



Original Article



A Hydrophilic/Hydrophobic Janus Membrane Based on Directionally Frozen Polyvinyl Alcohol Hydrogel for Dural Defect Repair

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Abstract

Background and objectives: Cerebrospinal fluid leakage and postoperative tissue adhesion are serious complications following dural injury. Current dural substitutes often lack the functional asymmetry of the native dura mater. This study aimed to develop a hydrophilic/hydrophobic Janus polyvinyl alcohol (PVA) hydrogel membrane with a directional structure and dual functionality for effective dural defect repair.

Methods: A PVA hydrogel with an aligned porous architecture was fabricated via directional freezing combined with salt leaching, and thermal annealing was applied to enhance mechanical strength and structural stability. The hydrogel was asymmetrically modified to obtain a Janus membrane. Morphology, mechanical properties, degradation, swelling, wettability, *in vitro* biocompatibility, and cell migration were evaluated by the NIH-3T3 mouse fibroblast cell line. *In vivo* biocompatibility was assessed using a rat subcutaneous implantation model, including blank control, Durepair®, frozen-salted PVA, and Janus-PVA groups, with 5 rats in each group. Dural repair efficacy was evaluated in a rat cranial dural defect model, including untreated defect control, frozen-salted-annealed PVA, and Janus-PVA groups, with 15 rats in each group.

Results: The Janus membrane exhibited high tensile strength (8.93 ± 1.46 MPa), slow degradation (1.42% mass loss at 28 days), and low swelling (58.13% water content at 28 days). It displayed distinct bilateral wettability, and effectively blocked fibroblast migration on both sides, acting as a physical barrier against fibroblast-driven adhesion. In the rat dural defect model, the Janus membrane reduced cerebrospinal fluid leakage and brain–dura adhesion compared with the untreated defect and frozen-salted-annealed PVA control groups.

Conclusions: The engineered hydrophilic/hydrophobic Janus PVA hydrogel membrane mimics the functional asymmetry of the native dura mater and may serve as a promising candidate for further evaluation as a dural repair material.

Keywords: Janus membrane; Polyvinyl alcohol hydrogel; Dural repair; Cerebrospinal fluid leakage; Surface modification; Directional freezing.

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Introduction

Cerebrospinal fluid (CSF) leakage is a serious and potentially life-threatening complication following neurosurgical procedures or head trauma, primarily arising from dural defects that compromise the integrity of the central nervous system's protective barrier.^{1,2} The dura mater not only maintains intracranial pressure homeostasis but also serves as a critical seal against CSF egress and a defense against microbial invasion. Persistent CSF leakage significantly increases the risk of meningitis, pneumocephalus, and wound dehiscence, leading to prolonged hospitalization, additional interventions, and heightened morbidity.^{3,4} Despite advances in surgical techniques, achieving a watertight

and durable dural closure remains a clinical challenge, particularly in cases involving large or complex defects. Current repair strategies rely heavily on autologous grafts, allografts, or synthetic dural substitutes. However, autologous tissues are limited by donor site availability and associated morbidity, while allografts carry risks of immune rejection and disease transmission. Synthetic materials, although readily available, often suffer from suboptimal biocompatibility, inadequate mechanical sealing, or a tendency to induce postoperative adhesions.^{5,6} These limitations underscore the urgent need for advanced dural repair materials that provide reliable, leak-proof closure, support tissue regeneration, and minimize complications.

Although both the inner and outer layers of the dura mater are primarily composed of collagen, fibroblasts, and extracellular matrix (ECM), differences in their compositional ratios confer significant biological asymmetry between the two layers.⁷ The outer layer (epidural or periosteal layer) is characterized by a dense network of collagen fibers that provide mechanical strength and anchor the dura to the inner surface of the skull. In contrast, the inner layer (meningeal or boundary cell layer) consists predominantly of tightly packed fibroblasts embedded in a relatively loose ECM.⁸ Fibroblasts play a dual role in maintaining dural homeostasis: on one hand, they actively participate in tissue repair and regeneration by secreting ECM components such as collagen; on the other hand, their abnormal activation and migration can lead to dural fibrosis, scar formation, and postoperative tissue adhesions.⁹ Therefore, when repairing dural defects, the two sides of the repair material require different functional properties. Theoretically, the side facing the brain tissue should inhibit fibroblast adhesion and migration to prevent excessive proliferation and subsequent adhesion to neural tissue. In contrast, the side adjacent to the dural defect should promote fibroblast migration and adhesion to facilitate collagen deposition and support dural regeneration, enabling the implanted material to be gradually replaced by newly formed tissue. Cell adhesion to material surfaces is related to ECM proteins. The adhesion of ECM proteins (such as collagen and fibrin) to hydrophobic surfaces is much lower than that to hydrophilic surfaces.¹⁰ Therefore, it is necessary to design an asymmetric structure with one hydrophilic side and one hydrophobic side—namely, a hydrophilic/hydrophobic Janus structure—to meet the different requirements of both sides of a dural repair material for promoting and inhibiting cell adhesion.

Polyvinyl alcohol (PVA), a synthetic polymer with excellent biocompatibility, tunable mechanical properties, and biodegradability, has been widely used in biomedical materials. Physically crosslinked PVA hydrogels, formed by freeze-thaw cycles that create stable crystalline domains as crosslinking points, avoid the use of chemical crosslinkers, significantly enhancing material safety.^{11,12} Notably, the directional freezing-salt leaching technique can induce ice crystal growth in a specific direction within the PVA solution, thereby guiding the ordered arrangement of polymer chains and forming a highly aligned porous structure. This method not only enables precise control over the morphology and interconnectivity of the pores but also significantly enhances the mechanical strength of the hydrogel due to the oriented polymer framework. This technique enables differential surface property distribution through interface engineering, providing a feasible pathway for constructing Janus membranes with specific functional zones.¹³

Based on these considerations, this study aimed to develop a hydrophilic/hydrophobic Janus PVA hydrogel membrane with a

directional structure and dual functionality for effective dural defect repair.

Materials and methods

Preparation of directional PVA hydrogels via directional freezing and salting-out

To prepare the directional PVA hydrogel, 1.5 g of PVA (Aladdin Reagent (Shanghai) Co., Ltd.) was first dissolved in 13.5 mL of deionized (DI) water in a 20 mL lidded glass bottle. The mixture was stirred at room temperature for 30 min, then heated in an oil bath with continuous stirring until the solution reached 95 °C and became clear and transparent. After cooling slightly, the solution was ultrasonicated to remove air bubbles. Next, a freezing container (self-made, [Supplementary Fig. 1](#)) was cleaned with anhydrous ethanol and air-dried (SCIENTZ-12N, Ningbo Scientz Biotechnology Co., Ltd.). A pre-cooled (−80 °C) ethanol bath was prepared, and the 10% PVA solution was slowly poured into the container's groove to fill it completely, taking care to avoid bubbles. The container was placed in the ethanol bath (with the ethanol level just covering the glass bottom and side insulation tape) and frozen for 1 h. The resulting hydrogel, designated frozen PVA (F-PVA), was then removed from the groove. Finally, F-PVA was immersed in a 1.5 mol/L sodium citrate solution (sodium citrate dihydrate, Aladdin Reagent (Shanghai) Co., Ltd.) for 24 h to complete the salting-out process, yielding the final frozen-salted PVA (FS-PVA) hydrogel.

Preparation of Janus membrane via post-treatment of hydrogels

Thermal annealing was performed: F-PVA and FS-PVA hydrogels were placed in an oven preheated to 100 °C for 1 h. After turning off the oven, the temperature was allowed to cool slowly to room temperature, and the hydrogels were retrieved and labeled as FA-PVA and frozen-salted-annealed PVA (FSA-PVA) hydrogels, respectively.

Next, polydopamine (PDA, Beijing InnoChem Technology Co., Ltd.) coating was applied. The FSA-PVA hydrogel was immersed in DI water for 24 h (with water replaced three times) to remove residual sodium citrate. A PDA aqueous solution (pH 8.5) was prepared, and the FSA-PVA hydrogel was incubated in it at 37 °C for 24 h to induce oxidative self-polymerization of PDA on its surface, forming a PDA coating. The resulting hydrogel was named PDA-FSA-PVA. The relationship between the intermediate products is shown in [Supplementary Figure 2](#).

A hydrophobic coating was added as follows: Solutions of 0.5 M γ -aminopropyltriethoxysilane (APTES, Beijing InnoChem Technology Co., Ltd.) in ethyl acetate (EtOAc, Sinopharm Chemical Reagent Co., Ltd.) and 0.5 M stearoyl chloride (Beijing InnoChem Technology Co., Ltd.) in EtOAc were prepared and sonicated to ensure uniform dispersion. The PDA-FSA-PVA hydrogel was plasma-activated for 10 s. Subsequently, it was immediately immersed in an APTES/EtOAc solution with only its bottom surface in contact, and allowed to react for 60 min. During this process, the hydrolyzed silanol groups from APTES underwent a condensation reaction with the hydroxyl groups (−OH) on the hydrogel surface, covalently grafting APTES onto the hydrogel. The hydrogel was dried at room temperature for 2 min to remove excess EtOAc, then immersed in a small amount of stearoyl chloride/EtOAc solution for another 60 min (bottom surface in contact). The amino groups of APTES reacted with the acyl chloride groups of stearoyl chloride, introducing the hydrophobic long carbon chain of stearoyl chloride onto the hydrogel surface. After drying at room tempera-

ture for 2 min, an asymmetric Janus membrane was obtained, with one side coated with APTES–stearoyl chloride–PDA and the other side coated only with PDA.

Material characterization

Thermal stability assessment

Thermogravimetric analysis (TGA) was used to evaluate the thermal stability of the synthesized hydrogels prior to high-temperature annealing. Hydrogels were crosslinked with excess glutaraldehyde (20 mL DI water, 200 μ L 25% wt glutaraldehyde, 100 μ L 38% wt HCl) at room temperature for 3 h, followed by 2-day DI water immersion to remove residual crosslinkers. Post-crosslinking samples were freeze-dried and analyzed using TGA (Pyris 1, PerkinElmer Instruments) from 30 °C to 400 °C at a heating rate of 10 °C/min.

Crystallinity measurement

Differential scanning calorimetry (DSC, Diamond DSC, PerkinElmer Instruments) was performed to assess crystallinity after crosslinking and freeze-drying. Hydrogels (F-PVA, FS-PVA, FSA-PVA) were analyzed under N₂ flow (35 mL/min) from 50 °C to 250 °C at 10 °C/min. Residual water mass (M_{residual}) and crystalline domain mass (M_{crystal}) were calculated using:

$$M_{\text{residual}} = M_{\text{total}} \times \frac{H_{\text{residual}}}{H_{\text{water}}}$$

$$M_{\text{crystal}} = M_{\text{total}} \times \frac{H_{\text{crystal}}}{H_{\text{PVA}}}$$

(H_{water} is the enthalpy of evaporation of water, 2,260 J/g. H_{PVA} is the enthalpy of fusion of PVA, 138.6 J/g.

Crystallinity (X_{dry}) was calculated as:

$$X_{\text{dry}} = \frac{M_{\text{crystal}}}{M_{\text{total}} - M_{\text{residual}}} \times 100\%.$$

Morphological analysis

Scanning electron microscopy (SEM)

SEM (SU8010, Hitachi Ltd.) was used to observe hydrogel cross-sections. Samples were freeze-dried (−80 °C, 24 h), cryo-fractured in liquid nitrogen, sputter-coated with gold (1 min), and imaged at 10 kV/10 μ A.

Mechanical testing

Hydrogels were swollen in DI water for 2 h before tensile testing. Bone-shaped samples (30 mm $\times$ 10 mm central section) were tested at a 0.100 mm/s strain rate using a universal testing machine (IBTC-500). Stress–strain curves were derived from force–displacement data.

In vitro degradation and swelling

Hydrogel (1 cm²) samples were incubated in artificial CSF (125 mM NaCl, 26 mM NaHCO₃, etc.) at 37 °C. After 7, 14, 21, and 28 days, samples were rinsed, dried, and analyzed for degradation rate ($DR = (M_i - M_d)/M_i \times 100\%$, where M_i is initial mass and M_d is dry mass) and moisture content ($MC = (M_s - M_d)/M_s \times 100\%$, where M_s is swollen mass and M_d is dry mass).

Hydrophilicity evaluation

Static water contact angles (CAs) were measured on FSA-PVA,

PDA-FSA-PVA, and Janus-PVA surfaces using a goniometer (20 μ L droplet, recorded at 1, 10, and 20 s).

Cellular experiments

Cell culture

NIH-3T3 cells (Stem Cell Bank, Chinese Academy of Sciences) were cultured in Dulbecco's modified Eagle medium (DMEM) (10% fetal bovine serum), 1% penicillin–streptomycin) at 37 °C and 5% CO₂. Medium was replaced every 48 h; cells were passaged at ~80–90% confluence.

Cytotoxicity assessment

Live/Dead Staining: Extracts (100 mg/mL hydrogel in DMEM) were prepared per ISO 10993-5. NIH-3T3 cells (1.5×10^4 /well) were incubated with extracts for 24 h and stained with Calcein-AM/PI (Beyotime Biotech Inc.).

Cell Counting Kit-8 (CCK-8) assay

Cell viability was quantified using CCK-8 (Beyotime Biotech Inc.) by measuring absorbance at 450 nm after 12, 24, and 48 h.

$$\text{Relative metabolic activity (\%)} = \frac{OD_{\text{test}} - OD_{\text{blank}}}{OD_{\text{control}} - OD_{\text{blank}}} \times 100\%$$

Transwell migration assay

NIH-3T3 cells (2×10^4 /mL) were seeded in Transwell inserts (12 μ m pore, 200 μ L) with Janus-PVA membranes (PDA side facing up). Migration was assessed after five days using crystal violet staining.

Animal studies

All animal experiments were performed using adult male Sprague–Dawley (SD) rats. A total of 65 adult male SD rats were used in this study, including 20 rats for the subcutaneous implantation experiment and 45 rats for the cranial dural defect model. The animal procedures were approved by the Animal Ethics Committee of the Hubei Provincial Center for Food and Drug Safety Evaluation, China. The animal ethics approval number was Safety Evaluation Center Animal (Welfare) No. 20252-6358. Rats were housed in a temperature-controlled environment at 22 ± 2 °C with $50 \pm 10\%$ relative humidity under a 12 h light/dark cycle. All animals had ad libitum access to standard laboratory chow and sterilized water. Surgical procedures were performed under general anesthesia induced by intraperitoneal injection of pentobarbital sodium (50 mg/kg). Postoperative pain was minimized using buprenorphine (0.05 mg/kg, subcutaneously) every 12 h for 48 h after surgery. Rats were randomly assigned to experimental groups using a random number table. To ensure objectivity, histological assessments and adhesion grading were performed by two independent blinded observers. At predetermined time points, rats were humanely euthanized by an overdose of pentobarbital sodium (150 mg/kg, i.p.), followed by cervical dislocation to ensure death.

Experimental grouping and subcutaneous implantation

For the subcutaneous implantation experiment, 20 SD rats weighing 200–300 g were randomly assigned to four groups: the blank control group, commercial dural substitute group, FS-PVA hydrogel group, and Janus-PVA hydrogel membrane group. In the commercial dural substitute group, Durepair® membranes (Integra LifeSciences (Shanghai) Co., Ltd.) were implanted. In the FS-PVA

and Janus-PVA groups, FS-PVA hydrogels or Janus-PVA hydrogel membranes were implanted, respectively. Each implanted sample was cut to a size of approximately 1 cm². In the blank control group, no material was implanted.

Briefly, after anesthesia and skin disinfection, a small dorsal incision was made, and a subcutaneous pocket was created by blunt dissection. The corresponding material was inserted into the subcutaneous pocket, followed by wound closure. Fifteen days after implantation, the rats were euthanized, and the implantation sites together with surrounding tissues were harvested. The collected tissues were fixed in 4% paraformaldehyde, embedded, sectioned, and subjected to hematoxylin and eosin (H&E) staining and Masson's trichrome staining to evaluate inflammatory response, fibrous encapsulation, collagen deposition, material degradation, and tissue integration.

Rat dural defect model

For the dural defect model, SD rats weighing 200–250 g were randomly divided into three groups: the untreated defect control group, FSA-PVA hydrogel membrane group, and Janus-PVA hydrogel membrane group, with 15 rats in each group. In the control group, the dural defect was left unrepaired after craniotomy. In the FSA-PVA group, the defect was covered with the salting-out/annealed PVA hydrogel membrane. In the Janus-PVA group, the defect was repaired using the Janus-PVA hydrogel membrane, with the anti-adhesive side facing the brain tissue and the regenerative side facing the extracranial tissue.

Briefly, after anesthesia, the scalp was shaved and disinfected, and a midline incision was made to expose the skull. A circular cranial window with a diameter of approximately 6 mm was created using a dental drill. The dura mater within the defect region was carefully removed to establish a dural defect model while avoiding damage to the underlying brain tissue. The corresponding membrane was then implanted to cover the defect site. For the Janus-PVA hydrogel membrane, the hydrophobic (anti-adhesive) side was placed toward the brain surface to prevent adhesion, whereas the hydrophilic (tissue-regenerative) side was oriented outward to promote tissue repair. The scalp was then sutured, and the animals were allowed to recover under postoperative care.

Postoperatively, the rats were monitored for general condition, wound healing, infection, subcutaneous mass formation, CSF leakage, and neurological abnormalities. At predetermined time points, the defect region together with surrounding tissues was harvested for gross observation and histological analysis. Five rats from each group were scheduled for euthanasia at 7, 15, and 30 days after implantation. Because two rats in the untreated defect control group died before day 7, the actual numbers of control rats included in endpoint gross and histological analyses were 4, 4, and 5 at days 7, 15, and 30, respectively. Five rats were included at each time point in the FSA-PVA and Janus-PVA groups. The samples were fixed in 4% paraformaldehyde, embedded, sectioned, and stained with H&E and Masson's trichrome stains. The degree of tissue adhesion, inflammatory cell infiltration, fibrous capsule formation, collagen deposition, material degradation, and dural repair was evaluated.

Evaluation of adhesion and CSF leakage

The effectiveness of the implanted membranes in preventing tissue adhesion and CSF leakage was evaluated in the rat dural defect model. Gross observation was performed to assess subcutaneous fluid accumulation, mass formation, wound infection, and material displacement. The defect site and corresponding brain tissue were

examined to determine whether the implanted material adhered to the brain surface or surrounding tissues. Histological sections were further used to assess the interface between the material and host tissue, inflammatory response, fibrous tissue formation, and the presence of cavities resulting from material degradation.

Systemic toxicity evaluation

To evaluate the potential systemic toxicity of the implanted materials, major organs, including the heart, liver, spleen, lung, and kidney, were collected from representative rats after implantation. The organs were fixed in 4% paraformaldehyde, embedded, sectioned, and stained with H&E. Histopathological analysis was performed to assess whether the implanted materials induced inflammatory infiltration, necrosis, structural abnormalities, or other pathological changes in major organs.

Data analysis

All quantitative data were analyzed using GraphPad Prism 8, Origin 2022, and SPSS 24. Results are presented as mean $\pm$ standard deviation. For comparisons between two groups, statistical significance was determined using Student's *t*-test. For comparisons among multiple groups, one-way analysis of variance was performed. When the data did not conform to a normal distribution, nonparametric tests were used. A value of *P* < 0.05 was considered statistically significant.

Results

Janus hydrogel membranes exhibit good thermal stability

TGA was employed to investigate the thermal stability of F-PVA hydrogels. The results are presented in [Supplementary Figure 3a](#). The glass transition temperature (*T*_g) of PVA ranges from 75 to 85 °C. As shown by the TGA curves, F-PVA hydrogels exhibited a weight loss of only 7.52% when heated from 30 °C to 210 °C, while a weight loss of 76.2% occurred between 210 °C and 400 °C. Since PVA typically undergoes thermal decomposition above 220 °C, producing acetic acid, water, and acetaldehyde,¹⁴ the weight loss below 210 °C is inferred to primarily result from the evaporation of residual water and intermolecular dehydration within the sample. In contrast, the weight loss above 210 °C is attributed to PVA decomposition, with the TGA curve remaining nearly flat between 210 °C and 250 °C. These findings indicate that the PVA used in this study exhibits favorable thermal stability below 250 °C, which satisfies the temperature requirements for thermal annealing, high-pressure steam sterilization, daily transportation, storage, and practical applications.

To further evaluate the effect of thermal annealing on the crystallinity of the prepared PVA hydrogels, DSC was performed, and the results are shown in [Supplementary Figure 3b](#). By integrating the peak areas of the DSC curves, the masses of residual water and crystalline domains were estimated to calculate the crystallinity of PVA in each sample. The crystallinity of PVA in F-PVA samples was determined to be 1.07% $\pm$ 0.52%, whereas that in FS-PVA samples was 3.25% $\pm$ 1.83%. No significant difference was observed between F-PVA and FS-PVA, suggesting that salt precipitation with sodium citrate does not promote PVA crystallization. Although sodium citrate decomposes at 200 °C to produce water, carbon dioxide, and sodium carbonate, the residual sodium citrate in the samples after soaking in DI water for two days was minimal, thus exerting no significant impact on the calculation of PVA crystalline domain mass. Notably, FSA-PVA samples displayed a

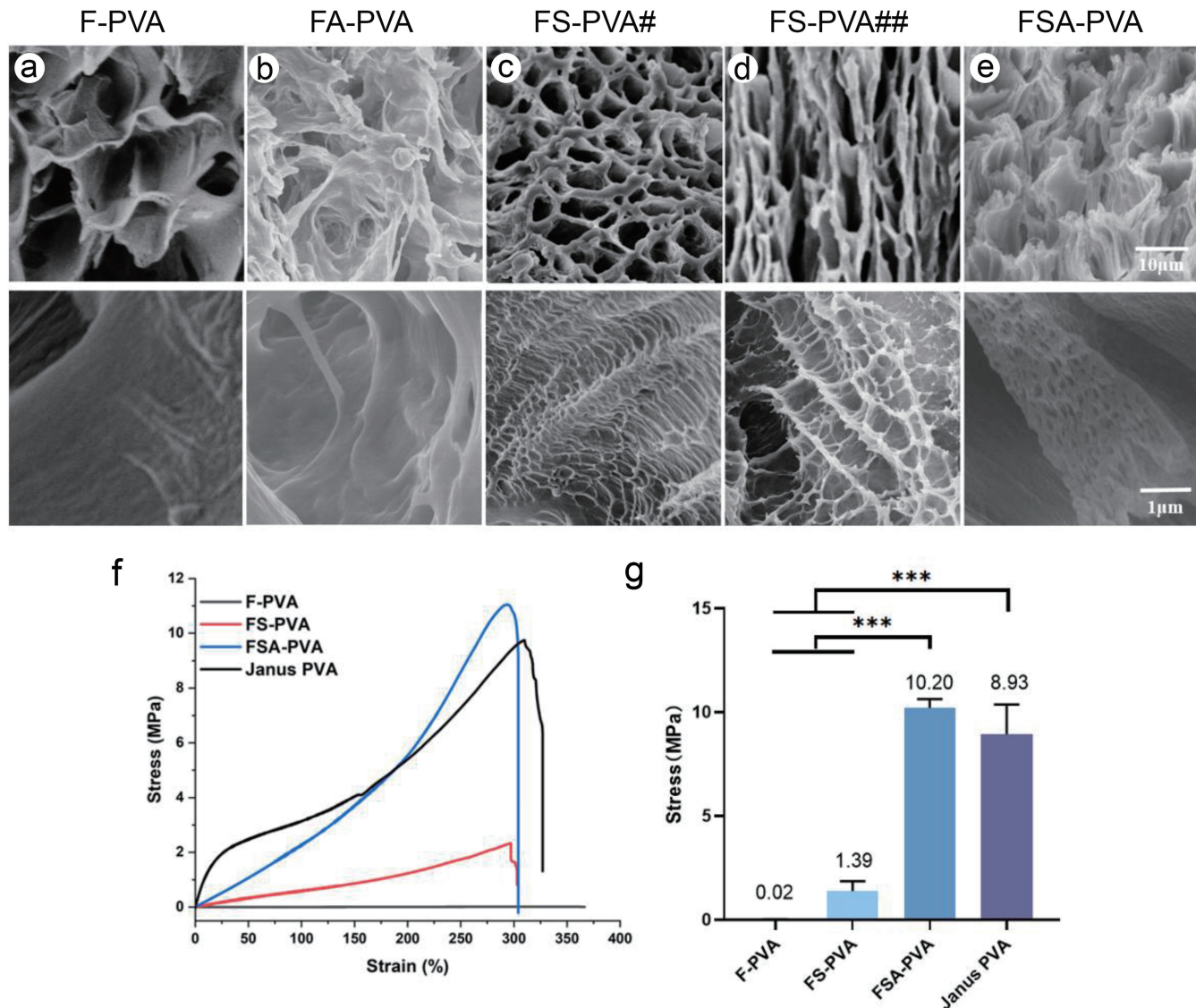


Fig. 1. Cross-sectional SEM images and mechanical property measurements of the hydrogels. (a–e) SEM images of the hydrogels. FA-PVA refers to the PVA hydrogel prepared by ice templating without salting-out and directly subjected to thermal annealing. Symbols # and ## denote cross-sections perpendicular and parallel to the temperature gradient, respectively. The scale bar applies to all images in the same row. (f) Stress–strain curves of the four hydrogels. (g) Maximum stress of the four hydrogels. Error bars represent standard deviation ($n = 3$; *** $P < 0.001$). FA-PVA, frozen-annealed polyvinyl alcohol; F-PVA, frozen polyvinyl alcohol; FS-PVA, frozen-salted polyvinyl alcohol; FSA-PVA, frozen-salted-annealed polyvinyl alcohol; Janus PVA, Janus polyvinyl alcohol; SEM, scanning electron microscopy.

distinct sharp peak between 200 °C and 250 °C, with the integrated peak area indicating a PVA crystallinity of $29.30\% \pm 2.47\%$. This demonstrates that thermal annealing significantly enhances the crystallinity of FSA-PVA samples.

Janus hydrogel membranes exhibit superior mechanical strength to natural dura mater

To investigate the effects of salt precipitation and thermal annealing on the microstructure of hydrogels, SEM was used to observe cross-sectional morphologies, and a universal testing machine was employed to measure tensile strength. As shown in Figure 1, PVA hydrogels crosslinked via ice templating all displayed porous structures. F-PVA hydrogels (Fig. 1a) featured uniformly sized

pores with thin walls and smooth inner surfaces. FS-PVA hydrogels (Fig. 1b) showed highly irregular morphologies with nearly vanished pores, likely due to high initial water content. FSA-PVA hydrogels exhibited aligned, ordered pore walls perpendicular to the temperature gradient (Fig. 1c and d), confirming directional ice crystal growth. Hofmeister effects—where salt solutions enhance molecular aggregation in hydrogels—reduced pore size and thickened pore walls in salt-leached hydrogels.¹⁵ Additionally, nanoscale networks replaced the smooth inner surfaces of F-PVA, further improving toughness; these nanonetworks persisted after annealing (Fig. 1e).

To validate the impact of these microstructures on mechanical performance, stress–strain curves and maximum tensile strengths

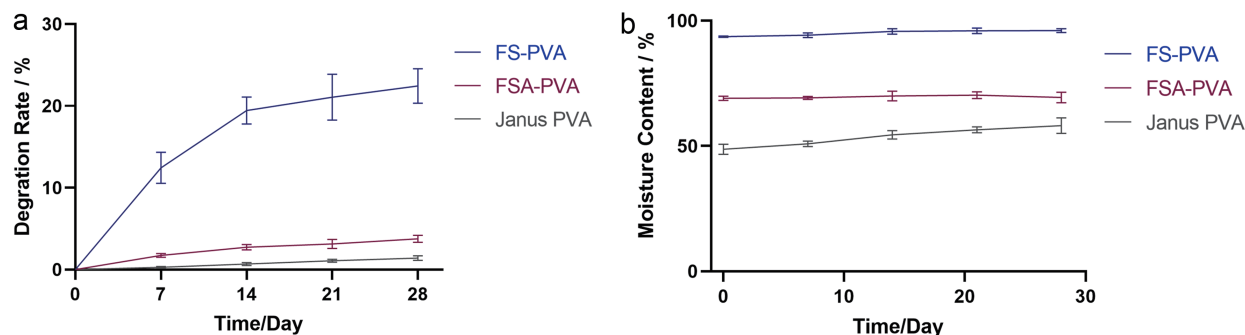


Fig. 2. *In vitro* degradation results of the three hydrogels. (a) Degradation rate curves of FS-PVA, FSA-PVA, and Janus PVA hydrogels. (b) Moisture content of FS-PVA, FSA-PVA, and Janus PVA hydrogels after hydration at 0, 7, 14, 21, and 28 days of degradation. Error bars represent standard deviation ($n = 3$). FS-PVA, frozen-salted polyvinyl alcohol; FSA-PVA, frozen-salted-annealed polyvinyl alcohol; Janus PVA, Janus polyvinyl alcohol.

were derived from universal tensile testing (Figs. 1f and g). F-PVA displayed near-linear stress-strain behavior with a low maximum strength of 20 ± 5.7 kPa, indicating weak mechanical properties. FS-PVA showed a dramatic strength increase to 1.38 ± 0.80 MPa, attributed to sodium citrate-induced polymer chain aggregation into nanofiber networks that better withstand tensile stress.^{16,17} FSA-PVA further increased strength to 10.20 ± 0.73 MPa, significantly surpassing F-PVA and FS-PVA. Janus membranes with coatings maintained high strength (8.93 ± 1.46 MPa), comparable to FSA-PVA, showing minimal interference from coatings. The elastic modulus of Janus PVA was calculated as 218 ± 16 MPa.

In summary, thermal annealing successfully enhanced and stabilized hydrogel mechanical properties. The final Janus membranes exhibited maximum stress exceeding that of natural dura mater (3–4.5 MPa) and strain far exceeding that of dura mater (20%–64%), meeting the mechanical requirements for dura repair materials.

Janus hydrogel membranes exhibit asymmetric bilateral properties

To confirm successful coating, SEM was used to analyze cross-sections of PDA-FSA-PVA and Janus PVA hydrogels. As shown in Supplementary Figure 4, PDA and silane coatings were uniform (40.72 ± 2.46 μ m and 21.01 ± 2.43 μ m, respectively). Static CA measurements (Supplementary Fig. 4c) validated asymmetric wettability. Hydrophilic FSA-PVA (hydroxyl-rich) showed rapid water penetration, with a 20-s CA of $13.93 \pm 2.40^\circ$. PDA coating increased the CA to $42.7 \pm 3.37^\circ$ (beneficial for cell adhesion). Silane/long-chain alkane modification further enhanced hydrophobicity (20-s CA = $122.46 \pm 4.40^\circ$, CA $>90^\circ$), with no significant spreading from 1–20 s. This asymmetry meets the requirements for dural repair. These results confirmed successful Janus membrane construction.

Janus hydrogel membranes exhibit slow degradation and anti-swelling properties

To evaluate biodegradability, hydrogels were immersed in artificial CSF (37 $^\circ$ C, shaking), and degradation rates were calculated (Fig. 2a). FS-PVA degraded the fastest initially, reaching $22.44\% \pm 3.65\%$ at 28 days. FSA-PVA and Janus PVA showed slower degradation, with 28-day rates of $3.75\% \pm 0.74\%$ and $1.42\% \pm 0.51\%$, respectively. This disparity is attributed to annealing-enhanced crystallinity and silane coating. Because dural reconstruction may require a prolonged period, the slow degradation of Janus PVA is desirable for dural repair applications.

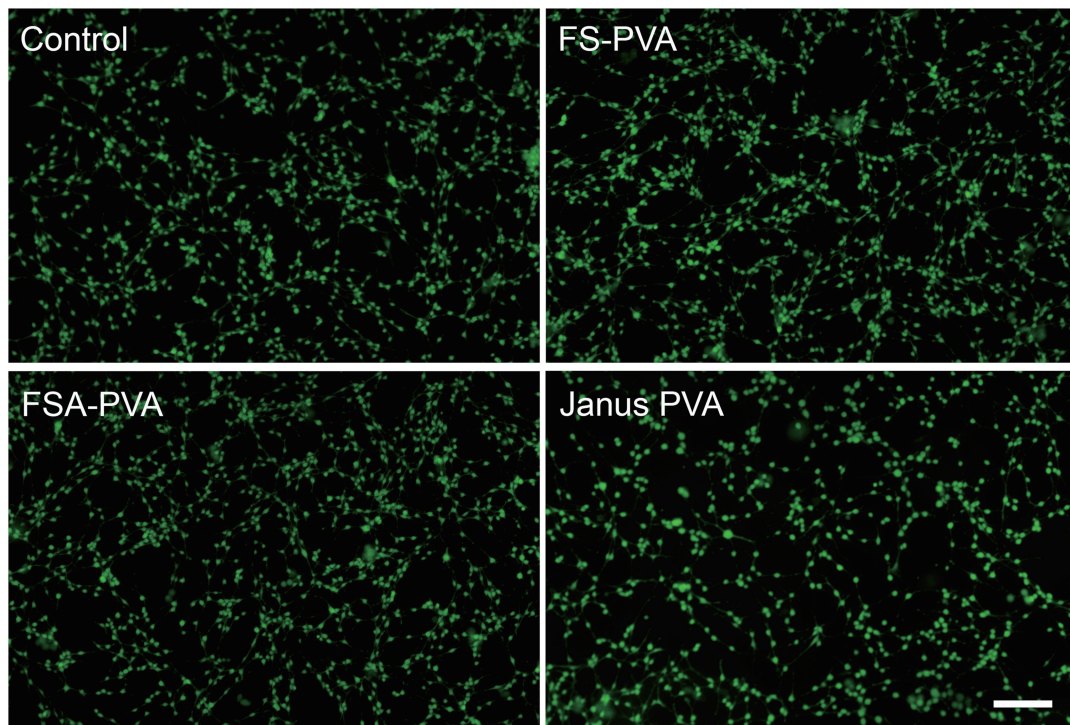
For swelling assessment, water content was measured to quantify swelling behavior (Fig. 2b). All hydrogels showed increasing water content over time: FS-PVA reached $96.01\% \pm 0.29\%$ at 28 days; FSA-PVA, $69.40\% \pm 1.69\%$; and Janus PVA increased from $48.74\% \pm 8.47\%$ (day 1) to $58.13\% \pm 5.31\%$ (day 28). Annealing and coating effectively reduced water absorption. Despite gradual swelling, Janus PVA maintained anti-swelling capacity, enabling pre-surgical trimming without significant volume change and minimizing postoperative compression risks to brain or spinal tissues.

Janus hydrogel membranes exhibit favorable biocompatibility

The biocompatibility of Janus hydrogel membranes was first evaluated *in vitro* using live/dead staining and the CCK-8 assay. Cell cytotoxicity was assessed via an indirect contact method, in which hydrogel extracts were co-incubated with cells. In the live/dead staining assay (Fig. 3a), after 24 h of co-culture with either hydrogel extracts or DMEM medium, fibroblasts in all groups displayed spindle-shaped morphology, formed confluent cell layers, and showed no visible red-stained dead cells, indicating healthy cell growth. Consistent with this, CCK-8 results (Fig. 3b) showed that the relative cell viability of FS-PVA, FSA-PVA, and Janus PVA hydrogels remained above 80% after 12, 24, and 48 h of co-culture with their respective extracts. These *in vitro* findings collectively suggest that FS-PVA, FSA-PVA, and Janus PVA hydrogel membranes exhibit favorable biocompatibility, providing preliminary evidence for their safety in potential applications.

To further investigate *in vivo* degradation behavior and biocompatibility, subcutaneous implantation experiments in rats were conducted. Histological analysis using H&E and Masson's trichrome staining at day 15 post-implantation revealed distinct outcomes across groups (Fig. 4). In the control group, H&E staining showed extensive infiltration of neutrophils, macrophages, and fibroblasts; Masson staining revealed irregular collagen fiber proliferation (Fig. 4a and b). Most of the commercial collagen patch group had degraded by day 15, and no obvious neutrophil or macrophage infiltration was observed, leaving cavities after degradation (Fig. 4c and d). The frozen-salted PVA hydrogel group displayed noticeable degradation and marked inflammatory cell infiltration, indicating a robust inflammatory response (Fig. 4e and f). Notably, the prepared Janus PVA hydrogel membrane showed no obvious degradation or inflammatory cell infiltration and maintained a relatively complete structure. Newly formed collagen fibers were regularly arranged, and the boundary between the implanted hydrogel and surrounding tissue was clear (Fig. 4g and h). These results demonstrate that the Janus PVA hydrogel membrane degrades slowly *in vivo*, preserving

a



b

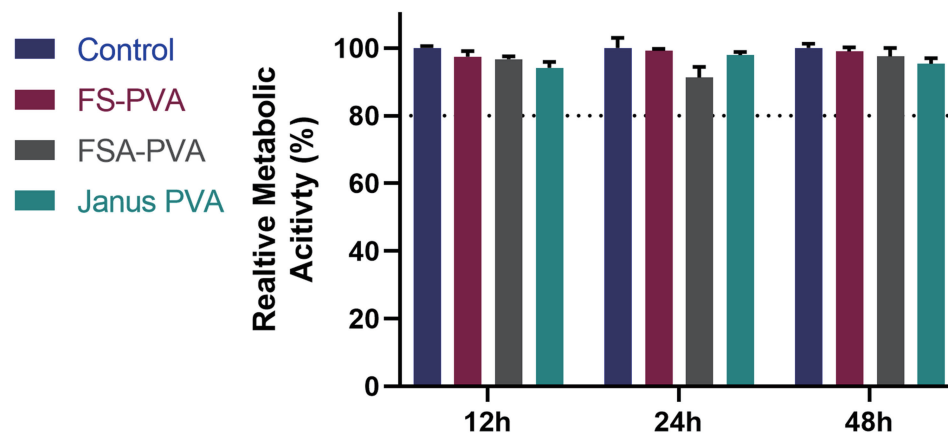


Fig. 3. Results of co-culture of hydrogel extracts with NIH-3T3 cells. (a) Fluorescence microscopy images of LIVE/DEAD staining after 24 h of co-culture with the extracts. The scale bar (200 μ m) applies to all images. (b) Relative cell viability (compared with the control group) measured by CCK-8 assay after 12, 24, and 48 h of culture. The dashed line corresponds to a vertical coordinate value of 80%. Error bars represent standard deviation ($n = 5$). CCK-8, Cell Counting Kit-8; FS-PVA, frozen-salted polyvinyl alcohol; FSA-PVA, frozen-salted-annealed polyvinyl alcohol; Janus PVA, Janus polyvinyl alcohol; NIH-3T3, mouse embryonic fibroblast cell line.

structural integrity over the period required for dural reconstruction. Its slow degradation rate also mitigated inflammatory reactions, confirming its excellent *in vivo* biocompatibility.

To assess systemic organ toxicity, rats with dural defects were euthanized at day 30, and tissues from the heart, liver, spleen, lung, and kidney were harvested for histological examination. As shown in [Supplementary Figure 5](#), myocardial fibers, hepatic lobules, splenic lymphoid follicles, lung parenchyma, and renal glomeruli in the implant group all maintained intact structures with no appar-

ent pathological changes. These findings suggest that the prepared hydrogels did not cause histopathological abnormalities in major organs within the 30-day observation period. Longer-term systemic safety still requires further evaluation.

Janus hydrogel membrane effectively prevents tissue adhesion and CSF leakage

To evaluate the ability of the Janus hydrogel membrane to prevent fibroblast infiltration and subsequent adhesion, a cell migration as-

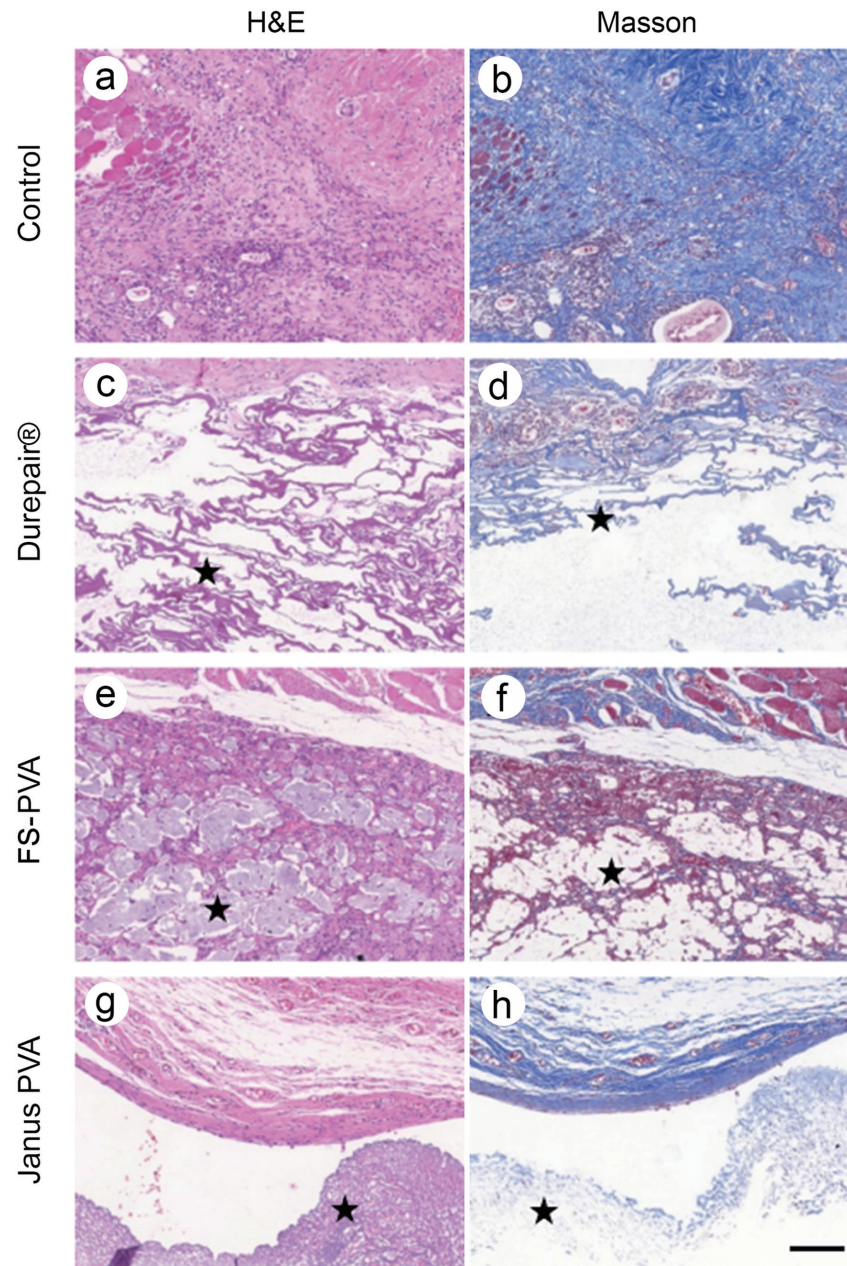


Fig. 4. Results of rat subcutaneous implantation for 15 days. From top to bottom: non-implanted control group, Durepair® group, FS-PVA group, and Janus PVA group. The black stars indicate the implanted materials or void regions left after material degradation. The scale bar (100 μ m) applies to all images. FS-PVA, frozen-salted polyvinyl alcohol; H&E, hematoxylin and eosin; Janus PVA, Janus polyvinyl alcohol; Masson, Masson's trichrome stain.

say was performed. Three groups were tested: blank control, the hydrophobic side of the Janus PVA hydrogel, and the PDA-coated (hydrophilic) side. Cells in the lower chamber were stained with crystal violet ([Supplementary Fig. 6](#)). Distinct spindle-shaped NIH-3T3 fibroblasts were observed only in the control group ([Supplementary Fig. 6a](#)), while no significant cell migration was detected on either side of the Janus membrane ([Supplementary Fig. 6b and c](#)). These results indicate that the Janus hydrogel effectively blocks fibroblast penetration under the tested conditions, demonstrating its potential as a physical barrier against fibroblast-driven adhesion and collagen overproduction, which may contribute to brain–scalp

adhesion. This hypothesis requires further *in vivo* validation.

To assess *in vivo* efficacy, a rat dural defect model was established. Within 30 days post-implantation, 6 of 15 rats in the control group developed palpable subcutaneous masses, and 2 died from wound infection; these animals were excluded from endpoint gross and histological analyses but were retained in the postoperative complication summary. In the FSA-PVA group, 2 rats exhibited subcutaneous masses, but no infection was observed. Notably, no masses or infections occurred in the Janus PVA hydrogel group. Incision of the masses revealed accumulated CSF, confirming the

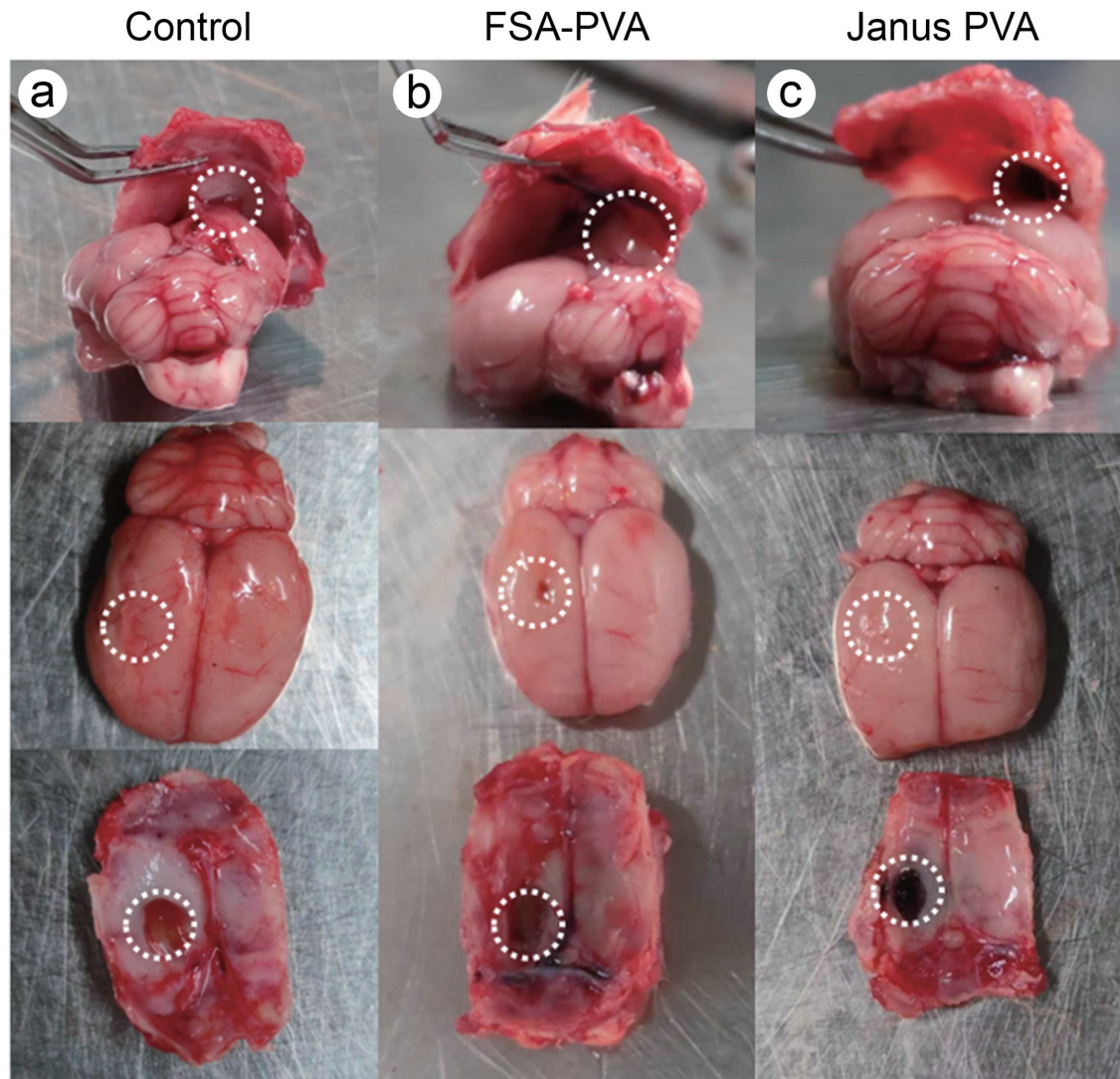


Fig. 5. Gross results of the rat dural defect model. (a–c) Representative images at 30 days post-implantation. The white circle indicates the dural defect site and the corresponding brain tissue. FSA-PVA, frozen-salted-annealed polyvinyl alcohol; Janus PVA, Janus polyvinyl alcohol; PVA, polyvinyl alcohol.

effectiveness of the Janus membrane in preventing CSF leakage.

At 30 days, rats were euthanized. The brain and overlying skull were carefully separated to evaluate adhesion. As shown in [Figure 5](#), significant tissue adhesion was observed in the control ([Fig. 5a](#)) and FSA-PVA groups ([Fig. 5b](#)), with visible brain tissue defects at the dural defect site upon separation. In contrast, the Janus PVA hydrogel group ([Fig. 5c](#)) showed minimal adhesion, allowing easy separation of the skull and brain, with a smooth brain surface and no apparent tissue defects.

Histological analysis (H&E and Masson's trichrome staining) was performed at 7, 15, and 30 days post-implantation ([Fig. 6](#)). The control group exhibited significant inflammatory cell and fibroblast infiltration at 7 and 15 days, along with disorganized collagen deposition (blue fibers), likely due to CSF leakage-induced inflammation. At 30 days, newly formed collagen fibers remained intermingled with brain tissue, confirming persistent adhesion. The FSA-PVA group showed discontinuous collagen at 7 days, irregular fibrous encapsulation at 15 days, and minimal material

degradation at 30 days, accompanied by sustained inflammation and thick fibrous encapsulation. In contrast, the Janus PVA hydrogel remained intact throughout the 30-day period. Newly formed collagen above the membrane was continuous and non-adherent. H&E staining at 30 days revealed minimal cell attachment on the hydrophilic surface, and Masson's staining showed a thin fibrous capsule with a mild inflammatory response.

It is hypothesized that unsealed CSF leakage in the control and annealed hydrogel groups led to severe inflammation and disorganized granulation tissue formation. In contrast, the Janus membrane effectively sealed the defect, preventing CSF leakage. In conclusion, the fabricated Janus hydrogel membrane demonstrates excellent anti-adhesion and CSF leakage-prevention properties.

Discussion

In this study, we developed a hydrophilic/hydrophobic Janus PVA hydrogel membrane for dural defect repair using directional freez-

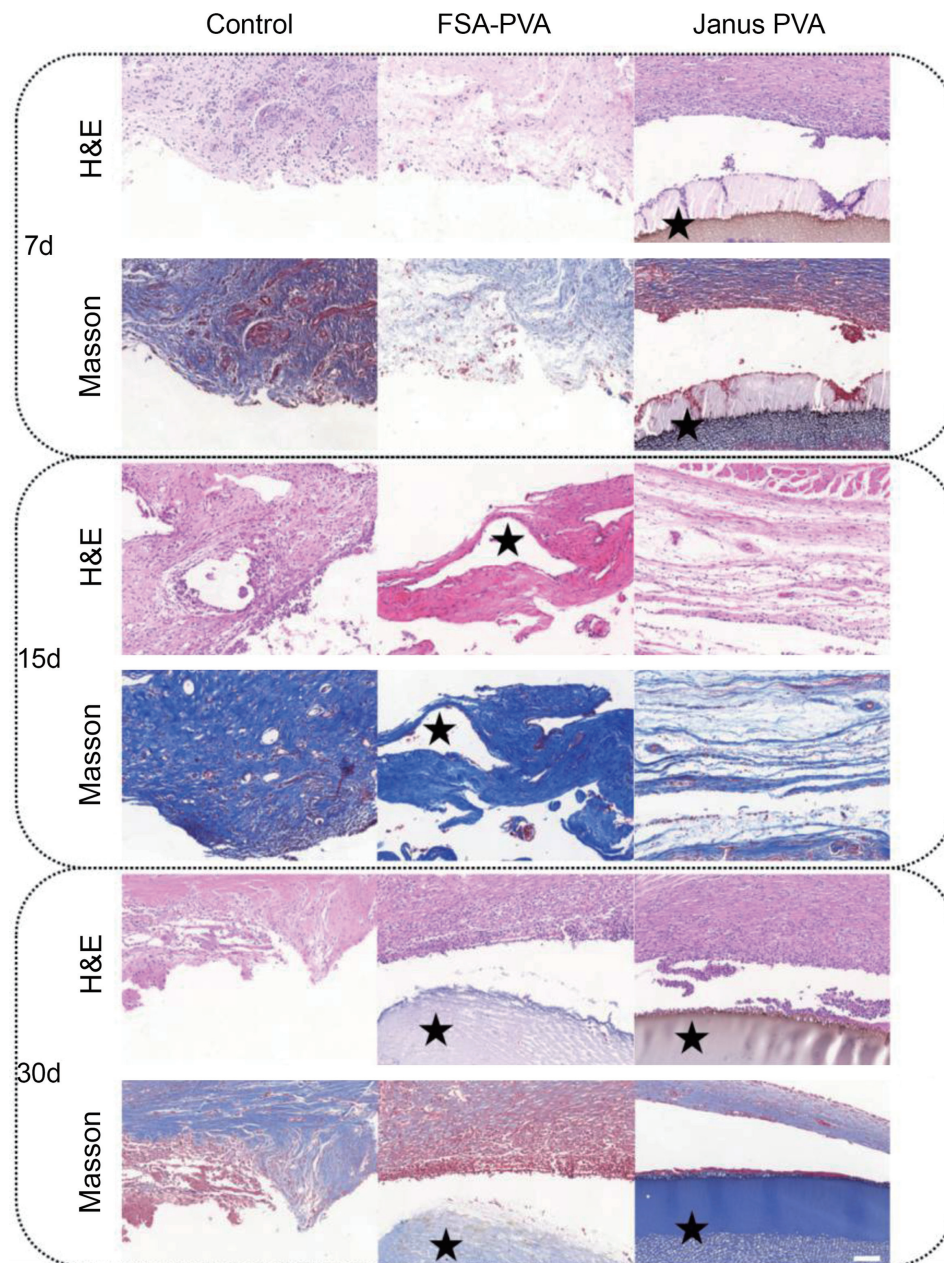


Fig. 6. Histological sections of the rat dural defect model. Representative images at 7, 15, and 30 days post-implantation. The stars indicate the implanted material and the cavities formed after material degradation. The scale bar (100 μ m) applies to all images. For endpoint gross and histological analyses, the actual numbers of rats in the untreated defect control group were $n = 4, 4,$ and 5 at 7, 15, and 30 days, respectively; in the FSA-PVA and Janus-PVA groups, $n = 5$ at each time point. FSA-PVA, frozen-salted-annealed polyvinyl alcohol; H&E, hematoxylin and eosin; Janus PVA, Janus polyvinyl alcohol; Masson, Masson's trichrome stain; PVA, polyvinyl alcohol.

ing, salt leaching, and thermal annealing. This strategy enhanced the mechanical strength and toughness of the hydrogel while maintaining low swelling and slow degradation. The resulting Janus membrane showed asymmetric bilateral wettability, favorable *in vitro* and *in vivo* biocompatibility, and reduced CSF leakage and brain–dura adhesion compared with the untreated defect and FSA-PVA control groups in a rat dural defect model. These findings suggest that asymmetric surface design may be a feasible strategy for balancing dural tissue integration and anti-adhesion require-

ments in experimental dural repair.

Clinically used dural substitutes are intended to provide coverage and facilitate dural closure, but postoperative CSF leakage and infection remain important concerns,^{3,4} and dural repair with autologous and nonautologous substitutes is still associated with moderate complication rates.⁵ Therefore, an ideal dural substitute should not merely cover the defect but should also provide reliable watertight closure, appropriate flexibility, minimal swelling, low immunogenicity, anti-adhesive properties, and controllable degra-

dation that matches the process of dural regeneration.⁶

PVA was selected as the base material because of its biocompatibility, processability, low cost, and tunable hydrogel properties. Directionally F-PVA hydrogels can form ordered porous structures that may facilitate cell migration and tissue regeneration. However, conventional PVA hydrogels may have insufficient mechanical strength, high swelling, and relatively rapid degradation, which limit their use in dural repair under dynamic intracranial conditions.¹⁸

To overcome these limitations, we employed a directional freezing–salt leaching–annealing strategy to enhance the mechanical performance and structural stability of the hydrogel. Although directional freezing combined with salt leaching can improve hydrogel tensile strength and toughness,^{16,19} our preliminary experiments revealed that the mechanical enhancement was not sustained upon exposure to aqueous environments. This finding supported the need for an additional stabilization step before *in vivo* application.

To address this issue, we introduced a thermal annealing step as a critical post-treatment. Annealing promotes molecular chain rearrangement and crystallization of PVA, forming a denser and more stable physically crosslinked network that effectively “locks in” the salt-induced structural reinforcement. Using this approach, we successfully fabricated a PVA hydrogel with outstanding mechanical properties: an average tensile strength of 8.93 ± 1.46 MPa and elongation at break ranging from 250% to 350%. These values exceed those reported for native dura mater (tensile strength ~ 3.5 – 5 MPa, elongation at break ~ 20 – 62%),²⁰ indicating that the material had sufficient mechanical strength and elasticity for experimental dural repair. Both *in vitro* and *in vivo* degradation tests indicated that the material maintained relatively low swelling during gradual degradation, which may help reduce swelling-related compression risk and support short-term structural stability.

Nevertheless, in animal implantation studies, we observed a degree of foreign body reaction and fibrous encapsulation, likely due to a significant modulus mismatch between the implant and host tissue. Such modulus mismatch may trigger local immune responses and fibroblast accumulation, potentially impairing tissue integration. Therefore, future studies should further optimize biomechanical matching between the Janus PVA membrane and native dura mater.

Dural repair involves a complex biological process. Current understanding suggests that fibroblasts, vascular endothelial cells, and inflammatory cells play key roles: fibroblasts secrete collagen to reconstruct the dural matrix, endothelial cells mediate neovascularization to support tissue regeneration, and inflammatory responses contribute to early cell recruitment and debridement.^{21,22} However, excessive fibroblast activation can lead to epidural fibrosis and adhesion to brain tissue, severely compromising postoperative recovery.^{23,24} Therefore, functional compartmentalization is important for dural substitutes: the side facing the dural defect should support cell adhesion and tissue regeneration, whereas the side facing the brain should inhibit cell attachment and reduce adhesion.^{25,26} Additionally, the material must exhibit excellent watertightness to effectively prevent CSF leakage.

This study successfully constructed a Janus membrane with a gradient pore structure and differential surface wettability using directional freezing. SEM revealed that one side of the membrane exhibited large, interconnected pores conducive to cell infiltration, while the other side formed a dense layer that effectively blocked fluid penetration. CA measurements further confirmed a significant difference in surface wettability between the two sides. Cell migration assays demonstrated that the Janus membrane effectively blocked fibroblast infiltration on both sides, confirming

its capability as a physical barrier against cell penetration. *In vivo* experiments showed that the Janus membrane reduced tissue adhesion and CSF leakage compared with the untreated defect and FSA-PVA control groups, supporting the rationale of the asymmetric structural design.

The *in vivo* maintenance of the Janus properties may be related to the membrane's intrinsic asymmetric structure rather than a simple surface coating. The porous hydrophilic side may promote cell infiltration and tissue integration, whereas the dense hydrophobic side may limit cell adhesion and fluid penetration. Annealing likely stabilizes this architecture by enhancing PVA crystallization and physical crosslinking, thereby reducing swelling and structural relaxation. During degradation, the porous side may be gradually replaced by regenerated dura-like tissue, while the dense side may persist longer as an anti-adhesive barrier. However, protein adsorption, inflammation, mechanical stress, and degradation may progressively weaken this asymmetry. Future studies should evaluate time-dependent changes in wettability, microstructure, degradation, and anti-adhesion performance after implantation.

Biological safety is a prerequisite for clinical use of any biomaterial. In this study, we systematically evaluated the biocompatibility of the material using multiple assays. CCK-8 cytotoxicity tests showed that cell viability remained above 80% when cultured with hydrogel extracts, and live/dead staining revealed no obvious increase in cell death, indicating acceptable *in vitro* cytocompatibility. Subcutaneous implantation and histopathological examination of major organs showed no apparent severe inflammatory response, necrosis, or major-organ pathological abnormalities within the 30-day observation period. However, longer-term systemic safety during degradation still requires further evaluation.

Limitations

This study has several limitations. First, as an exploratory study, the comparative evaluation with clinically used commercial dural substitutes, such as Durepair®, was limited. Except for the subcutaneous implantation experiment, commercial materials were not included as controls in the assessments of material properties, *in vitro* biocompatibility, dural defect repair efficacy, or postoperative tissue adhesion. Instead, the present work mainly focused on comparing the modified Janus PVA membrane with its precursor materials to clarify the effects of directional freezing, salt leaching, annealing, and asymmetric surface modification. This design limits the ability to draw conclusions regarding comparative performance relative to existing clinical products. Second, the lack of validation in large animal models limited the assessment of suturability and surgical handling. Third, the 30-day *in vivo* follow-up period was insufficient to evaluate long-term degradation, chronic inflammation, late-stage fibrosis, changes in mechanical properties, and *in vivo* stability of the Janus structure. Finally, the long-term interaction between the material and brain tissue, as well as its potential effects on neurological function, remains to be investigated. Further systematic comparisons with commercial dural substitutes and longer-term large-animal studies are needed to evaluate the safety and practical feasibility of this material for dural repair.

Conclusions

In this study, a hydrophilic/hydrophobic Janus membrane was developed via directional freezing, salt leaching, and annealing of a PVA hydrogel for dural repair. The synergistic strategy enhanced mechanical strength and toughness while maintaining structural

stability under physiological conditions. The Janus architecture was designed to support tissue integration on the hydrophilic side and reduce tissue adhesion on the hydrophobic side, contributing to reduced CSF leakage and tissue adhesion in a rat dural defect model. The membrane also showed favorable biocompatibility, slow degradation, and low swelling under the current experimental conditions. These findings suggest that the engineered PVA-based Janus membrane may serve as a promising candidate for further evaluation as a dural repair material.

Supporting information

Supplementary material for this article is available at <https://doi.org/10.14218/NSSS.2025.00045>.

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Conflict of interest

XJ has been an Executive Associate Editor of *Neurosurgical Subspecialties* since July 2024. The authors declare that they have no other conflict of interest.

Author contributions

Contributed to the study concept and design (XJ, HJ), acquisition of data (SW, HL), performance of assays and data analysis (HL, SW, BZ), drafting of the manuscript (SW, HL, BZ), critical revision of the manuscript (XJ, HJ), and supervision (XJ, HJ). All authors made significant contributions and approved the final version of the manuscript for publication.

Ethical statement

This study did not involve human participants. All animal procedures were approved by the Animal Ethics Committee of the Hubei Provincial Center for Food and Drug Safety Evaluation, China (Safety Evaluation Center Animal [Welfare] No. 20252-6358). All animal experiments were conducted in accordance with institutional guidelines and applicable national regulations for the care and use of laboratory animals. All efforts were made to minimize animal suffering and reduce the number of animals used.

Data sharing statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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