Wu et al. BioMed Eng OnLine (2024) 23:112
https://doi.org/10.1186/s12938-024-01302-3

BioMedical Engineering OnLine

RESEARCH Open Access

Human acellular amniotic membrane/polycaprolactone vascular grafts prepared by electrospinning enable vascular remodeling in vivo

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Abstract

Background: Vascular transplantation is an e□ective treatment for severe vascular lesions. The design of the bioactive and mechanical properties of small-caliber vascular grafts is critical for their application in tissue engineering. In this study, we sought to develope a small-caliber vascular graft by electrospinning a mixture of a human acellular amniotic membrane (HAAM) and polycaprolactone (PCL).

Results: Mechanical tests showed that the vascular grafts were strong enough to endure stress from adjacent blood vessels and blood pressure. The biocompatibility of the HAAM/PCL vascular grafts was evaluated based on cell proliferation in vitro. The tubular formation test demonstrated that vascular grafts containing HAAM could improve human umbilical vein endothelial cell function, and in vivo implantation was performed by replacing the rat abdominal aorta. The HAAM/PCL vascular graft was found to promote attachment and endothelial cell retention. The regenerated smooth muscle layer was similar to native arteries' smooth muscle layer and the endothelium coverage was complete.

Conclusions: These results suggest that our constructs may be promising vascular graft candidates and can potentially be used to develop vascular grafts that can endothelialize rapidly in vivo.

Keywords: Human amnion membrane, Polycaprolactone, Small-caliber vascular graft, Endothelialization, Angiogenesis, Electrospinning, In vivo

Introduction

Cardiovascular disease has one of the highest incidence and mortality rates of any disease worldwide. According to the World Health Organization, the projected number of fatalities from cardiovascular disease will reach 23.3 million by 2030 [1]. Vascular transplantation is an e ective treatment for severe vascular lesions, and autologous blood vessels are the most ideal vascular substitutes [2]. However, autologous blood vessels

are di cult to obtain owing to their poor quality and insu cient quantity; therefore, research and development of artificial vascular grafts is essential.

Small-caliber vascular grafts (diameter < 6 mm) have been the focus of research for many years [3, 4]. However, small-caliber vascular grafts are prone to thrombosis owing to their slow local blood-flow velocity, small vessel diameter, complex blood-flow environment, and low intraluminal blood pressure [5]. Consequently, the long-term patency rate of small-caliber vascular grafts is poor. e physical and chemical properties and biocompatibility of materials are important factors to be considered in the preparation of ideal small-caliber vascular grafts. Vascular graft materials must have good biocompatibility and be conducive to cell adhesion and proliferation [6]. Furthermore, they must be non-immunogenic, non-inflammatory, nontoxic, stable, and easy to store.

Artificial vascular grafts are commonly fabricated through in situ tissue-induced regeneration processes. [7]. After preparation, the vascular graft is implanted into the body to provide a three-dimensional vascular graft for vascular regeneration and cell infiltration [8, 9]. In recent decades, small-caliber vascular grafts constructed from polymers and natural materials have been developed [10, 11]. However, owing to limitations in biocompatibility, degradation, and induction of inflammatory reactions by the materials, no well-established preparation method for small-caliber vascular grafts have been commercialized.

Natural materials, such as collagen, chitosan, fibrin, and acellular vascular matrix, have been widely used as the biomaterial backbone of the vascular graft. Usually, these natural ECMs are harvested from xenogenic, digested ECMs that can be triggered to re-crosslink. Furthermore, xenogeneic natural materials can carry antigens and pathogens such as galactose-alpha-1,3-galactose [12, 13], which could induce inflammatory reactions after implantation [14–17]. Consequently, the application of natural biomaterials for the preparation of small-caliber vascular grafts is limited. e preparation of materials with good biocompatibility and the modification of their surface activities needs to be studied.

e human amnion membrane (HAM) is a layer of the fetal membrane with a thickness of 20–50 μm [18]. HAM is a translucent membrane including five-layered structure. Amniotic membranes are widely used in regenerative medicine owing to their beneficial functions and characteristics [19]. e human acellular amniotic membrane (HAAM), the extracellular matrix of the HAM, does not contain amniotic epithelial cells but preserves the beneficial properties of HAM [20]. HAAM is composed of collagen III, IV, and V, fibronectin, elastin, proteoglycans, transforming growth factor-beta, and epidermal growth factor [21].

In previous studies, we successfully prepared a HAAM and found that it had good biocompatibility and no immunogenicity [20]. However, following acellular treatment, the mechanical properties of the amniotic membrane deteriorated, making it di cult to prepare small-caliber vascular grafts.

Polycaprolactone (PCL) is a nontoxic polymer with good mechanical properties that can extend to 1000% of its length before rupturing after dissolution in chloroform [22]. It is an in vivo vascular graft material with strong hydrophobicity and degrades at a slower rate than other materials [23]. ese problems can be solved by combining natural materials, such as gelatin, silk fibroin, and collagen, with synthetic polymers. e inclusion of

natural materials could enhance the biocompatibility of the vascular grafts. To improve the biocompatibility of polymers-based grafts, PCL is blended with collagen and formed into network structure by electrospinning. Ma et al. and Lu et al. demonstrated that polymer/natural materials combination grafts are a promising material for vascular tissue engineering [24, 25]. HAAM not only contains collagen, but also vasoactive substances.

e combination of HAAM-PCL could enhance biocompatibility and promote vascular regeneration. LIU et al. constructed a graft by shaping the HAM membrane into a tubular structure and then wrapping the electrospun PCL/silk fibroin around it to form the luminal surface [26]. ey use HAM as the inner-face of the grafts, while PCL/SF ensures a stable vascular framework. Currently, there is no research on directly mixing HAM and PCL for the preparation of blood vessels, which could potentially make the process more convenient.

In this study, an artificial vascular graft was prepared by electrospinning a mixture of HAAM and PCL, and in vivo and in vitro experiments were performed to explore the mechanical properties, biocompatibility, and e ects of vascular grafts on cell migration, proliferation, and di erentiation.

Results

Morphology and mechanical properties of vascular grafts

HAM was peeled o by blunt dissection. ere were epithelial cells on the HAM (Fig. 1a). Following the decellularization process, H&E staining (Fig. 1b) confirmed the movement of cells. HAAM/PCL-composite vascular grafts were prepared by electrospinning (Fig. 1d). e inner diameter of the vascular grafts was 3 mm and the average wall thickness was ~ 0.5 mm. e graft consisted of randomly distributed fibers with a diameter of 1–4 μm (Fig. 1C). A suitable vascular graft must have appropriate

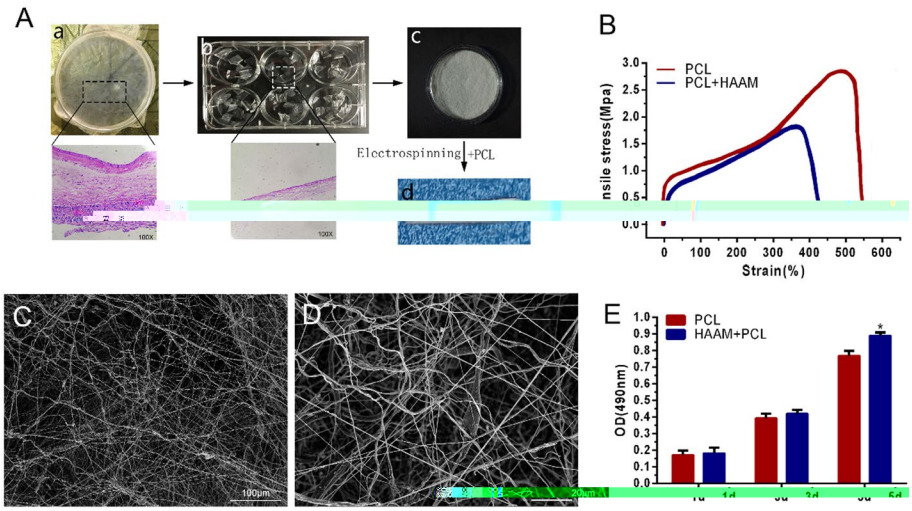

Fig. 1 **A a** HAM after blunting dissection. **b** After dissociating with 0.02% EDTA and scraping, the human acellular amniotic membrane (HAAM) was cut into small pieces. Hematoxylin and eosin (H&E) staining confirmed that the human amnion membrane epithelial cells had been removed. **c** HAAM was crushed in a ball mill. **d** HAAM/PCL-composite vascular grafts were prepared by electrospinning. **B** Representative stress–strain curves of di erent vascular grafts. **C**, **D** Scanning electron microscopy images for the HAAM-polycaprolactone (PCL) vascular grafts. **E** OD value was calculated using the methylthiazol tetrazolium (MTT) assay every 2 days. *$p < 0.05$

mechanical properties; the better the mechanical properties, the higher the reliability of the vascular graft. A representative stress–strain curve is shown in Fig. 1B. e mechanical properties of the vascular grafts are shown in Table 1. e Young's modulus of the HAAM/PCL vascular graft was about 8.05 ± 1.12 MPa, whereas the strain and stress at break were 421.2 ± 21.2% and 1.76 ± 0.21 MPa. e suture strength was 1.42 ± 0.28 MPa (Table 1). is indicates that the ultimate tensile strength of the mixed-material vascular graft was slightly lower than that of the PCL-only vascular graft. Compared to native arteries, the mechanical properties of these vascular grafts were su ciently strong to endure stress from adjacent blood vessels and blood pressure.

Cytocompatibility

e proliferation of HUVECs in the artificial vascular grafts were tested. Cells were cultured on vascular graft disks and the OD value was determined using the MTT assay. As shown in Fig. 1E, HUVECs grew significantly faster on HAAM-PCL vascular grafts than on PCL vascular grafts.

E ects of HAAM/PCL vascular grafts on angiogenesis in vitro

e e ects of HAAM/PCL vascular grafts on the angiogenesis in vitro were determined (Fig. 2). e tube length and number of nodes were significantly better for HAAM/PCL vascular grafts than for PCL vascular grafts and blank group at 6 h. Furthermore, the node number in the HAAM/PCL vascular grafts was significantly higher than that in the PCL vascular grafts and blank group at 12 h. ere are no significantly di erence between the PCL vascular grafts and blank group. In both vascular grafts, peak tube formation occurred at 6 h, indicating that vascular grafts containing HAAM could improve HUVEC functions, such as tube formation.

Cell migration assay of HUVECs in vitro

In the cell migration assay (Fig. 3), cells migrated 48.76 ± 16.19% and 38.33 ± 14.41% of the wound distance in the HAAM/PCL and PCL vascular grafts, respectively. Although vascular grafts containing HAAM improved cell migration, no significant di erences were observed between the two types of vascular grafts.

In vivo tests

We used an abdominal aorta transplantation model in rats to evaluate the performance of vascular grafts in vivo and harvested the implants at 4 weeks. A PCL vascular graft was used as control. No thrombosis or aneurysms were observed in either group. Both groups of vascular grafts maintained their shape before implantation (Fig. 4A, B).

Table 1 Mechanical properties of the vascular grafts

Measurement ($n = 3$)	HAAM/PCL	PCL
Young's modulus (MPa)	8.05 ± 1.12	7.19 ± 0.34
Maximum stress (MPa)	1.76 ± 0.21	2.87 ± 0.13
Strain at rupture (%)	421.2 ± 21.2	553.0 ± 13.2
Suture strength (MPa)	1.42 ± 0.28	2.03 ± 0.43

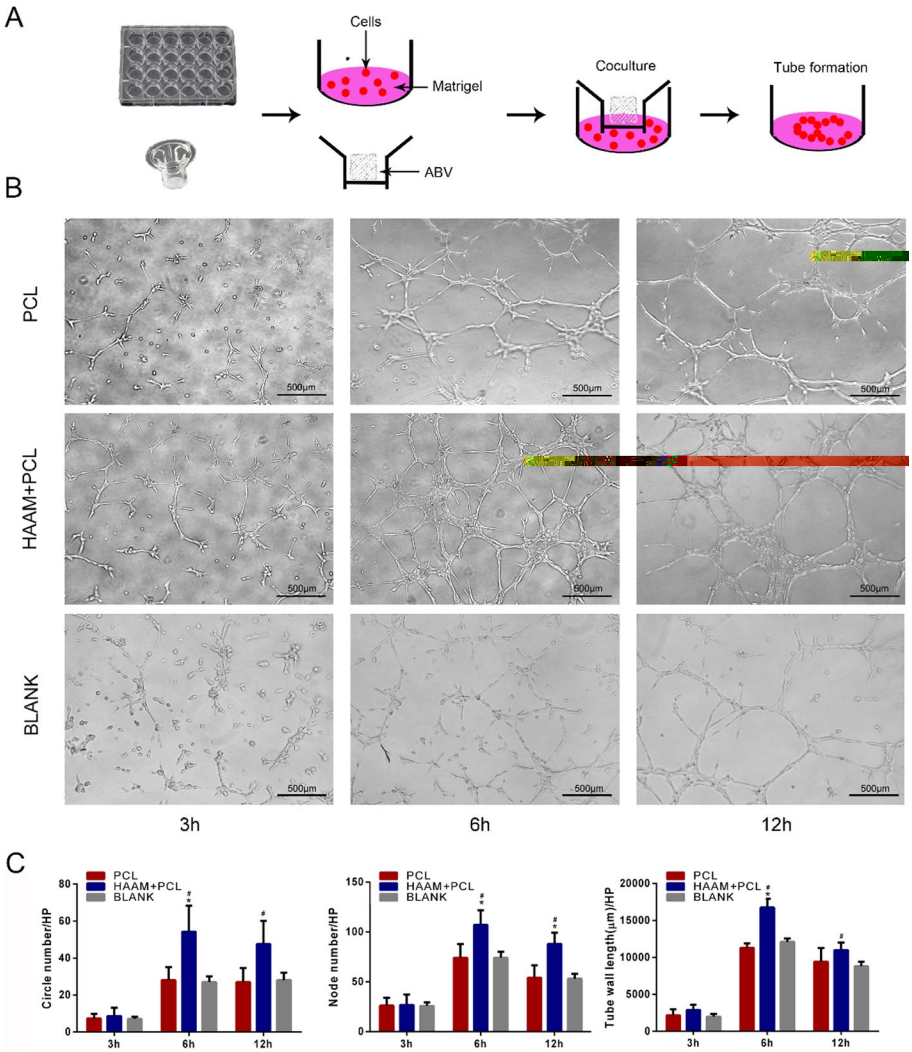

Fig. 2 Human umbilical vein endothelial cells (HUVECs) were co-cultured with HAAM-PCL vascular grafts and PCL vascular grafts. Tubule formation was analyzed. **A** Schematic illustration of culture design. **B** Optical microscopy images of tubular formation. **C** Tubular formation was assessed in terms of number of circles, tube wall length and number of nodes. *$p < 0.05$ between PCL and HAAM + PCL; #$p < 0.05$ between HAAM + PCL and BLANK

Ultrasonography also indicated that the vascular grafts were free of thrombi (Fig. 4C, D). Hematoxylin and eosin staining confirmed that vascular grafts were patent (Fig. 5).

e endothelium plays an important role in the maintenance of vascular homeostasis. At 4 weeks, the H&E and SEM images showed more endothelium in the HAAM/PCL group (Figs. 5, 6) than in the PCL group. CD31 staining showed that the monolayer had an endothelial coverage of 79.87 ± 10.59% and 46.43 ± 6.96% in the HAAM/PCL and PCL vascular grafts, respectively. ese results indicated that the HAAM/PCL vascular graft promoted endothelialization in vivo (Fig. 7E).

Furthermore, we performed immunofluorescence staining with α-SMA antibodies to examine the e ect of HAAM/PCL vascular grafts on SMC regeneration. e average thickness of α-SMA was 30.24 ± 7.52 and 13.18 ± 4.11 μm in the HAAM/PCL and

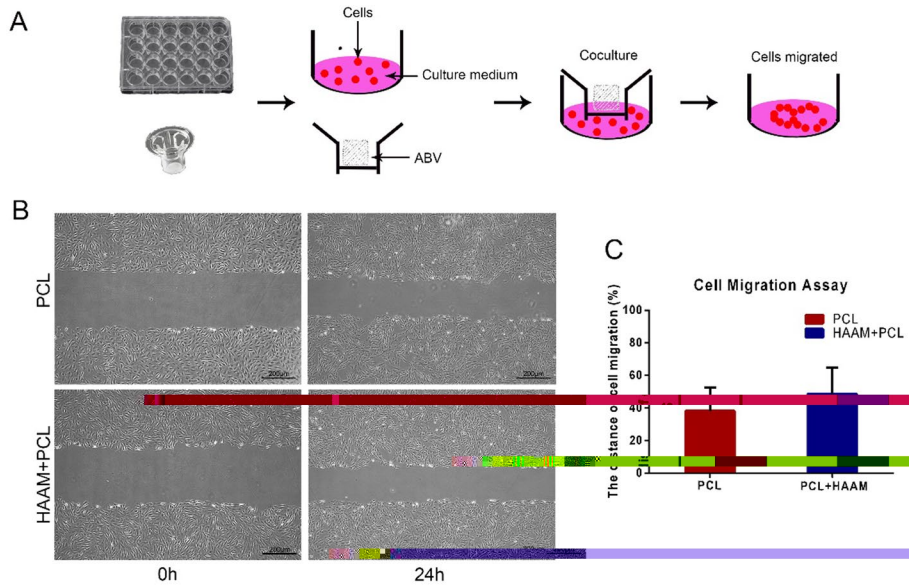

Fig. 3 Cell migration assay of human umbilical vein endothelial cells (HUVECs) was analyzed. **A** Schematic illustration of culture design. **B** Optical microscopy images of cell migration among two groups. **C** Cell mobility was calculated in two groups. No significant di erence was observed between the two vascular grafts

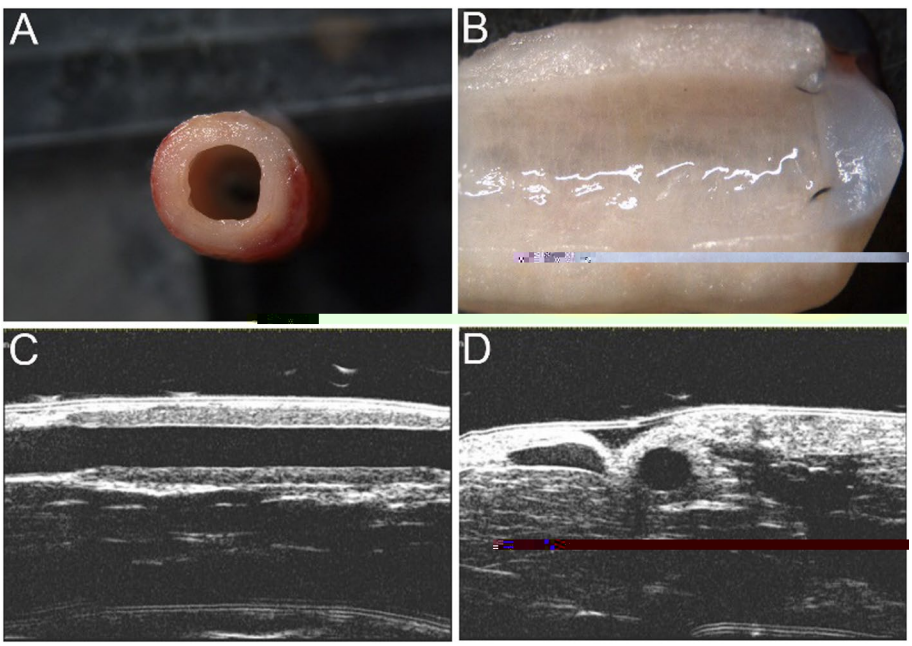

Fig. 4 Evaluation of the vascular graft in vivo. **A**, **B** The luminal morphology of the human acellular amniotic membrane (HAAM)-polycaprolactone (PCL) vascular graft at 4 weeks was observed under a stereomicroscope. **C**, **D** Ultrasound image of the HAAM-PCL vascular graft at 4 weeks

PCL vascular grafts, respectively (Fig. 7F). SM-MHC immunofluorescence staining is a test for the mature SMC regeneration. e thickness of SM-MHC was 27.25±6.97 and 9.59±3.98 μm in the HAAM/PCL and PCL vascular grafts (Fig. 7I).

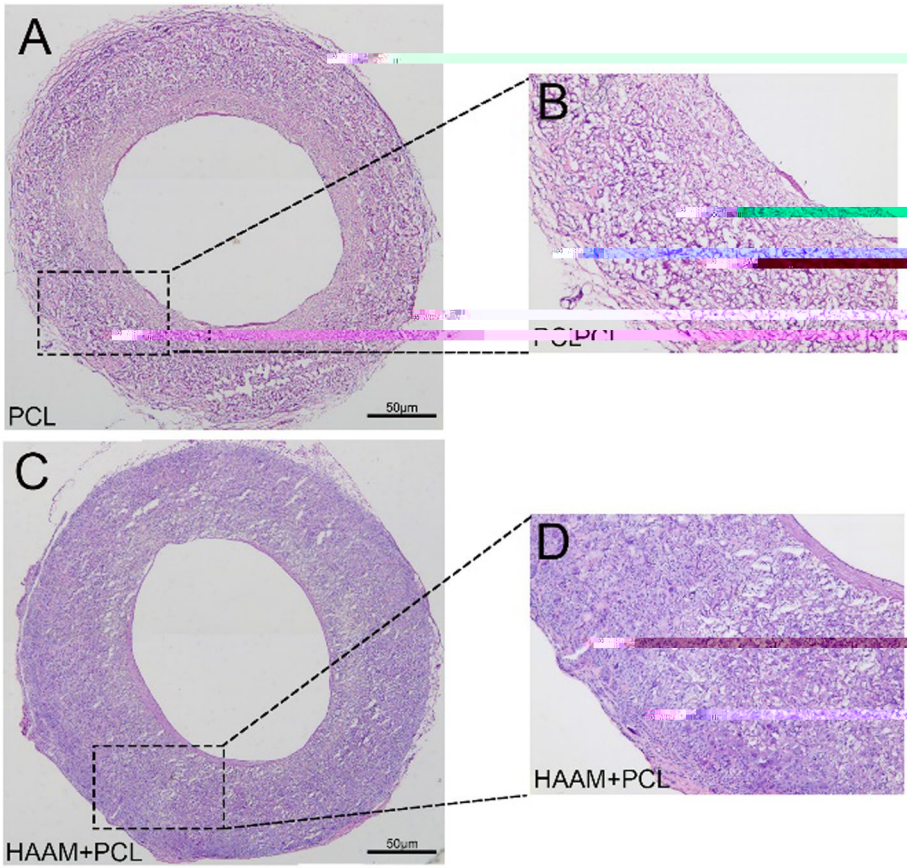

Fig. 5 Regeneration of vascular media layer within the vascular graft during the implantation time. **A**, **C** Transverse sections of the polycaprolactone (PCL) and human acellular amniotic membrane (HAAM)/PCL vascular grafts stained by hematoxylin and eosin staining. **B**, **D** H&E revealed more endothelium in the HAAM/PCL group

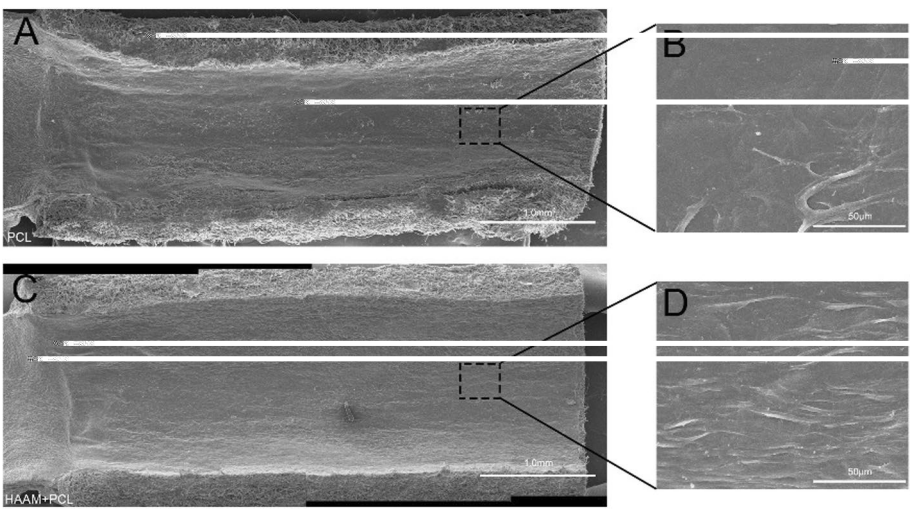

Fig. 6 Endothelialization of the luminal surface of vascular grafts. **A**, **C** Scanning electron microscopy image of the interior surface of vascular grafts cut in half longitudinally. **B**, **D** High magnification image of the surface

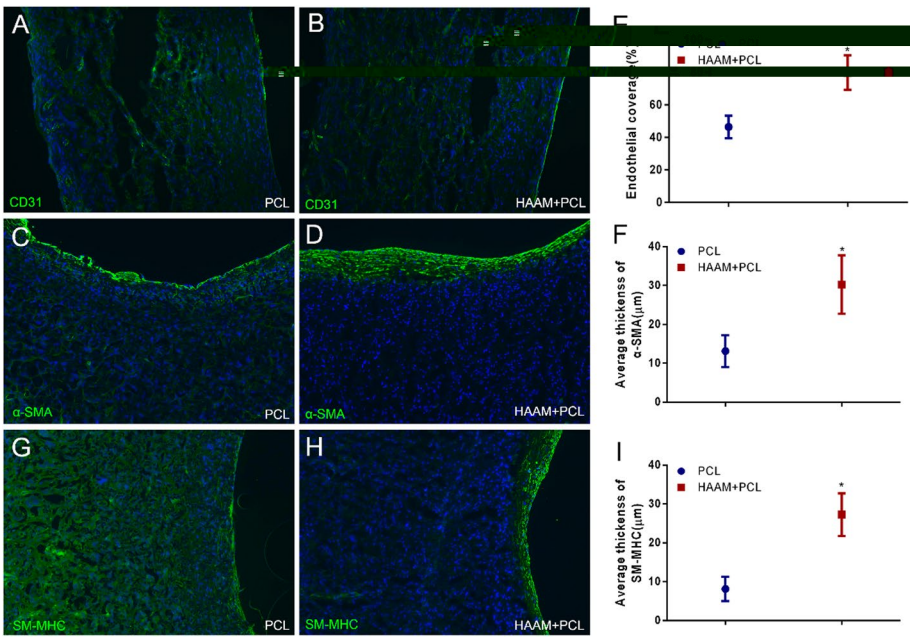

Fig. 7 **A**, **B** Images of immunofluorescent staining of vascular grafts using the CD31 antibody. **E** At 4 weeks after implantation, 79.87 ± 10.59% of the surface was covered by CD31 + cells in the in human acellular amniotic membrane (HAAM)/polycaprolactone (PCL) vascular grafts, whereas 46.43 ± 6.96% was covered in the PCL vascular grafts. **C**, **D** Immunofluorescence images of α-SMA. **F** The average thickness of α-SMA was 30.24 ± 7.52 μm in the HAAM/PCL vascular grafts, whereas it was 13.18 ± 4.11 μm in the PCL vascular grafts. **G**, **H** Immunofluorescence images of SM-MHC. **I** SM-MHC between two groups. *$p < 0.05$

Discussion

Numerous studies have focused on developing appropriate vascular grafts for the treatment of cardiovascular diseases; however, this remains challenging as an e ective vascular graft should mimic the in vivo environment, both structurally and functionally.

PCL is an in vivo vascular graft material with excellent mechanical properties and biocompatibility as well as strong hydrophobicity and biological inertia [27]. Because of their inability to induce cell proliferation and migration, vascular grafts composed solely of PCL are not ideal candidates for vascular transplantation. While some studies have improved the bioactivity of PCL through chemical modifications, this is a time-consuming and expensive process, which limits its future clinical applications [28].

Some vascular grafts can also originate from decellularized xenogenic tissues, typically sourced from pigs [29]. e advantage of decellularization over synthetic materials is that it preserves the native components of the vascular ECMs, potentially facilitating a more rapid vessel remodeling. However, there can be severe immune reactions to xenogeneic cells and materials. Despite advancements in decellularization techniques that have reduced the presence of immune reactions, the complete removal of immunogenic biomolecules remains a significant challenge [14]. HAM, as an allogeneic biomaterial, is preferred for vascular tissue engineering templates due to its endothelialization [30]. Furthermore, HAM demonstrates no immunogenicity following decellularization.

In this study, a bioactive vascular graft was developed by mixing HAAM with PCL. After decellularization, the HAAM preserved the components responsible for the structural integrity and bioactivity of the amniotic membrane matrix. In previous studies, we

found that HAAM improved the adhesion and growth of bone marrow mesenchymal

vascular grafts will have better thrombosis performance. After implantation, endothelialization takes place through the migration of endothelial cells from the anastomotic sites. Nevertheless, achieving complete endothelialization, particularly in the center of the grafts, is challenging. To overcome this, several studies have focused on applying growth factors to the surface of vascular grafts in order to promote endothelialization [39, 40]. Koobatian et al. presented an acellular vascular graft constructed using small intestinal submucosa. After functionalization with heparin and VEGF, the graft achieved rapid endothelialization [41]. In the future, the application of growth factors to the inner surface of HAAM/PCL vascular grafts may enhance their capacity for rapid endothelialization.

Four weeks after implantation, a layer of SMCs was observed on both HAAM/PCL and PCL vascular grafts without thrombus. e average thickness of the SMC layer in the HAAM/PCL vascular grafts was approximately 30.24 ± 7.52 μm, which was thicker and smoother than that in the PCL vascular grafts. However, vascular injury leads to the dedi erentiation of smooth muscle cells, which contributes to the development of atherosclerosis and neointima formation. SM-MHC immunofluorescence staining is a test for the mature SMC regeneration. e average thickness of the mature SMC layer in the HAAM/PCL vascular grafts was thicker than that in the PCL vascular grafts.

e mature SMC phenotype maintains quiescence and is more inclined to express contractile proteins, such as SM-MHC (myosin-11). e regeneration of mature SMCs is deemed beneficial for vascular graft implantation due to their role in vascular contraction and relaxation, extracellular matrix composition, and preserving EC stability [42].

is di erence may be attributable to enhanced cellular infiltration. Zoe et al. reported that vascular endothelial growth factor recruits SMCs and ECs to vascular grafts [43]. HAAM is rich in VEGF and other bioactive factors that accelerate the infiltration and recruitment of SMCs in vivo. Physiological phenotype of SMCs can be maintained by ECs. SMCs and ECs work together to prevent thrombosis.

Conclusion

In summary, the HAAM/PCL vascular grafts exhibited good biocompatibility and their mechanical properties provided good in vivo support. Furthermore, the vascular grafts promoted the infiltration and migration of ECs and SMCs into the vascular graft in vivo. is study provides a foundation for the future clinical applications of HAAM/PCL vascular grafts.

Methods

Materials

e study was approved by the institutional review board of Fuwai Hospital, Beijing, China. Before placenta collection, the written informed consent was obtained from the donors. Human placentas were obtained at the time of cesarean section from healthy donors in accordance with the Declaration of Helsinki. All the procedures were performed under aseptic conditions. PCL (Mw = 80,000) was purchased from Sigma-Aldrich (St. Louis, USA).

Preparation of HAAM/PCL mixture

HAAM was prepared as described previously [20]. Briefly, HAM was peeled o by blunt dissection. Subsequently, it was incubated at 37 ℃ for 1 h with 0.02% EDTA. en using a cell scraper to remove the epithelial. e resulting HAAM was then dried in a vacuum freeze dryer for 24 h, cut into 2×2 cm pieces, and crushed in a ball mill to prepare HAAM particles with a diameter of ~ 40 μm. Subsequently, amniotic membrane and PCL (1/1, w/W) were mixed and dissolved in hexafluoroisopropanol to prepare a mixed solution with 10% concentration (w/V). e mixed solution was then taken in a 20-mL glass syringe (21-gauge needle). ereafter, the flow rate of the syringe pump was set to 4 mL/h. e collector was set at a distance of 13 cm, and a voltage of 17 kV was applied. To construct a vascular graft, a stainless-steel rod rotating mandrel (3-mm diameter) was used as the collector. We obtained a vascular graft by removing the mandrel. Additionally, PCL vascular grafts were fabricated and used as controls.

Mechanical test

e longitudinal mechanical properties were measured by using a tensile testing machine (100 N, Germany Shenke Co., Ltd. M1600). Vascular grafts ($n=3$) were clamped 1 cm apart. e vascular graft was pulled longitudinally at 10 mm/min until rupture. e maximum stress and strain at the time of the vascular graft rupture were recorded and the corresponding stress–strain curve was drawn based on the measurement results. Suture retention strength was measured using a 6-0 suture placed 2 mm away from the edge of the vascular grafts with a constant elongation as well as tension test until the grafts or sutures was fractured.

Microstructure of vascular graft

For scanning electron microscopy (SEM), the vascular grafts were freeze-dried for 48 h. After drying, the sample was installed on an aluminum plate, coated with gold, and examined using a scanning electron microscope (TECNAI G2 F30, Fei, Ned).

Cell proliferation in vitro

Human umbilical vein endothelial cells (HUVECs) (PCS-100-010, ACTT) were cultured in an Endothelial Cell Medium (ScienCell, USA). e vascular grafts ($n=3$) were cut open (disk inner diameter = 5 mm) and rehydrated in complete medium for 24 h. Subsequently, 2×10^3 cells (HUVSCs) were cultured on a 96-well plate for 36 h. e medium was changed every 48 h. On days 1, 3, and 5, the methylthiazol tetrazolium (MTT) assay was performed to assess cell metabolic activity.

Cell migration assay of HUVECs in vitro

HUVECs were inoculated in 24-well Petri dishes. After the cells were fully fused, a wound was made using the tip of a 1-ml sterile pipette. e isolated cells were then washed with PBS. A Transwell insert with vascular grafts ($n=3$) was then placed in the upper part of each hole and images were acquired immediately using an inverted microscope (Olympus Corporation, Tokyo, Japan). After incubation for 24 h, cells that migrated to the scratched area were photographed under an inverted microscope. e

cell mobility was calculated as follows: cell mobility = (wound length at 0 h − wound length at 24 h)/wound length at 0 h × 100.

Tubular formation of HUVECs in vitro

e cell tube formation assay was performed as described previously [20]. Briefly, a tubular formation test was performed using Matrigel (BD Bioscience, USA). 24-well plates were coated with Matrigel. A total of 1 × 104 cells were cultured in each well of a 24-well plate and the Transwell insert with the vascular grafts ($n = 3$) was placed on the upper part of each well. Blank group only coated with Matrigel. At specific time points (3, 6, 12 h), the random microscopic images of cells were photographed by using an inverted light microscope (Olympus Corporation). Mesh-like circles (circles), number of branch points (nodes), and total tubule length were tested.

In vivo implantation

An abdominal aorta transplantation model was used to evaluate the performance of vascular grafts in vivo. e study was approved by the institutional review board of Fuwai Hospital, Beijing, China. Sprague–Dawley rats (males, 280–320 g) were injected with heparin (100 units/kg) through the caudal vein before surgery. Tubular vascular grafts (3.0-mm inner diameter, 450-mm thickness, 1.0-cm length) were used as arterial substitutes. Aspirin was administered daily as an anticoagulant for 1 week postoperatively (2 mg/kg). Each group had five parallel rats. Vascular graft patency was examined 1 month after implantation, and vascular patency was examined by ultrasound after anesthesia.

e rats were killed after 1 month, and the vascular grafts were removed for analysis.

Histological staining

e vascular grafts were fixed with 10% natural bu ered formalin, dehydrated by gradually increasing ethanol, and embedded in para n. e vascular grafts were cut into 6-μm slices. Subsequently, the samples were stained with hematoxylin and eosin.

Immuno uorescence staining

Endothelial cells (ECs) were identified using an anti-CD31 antibody (1:70; Abcam). Furthermore, smooth muscle cells (SMCs) were identified using mouse anti-α-SMA (α-SMA; 1:100, Abcam) and mouse anti-smooth muscle myosin heavy chain I (SMMHC, 1:100, Abcam) antibodies. Goat anti-mouse IgG (1:200; Invitrogen) was used as a secondary antibodies. Frozen sections were fixed in formaldehyde for 5 min. After washing with PBS, the sections were incubated with 5% normal goat serum (Zeye Biotechnology Co., Ltd., China) for 1 h at 4 ℃. e sections were incubated with mouse anti- α-SMA and anti-CD31 (1:70, Abcam) antibody at 4 ℃ overnight. Subsequently, the slices were washed five times with PBS and then incubated with goat anti-mouse IgG in PBS for 2 h. After washing with PBS, nuclei were counterstained with 4,6-diamino-2-phenylindole (ermo Fisher Scientific Inc. USA). e images were captured using a fluorescence microscope (Olympus Corporation, JPN). e endothelial coverage (the length of the EC layer/cm) was determined using ImageJ. e average thickness of the SMC layer was determined by dividing its area by its length. Each sample was tested in triplicates.

Statistical analysis

All of the data are expressed as mean ± SD. Statistical analyses were performed using a two-tailed unpaired *t*-test and one-way analysis of variance. Statistical significance was set at p value < 0.05.

Author contributions

Authors' contributions KT and JW contributed to conception and design of the study. LD is the surgeon of operation for animals. SL organized the data. YC conducted the cell experiments. JW wrote the first draft of the manuscript. All authors read and approved the final version of the manuscript.

Funding

This work was financially supported by the Fundamental Research Funds for the Central Universities (3332022019).

Availability of data and materials

No datasets were generated or analyzed during the current study.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethical committees and Internal Review Boards of Fuwai Hospital, Beijing, China. The written informed consent was obtained from the donors. Human placentas were obtained in accordance with the Declaration of Helsinki.

Competing interests

The authors declare no competing interests.

Received: 20 May 2024 Accepted: 25 October 2024
Published online: 06 November 2024

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