The lyophilized form of both CultiSpher® microcarriers and mesenchymal stromal cells offers substantial practical advantages, enabling the fabrication of a pre-assembled, ready-to-use bioengineered component with prolonged shelf stability that does not require special storage conditions.[22,23]

The conclusions of this study align with earlier investigations in regenerative endodontics, corroborating the crucial contribution of the synergistic interplay between extracellular matrices and stromal cells to successful tissue regeneration.[24,25] The tri-component bioengineered material developed in this work could serve as a promising platform for vital pulp therapy and for promoting regeneration of the pulp–dentin complex.

CONCLUSIONS

The development of a bioengineering algorithm represents a multistage, technologically demanding process that requires the iterative optimization of cellular, scaffold, and matrix components to achieve a functional synergistic effect. The present study demonstrated the distinct odontogenic and regenerative potential of the formulated bioengineered material, providing a robust basis for subsequent preclinical validation and translational application in regenerative endodontics.

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