Enhancing compliance and extracellular matrix properties of tissue-engineered vascular grafts through pulsatile bioreactor culture

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Abstract (278 words)

Purpose: Materials science and regenerative medicine are promising avenues for production of tissue-engineered vascular grafts (TEVGs) with biomimetic extracellular matrices (ECMs). However, many TEVGs exhibit poor mechanical compliance, with studies often overlooking the complex role of ECMs. Here, highly compliant TEVGs were cultured in pulsatile bioreactors using porous polymer scaffolds as substrates for tissue growth. For 6-weeks in vitro we studied matrix progression and mechanics of TEVGs cultured with mesenchymal stem cells (MSCs) and smooth muscle cells (SMCs) in static or dynamic conditions, with post-processing methods assessed for development of readily-available grafts.

Methods: Small diameter tubular scaffolds produced from medical polycaprolactone (PCL) via melt electrowriting (MEW) were engineered to exhibit biomimetic mechanics with precise sinusoidal fibre architecture. MSCs and SMCs were cultured on scaffolds for 6 weeks in static or dynamic conditions, prior to decellularization and lyophilization. Biochemical analyses, mechanical testing, histology and immunofluorescence imaging enabled assessment of engineered vascular tissue matrices.

Results: In 6-weeks cells and ECM completely filled scaffold pores. Pulsatile stimulation successfully maintained high scaffold compliance (12.4±0.8% per 100mmHg) with negligible loss of mechanics after decellularization. Dynamic TEVGs exhibited burst pressure (1225±196mmHg) and suture strength (3.1±0.3N) significantly greater than static TEVGs owing to enhanced ECM. MSCs produced more dense and collagen-rich ECM reflected by greater GAG and hydroxyproline content. TEVGs were effectively decellularized via TX100 and lyophilized, with negligible influence on ECM performance. Finally, endothelial cell seeding of rehydrated TEVGs achieved intimal endothelium formation in 7 days.

Conclusion: Highly compliant polymer scaffolds cultured in pulsatile conditions enabled biofabrication of TEVGs with physiological mechanics and enhanced ECMs which, in addition to decellularization and lyophilization, provided positive indications toward future preclinical testing for small diameter bypassing applications.

Advanced Orthodontic Adhesive Modified by Nano-Calcium-Phosphate and Nano-Silver: Antibacterial and Remineralizing for Enamel Demineralization Prevention

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Abstract:

During fixed orthodontic treatment, white spot lesions are prevalent issues associated with cariogenic bacteria. This study aims to construct an orthodontic adhesive containing nanoparticles of amorphous calcium phosphate-polydopamine-Ag (NPA) fillers to combat white spot lesions. The NPA fillers were prepared and characterized by scanning electron microscopy (SEM), transmission electron microscopy (TEM), Fourier transform infrared spectroscopy (FTIR), and X-ray photoelectron spectroscopy (XPS). The biocompatibility of the fillers was evaluated. A colony counting test evaluated the antibacterial properties of the fillers against Streptococcus mutans (S. mutans). NPA fillers were mixed with orthodontic adhesive at different weight ratios (0, 1, 3, and 5 wt.%). The shear bond strength and antibacterial properties were then further investigated. The results showed that NPA was prepared successfully, with good antibacterial and remineralization properties. The cell survival rate of all groups of fillers was higher than 70%, showing good biocompatibility. Moreover, the shear bond strength of the orthodontic adhesive with 3 wt.% NPA fillers was 8.65 ± 1.41 MPa, meeting the minimal clinical bond strength requirements of 7.8 MPa. Furthermore, the orthodontic adhesive resin blocks and the extract displayed good antibacterial properties, with the number of colonies decreasing significantly ($p < 0.001$). Taken together, we think that an orthodontic adhesive with NPA may have a good application potential for the prevention and treatment of white spot lesions.

Graphic:

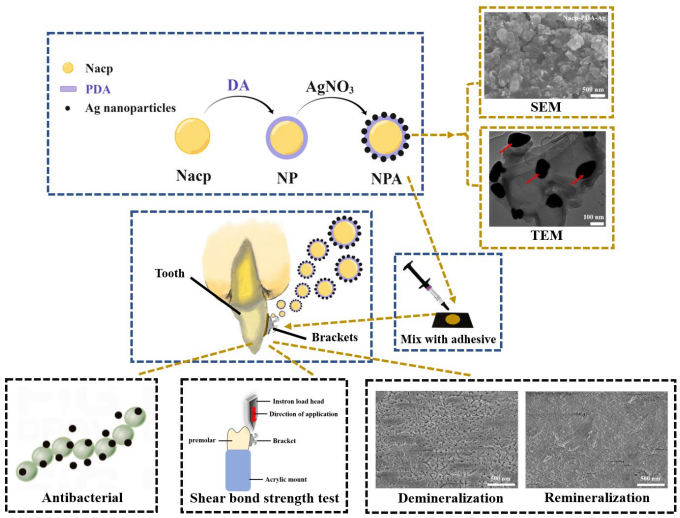

Figure 1. Schematic of the synthesis process of the NPA fillers and orthodontic adhesive containing NPA fillers with both antibacterial properties and reasonable shear bond strength.

Efficacy of Low-dose and Short-term Oral Olanzapine in Reducing Significant Perioperative Anxiety in Primary Total Joint Arthroplasty: A Prospective, Randomized Controlled Trial

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Abstract:

Background: Significant perioperative anxiety can lead to additional discomfort, more pain, and poor joint function recovery in patients undergoing total joint arthroplasty (TJA). Recent studies have shown that olanzapine has a favorable anxiolytic effect, improves sleep quality, and treats clinical chronic pain. However, the above efficacy of olanzapine has not been reported in orthopedics. Therefore, we aimed to apply for this new clinical application in orthopedics and investigate the above effects of olanzapine in these high-risk patients undergoing primary TJA.

Methods: We prospectively enrolled 101 patients undergoing primary THA/TKA who have significant perioperative anxiety (State-Trait Anxiety Inventory-State, STAI-S≥40). Patients were randomized to the olanzapine group (2.5 mg qn for 5 days starting on the day of admission) or the control group. The STAI-S score, the Visual Analogue Scale-Sleep disorder (VAS-S), the VAS-Pain score were measured. Postoperative opioids consumption, Range of motion (ROM) of hip and knee, Harris Hip Score/Hospital for Special Surgery Knee Score (HHS/HSS), length of stay (LOS), and other adverse events related to olanzapine were recorded.

Results: The STAI-S score in olanzapine group was significantly lower than that of control group on the night before surgery, the postoperative day (POD) 1 and POD 3. The olanzapine group also had lower VAS-S and resting VAS-P from POD 1-3. Furthermore, the olanzapine group showed a less postoperative consumption of opioids. Patients in olanzapine group exhibited better hip function, including HHS, hip flexion and abduction ROM. No significant difference was observed in adverse events between two groups.

Conclusion: Low-dose and short-term oral olanzapine can reduce anxious patient's anxiety level, sleep disorder and postoperative pain and enhance recovery in patients undergoing primary TJA. Thus, we recommend anxious patients receive this new clinical application for the optimization of perioperative experience and TJA outcomes.

Investigating the Role of Bacterial and Host-Derived Extracellular Vesicles in Periodontitis diagnosis

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Introduction

Extracellular vesicles (EVs) are nanoscale lipid-bilayer particles derived from most cells of different species, including host and bacterial-derived EVs (BEVs) [1]. Oral bacterial-derived BEVs contain a variety of microbial molecules, including enzymes, toxins, and microbial-associated molecular patterns (MAMP) [1], that can be transported to recipient host cells locally and systematically to cause periodontitis or other systemic diseases [1, 2]. In terms of host response, host-derived EVs with encapsulated pro-inflammatory cytokines may contribute to the modulation of immune and inflammatory processes in oral disease pathogenesis [3]. Limited studies explored both dental plaque derived BEVs and saliva host EVs cytokine profiles. This study aims to a) understand the BEV component by comparing 16S sequencing profiles from 3D-mimicking saliva biofilm and b) assess the potential of immunoaffinity-enriched host EVs from saliva as diagnostic markers for periodontitis.

Methods

For BEV profiling, oral biofilms were cultured on 3D polycaprolactone (PCL) scaffolds and 2D plates. BEVs were isolated using size exclusion chromatography (SEC) and characterized by multiple techniques, followed by genomic DNA qPCR and 16S sequencing. Simultaneously, host-derived EVs were enriched from 12 non-periodontitis and 20 periodontitis patients' saliva using SEC and bead-based immunoaffinity capture. After saliva-EVs characterization, inflammatory cytokines (IL-6, IL-1β, IL-8 and IL-10) in host EVs were compared between non-periodontitis (n=12) and periodontitis (n=20) groups.

Results and Discussion

16s sequencing results suggest that BEVs exhibit strong enrichment ability and sensitivity with genera *Capnocytophaga, porphyromonas* and *veillonella*, phylum *Firmicutes* and *Bacteroidota,* and species *Alloprevotella_tannerae*, *Capnocytophaga_sputigena*, *Veillonella_atypica* and *Prevotella_melaninogenica*. Moreover, immunoaffinity-enriched salivary EVs from periodontitis patients displayed elevated pro-inflammatory cytokines (IL-6, IL-8) and reduced anti-inflammatory IL-10 compared to non-periodontitis individuals.

Conclusion

Investigating BEVs from oral biofilm and cytokine signatures in salivary host EVs could enhance our understanding of periodontitis, leading to more accurate diagnosis and targeted therapeutic interventions.

Injectable Gelatin-Pectin Hydrogel for Enhanced Angiogenesis and Antibacterial Efficacy in Pulpitis Therapy

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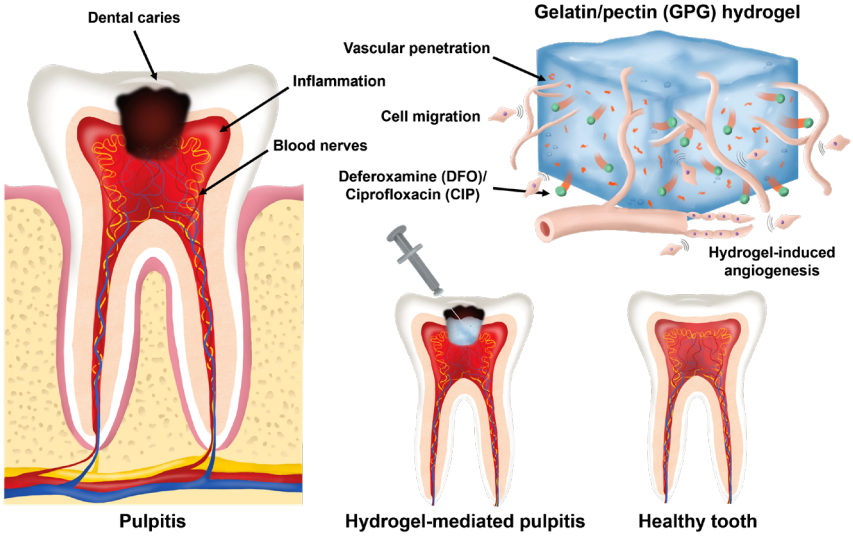
Abstract:
Pulpitis is inflammation of the dental pulp, often caused by bacterial infection from untreated cavities, leading to pain. The main challenge in treatment is eliminating infection while preserving tooth vitality. This study aimed to address this challenge by developing a hydrogel for convenient insertion into the root canal system, securely attaching to dentin walls. We developed an injectable hydrogel system by chemically cross-linking natural polysaccharide pectin with gelatin (GPG) through reversible Schiff base reaction. The GPG system was then assessed for its ability to encapsulate and release drugs, such as ciprofloxacin (CIP) for infection prevention and deferoxamine (DFO) for promoting blood vessel proliferation and reducing inflammatory reactions. The GPGs absorbed significant amounts of CIP and DFO, enabling sustained release over a ten-day period. When subcutaneously implanted, the GPGs formed stable gel depots, with only 50% of the gels degrading after 3 weeks, indicating a sustained biodegradation pattern. Additionally, the GPG system demonstrated excellent antibacterial activity against both gram-negative and gram-positive bacteria. Results from *in vitro* scratch healing tests and *in ovo* chorioallantoic membrane chick model tests showed promising biocompatibility and promotion of vascular proliferation by the GPG. This study heralds an innovative frontier in endodontic therapeutics, poised to revolutionize dental pulp regeneration.

Graphic:



Transcriptome-guided hydrogel design of a stem cell niche for enhanced tendon regeneration

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Abstract:
Bioactive hydrogels have emerged as promising artificial niches for enhancing stem cell-mediated tendon repair. However, a substantial knowledge gap remains regarding the optimal combination of niche features for targeted cellular responses, which often leads to lengthy development cycles and uncontrolled healing outcomes (Figure 1A). To address this critical gap, we developed an innovative, data-driven materiomics strategy. This is based on our in-house RNA-seq data that integrates bioinformatics and mathematical modeling, which is a significant departure from traditional trial-and-error methods. It aims to provide both mechanistic insights and quantitative assessments and predictions of the tenogenic effects of adipose-derived stem cells induced by systematically modulated features of a tendon-mimetic hydrogel (TenoGel) (Figure 1B). The knowledge generated has enabled a rational approach for TenoGel design, addressing key considerations, such as tendon extracellular matrix concentration, uniaxial tensile loading, and *in vitro* pre-conditioning duration. Remarkably, the optimized TenoGel demonstrated robust tenogenesis *in vitro* and facilitated tendon regeneration while preventing undesired ectopic ossification in a rat tendon injury model (Figure 1C). These findings shed light on the importance of tailoring hydrogel features for efficient tendon repair. They also highlight the tremendous potential of our innovative materiomics strategy as a powerful predictive and assessment tool in biomaterial development for regenerative medicine.

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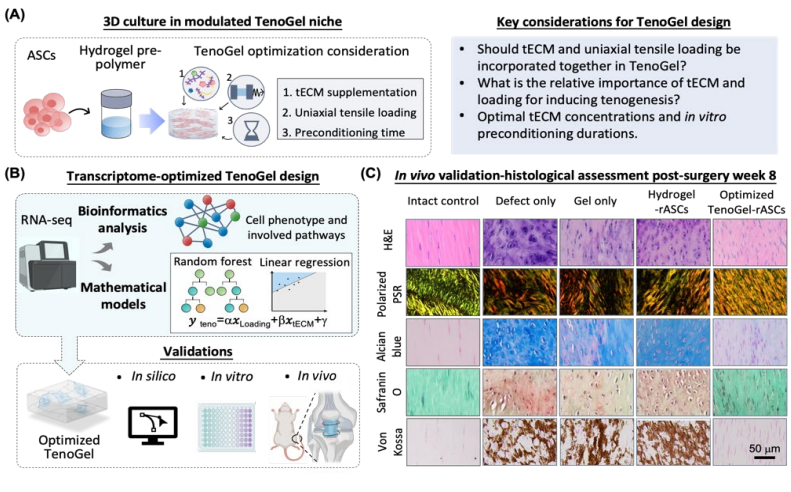

Figure 1 Optimized TenoGel developed through a materiomics strategy that integrates bioinformatics analysis and mathematical modeling to enhance stem cell-mediated tendon repair. (A) Modulation of tendon extracellular matrix (tECM) and tensile loading in TenoGel, along with key design considerations. **(B)** Materiomics analysis utilizing in-house RNA-seq data: (1) Bioinformatics provides mechanistic insights into cellular responses to various hydrogel features. (2) Mathematical modeling quantitatively assesses and predicts the tenogenic effects of the hydrogel design. The optimized TenoGel was further validated through *in silico*, *in vitro*, and *in vivo* analyses. **(C)** The optimized TenoGel with rat adipose-derived stem cells (rASCs) facilitates effective tendon repair while inhibiting ectopic bone formation in a rat tendon defect model, as demonstrated by histological analysis at week 8.

Delayed jaw bone healing in a rat model of collagen induced arthritis and its relationship with gut microbiota imbalance

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Abstract:
Periodontal bone defects, resulted from severe periodontitis, remains a challenge for dentists. A close link between periodontitis and rheumatoid arthritis (RA) has been demonstrated. However, there's limited understanding of the effects of RA on periodontal healing and the underlying mechanism. In order to solve this problem, we constructed periodontal fenestration defects and established collagen induced arthritis (CIA) in 6-weeks-old male Sprague Dawley rats (n=60). Micro-architecture of bone tissue in both the jaw and the back paw was determined by micro-computed tomography (μCT). The results showed that CIA could worsen bone defects in the rat jaw after 1, 3 and 6 weeks, while no significant difference of bone resorption was observed in paw joints between the rats with or without periodontal fenestration defects. 16S rRNA high-throughput sequencing was obtained to analyze gut microbiota. It is revealed that, comparing to the control group, gut microbiota imbalance was observed in the periodontal defects group, the CIA group and the two diseases group (rats with both periodontal fenestration and CIA). Moreover, comparing to the periodontal defects group, the accumulation of Eubacterium was significantly increased. Collectively, CIA slowed the healing of periodontal bone regeneration and the mechanism might be related with gut microbiota modulation. The results reveal potential insights into the association between periodontal tissue regeneration and RA, and build theoretical foundation for promoting periodontal repair via gut-bone axis.

Acknowledgments:
The authors acknowledge the financial support received from the National Natural Science Foundation of China (82301101); Natural Science Foundation of Jiangsu (BK20230159); ‘‘3456’’ Cultivation Program for Junior Talents of Nanjing Stomatological Hospital, Medical School of Nanjing University (0222R210); Nanjing Postdoctoral Fellowship Research Funding; Jiangsu Provincial Medical Key Discipline Cultivation Unit (JSDW202246) respectively.

High-efficient photothermal Fe3O4-based nanoparticles for efficient biofilm eradication against periodontitis

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Abstract:

Periodontitis is a common condition characterized by a bacterial infection and the disruption of the body's immune-inflammatory response, which causes damage to the teeth and supporting tissues and eventually results in tooth loss. However, the efficacious delivery of antibiotic to intractable oral biofilms and bacteria resistance significantly increased the difficulty of curing the infectious diseases. Herein, the Fe_3O_4-based core-shell structure covered with ZnO and epsilon-polylysine (EPL) with biofilm penetration, antibacterial/antibiofilm and anti-inflammatory activities were fabricated. The Fe_3O_4 core induced efficient photothermal effects to cause dense biofilm dispersal, which dramatically promoted the adsorption and penetration of ZnO and EPL into the bacterial cells to thoroughly kill bacteria in biofilms *in vitro* with the enhanced sterilization ability. More importantly, the positively charged FZE NPs can precisely adsorb onto the surface of negatively charged bacterial membranes which can effectively control the inflammatory response with no damage to normal tissues. *In vitro* antibacterial effects of Fe_3O_4/ZnO/EPL (FZE NPs) were investigated in *porphyromonas gingivalis* (*P. gingivalis*) which is a well recognized periodontal pathogenic bacterium, and *in vivo* anti-periodontitis effects were evaluated using Sprague–Dawley (SD) rats with ligature-induced periodontitis. The obtained FZE NPs exhibited efficient photothermal antibacterial activity against periodontal pathogens under near-infrared (NIR) light irradiation. We provided a new strategy for the therapy of periodontitis based on FZE NPs, which would have great application prospects in the development of nanodrugs in the treatment of periodontal-related diseases.

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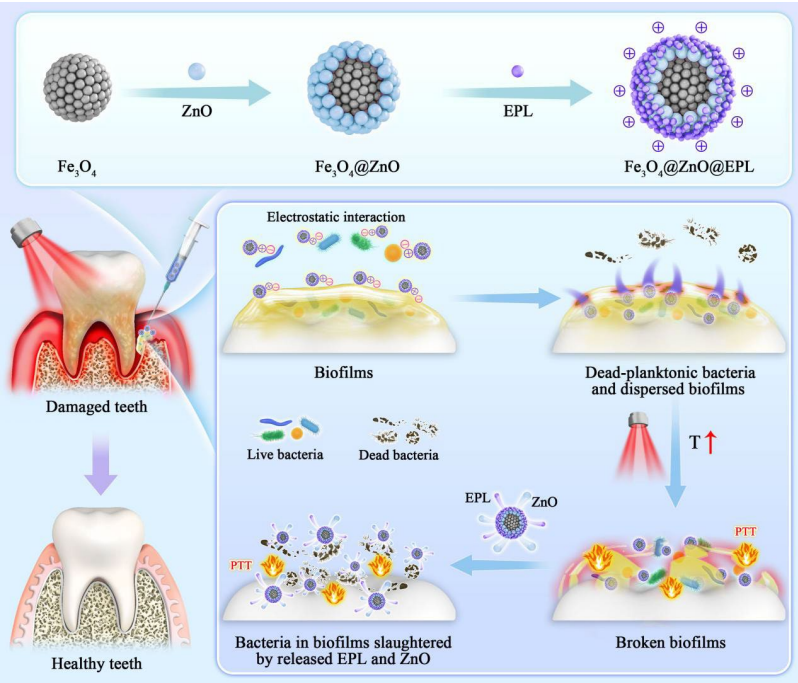

Scheme 1. Schematic illustrating of the step-by-step preparation process of the designed FZE NPs and the working mechanisms for periodontitis therapy.

Stroke Risk Stratification for Patients with Atrial Fibrillation by Assessing Atrial Deformation and Blood Flow

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Abstract:
Atrial Fibrillation (AF) is the most common cardiac rhythm disorder which is characterized by irregular and often rapid heartbeats, leading to ineffective atrial contraction and consequently cause irregular atrial motion and deformation. The changes in atrial motion can further increase the risk of adverse cardiovascular events, such as stroke and heart failure. Clinically, the CHA_2DS_2-VASc score is widely accepted for assessing stroke risk in patients with atrial fibrillation. Since it solely relies on demographic and clinical factors, important information embedded in heart deformation and blood flow is often ignored. Our object is to explore effective stroke risk stratification parameters. A mesh regularized sub-volume tracking method was proposed to calculate atrial wall displacements and strain and via 4D-CTA images [1]. Subsequently, patient-specific computational fluid dynamic models simulating blood flow in left atrium were developed. Boundary conditions at pulmonary veins (pressure) and mitral valve ring (flow rate) were computed via heart morphology data derived from 4D-CTA. Statistics analysis was performed to explore the effectiveness of using 3D left atrial surface strain and blood flow data for stroke risk stratification. Our work has great potential in stroke event prevention and optimizing treatment procedures for patients with atrial fibrillation.

References:
[1] Han Yu, Zidun Wang, Hao Wu, Zhengduo Zhu, Jiaqiu Wang, Runxing Fang, Shanglin Wu, Hujin Xie, Xianjue Huang, Jessica Benitez Mendieta, Haveena Anbananthan, Zhiyong Li, In-vivo left atrial surface motion and strain measurement using novel mesh regularized image block matching method with 4D-CTA, Journal of Biomechanics, Volume 176, 2024, 112354

Deep Learning-Enabled Subtraction Coronary CT: Synthesizing Noncontrast Images from CTCA

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Abstract:
Introduction: Coronary artery calcium (CAC) causes beam hardening and blooming artifacts on CT Coronary Angiography (CTCA) images, leading to overestimation of luminal stenosis and reduced diagnostic specificity. The development of subtraction CT has been reported to be valuable for eliminating the artifacts by subtracting non-contrast images from contrast images. The precise alignment algorithm between the two images remains challenging.
Methods: To eliminate the complicated alignment process between two images and to reduce patient exposure to radiation, we proposed a deep learning-based adversarial diffusion model. This approach integrates concepts from generative adversarial networks (GANs) and diffusion models to generate synthetic non-contrast CT images from CTCA. Patients with high Agatston score (>400) were selected for model training and evaluation. The efficacy of the model was assessed using peak signal-to-noise ratio (PSNR) and Agatston score, with real non-contrast CT serving as the reference standard.
Results: A total of 6572 CTCA slices and 2591 non-contrast CT slices were extracted from 13 patients with both scans for model training and evaluation. The high PSNR indicated the model's remarkable ability to preserve the visual similarity of the generated images. Meanwhile, a strong positive correlation was observed between the Agatston scores of the synthetic and real non-contrast CT images.
Conclusion: This study establishes the feasibility of employing deep learning-based models to generate non-contrast CT images from CTCA, potentially enabling the acquisition of subtraction CT through a single CTCA imaging process. These findings have significant implications for improving diagnostic accuracy and reducing radiation exposure in coronary imaging.

Inorganic biomaterials promote innervated tissue regeneration

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Abstract:
Neural networks are densely distributed throughout many tissues and organs, which plays an essential role in tissue regeneration and functional recovery. Numerous neuropeptides and neurotrophic factors secreted from the neural system have been confirmed to be beneficial to tissue repair. However, the requirement of regenerating the neural components within the injury sites have been largely overlooked during the past decades. Silicate biomaterials have been proved to promote various tissue regeneration, owing to the positive effects of bioactive ions (Si, Zn, Ca, etc.) on osteogenesis, angiogenesis and neurogenesis. Moreover, the spatial topology structures of biomaterials can also provide physical cues to modulate cell behaviors. Hence, we have developed several silicate biomaterials with excellent bioactivities, and in combination with advanced manufacturing technology (including electrospinning, 3D printing and 3D bioprinting) to fabricate tissue regenerating scaffolds. The results showed that silicate biomaterials-based scaffolds could obviously promote tissue regeneration with neural integration. Besides, the physical cues of scaffolds also activated the PI3K-Akt signal pathway to promote the osteogenic differentiation of bone mesenchymal stem cells (BMSCs) and neurogenesis, resulting in innervated bone regeneration. Taken together, biomaterials with innervation properties can not only recapitulate the physiological microenvironment of damaged tissues but also rapidly integrate with host neural networks, resulting in accelerated functional tissue regeneration.

One-shot generation of universal stem cells expressing Goldilocks-level of HLA-I via B2M super-enhancer editing for allogeneic cell therapy

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Abstract:
Immune rejection caused by human leukocyte antigens (HLA) mismatch is a fundamental barrier to allogeneic cell therapy. Current strategies to create universal cells by multiple gene editing of HLA-I and natural killer (NK) cell inhibitory proteins are associated with various safety issues pertaining to gene stability and cellular cytotoxicity. Here, we identified an IFNγ-responsive B2M super-enhancer (B2M-SE) that plays a key role in regulating surface HLA-I expression in allogeneic immunological reaction. One-shot site-specific epigenetic repression of B2M-SE successfully created a surface HLA-I level that was below the threshold needed to activate allogenic T cells in MSCs, while still being at a sufficiently moderate level to evade NK cell-mediated attack. We named these **G**oldilocks-**L**evel **O**f **B**2M **E**xpression M**S**Cs (GLOBES). A combination of in vitro assays and humanized mouse models demonstrated that GLOBES elicited minimal immune activation and memory, while exhibiting extended in vivo survival and exerting superior therapeutic effects on LPS-induced acute injury lungs. Hence, epigenetic editing of the B2M-SE has strong potential in creating multiple off-the-shelf universal donor cell sources for allogeneic cell-based therapy.

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Wang F#, Li R#, Xu JY#, Bai XX#, Wang Y, Chen XR, Pan C, Chen S, Zhou K, Heng BC, Wu X, Guo W, Song Z, Jin SC, Zhou J, Zou XH*, Ouyang HW*, **Liu H***. Downregulating human leukocyte antigens on mesenchymal stromal cells by epigenetically repressing a β2-microglobulin super-enhancer. Nature Biomedical Engineering. 2024 Oct. DOI : 10.1038/s41551-024-01264-w.

Bioadaptable bioactive glass-β-tricalcium phosphate scaffolds with TPMS-gyroid structure by stereolithography for bone regeneration

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Abstract:
Bone defect repair remains a problem in orthopedics, which involves complex biological processes. Calcium phosphates have been widely used owing to their advantage of biocompatibility. However, single component and traditional fabrication methods cannot meet the requirements of bioadaptability during tissue repair process. In this work, 0%, 5%, 15%, 25% wt% of BG-TCP (bioactive glass-β-tricalcium phosphate) scaffolds with triply-periodic minimal surface (TPMS)-gyroid structure were prepared by stereolithography (SLA) technology. TPMS-gyroid structure provided an accurate mimicry of natural bone tissue, and the incorporation of BG improved the compressive strength of β-TCP matrix, matched with the defective bone (2-12 MPa). Rapid but tunable degradation kinetics of BG enabled the BG-TCP system to show adaptable biodegradability to new bone generation. In vitro studies showed that composite scaffolds have better mechanical properties (7.82 MPa), and could release appropriate contents of calcium, phosphorous, and magnesium ions, which promoted osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) and angiogenic ability of endothelial progenitor cells (EPCs). Moreover, the in vivo assessment of rat femoral defect revealed that TPMS-structure-based scaffolds accelerated bone ingrowth to the pores. Moreover, BG-TCP scaffolds, especially 15BG-TCP group, exhibited superior bone regeneration capacity at both 4 and 8 weeks, which achieved an optimal match between the rate of material degradation and tissue regeneration. In summary, this study provides insight into influences of bioactive components and bionic structures on the physical-chemical properties of materials, cell behavior and tissue regeneration, which offers a promising strategy to design bioadaptive ceramic scaffolds in the treatment of bone defects.

Effects of autologous platelet-rich plasma therapy on human thin endometrium: a comprehensive transcriptome analysis through single-cell RNA sequencing

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Abstract:

Background Therapeutic options of thin endometrium (TE) have emerged during recent years, of them autologous platelet-rich plasma (PRP) therapy gather patients' attention due to its promising clinical effects. To better know the precise function of PRP enhancing implantation, advanced technologies such as singe-cell RNA sequencing (scRNA-seq) are needed to disclose the underlying mechanisms. **Methods** 10 eligible TE patients were recruited for PRP infusion and endometrial thickness was evaluated. Biopsies of endometrial tissue pre- and post-PRP therapy (paired samples) were proceeded for scRNA-seq. Hematoxylin & eosin (HE) staining, and immunohistochemistry (IHC) were utilized for validating protein markers. **Results** PRP therapy evidently increased the endometrium thickness of TE patients. Based on scRNA-seq data, 11 major cell types have been shown in paired samples. Gene ontology (GO) and kyoto encyclopedia of genes and genomes (KEGG) pathway analyses supplied the most enriched pathways for 11 cell types. Cellular trajectory reconstruction analysis using gene counts and expression (CytoTRACE) scores predicted that high stemness cells were more enriched in proliferating stromal cells (pStr) or Str cells of post-PRP samples, while much higher stemness cells were detected in glandular cells (GE) and luminal cells (LE). Gene set variation analysis (GSVA) calculated significant differences of mesenchymal-epithelial transition (MET)-related gene signature scores between paired samples. Epithelial cells of post-PRP patients displayed relatively less expression of vimentin (VIM), while similar or higher expression of cytokeratin 8 (KRT8). With increased number of macrophages in post-PRP samples, a greater amount of M1 type macrophages was also detected by cell clustering analysis. Various protein markers of cell stemness, MET pathway and macrophage polarization were confirmed by HE and IHC. **Conclusions** As the first one reporting the effects of PRP therapy via transcriptome analysis, our results may uncover its mechanisms involving three aspects: improve stem cell potential, stimulate MET transformation, and increase macrophage function.

Upscaling the generation of cartilage microtissues within a microwell/mesh system by optimizing chondrogenic protocols

Jillis Ernst, Dr. Angus Weekes[1], Jordan Davern[1], Udhaya Nedunchezhiyan[1], Dr. Debby Gawlitta[2], Dr. Mike Doran[1], Dr. Kathryn Futrega[1], Prof. Travis Klein[1]
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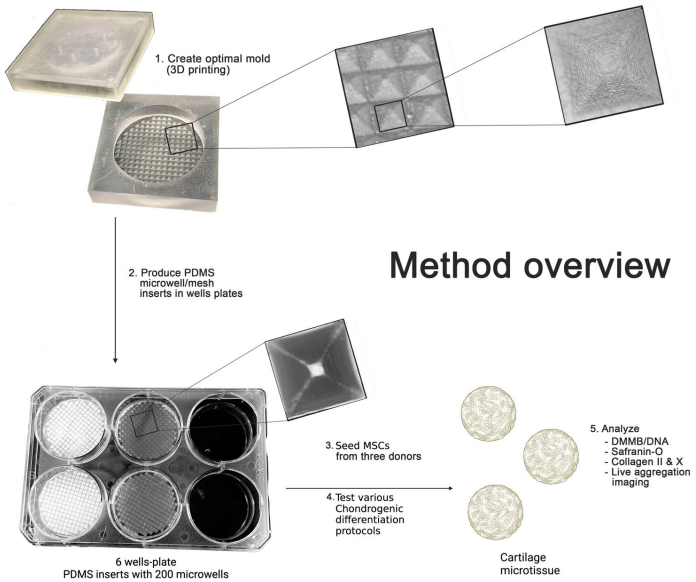
University Medical Centre Utrecht, Utrecht, Netherlands

Abstract:

Hypertrophic cartilage microtissues (CMs) are promising building blocks for bone-implants and are typically produced through the chondrogenic differentiation of Mesenchymal Stromal Cells (MSCs). After implantation, CMs are remodeled into patient-own bone through endochondral ossification, and thus can be used to treat bone defects[1–3]. Currently, there is no production method capable of producing sufficient hypertrophic CMs to treat a human-sized bone-defect. Microwell systems are one of various methods being explored, as they enable discrete microtissue differentiation, preventing microtissue aggregation associated with bioreactor cultures. Several commercial microwell systems are available, although their use is limited because of frequent dislocation of microtissues, resulting in aggregation. A more practical system called the microwell/mesh was developed at the QUT that locks microtissues in the microwell with a covering mesh, preventing this issue[4,5]. This study will find out what the optimal chondrogenic growth factor regimen is for hypertrophic CM production in this system, and what the effect of growth factors is on the aggregation of MSCs.

To do so, several moulding methods have been evaluated to generate PDMS pyramidal microwell arrays for cell culture in 6- and 24-well plates. Cells were effectively pelleted in these microwells. MSC microtissue formation and development will be assessed using fluorescent live-cell imaging in an incubator with the Etaluma LS850 microscope. Different chondrogenic protocols will be evaluated by comparing five different growth factor regimens over a 21 day hypoxic culture. DMMB/DNA assay, Safranin-O staining, Collagen type II and X staining are used to visualize and quantify the effect of the chondrogenic protocols on the microtissues. Last of all, this project will explore the scalability of the microwell/mesh system by increasing the surface area using larger cultureware. Altogether, this study aims to optimize the production of hypertrophic cartilage microtissues, which can advance the development of larger, clinically relevant bone-regenerative implants.



Application of plasmatrix in bone augmentation for dental implantistry

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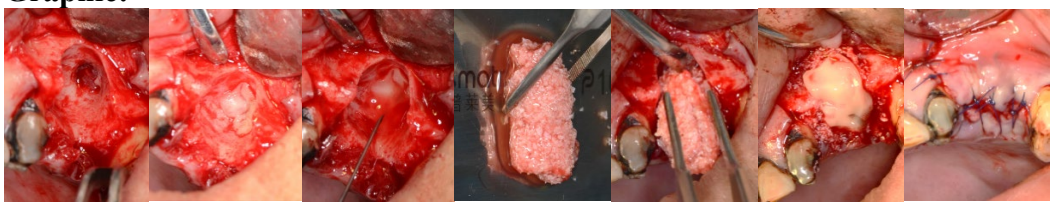
Abstract:
Lack of bone for dental implant placement is a huge challenge for dentist, especially in East Asian population. In order to complete the implant restoration for those patients, the dentist have to perform complicated bone augmentation surgeon, which lead to severe post-operation reactions and complications, including pain, swelling and bruise, also higher financial burden for patients. For both social and economic benefits, our clinic had applied the fourth generation of plasmatrix products developed by Dr. Yufeng Zhang group in the guided bone regeneration GBR approach and realized ideal results in bone augmentation. Briefly, whole blood collected from patients bow vein had been distributed to hydrophilia and hydrophobic tubes respectively and gently centrifuged for 3 minutes. After one time centrifuge, both solid (in hydrophilia tubes) and liquid (in hydrophobic tubes) plasmatrix products could been collected. Then, the solid products were compressed into membrane appearance and mixed with bone substituted materials or autogenous bone granules as bone block to fill into the bone defect sites. The liquid plasmatrix could be used as the glue to enhance the mechanical strength of bone blocks. We had observed that the high quality of bone regeneration during less waiting period, as well as less complains from patients about the adverse reactions. The operation processes had been simplified and the time of operation had also been reduced compared with the traditional GBR.

Graphic:



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Novel fiber-reinforced hydrogel promotes periodontal bone regeneration and its mechanism

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Abstract:
Periodontitis is a common oral disease affecting a large proportion of the population, exhibiting periodontal inflammatory bone destruction and tooth loss. Clinically, the inflammation is suppressed by periodontal treatment, but the inflammation cannot be completely eliminated. The imbalance of the periodontal microenvironment often leads to difficulties in bone regeneration. Therefore, effective therapeutic strategies are needed to modulate the periodontal microenvironment and promote periodontal bone regeneration. In previous studies, we found that Yoda1 bilayer membrane could accelerate the bone regeneration process through the activation of Piezo1 channel, and that 0.04 μmol/L Yoda1 promoted the gene expression of M2-phenotype macrophage markers, consistent with the interleukin 4 (IL-4) effect. However, the Yoda1 released by the fiber membrane is difficult to reach the irregular periodontal bone defect area under the barrier of the bone replacement material. Therefore, in this study, a novel fiber-reinforced hydrogel scaffold material was constructed by preloading Yoda1 with electrospinning technology and mixing a certain proportion of Yoda1-loaded fiber fragments with the hydrogel solution. Biphasic regulation of hydrogel stiffness and bone induction activity by changing the ratio of hydrogel polymer and Yoda1-loaded fiber fragments to achieve material degradation / osteoconversion equilibrium. Moreover, the specific mechanism of novel fiber-reinforced hydrogel to regulate periodontal microenvironment and promote periodontal bone regeneration was explored, so as to provide theoretical basis and experimental basis for optimizing bone replacement materials.

Three-Dimensional Olfactory Ensheathing Cells Promote Directed Neurite Outgrowth: A Promising Approach for Neuronal Regeneration

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Traumatic nerve injuries can lead to permanent loss of motor, sensory, and autonomic functions, with no effective treatments currently available. Olfactory ensheathing cells (OECs) have emerged as strong candidates for neuron regeneration due to their unique capacity to promote nerve repair. In this study, we explored the regenerative potential of 3D-cultured OECs and investigated the underlying molecular mechanisms using RNA sequencing (RNA-Seq). RNA-Seq analysis identified significant gene expression changes linked to axonal growth, cell adhesion, and neurotrophic signalling pathways, as indicated by KEGG pathway results. Co-culturing OEC spheroids with dorsal root ganglia (DRG) revealed that 3D OECs demonstrated an enhanced ability to guide directed neurite growth compared to the absence of OECs. These findings highlight both the physical guidance and molecular mechanisms by which 3D OECs facilitate directed neurite outgrowth, reinforcing their potential as a promising cell-based therapy for treating peripheral nerve injuries and spinal cord repair.

Spheroid culture of DESC for enhanced dentin regeneration

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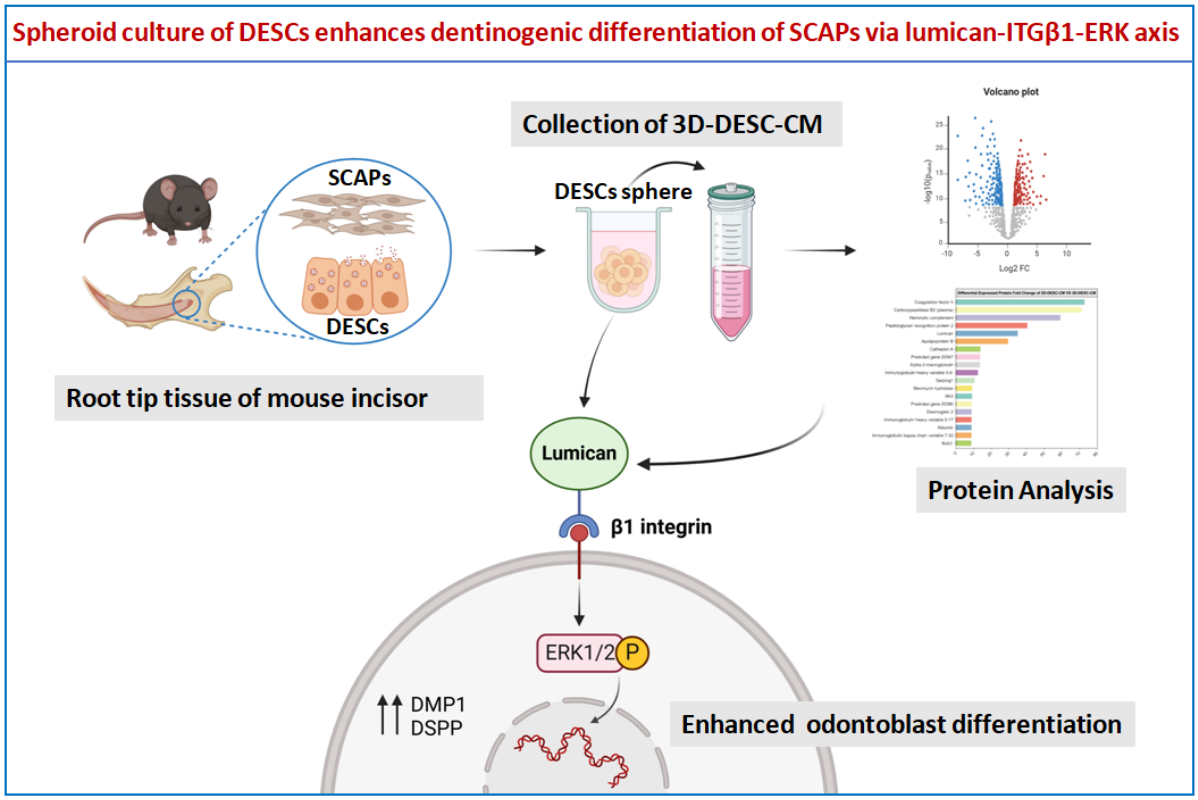
Abstract:

This study investigates the application of spheroid culture for dental epithelial stem cells (DESCs) in the context of dentin regeneration. The pulp-dentin complex, a functional unit composed of dental pulp and dentin, relies heavily on the differentiation of dental papilla stem cells (SCAP) into odontoblasts for its development and repair. During tooth development, ameloblasts release a range of signaling molecules through epithelial-mesenchymal interactions, which stimulate the differentiation of DESCs into odontoblasts. However, the specific signaling molecules involved remain largely unexplored. In this research, we utilized DESCs derived from the root tips of rodent incisors to examine the biological changes that occur under spheroid culture compared to monolayer culture. Through label-free mass spectrometry and bioinformatics analyses, we uncovered, for the first time, the crucial role of Lumican—a key protein significantly secreted by DESCs in spheroid culture—in promoting the odontoblastic differentiation of SCAP. Further in vitro and in vivo assays elucidated the potential mechanisms by which Lumican contributes to the regeneration of the pulp-dentin complex. This study identifies novel molecular targets and mechanisms that could enhance the regeneration of the pulp-dentin complex, paving the way for future therapeutic applications.

Graphical abstract:



Periodontitis-associated gut microbiota impairs the glucose homeostasis of germ-free mice

Li LILI[#], Xu ZHONGHAN[#], Liu HAOTIAN, Du MENG, Wang XINYUE, Jia HUI, Bao JUN, Tong XIN, Yan FUHUA*

Nanjing Stomatological Hospital, Affiliated Hospital of Medical School, Research Institute of Stomatology, Nanjing University, Nanjing, China

Abstract:
Periodontitis is not only the leading cause of tooth loss in adults, but also exacerbate various systemic diseases, especially diabetes. Patients with periodontitis have more than a fourfold increased risk of developing diabetes compared to periodontally healthy individuals. However, the underlying mechanism remains unclear. Our previous research indicated that regulating gut microbiota may mitigate the impact of periodontitis on glucose control. But it is not fully understood whether gut microbiota independently mediates the impact of periodontitis on glucose homeostasis. Therefore, this study aimed to explore whether periodontitis-associated gut microbiota could disrupt glucose homeostasis using germ-free mice. Initially, we confirmed that periodontitis affected blood glucose control, as fasting blood glucose (FBG), HbA1c, and glucose intolerant levels in the periodontitis group were significantly higher than in the control group, accompanied by alterations in gut microbiota. We then transplanted the gut microbiota into germ-free mice. Mice that received gut microbiota from the LIG group (GF-LIG) exhibited significantly higher levels of FBG, serum insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and β-cell function index (HOMA-β) than mice receiving gut microbiota from the CON group (GF-CON). Insulin sensitivity and glucose tolerance were significantly reduced in the GF-LIG group compared to the GF-CON group. Correlation analysis revealed that the relative abundance of the Lachnospiraceae_NK4A136_group, a group of short chain fatty acids (SCFAs) producer, was negative correlated with FBG and HOMA-β. We then supplemented SCFAs-producing bacteria to mice and found that the supplementation significantly reduced the FBG, HbA1c levels in mice with periodontitis. In conclusion, we suggest that gut microbiota mediates the effect of periodontitis on glucose homeostasis. The reduction of the Lachnospiraceae_NK4A136_group and SCFAs may play pivotal roles in this process.

2024 International Conference for MedTech & Regenerative Medicine and Dentistry
4 - 7 December 2024 | Gold Coast, Queensland, Australia
Rapid Oral Number: 21

"Gingival Soft Tissue Integrative" Lithium Disilicate Glass-Ceramics with High Mechanical Properties and Sustained-Release Lithium Ions

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Introduction:

Aiming at the clinical issues that "hard" all-ceramic materials are difficult to ideally integrate with "soft" tissue, we applied modified ion-exchange technology to "activate" the lithium disilicate glass-ceramics, via releasing lithium ions to promote multi-reparative functions of gingival fibroblasts. In addition, this strategy can also improve its mechanical properties, thus developing "Gingival soft tissue integrative" lithium disilicate glass-ceramics with high mechanical properties and sustained-release lithium ions.

Methodology:

Lithium disilicate glass-ceramics were prepared and added with a mixed salt of 98 wt.% KNO_3 and 2 wt.% NaOH for ion-exchange. The Physicochemical properties were characterized by SEM, XRD, XPS and EDS. The fracture strength and Vickers hardness were characterized by universal mechanical tester and digital micro-hardness tester. The lithium release was measured by ICP-OES. The multi-reparative functions of gingival fibroblasts were measured by CCK-8, RT-qPCR, IF staining and cell function assays.

Results:

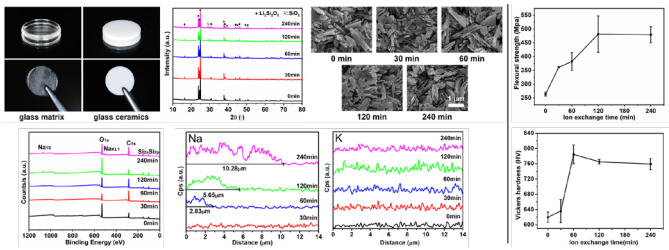


Fig1. The preparation of modified lithium disilicate glass-ceramics and the physicochemical properties.

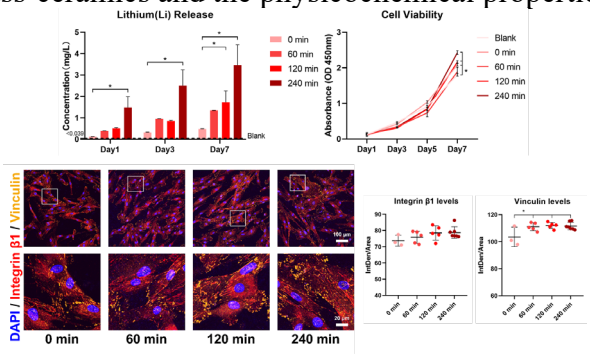


Fig2. The lithium ions release and the cell viability and cell adhesion function of gingival fibroblasts.

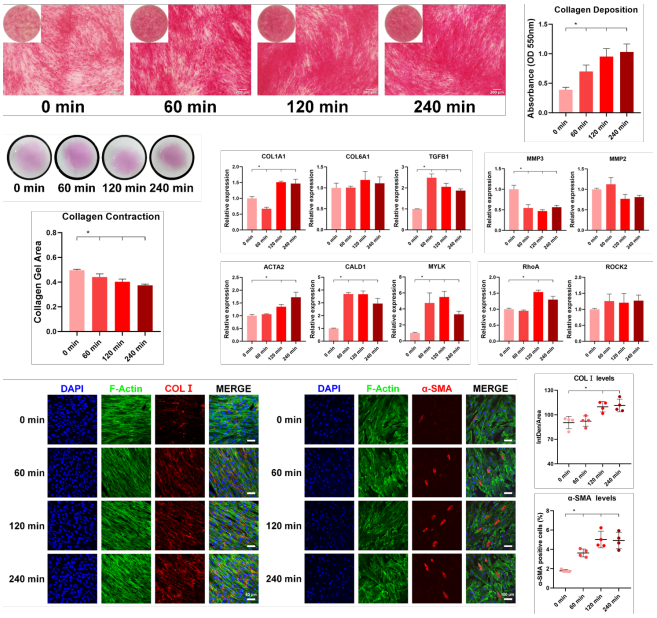
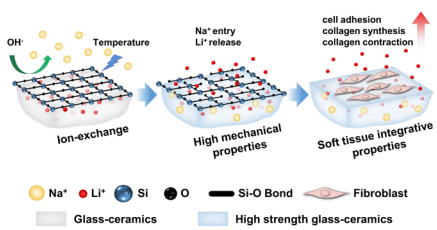


Fig3. The extracellular matrix organization and collagen contraction function of fibroblasts on modified lithium disilicate glass-ceramics.

Conclusions:



This successful case in simultaneous improvement of mechanical properties and biological activity prove the feasibility of developing "soft tissue integrative" all-ceramic materials with high mechanical properties, which provide a new direction for future development of advanced all-ceramic soft tissue materials.

Intra-articular Metformin Delivery of ROS Responsive Mesoporous Nanomotors Alleviate Osteoarthritis Pain and Cartilage Damage

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Abstract:

Introduction: The most common chronic and crippling joint disease, osteoarthritis (OA) imposes significant financial and medical burdens on sufferers. The quick clearance of intra-articular administration contributed to the failure of pain management in OA patients. Nanomotors represent a promising class of drug delivery carriers, capable of converting surrounding chemical energy into mechanical power, enabling autonomous movement, offering significant potential for enhancing drug penetration across cellular and tissue barriers.

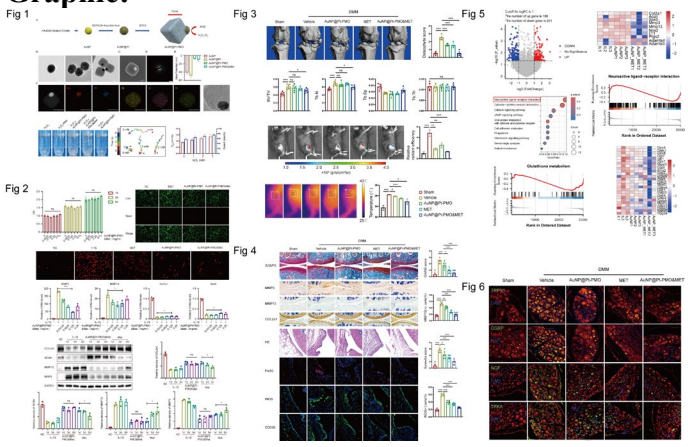
Objective: Herein, a dual-source-driven AuNP@Pt-PMO&MET Janus nanomotor (NM@MET) is prepared by an interfacial energy-mediated anisotropic growth strategy for synergistic osteoarthritis therapy. The generation of oxygen in the process of reactive oxygen species (ROS) decomposition catalyzed by Pt ensures the chemotactic and anti-inflammatory effects of the nanomotors. It has been well-evidenced that metformin (MET) has therapeutic effects on osteoarthritis. This study aims to investigate the extension of the effects and mechanism of metformin on OA by nanomotors.

Method: Mice were given intra-articular injection of nanomotors with or without metformin following destabilize the medial meniscus (DMM) surgery. After behavioral assessment, knee samples and dorsal root ganglion (DRG) were then collected for histological analysis and CT scanning. Primary mouse chondrocytes and bone marrow-derived macrophages (BMDMs) were cultured in vitro to detect the effects and mechanism of nanomotors and metformin.

Result: After receiving nanomotor treatment, DMM mice showed reduced cartilage degeneration, alleviated synovitis, decreased osteophyte formation, lower OARSI scores and reduced pain. NM@MET inhibited sensory neurite expansion in synovial tissues and DRG. Nanomotor enhances cartilage penetration and prolonged the intra-articular residence time of metformin. RNA sequencing analysis showed NM@MET regulated Glutathione Metabolic signaling pathway, which regulated ROS production.

Conclusion: These findings provide a drug delivery strategy that addresses both pain symptoms and cartilage loss in OA by dual-drive Janus nanomotors based on dual noble metal nanozymes.

Graphic:



Multi-quantifying maxillofacial traits via a demographic parity-based AI model

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Introduction:

The multi-quantification of the distinct individualized maxillofacial traits, that is, quantifying multiple indices, is vital for diagnosis, decision-making, and prognosis of the maxillofacial surgery. While the discrete and demographic-disproportionate distributions of the multiple indices restrict the generalization ability of AI-based automatic analysis, this study presents an approach for demographic-parity strategy-based multi-quantification AI model with greater model generalization ability.

Methodology:

The aesthetic-concerning maxillary alveolar basal bone which require quantifying a total of nine indices from length and width dimensional, this study develops a deep learning model composed of backbone and multiple regression heads with fully shared parameters to intelligently predict these quantitative metrics. The sensitive attribute was identified and the dataset was subdivided to train new sub-models. Then sub-models trained from respective subsets were ensembled for final generalization.

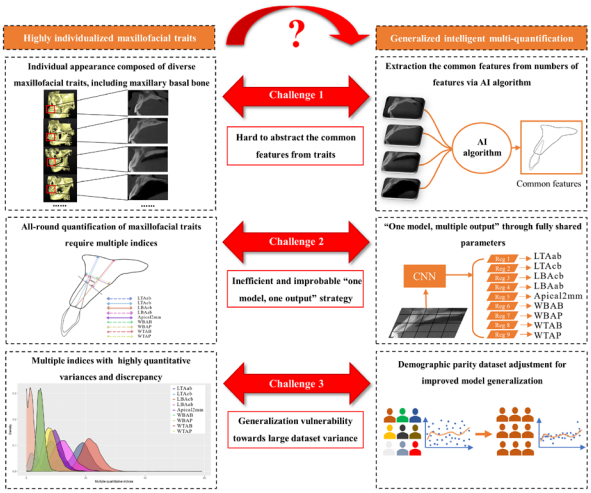

Fig. 1. The schematic of the challenges in highly variable maxillofacial traits versus generalized intelligent multi-quantifications.

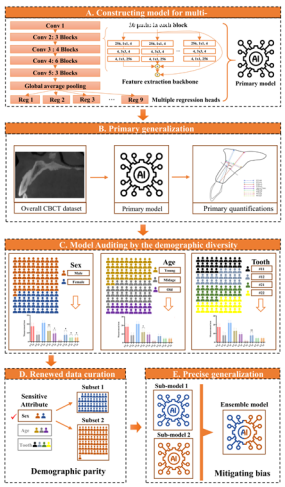

Fig. 2. The schematic of the workflow of the deep learning-based multi-quantifications of the variable maxillary basal bone via the demographic parity-based strategy.

Conclusion:

This work validates that the demographic parity strategy enables the AI algorithm with greater model generalization ability, even for the highly variable traits, which benefits for the appearance-concerning maxillofacial surgery.

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CMC/ACP - TLR4 Interaction Influenced the Immunomodulation of Biomineralized Collagen Matrix

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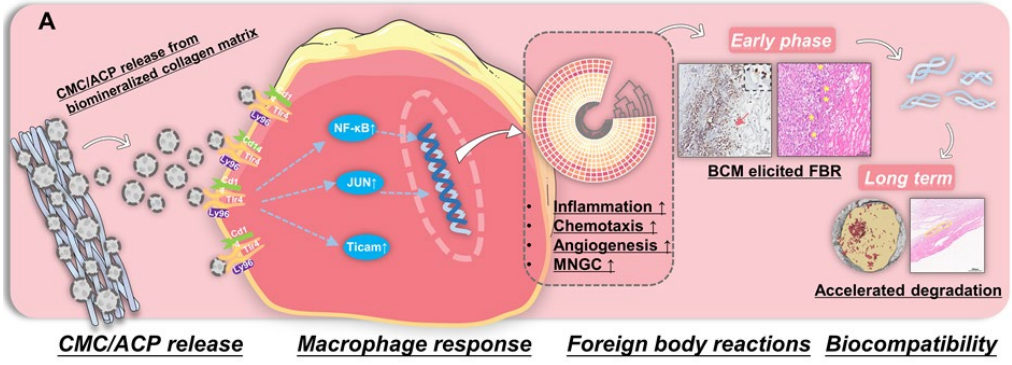
Abstract:
Objectives: Calcium phosphate-based biomineralized materials have broad application prospects in oral bone regeneration because of their unique intra- and extra-fibrillar mineralization structures close to the natural bone. Their biocompatibility and foreign body reactions have drawn attention these years. Based on the effect of immune microenvironment optimization on biocompatibility, it is of great importance to clarify the immunomodulation property of biomineralized materials and unveil the related mechanism.
Methods: This study has prepared the collagen matrix (CM) and carboxymethyl chitosan (CMC)-mediated biomineralized collagen matrix (BCM), then characterized the chemical composition, morphology, and cytotoxicity of CM and BCM. Their immunomodulation on macrophages was explored through transcriptomic analysis and verified *in vitro*. Meanwhile, the animal model was established to investigate the immunomodulatory properties and biocompatibility of CM and BCM *in vivo*. The key immunomodulation factor of BCM was clarified by screening the physical and chemical properties, adsorption factors, and release effects. The activated signal pathways were enriched through transcriptomic analysis, measured by Reactome enrichment analysis, and verified *in vitro*.
Results: Both the CM and BCM contained the chemical characteristics of collagen with no cytotoxicity ($p < 0.05$), and the BCM achieved the intrafibrillar and extrafibrillar deposition of minerals. The transcriptomic analysis showed the BCM-induced inflammation and foreign body reactions ($p < 0.01$). The semi-quantitative analysis showed the BCM group had more inflammatory cells and multinuclear giant cells and accelerated degradation rate than the CM group ($p < 0.0001$). Later, the key immunomodulation factor as carboxymethyl chitosan/amorphous calcium phosphate (CMC/ACP) nanocomplex and activated TLR4-MAPK/NF-κB signaling pathway were clarified.
Conclusions: The BCM activated the TLR4-MAPK/NF-κB signaling pathway by releasing the CMC/ACP nanocomplex, causing the early stage of inflammation and cascade foreign body reactions. Controlling the release of CMC/ACP nanocomplex to accord with the temporal regenerative demands is key to developing advanced calcium phosphate-based biomineralized materials.

Graphic:



Two-dimensional ferroelectric materials on the applications of next-generation electronics

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Abstract:
Effective manipulation for physical properties of nano-materials is fundamental for the development of next-generation electronic devices and has attracted numerous research interests. Two-dimensional (2D) ferroelectrics (FE) stand out as excellent candidates due to the promising properties of high density of storage and low-energy-consuming, which are expected to play an essential role in developing functional nano-scale electronic devices. In this presentation, by using the state-of-art density functional theory (DFT) and micromagnetic simulations, we systematically studied the impacts of stacking engineering and ferroelectric polarization on the physical properties of 2D materials, including GeSe/SnS heterobilayers, bilayer NiI_2 and monolayer $CuCrP_2Te_6$. The ultimate aim of this presentation is to manipulate the physical properties of 2D functional materials and explore the applications in electronics. The obtained knowledge is expected to guide and inspire experimental research and promote the development of nano-scale FE electronics.

Versatile hybrid nanoplatforms for treating periodontitis with chemical/photothermal therapy and reactive oxygen species scavenging

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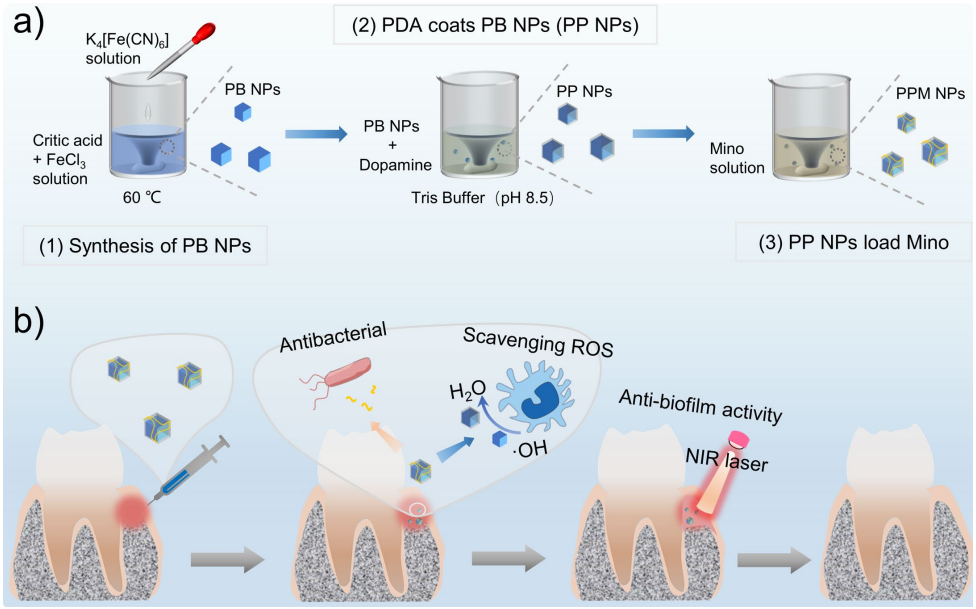
Abstract:

Given the limitations of clinical curettage for periodontitis, the thorough removal of dental plaque at deep periodontal pockets and periodontal tissue repair require improvement with the assistance of appropriate medical therapy. Despite the significant developments of various local drug delivery systems (LDDSs) for adjuvant periodontitis therapy, several issues exist, such as the relatively low anti-biofilm effect and the tissue damage caused by excessive reactive oxygen species (ROS). To address the issues, we fabricated the versatile nanoplatforms (PPM NPs) via coating polydopamine (PDA) on the surface of monodispersed Prussian blue nanoparticles (PB NPs) through the facile yet efficient self-polymerization of dopamine (PP NPs), and then loading minocycline (Mino). Notedly, these integrative nanocomposites-based PB NPs as photothermal agents enhanced the therapeutic effect of plaque biofilms in vitro utilizing the antibacterial photothermal therapy (PTT) under irradiation of NIR laser. Further, the designed nanocomposites efficiently scavenged ROS over oxidative stress Raw267.4 cells and human periodontal ligament cells, attributing to the enzyme-like activity of PB nanozymes and the reducibility of catechol in PDA. In vitro and in vivo consequences demonstrate the significantly augmented antibacterial and anti-inflammatory effects from the live/dead staining of biofilms and western blot results of inflammatory factors compared with free Mino solution in periodontitis. Our fabricated nanoplatforms-based PB NPs conveniently modified with PDA not only significantly improved the antibacterial effect via the combinational therapies but also efficiently scavenged cellular ROS utilizing the enzyme-like activity of nanozymes contributing to the treatment of periodontitis.

Graphic:



Scheme 1. Schematic illustrating of a) the step-by-step preparation process of the designed PPM NPs and b) the working mechanisms for periodontitis therapy.

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4 - 7 December 2024 | Gold Coast, Queensland, Australia
Rapid Oral Number: 27

Cell-free immunomodulatory biomaterials mediated in situ periodontal multi-tissue regeneration and their immunopathophysiological processes

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[1]Hospital of Stomatology, Guanghua School of Stomatology, Sun Yat-sen University, and Guangdong Provincial Key Laboratory of Stomatology, Guangzhou,Guangdong, China

Introduction:

Achieving cell-free biomaterial-induced multi-tissue regeneration is challenging; however, advanced immunomodulatory biomaterials offer a promising approach. Understanding immunopathophysiological mechanisms is crucial for effective immunomodulation. This study demonstrated that immune response critically regulates the regeneration outcome when immunoregulatory cell-free biomaterials are implanted into periodontal defects.

Methology:

This study employed porcine bone hydroxyapatite (PHA) to adsorb LPS/IFNγ and IL4, creating biomaterials with varying immunomodulatory capabilities. These were implanted into a rat periodontal defect model, and the acute inflammatory response, early tissue repair, and subsequent periodontal regeneration with immune-pathophysiological changes were assessed using histological staining and micro-CT.

Results:

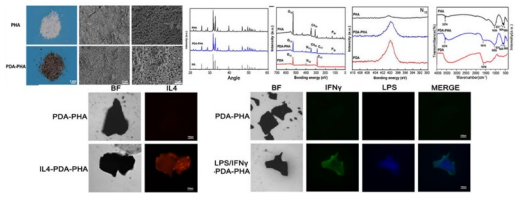


Fig1. PHA loaded with macrophage polarization stimuli factors constructs a cell-free immunomodulatory biomaterial.

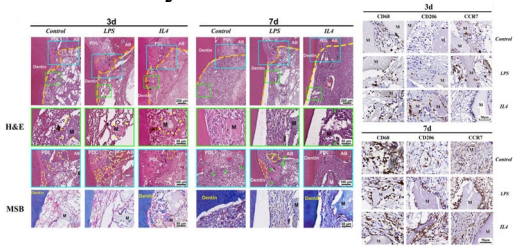


Fig2. The acute injury response and initial multi-tissue repair process following the implantation of immunomodulatory biomaterials.

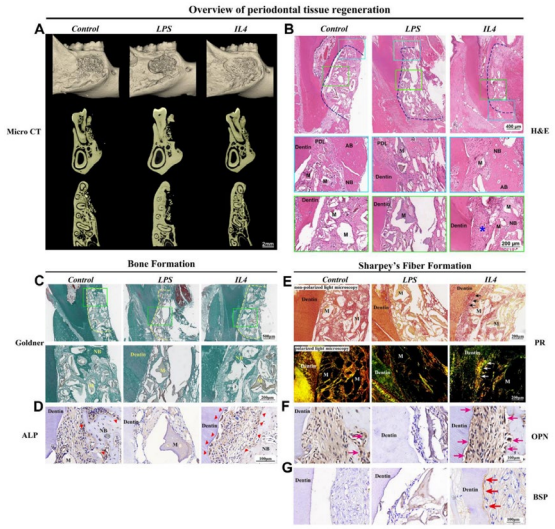
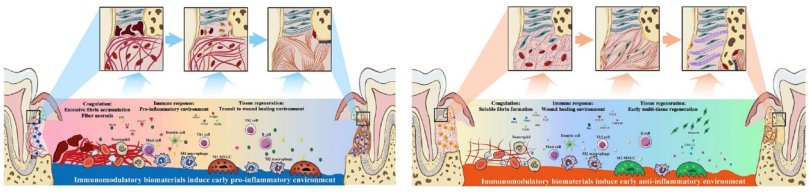


Fig3. The regenerative status of periodontal multi-tissues at week 4 under various immunological microenvironments.

Conclusions:



The multi-tissue regenerative outcome is intricately modulated by immune responses, and biomaterials with anti-inflammatory features can steer the immunopathophysiological processes to enhance periodontal tissue regeneration, including the periodontal ligament, cementum, and alveolar bone.

Comparative Analysis of Ruptured and Unruptured Intracranial Aneurysms Using Computational Fluid Dynamics

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Abstract:

Introduction: Intracranial aneurysms (IAs) are pathological dilations in the walls of cerebral arteries, posing significant health risks due to their potential to rupture and cause subarachnoid hemorrhage (SAH), a condition associated with high mortality and long-term disability rates. This study aims to determine the hemodynamic parameters of intracranial aneurysms using three-dimensional reconstruction via computational fluid dynamics (CFD) simulations. By comparing these parameters between ruptured and unruptured aneurysms, the research seeks to elucidate factors contributing to rupture risk. **Methods:** We utilized publicly available three-dimensional models of intracranial aneurysms from a cohort of 573 patients (Juchler et al., 2022) to conduct CFD simulations. A strategic sampling approach ensured a balanced representation of ruptured and unruptured aneurysms. These simulations facilitated the analysis of wall pressure and wall shear stress within the aneurysms. Traditional data analysis was complemented by advanced deep learning techniques, including point cloud and graph neural networks, to analyze the correlation between hemodynamic parameters and rupture status. **Results & Conclusion:** Preliminary analyses have identified differences in hemodynamic parameters between ruptured and non-ruptured aneurysms, indicating their potential utility in assessing rupture risk. Future research will integrate both hemodynamic and morphological parameters, such as aneurysm diameter, aspect ratio, and irregularity, to enhance understanding of rupture risk. We plan to employ machine learning techniques to fuse these multimodal feature data, utilizing methods such as neural networks, to improve predictive accuracy for rupture risk assessment.

References:

Juchler, N., Schilling, S., Bijlenga, P., Kurtcuoglu, V., & Hirsch, S. (2022). Shape trumps size: image-based morphological analysis reveals that the 3D shape discriminates intracranial aneurysm disease status better than aneurysm size. *Frontiers in Neurology*, *13*, 809391.

Injectable Ultrasound-Powered Bone-Adhesive Hydrogel for Electrically Accelerated Bone Defect Healing

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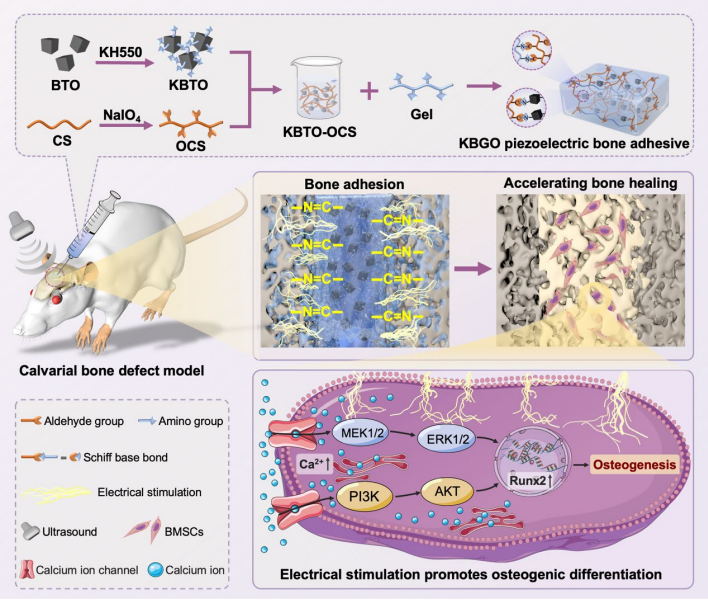
Abstract:
The treatment of critical-size bone defects with irregular shapes remains a significant challenge in the field of orthopedics. Piezoelectric materials, which mimic the mechano-electric response behavior of bone tissue, have been w extensively studied in bone regeneration research. However, these materials such as piezoelectric ceramics, piezoelectric films, and piezoelectric coatings are often pre-formed into fixed shapes, which present several limitations, including difficulty in shaping, a lack of adaptability to the contours of bone defects, and limited plasticity. Therefore, there is a pressing need to develop bone implants that are adaptable to complex bone morphologies, possess bone-adhesive properties, and exhibit potent osteogenic capabilities. In this study, we introduce a shape-adaptive, highly bone-adhesive, ultrasound-powered injectable nanocomposite hydrogel. This novel hydrogel is synthesized through dynamic covalent crosslinking of amino-modified piezoelectric nanoparticles and biopolymer hydrogel networks, designed to electrically accelerate bone healing. The interaction between the amino-modified piezoelectric nanoparticles and the bio-adhesive hydrogel network significantly enhances the bone adhesive strength of the hydrogel, exhibiting an approximately three-fold increase. In response to ultrasound radiation, the nanocomposite hydrogel generates a controllable electrical output (-41.16 to 61.82 mV), which facilitates osteogenic differentiation of bone mesenchymal stem cells by increasing calcium ion influx and up-regulating the PI3K/AKT and MEK/ERK signaling pathways. Additionally, *in vivo* studies using a rat critical-size calvarial defect model demonstrated accelerated bone healing with this bone glue. Overall, this study presents a novel wireless, ultrasound-powered, bone-adhesive nanocomposite hydrogel that broadens the therapeutic potential for treating irregularly shaped bone defects.

Graphic:



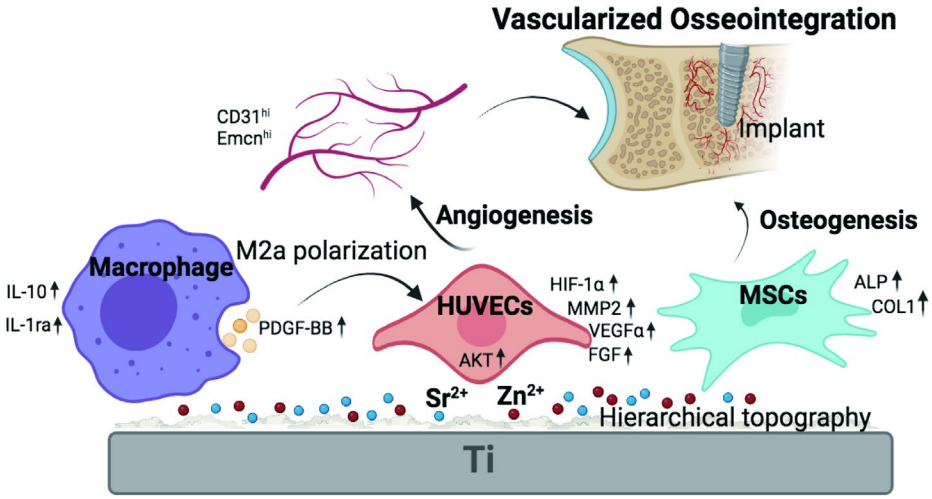
Comprehensive process optimization for rapidly vascularized osseointegration by dual ions effects

Wei Lu[1], Fuming He[2]
[1]Department of Periodontics, Stomatology Hospital, School of Stomatology, Zhejiang University School of Medicine, Clinical Research Center for Oral Diseases of Zhejiang Province, Key Laboratory of Oral Biomedical Research of Zhejiang Province, Cancer Center of Zhejiang University, Hangzhou 310000, China

[2]Department of Prosthodontics, Stomatology Hospital, School of Stomatology, Zhejiang University School of Medicine, Hangzhou 310000, China

Abstract:
Osseointegration involves a series of sophisticated physiological processes including osteoimmune responses, angiogenesis, and osteogenesis. However, a comprehensive process optimization to tackle the dilemma of the prolonged implant osseointegration still remains a challenge. In this study, we designed a micro/nanoscaled hierarchical topography and simultaneously incorporated strontium ions and zinc ions onto titanium surface (SLA-Sr/Zn). SLA-Sr/Zn exhibited potent pro-angiogenic capacity in vitro by expressing essential angiogenic genes and activating Akt/HIF-1α signaling pathway of human umbilical vein endothelial cells. Meanwhile, SLA- Sr/Zn exerted robust osteogenic potential by facilitating bone mesenchymal stem cells osteogenic differentiation. Furthermore, the continuous release of dual ions orchestrated a favorable osteoimmune microenvironment by modulating macrophage polarization towards M2a phenotype and up-regulated expression of platelet-derived growth factor. In vivo study corroborated the excellent efficacy of SLA-Sr/Zn implant on promoting vascularized osseointegration by augmenting type H vessel generation. Collectively, the distinct SLA-Sr/Zn titanium implant surface exerted versatile biological functions in angiogenesis, osteogenesis and osteoim-munomodulation, rendering its therapeutic potential for rapidly vascularized osseointegration.

Graphic:



Verteporfin-loaded exosomes ameliorate chymase deficiency-induced non-syndromic hereditary gingival fibromatosis by YAP/TAZ inhibition

Xin Chen[1], Yuqing Guo[1], Yangqiao Qing[1], Yang Cao[1], Chen Zhou[1], Weicai Wang[1]

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Abstract:
Hereditary gingival fibromatosis (HGF) is an inherited disease characterized by progressive fibrous hyperplasia of gingival tissues with significant genetic heterogeneity. However, the mechanisms underlying HGF are not yet fully understood. Here, based on a family pedigree with non-syndromic HGF, we reported a novel pathological mutation (c.114C>A) in the *CHYMASE* gene outside HGF-related loci. The *CHYMASE* variant decreased chymase expression in the patient's gingival fibroblasts, thus directly leading to extracellular matrix deposition via YAP/TAZ activation. Moreover, the specific YAP inhibitor verteporfin can abrogate chymase deficiency-induced extracellular matrix overproduction of gingival fibroblasts, suggesting its therapeutic potential against non-syndromic HGF. To improve solubility and in-vivo efficacy of verteporfin, we developed a HEK-293T exosome-based delivery platform for verteporfin. In the mouse model, verteporfin-loaded exosomes were shown to ameliorate chymase deficiency-induced tissue fibrosis. Our findings highlight the contributory role of chymase deficiency in non-syndromic HGF through YAP/TAZ pathway. Verteporfin loaded-exosomes are proposed as promising therapeutic agents to treat non-syndromic HGF.

Retinoic Acid Induces Dysfunction of Human Embryonic Palatal Mesenchymal Cells in Cleft Palate via Lhx6-mediated Mitophagy Suppression

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[1] Hospital of Stomatology, Guanghua School of Stomatology, Guangdong Provincial Key Laboratory of Stomatology, Sun Yat-sen University, Guangzhou, Guangdong, China

Abstract:
Retinoic acid (RA) is a nutrient necessary for normal embryonic development, but excessive administration of RA during the formation of the embryonic palate will lead to cleft palate in neonatal animals. Preliminary studies by our group have shown that RA leads to a decrease in the function of proliferation and migration of human embryonic palatal mesenchymal (HEPM) cells. In addition, Lhx6 is a vital transcription factor regulating embryonic development and cell fate determination and is expressed in the exogenous mesenchyme of the maxilla and mandible. In this study, we for the first time revealed that RA inhibited the proliferation and migration of HEPM by downregulating Lhx6 expression. Moreover, the cell mitochondria were characterized by abnormal mitochondrial number and structure, reduced energy production and increased levels of mitochondrial reactive oxygen species. On the other hand, the aberrant mitochondrial function, proliferation, and migration observed in RA-induced HEPM cells were ameliorated by overexpressing Lhx6. Mechanistically, Lhx6 is essential for mitochondrial homeostasis by modulating PINK1/Parkin-mediated mitophagy, thereby activating the MAPK signaling pathways. Downregulation of Lhx6 by RA transcriptionally disturbs the mitochondrial homeostasis, which in turn leads to the proliferation and migration defect in HEPM cells, ultimately causing the cleft palate. This study contributed a fresh perspective on the mechanism of RA-related craniomaxillofacial malformations, and Lhx6 is expected to be a gene target for cleft palate therapy.

Research on antibacterial treatment of periodontitis by the magnetic Fe_3O_4@PDA-Ag nanoparticles

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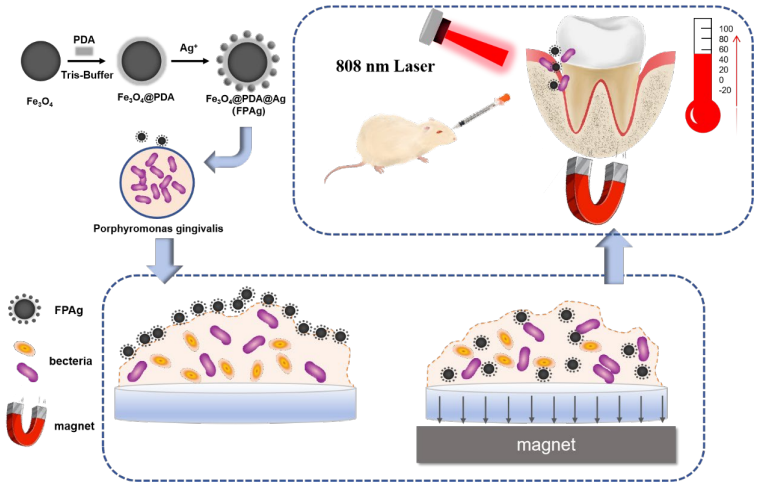
Abstract:

The key challenge in the treatment of periodontitis is the removal of plaque biofilm, and antibiotics routinely used in clinical treatment are difficult to penetrate plaque. Meanwhile, the misuse of antibiotics has become a concern. In order to solve these problems, we prepared multifunctional nano platform FPAg NPs by coating the polydopamine (PDA) formed by self-polymerization of dopamine (DA NPs) on the surface of ferric oxide nanoparticles (Fe_3O_4 NPs) and then loading nano silver (Ag), which can penetrate biofilm by magnetic field. Nano silver has a broad spectrum antibacterial effect, and as a photothermal agent, FP NP can enhance bactericidal effect by antimicrobial photothermal therapy (PTT). Scanning electron microscope (SEM), transmission electron microscope (TEM), mapping elemental analysis, laser particle sizer, magnetic targeting experiment and photothermal experiment were used to characterize their physical, chemical ,magnetic targeting and photothermal properties. Colony-forming units (CFU), MTT and live/dead staining of bacteria were used to show the good antibacterial properties of FPAg NPs on suspended bacteria and biofilm. The good physical penetration ability of FPAg NPs on biofilm was showed by laser confocal microscopy with the application of magnetic field. Through testing on rat models of periodontitis, the results of various histological sections, real-time quantitative PCR detecting system (q-PCR) and western blotting (WB) showed that FPAg NPs had good antibacterial effect in vivo, and the periodontal inflammation in rats was controlled. In this study, FPAg NPs was successfully prepared, and the three mechanisms of magnetic targeting of Fe_3O_4 NPs, photothermal action of Fe_3O_4 and PDA, and sterilization effect of nano silver were combined. This antibacterial agent has good biocompatibility and antibacterial performance, and can effectively treat periodontal inflammation in rats, providing reference for clinical treatment of periodontitis.

Graphic:



Summary of Ferriferrous oxide@polydopamine-silver (FPAg) experiments: including material synthesis, in vitro anti-suspended bacteria and anti-bacterial biofilm experiments , photothermal experiments and in vivo experiments of periodontitis caused by bacterial infection in rat models.

Highly efficient self-assembling tenogenic organoids boost tendon regeneration

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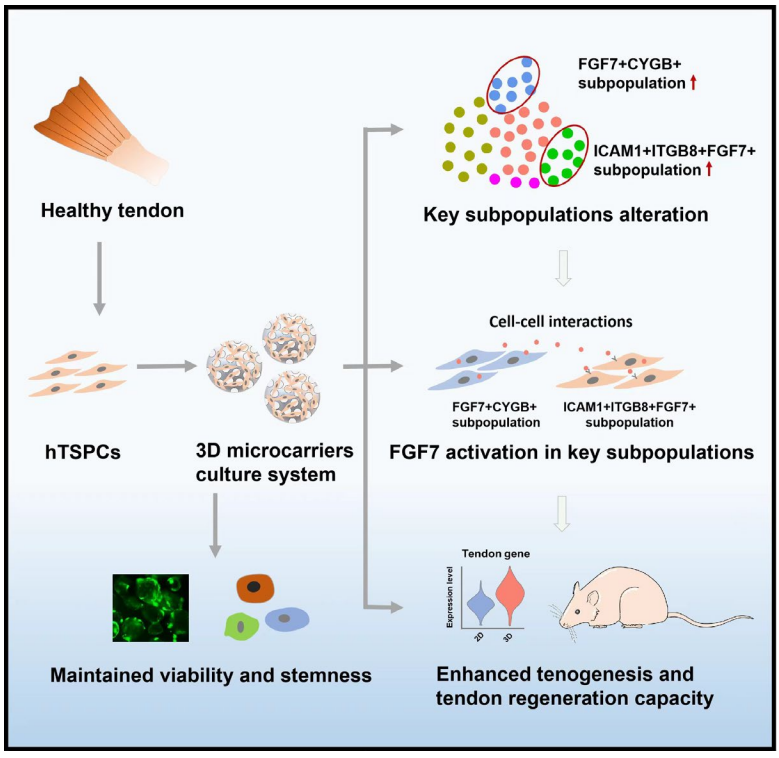
[1]Dr. Li Dak Sum & Yip Yio Chin Center for Stem Cell and Regenerative Medicine, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, China

Abstract:
Engineered organ models from stem cells show great promise in regenerative medicine. Traditional 2D cell cultures fail to mimic the in vivo environment, while 3D cell culture technology offers a more realistic microenvironment. A 3D multi-lacunar gelatin microsphere carrier, rich in collagen like the natural ECM of human tendons, provides mechanical support and enhances cell-ECM interactions, triggering positive differentiation signals in human tendon-derived stem/progenitor cells (hTSPCs). Using scRNA seq and functional analysis, we found key cell subpopulations and downstream signaling pathways essential for tendon differentiation and regeneration in 3D environments. However, achieving true human tendon organoids requires excellent stem cell proliferation ability in vitro. By decoding the cytokine pathway that promotes hTSPC proliferation and ECM enrichment, we established a culture system that maintains stem cell proliferation and facilitates ECM connection. This strategy produces over 3 cm tendon microtissue, enhances stem cell proliferation by 30 times, retains high youth characteristics, and significantly improves injured tendons' mechanical properties and collagen microstructure after implantation.This research not only offers new possibilities for the treatment of tendon injuries but also provides significant insights and guidance for constructing other types of organ models using stem cells and 3D cell culture technology

Graphic:



Nanotopographic micro-nano forces finely tune the conformation of macrophage mechanosensitive membrane protein integrin β2 to manipulate inflammatory responses

Yong AO[1], Yuanlong Guo[1], Chen Ye[1], Ruidi Xia[1], Zetao Chen[1*]

[1]Hospital of Stomatology, Guanghua School of Stomatology, Sun Yat-sen University, and Guangdong Provincial Key Laboratory of Stomatology, Guangzhou, Guangdong, China

Introduction:
Mechanosensitive membrane protein integrin β2 is deeply involved in inflammatory responses. Finely tuning conformation of integrin β2 and its consequent activity holds great potential in precisely controlling inflammatory responses. This study employed three specially designed low-aspect-ratio nanotopographic structures to generate micro-nano forces to manipulate conformation change of integrin β2, thereby regulating macrophage inflammatory responses.

Methology:
Steered molecular dynamics simulation was first applied to reveal the required force for conformational activation of integrinβ2. Replica molding was used to fabricate three low-aspect-ratio nanotopographic structures. Finite element analysis was performed to analyze the generation of nanotopographic micro-nano forces. Bioinformatic analysis and experimental verification were carried out to unveil the underlying mechanotransduction pathway.

Results:

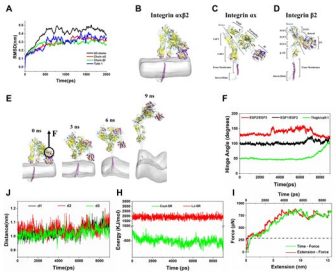


Fig1. The effect of direct interactions between micro-nano forces and integrin $\alpha x\beta_2$.

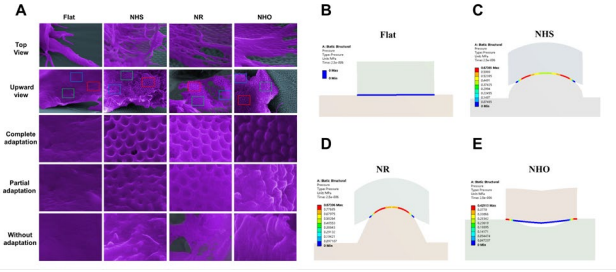


Fig3. Finite element analysis reveals the contact pressure on cell membranes after cell adhesion.

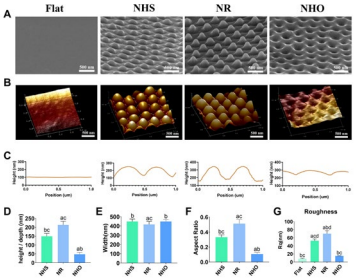


Fig2. Fabrication and characterization of three low-aspect-ratio nanotopographic structures.

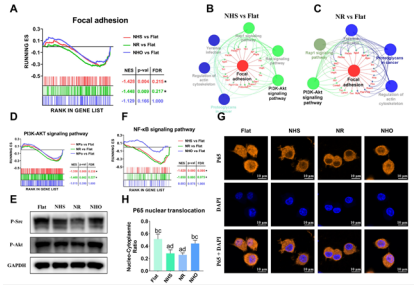
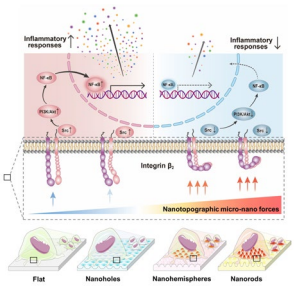


Fig4. The probable signaling pathway underlying mechano-regulation of inflammatory responses by nano-structures

Conclusions



Compared to the nanoholes, the nanorod and nanohemisphere surfaces induce bigger contact pressures, which inhibit conformational extension of integrin$\alpha x\beta_2$ and its consequent activity. This result in down-regulated focal adhesion activity and the downstream PI3K-Akt signaling pathway, ultimately reducing NF-κB signaling and macrophage inflammatory responses.

Sulfated polysaccharide directs therapeutic angiogenesis via endogenous VEGF secretion of macrophages

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Abstract:
Notwithstanding the remarkable progress in the clinical treatment of ischemic disease, proangiogenic drugs mostly suffer from their abnormal angiogenesis and potential cancer risk, and currently, no off-the-shelf biomaterials can efficiently induce angiogenesis. Here, we reported that a semisynthetic sulfated chitosan (SCS) readily engaged anti-inflammatory macrophages and increased its secretion of endogenous vascular endothelial growth factor (VEGF) to induce angiogenesis in ischemia via a VEGF-VEGFR2 signaling pathway. The depletion of host macrophages abrogated VEGF secretion and vascularization in implants, and the inhibition of VEGF or VEGFR2 signaling also disrupted the macrophage-associated angiogenesis. In addition, in a macrophage-inhibited mouse model, SCS efficiently helped to recover the endogenous levels of VEGF and the number of $CD31^{hi}Emcn^{hi}$ vessels in ischemia. Thus, both sulfated group and pentasaccharide sequence in SCS played an important role in directing the therapeutic angiogenesis, indicating that this highly bioactive biomaterial can be harnessed to treat ischemic disease.

References

1. Yuanman Yu, Shuang Wang, Xinye Chen, Zehua Gao, Kai Dai, Jing Wang*, Changsheng Liu*. Sulfated oligosaccharide activates endothelial Notch for inducing macrophage-associated arteriogenesis to treat ischemic diseases. *PNAS*, 2023, 120(46), e2307480120.

2. Yuanman Yu, Kai Dai, Zehua Gao, Wei Tang, Tong Shen, Yuan Yuan, Jing Wang*, Changsheng Liu*. Sulfated polysaccharide directs therapeutic angiogenesis via endogenous VEGF secretion of macrophages. *Science Advances*, 2021, 7(7), eabd8217.

Spatial transcriptome combined with an engineered atherosclerotic plaque model reveal strain-mediated death of macrophage

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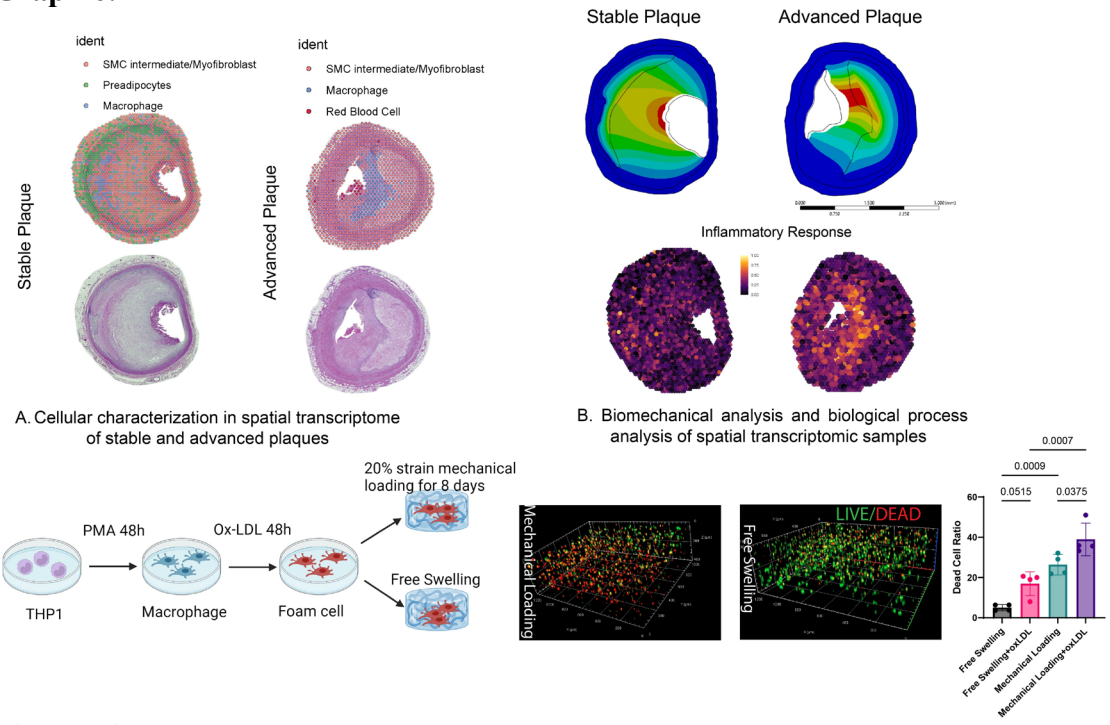
Abstract:

Introduction: Atherosclerosis is the primary cause of cardiovascular events. Oxidized LDL (oxLDL) plays a crucial role in atherosclerotic plaque formation by promoting inflammation, foam cell formation, contributing to plaque progression and instability. Radial wall strain (RWS) has been identified as a potential marker for predicting cardiovascular events. The impact of radial strain on plaque development and its link to key risk factors, such as inflammatory cell infiltration and cell death, remains under investigation. **Aim:** Construct a 3D engineered plaque model to understand how radial strain influences cellular behavior in the plaque. **Method:** Public spatial transcriptomics data of advanced and stable plaque was reanalyzed using SCTransform. Biomechanical characters of the tissue sections were then analyzed using Ansys. Next, a 3D plaque model was established with GelMA and oxLDL. A compressive strain of 20% for 2 hours at 1 Hz was applied using the custom bioreactor for 8 days. Finally, live/dead staining and flow cytometry were used to assess the proportion of dead cells. **Result**: The advanced plaque was observed with increased infiltration of macrophages. It also exhibited greater deformation and stronger inflammatory responses. In the 3D engineered plaque model, mechanical loading resulted in approximately a 20% increase in macrophage death compared to the group without mechanical stimulation. **Conclusion**: Our study indicated that cyclic compression of the plaque may be a significant factor contributing to macrophage death in atherosclerosis.

Graphic:



A. Cellular characterization in spatial transcriptome of stable and advanced plaques

B. Biomechanical analysis and biological process analysis of spatial transcriptomic samples

C. Flowchart for establishing a 3D engineered plaque model

D. Live/Dead staining and flow cytometry analysis of dead macrophages

Janus Hydrogel Microrobots Loaded with Dual Bioactive Ions for the Regeneration of Gradients in Tendon-bone Interface

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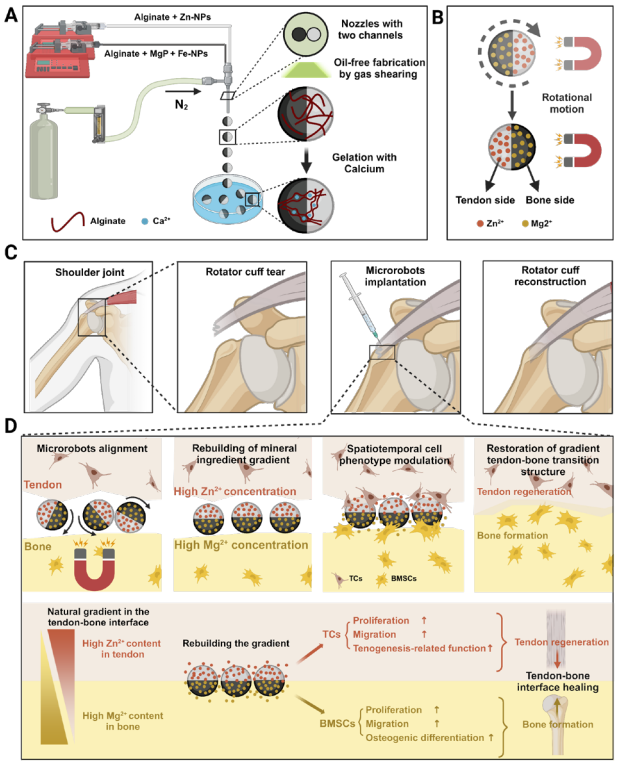
Abstract:
Regenerating the natural gradients in composition, cell phenotype and structure of tendon-bone interface (TBI) poses a significant challenge in reconstruction of rotator cuff tear (RCT). In this study, we developed hydrogel microspheres with Janus design using a novel biofriendly gas-shearing microfluidic platform to address this challenge. These alginate-based microspheres can function as microrobots that could be manipulated by magnetic force to match the TBI orientation during RCT reconstruction surgery. By separately loading Mg2+ and Zn2+, the microrobots facilitated the immediate restoration and long-term maintenance of natural mineral gradient in TBI after implantation and alignment. In vitro studies confirmed that hemispheres loaded with Mg2+ and Zn2+ could promote the proliferation, migration, and function of bone mesenchymal stem cells and tenocytes, respectively, demonstrating the spatiotemporal cell phenotype modulation effect of microrobots. In a rat RCT model, microrobots synchronously enhanced the bone and tendon regeneration, increased the mechanical properties of repaired TBI tissue, improved the rats' limb function and promoted the restoration of gradient tendon-bone transition structure in TBI. Overall, through rebuilding the Mg2+/Zn2+ mineral gradient, cell phenotype gradient and structure gradient of TBI, magnetic Janus microrobots loaded with Mg2+/Zn2+ offer a promising strategy for the promotion of TBI healing in RCT reconstruction surgery.

Graphic:



Comparison of host immunomodulatory response to emerging biological meshes in ventral hernia repair

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[2] Department of Hernia and Abdominal Wall Surgery, Shanghai East Hospital, TongJi University, 150 Ji Mo Road, Shanghai 200120, P.R. China

[3] Department of General Surgery, Ninth People's Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai 200011, P.R. China

[4] School of Chemical Engineering, The University of Queensland, Brisbane, QLD 4072, Australia

Abstract:

Consensus on the treatment for ventral hernia using biological meshes remains elusive based on varying repair outcomes, especially with the influx of new candidates, posing challenges for clinical managements. Host immunomodulatory response is a critical determinant of repair success or failure by orchestrating cellular activities in remodeling events, necessitating to be elaborated for prognosis improvement. This study compared a small intestinal submucosa (SIS)-urinary bladder matrix (UBM) mesh and an electrospun poly (l-lactide-co caprolactone)-fibrinogen mesh to a paradigmatic SIS mesh in a ventral hernia model, focusing on their immunomodulatory features. Compared to the SIS mesh, the SIS-UBM mesh provided superior biocompatible microenvironments for cellular activities due to UBM surface layer. However, it exhibited a reduced cascade of bioactive factors in its milieu owing to through decellularization. In vivo studies revealed that both SIS-UBM and SIS meshes induced less-intensive intraperitoneal adhesion along with a histologically milder inflammatory response than the electrospun mesh after 8 weeks. No macroscopic differences were observed between SIS-UBM and SIS meshes, whereas the electrospun mesh induced significant fibrotic encapsulation. Within the immunomodulatory response, both SIS-UBM and SIS meshes initially triggered similar pro-inflammatory responses, whereas SIS meshes facilitated an earlier transition to modulate macrophage polarization toward an anti-inflammatory phenotype after 2 weeks, creating a favorable microenvironment for constructive remodeling. Comparatively, the SIS-UBM mesh switched to a similar macrophage polarization at 4 weeks, promoting a pro-remodeling state with upregulated anti-inflammatory cytokines and gene expression. The electrspun mesh maintained a pro-inflammatory state throughoutly, regardless of a more favorable geometry for cell infiltration than the SIS and SIS-UBM meshes. The temporal and directional differences in immunomodulation among diverse meshes were supported by the analysis of vascularization and collagen deposition over the integration process. The exploration of newly developed meshes upon immunomodulation offers insights for further modification to optimize the mesh-aid hernia repair.

Naturally Derived Flexible Bioceramics: Biomass Recycling Approach and Advanced Function

Zhibo Yang , Jianmin Xue , Chengtie Wu
Shanghai Institute of Ceramics, Chinese Academy of Sciences, Shanghai, China

Abstract:

Bioceramics, as one of the typical functional materials, find extensive use in the field of tissue regeneration due to their excellent biocompatibility and bioactivity. However, the high-temperature sintering process and the intrinsic brittleness of bioceramics significantly constrain their manufacturing processes, mechanical performance, and clinical applications. Therefore, developing bioceramics combining low temperature fabrication, flexibility, bioactivity is great challenge. *Euplectella aspergillum (Ea)*, a deep-sea inorganic sponge which possessing high strength and flexibility, attracted broad attention. Here, a biomass recycling strategy based on *Ea* was proposed to fabricate the thin and flexible naturally derived silica-based bioceramics. The mechanical properties and bone-forming bioactivity were further investigated.

Specifically, the sponge were used as natural source of silicon and immersed in solution calcium hydroxide to *in situ* mineralize calcium silicate on the surface of the natural sponge at hydrothermal condition (100 ℃). The silicon dioxide on the surface of sponge skeleton matrix was transferred into bioactive calcium silicate. The naturally derived calcium silicate mineralized sponge skeleton remained the mechanical properties of natural skeleton, exhibiting remarkable flexibility and machinability, which were superior to those of traditional inorganic biomaterials. Interestingly, the inert sponge was successfully activated through hydrothermal mineralization process, which could released bioactive Ca and Si ions. Due to the efficient ions release properties, the naturally derived flexible bioceramics possessed the capacity for promoting osteogenesis and angiogenesis *in vitro.* Finally, these bioceramics demonstrated excellent vascularized bone forming ability in the repair of flat bones (calvarial bone). Such a strategy successfully transformed discarded natural biomass into high value-added biomedical material, while provides a feasible approach to the manufacturing advanced functional bioceramics.