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Research article

Urinary bladder matrix scaffold improves the impact of adipose-mesenchymal stem cells on the function and structure of transplanted rat ovaries

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ABSTRACT

Ovarian transplantation presents significant advantages for the preservation of female fertility. Nonetheless, a substantial number of follicles are apoptosis during the process of ovarian tissue transplantation as a result of ischemic conditions. This study aimed to assess whether adipose-derived mesenchymal stem cells combined with urinary bladder matrix (ADSC/UBM) confer a greater therapeutic benefit compared to ADSCs alone. To achieve this, ADSC/UBM was applied during the autotransplantation of rat ovaries. Thirty rats were divided into five sets of six: the untreated control group (Normal), the oophorectomy group, the autograft group, the autograft + ADSCs group (ADSC), and the autograft + ADSC/UBM group (ADSC/UBM). After transplantation, the number of follicles in the ADSC/UBM group was significantly higher than that in the autograft group. Angiogenesis was enhanced following ADSC/UBM transplantation. Follicle-stimulating hormone (FSH) levels were significantly lower, and Anti-Müllerian hormone (AMH) levels were significantly higher in rats in the ADSC/UBM group than in the Autograft group. The apoptosis rate in the ADSC/UBM group decreased. The estrous cycle in the ADSC/UBM group recovered more quickly than the ADSC group. The data indicate that UBM improves ADSC retention in graft ovaries and aids in permanently restoring ovarian function, making ADSC/UBM a promising option for ovarian transplantation.

1. Introduction

In recent years, there has been an observed rise in the prevalence of cancer among young women [1], with chemotherapy and radiotherapy treatments leading to adverse impacts on ovarian function and subsequent infertility [2]. Currently, ovarian tissue transplantation serves as a significant strategy for preserving fertility in young women undergoing chemotherapy or radiation therapy [3]. In 2004, the first successful pregnancy from ovarian tissue transplantation proved the technique's clinical effectiveness. By 2017, the number of live births resulting from this procedure had exceeded 130, representing a substantial increase over the preceding two years [4]. The grafting process loses 20 %–65 % of follicles, so further refinement is needed [5]. Ischemia of ovarian tissue precedes

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reperfusion, leading to follicular apoptosis. The primary obstacle in ovarian transplantation is ischemic tissue injury [6]. Malek et al. [7] demonstrated that the transplantation of ADSCs improve the functionality of grafted rat ovaries by promoting angiogenesis; The limited application of stem cell is attributed to challenges such as poor stem cell implantation in the host [8],susceptibility to immune response, and inadequate growth signals. Bioscaffolds offer a three-dimensional framework that supports stem cell growth and differentiation by providing essential growth factors, cell adhesion sites, and signaling molecules [9]. The application of scaffolds for the delivery and support of grafted cells represents a promising strategy for the preservation of stem cells within transplanted organs [10].

The extracellular matrix (ECM) is a intricate three-dimensional framework composed of proteins, polysaccharides, and other molecules that provide structural and functional support to cells in tissues and organs [11]. ECM plays a crucial role in maintaining tissue integrity, facilitating cell adhesion, migration, and signaling. It is commonly utilized in clinical settings for applications such as reinforcing abdominal wall repair [12],.diabetic ulcers treatment [13], and the deep wounds treatment [14]. UBM is a kind of ECM that exhibits non-immunogenic properties and serves as a biological scaffold for neovascularization. According to research, UBM promotes stem cell differentiation in tissue healing [12]. In this study, autografting of ovaries within the rat kidney capsule was conducted, with the subsequent transfer of ADSCs to the graft site using UBM. An analysis was performed to assess whether the combination of UBM and ADSCs could improve the outcomes of ovarian transplantation.

2. Materials and methods

2.1. Chemicals and reagents

The ethics committee of the Shanghai Public Health Clinical Centre reviewed and approved each animal experiment (Ethical assessment 2023-A045-01). In the Second Military Medical University's SPF animal room, 8-week-old female SD rats weighing 160–180 g with normal estrous cycles were selected and fed following established protocols. Five experimental groups with random distributions of rats were created: 1. The normal group (n = 6) consists of the untreated normal group. 2. The rats in the Oophorectomy group underwent ovariectomy. 3. Rats in the autograft group (n = 6) received solely autograft. 4. Autograft with ADSC treatment in the ADSC group (n = 6), 5. Autograft with the treatment of ADSC/UBM in the ADSC/UBM group (n = 6). UBM was purchased from ZhuoRuan Medical Technology Co., Ltd. (China).

2.2. Isolation and identification of ADSC

Rat ADSCs were isolated and cultured according to previous methods described previously [15]. Adipose tissues were briefly removed from the male inguinal region of SD rats when they were 8–10 weeks old. The extracted ADSC cells were grown in 10 % FBS and 1 % penicillin-streptomycin high glucose DMEM (Gibco, Carlsbad, CA) media. The third generation of ADSCs were subjected to flow cytometry analysis (Becton Dickinson, USA) to ascertain cellular features. CD73, CD90, CD44, CD45, CD11b, and CD34 antibodies were found (BD Pharmingen, USA).

2.3. CCK8 assay

CCK8 assay was performed to indicate the proliferation-promoting effect of UBM on ADSCs. 96-well plate (n = 3) was used to prepare the UBM before incubating at 37 °C for 24 h. ADSCs were seeded on the UBM surface and the plate at a density of 10,000 cells/well and cultured with the medium, and ADSCs cultured with the medium only was the control group (n = 3). 48 h later, proliferation of ADSCs on the UBM were analysed with CCK8(Biyuntian, Shang Hai,China), according to the manufacturer's instructions. Briefly, 1, 3, 5, and 7 days after ADSCs were cultured, 10 μl CCK-8 was added to each well, 1.5 h later, the absorbance wavelength was obtained at 490 nm (ThermoWellscan MK3, USA).

2.4. Ovarian autografting

Rats in the ADSC/UBM, ADSC, and autograft groups received 3 % pentobarbital sodium of intraperitoneal injections (Shanghai Siyu Biotechnology, China, 0.1 ml/100 g) to induce anaesthesia. The ovary was removed in an aseptic setting. The two separated ovarian tissue pieces were then positioned beneath the ipsilateral renal capsule through a little incision made in the renal capsule. Per ovarian tissue in the autograft group, 40μLof phosphate-buffered saline (PBS) (Biyuntian, Shang Hai,China) were administered. For the ADSC group, 1×10^6 ADSCs were injected into each ovarian tissue in 40μLof PBS. The 3×3 mm^2 UBM/ADSC group received 1×10^6 suspended ADSCs.

2.5. CM-Dil-labeled ADSC tracing in vivo

When ADSCs reached 90 % confluency, the medium containing 2 mg/l chloromethyl dialkylcarbocyanine (CM-Dil) (1:200; Invitrogen; Thermo Fisher Scientific, Inc.) was used to continue the culture and the labeled cells were monitored using the Olympus BX51 microscope. To identify the ADSCs survival in vivo, rats were divided into ADSC group and ADSC/UBM group. Ovarian tissue transplantation procedure was conducted as describes previously. CM-Dil-labeled ADSCs were injected in the autograft ovary, and ADSC/UBM group received 1×10^6 CM-Dil-labeled ADSCs suspended on 3×3 mm^2 UBM.7 days after transplantation, The ovary tissues were sectioned, and were stained with DAPI monitor the ADSCs survival.

2.6. Number of follicles estimation

Rats were put under anaesthesia twenty-eight days after the transplant, followed by removing of ovaries from the renal capsule, the ovaries were sectioned at a thickness of 5 μm, and follicle counts were made after eosin and hematoxylin staining. The ovaries were cut into 5 μm sections, with three representative sections chosen from each ovary (n = 6). Every fifth segment of each autografted ovarian tissue was analysed in order to prevent repeatedly assessing the same follicle. Follicle assessment and follicle counting were carried out in accordance with established published criteria. These are categorized as primordial, primary, secondary, and antral follicles [16].

2.7. Hormone assay and vaginal smear examination

After 28 days of transplantation, Blood samples were collected. The level of FSH, and AMH hormone were assessed in accordance with the manufacturer's instructions using ELISA test kits from Xi Tang in China. After autograft, each rat's vaginal wall was carefully cleaned with sterile pipettes. The cells were then applied to a glass plate and observed with a light microscope (BX51; Olympus).

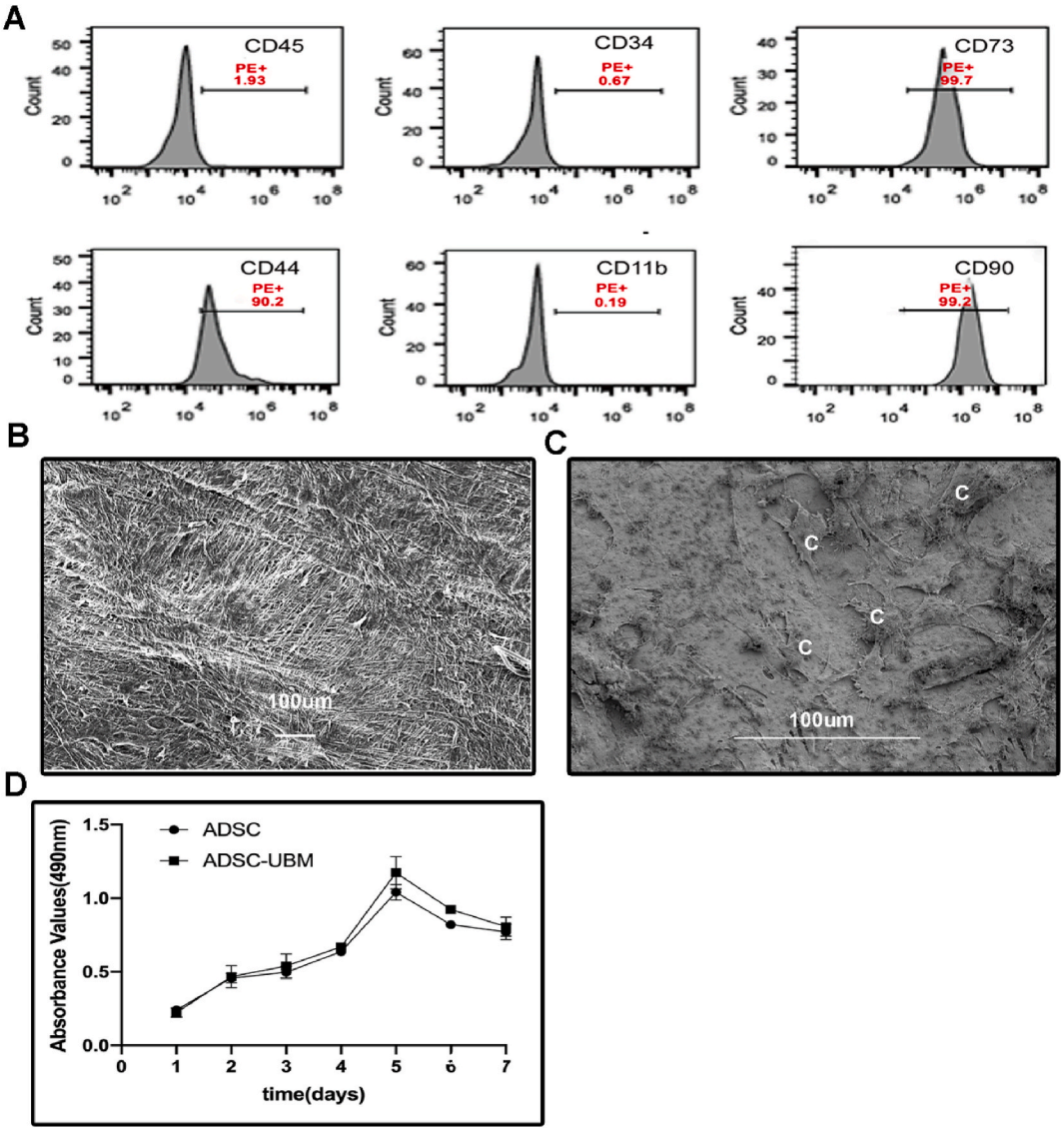

Fig. 1. Characterization of ADSCs and ADSCs grew well on UBM. A: Flow cytometric characterization of ADSCs. ADSCs were negative for CD45, CD11b, and CD34 and positive for CD44,CD90, and CD73. B: The SEM image of the UBM showed that it was porous, loose, and composed of sheet-like connective tissue and fibrous strands. C:The SEM image of ADSCs cultured on UBM showed that ADSCs grow well on UBM(c represents ADSC). D: ADSCs cultured on UBM presented the same proliferation rate with ADSCs cultured in DMEM medium by CCK8.

2.8. Immunofluorescence

CD31 was found in ovarian autografts that were 7- and 28-days post-transplant utilising immunohistochemical methods. Briefly, primary rabbit anti-CD31 (Bioworld, USA) was incubated on slides. Hoechst 33,342 was used as a counterstain (1:200; Sigma-Aldrich) on the nuclei. Fluorescent microscope (Nikon Eclipse, Japan) set at 200× magnification, and images were successively captured [7].

2.9. VEGFR2 assay

7- and 28-days post-ovary autografts, the ovarian tissues were harvested for Western blot and immunohistochemistry. For Western blot, ovarian tissues were sealed with RIPA buffer with protease inhibitor cocktail on ice, and the protein lysates were quantified. The antibodies we used in this study were VEGFR.After incubation, a secondary antibody coupled to horseradish peroxidase was applied to the membranes at room temperature for 1 h. For immunohistochemistry, the ovaries were sectioned into 5 μm sections, and then incubated with the primary anti-VEGFR2 (mouse, 1:25, Xi Tang, China), at 4 °C overnight and then placed in a secondary antibody and DAB (Merck, Germany).

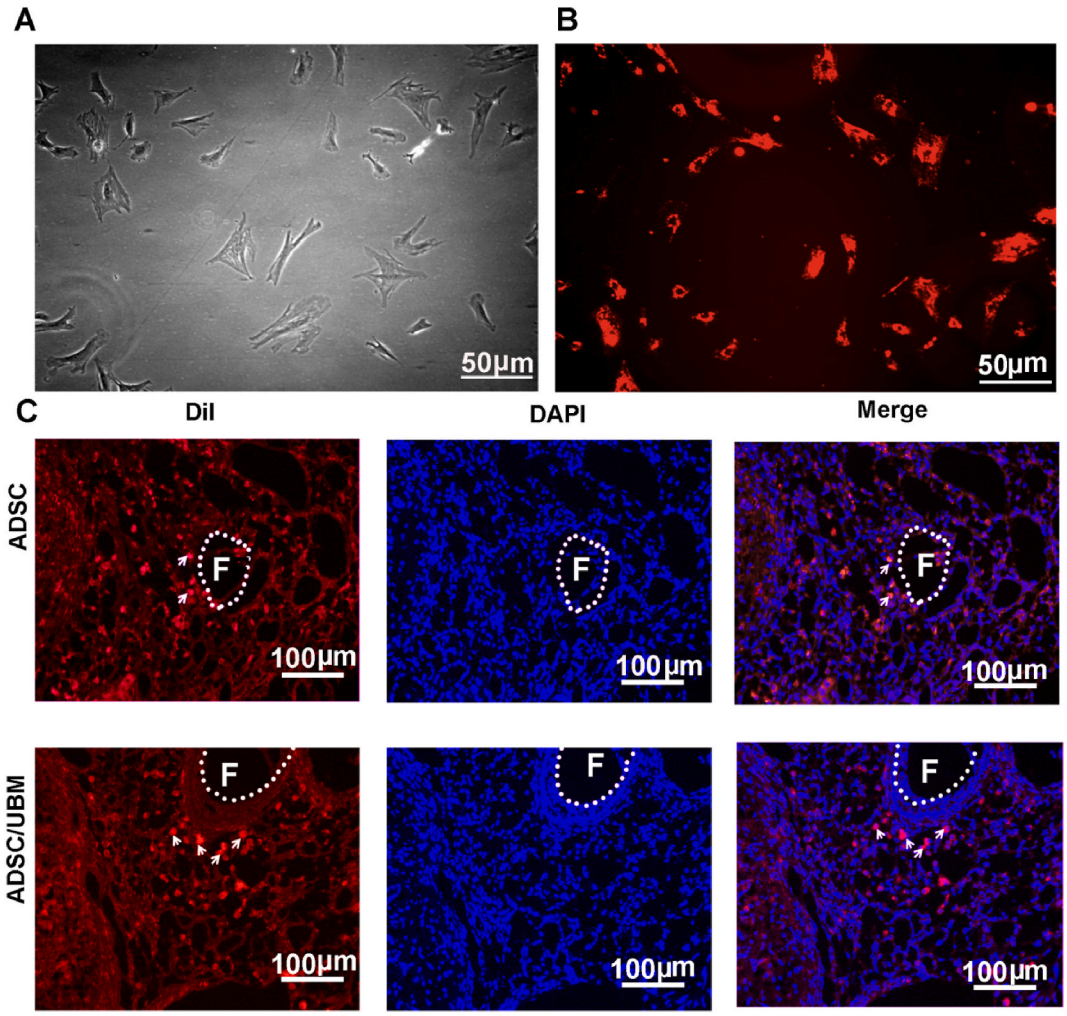

Fig. 2. Homing of cm-Dil stained ADSCs in transplanted ovarian tissue seven days after transplantation. A: ADSCs were cultured in DMEM medium 3 weeks after differentiated from adipose tissue. B: ADSCs were labeled with CM-Dil. C: The localization of cm-Dil stained ADSCs in transplanted ovarian tissue seven days after transplantation. Seven days after transplantation, more cm- Dil labeled ADSCs were found around the follicles in ADSC/UBM group. Immunofluorescence staining showed that CM-Dil labeled ADSCs (red) was more visible near follicles in the ADSC/UBM group compared to the ADSC group. Nuclei were stained with DAPI (blue). Arrow, CM-Dil labeled ADSCs.F, ovarian follicle. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.10. TUNEL analysis

The apoptosis rate was calculated by TUNEL assay 28 days after ovarian autografting (In Situ Cell Death Detection Kit; Roche). Software of Image-Pro Plus 6 (Media Cybernetics, USA) was used to estimate the apoptotic rate.

3. Results

3.1. ADSCs characteristics

According to the flow cytometry results, the cell markers of ADSCs were expressed as follows: positive markers were CD73, CD44, and CD90; and the negative markers were CD34, CD11b, and CD45. The results were consistent with the characteristics of adipose mesenchymal stem cells (Fig. 1A).

3.2. ADSCs grew well on the UBM

Under SEM, UBM showed loose three-dimensional structure (Fig. 1B). Filopodia on UBM were seen, and ADSCs were determined to be well-developed with long cytoplasmic processes (Fig. 1C). CCK8 showed that the proliferation of ADSC inoculated on UBM was the same as that in DMEM culture, which indicated that UBM could promote the proliferation of ADSCs (Fig. 1D).

3.3. Distribution of ADSCs in the autograft ovaries

Isolated cells were analysed by light microscopy (Fig. 2A) and we used cm-Dil to label ADSCs (Fig. 2B)and tracked the distribution 7days after transplantation. The ADSCs were found around the follicles. The fluorescence area of the ADSC/UBM group was substantially greater than the fluorescence area of the ADSC group (4.25 ± 0.25vs. 1.02 ± 0.06, $P < 0.001$). The results indicated that the addition of UBM increases the number of ADSCs retaining in the autograft ovaries (Fig. 2C).

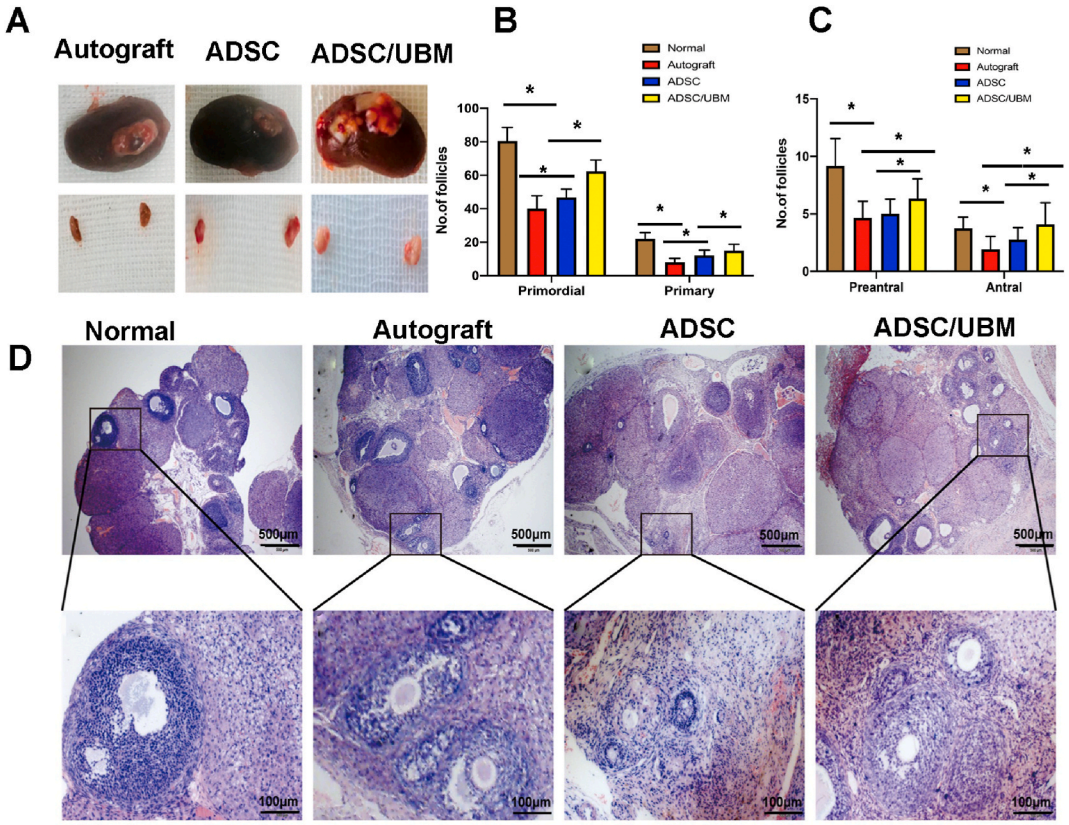

Fig. 3. Twenty-eight days after ovarian autografting and follicle evaluation. A:Ovarian tissue transplanted under the renal capsule and ovarian tissue removed from the renal capsule from various groups. B–C: The average number of primordial, primary, secondary, and antral follicles per section (n = 6). The values are given as mean SD. The *t*-test is used to calculate significance. *$P < 0.05$. D: H&E-stained representative sections of ovaries from various categories.

3.4. ADSC/UBM increases the number of follicles

The kidney was exposed to examine the transplanted ovaries on the 28th day following surgery. In each group, all autografted ovarian tissues survived, and new vessels sprouted from the kidney to the outer layer of graft. Fresh and living ovarian tissues were observed in the autograft. Rats in the ADSC and ADSC/UBM groups had more vessels than those in the autograft. In the group of ADSC/UBM, there was greater neovascularization in the rats (Fig. 3A). The mean number of follicles in each group was examined and counted 28 days following the autograft. The number of follicles in all stages of development was higher in the Normal group than in the other groups. The Autograft group had a significantly lower number of follicles in each stage, notably the primordial stage, as compared to the Normal group ($P < 0.05$). In comparison to the Autograft group, the number of follicles increased in the ADSC/UBM and ADSC groups ($P < 0.05$), with the ADSC/UBM rats having considerably more follicles ($P < 0.05$; Fig. 3B–D)., especially in primordial follicles. It indicated that ADSC/UBM decreased follicle loss during ovary transplantation.

3.5. ADSC/UBM improves the endocrine function of the autograft ovary and accelerate the recovery of the estrus cycle

After the autograft, the FSH serum level was significantly higher in the autograft group, ADSC group, and ADSC/UBM group than in the control. The FSH level was drastically lowered in the ADSC/UBM than in the autograft group ($P < 0.05$). Similarly, the AMH serum level was lower significantly in rats in Autograft, ADSC and ADSC/UBM group than in Oophorectomy group ($P < 0.05$), and higher in rats in the ADSC and ADSC/UBM groups than Autograft group ($P < 0.05$; Table 1). It indicated that the autografted tissue was effective, and compared to the Autografted group, ovary tissue function was better preserved in ADSC/UBM group. All rats that had ovary autograft surgery recovered their estrous cycles, although rats in the ADSC/UBM group began their estrous cycles considerably earlier than with the Autograft group ($P < 0.05$; Table 1).

3.6. ADSC/UBM promotes angiogenesis and expression of VEGFR2

Rats in the ADSC group had significantly higher CD31 expression on day 7 post-autograft than did rats in the autograft group (Fig. 4A). Rats receiving ADSCs alone had significantly lower CD31 expression than rats receiving ADSCs and UBM ($P < 0.05$). Rats in each group had more CD31-positive cells on day 28 post-autograft, but UBM/ADSC rats had significantly more CD31 expression than the rats in the other two groups ($P < 0.05$). Immunohistochemical staining for VEGFR2 showed strong expression in oocytes and granulosa cells of the ADSC/UBM group compared to that of the Autograft group (Fig. 4B). The expression of VEGFR2 in the ADSC/UBM group was significantly elevated compared to the Autograft Group at 7 days post-ovarian transplantation, with this difference becoming even more pronounced at 28 days post-transplantation (Fig. 4C; Uncropped supplementary mage Fig. 4c).

3.7. ADSC/UBM inhibits apoptosis

Using Image-Pro Plus 6 software , the apoptotic rate was estimated. The apoptotic rate was lower when transplanted with ADSCs than it was in the autograft group ($P < 0.05$). The apoptotic rate was considerably lower in the UBM-transplanted group than in the other two ($P < 0.05$; Fig. 5).

4. Discussion

For adolescents and women needing immediate cancer treatment, ovary transplantation is the sole option for preserving fertility [17]. However, ischemia and hypoxia before vascular regeneration after transplantation induced follicle loss [18]. It is important to decrease the duration of the ischemic period and to provide rapid vascularization in order to increase the success rate of transplantation。

ADSCs and UBM scaffold represent key components utilized in tissue engineering and regenerative medicine, particularly in tissue repair and regeneration. The advantages of ADSCs include their easy isolation and culture as well as their low immunogenicity, making them a hot topic in clinical and scientific research. ADSCs have been shown to promote angiogenesis in the course of tissue repair and wound healing [19]. Recent studies have demonstrated that ADSCs have the ability to stimulate angiogenesis in transplanted mouse ovaries [7]. However, Stem cells were administered via intravenous or intramuscular injection on a regular basis. The viability of these cells may have been compromised due to the delivery methods employed. Furthermore, the hostile microenvironment surrounding the

Table 1
Follicular stimulating hormone and anti-Mullerian hormone levels measured 28 days after ovarian tissue autograft.

Group	AMH (ng/ml)	FSH (ng/ml)	Starting day of estrous cycle (days)
Autograft	0.60 ± 0.33^{bc}	13.64 ± 1.97^{bc}	12 ± 0.82^{b}
ADSC	0.87 ± 0.28^{ac}	7.47 ± 2.34^{ac}	10 ± 0.51^{a}
ADSC/UBM	0.98 ± 0.32^{abc}	6.38 ± 1.45^{abc}	10 ± 0.34^{a}
Oophorectomy	0.40 ± 0.11^{ab}	29.14 ± 3.84^{ab}	–

Values are means ± SD. [a] Compared with the autograft group; [b] Compared with the ADSC group, P <0.05; [c] Compared with the Oophorectomy group, P <0.05 (one-way ANOVA and Tukey's test, P <0.05).

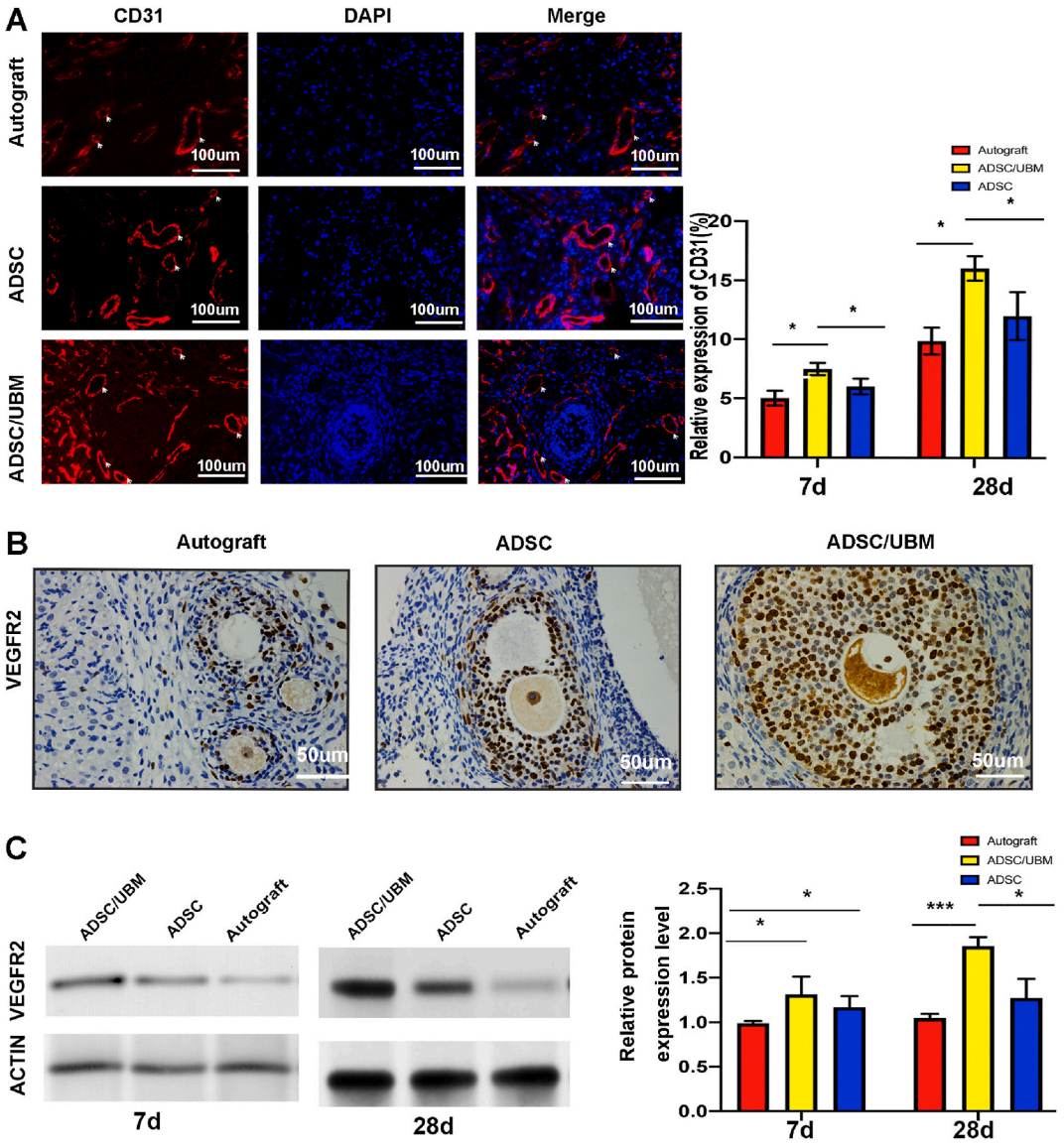

Fig. 4. CD31 and VEGFR2 expression in different groups after transplantation in ovaries. A: Immunohistochemical staining of CD31 in rats 7 days post-autograft, neovascularization (white arrow) was observed in each group, and the number of blood vessels in the ADSC/UBM group was significantly more than that in the Autograft group. CD31 expression in rats 7 and 28 days post-autograft (n = 6). $^{*}P < 0.05$. B: Immunohistochemistry showed high expression of VEGFR2 in ADSC/UBM group compared to the Autograft and ADSC group in follicles. C: The protein level of VEGFR2 in rats 7 and 28 days post-autograft was detected by western blotting. $^{*}P < 0.05$,$^{***}P < 0.001$. Uncropped supplementary image Fig. 4c is provided.

site of stem cell transplantation, characterized by inflammation, trauma, and oxidative stress, hinders the survival and differentiation of stem cells, ultimately diminishing their therapeutic efficacy [20]. Many researchers have reported ADSC loss after injection [21]. In this sector, Within the host, UBM generates a collagen-rich scaffold for long-term differentiation of stem cells, revascularization, and tissue regeneration.

UBM is a kind of ECM, which is widespread biomaterials used in surgical practice as tissue reinforcement and tissue regeneration. Previous study has confirmed that ADSC differentiation needs stimuli from the external microenvironment [22], such as growth factors and cytokines in UBM [23]. ADSCs can invade the scaffold and develop into specialised cells via biomaterials. According to reports, the combination of ADSCs with UBM promotes the growth of new blood vessels during tissue repair [24]. Overall, stem cells have been shown to anchor, move, and operate effectively on UBM [25]. UBM scaffold is a biologic material generated from an animal's urine bladder. Because of its natural composition and structural qualities, it is frequently employed as a tissue engineering scaffold. The three-dimensional framework provided by UBM scaffold allows for cell adhesion, proliferation, and tissue regeneration. Extracellular matrix components, growth factors, and structural proteins all contribute to cell behaviour and tissue creation. To enable its use in

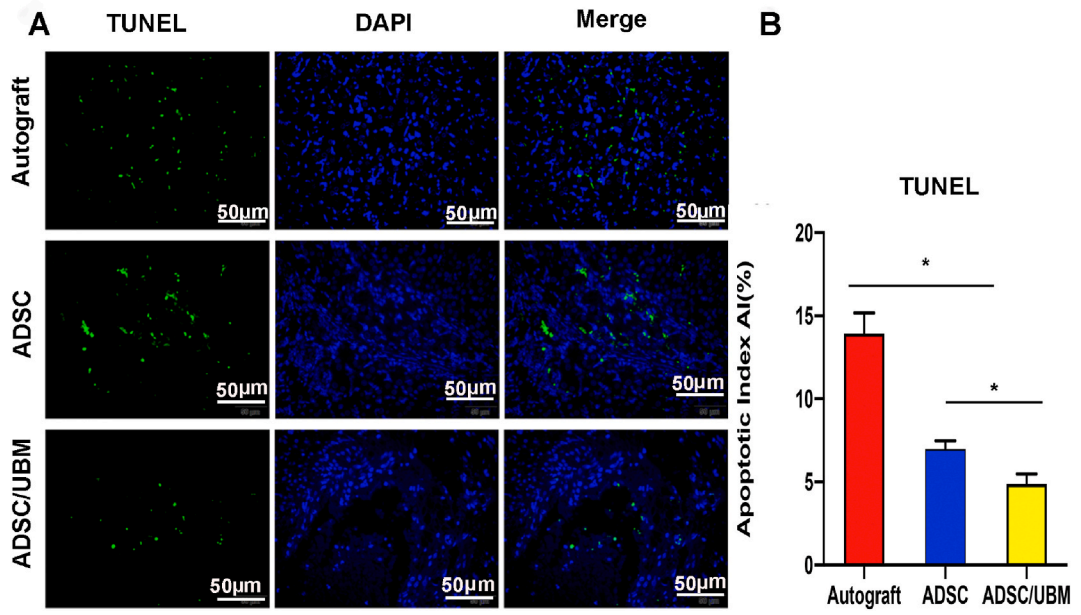

Fig. 5. TUNEL analysis. A: TUNEL tests were performed 28 days after the autograft; B: Apoptosis rate 28 days after the autograft (n = 6). *$P < 0.05$.

diverse tissue engineering applications, UBM scaffold can be manufactured into various forms such as sheets or powders. we propose that UBM will effectively host more ADSCs and provide a better environment for there differentiation due to its uniform distribution and high interconnectivity.

This research initially shown that ADSCs grow well on the UBM. SEM verified cells were able to adhere to UBM and CCK8 indicated that the proliferation of ADSCs on UBM was the same as that in DMEM medium. This is agreement with other studies [26]. Detecting trans-planted ADSCs was achieved using a labeling method using cm-Dil, which has been used in previous studies. Labeled cells were detected in the transplanted ovary 7 days post-transplantation, confirming their ability to migrate from the surrounding environment into the ischemic tissue. Finally, after ovary auto transplantation, the impact of ADSCs paired with the UBM on ovarian tissue grafted into a rat model was analysed. After 28 days post-transplantation, the quantity of follicles in the ADSC group surpassed that of the autograft group, while the number of follicles in the ADSC/UBM group exceeded that of the ADSC group. In the ADSC group,a reduction in the incidence of apoptosis was observed compared to the autograft group. Previous research has similarly reported decreased apoptosis rates following ADSC transplantation in various ischemic tissues. This phenomenon may be attributed to the capacity of ADSCs to generate cytokines possessing anti-apoptotic characteristics. The hormone levels of the rats and the number of follicles in the ADSC/UBM group were more than those in the autograft group 28 days after transplantation. Additionally, the ADSC/UBM group's estrous cycle recovered quicker than the Autograft group's did. The transplanted ovarian tissue was exposed to ischemic injury until angiogenesis. Five days following the transplant, according to a prior study, vascular connections between the host and the transplanted ovary can be seen [27]. Therefore, CD31 was detected 7 and 28 days after grafting to evaluate angiogenesis. The data confirmed the better proangiogenic effect of ADSC/UBM than of ADSC, and that the improved vascularization modulates the follicular density. Our study revealed that the rate of apoptosis was lower in the ADSC/UBM group than in the autograft group. In addition, our study confirmed that ADSC/UBM induced the upregulation of *vegfr2* in autograft ovarian tissues, which promoted endothelial cell proliferation, migration and tube formation [28]. The limitation of this study was lack of mechanism of stem cells promoting angiogenesis. In summary, this research shows that a UBM can encourage the attachment of external stem cells, draw in host stem cells, and create the perfect milieu for their proliferation and differentiation. ADSCs combined UBM application is effective to promote angiogenesis and expected to be used in clinic.

Ethics approval and consent to participate

The ethics committee of the Shanghai Public Health Clinical Centre reviewed and approved each animal experiment (Ethical assessment 2019-A018-02). Confirmed that all experiments were performed in accordance with relevant guidelines and regulations.

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Data availability

No data was used for the research described in the article.

CRediT authorship contribution statement

Yanyan Xing: Writing – original draft, Methodology, Investigation, Conceptualization. **Yuqi Li:** Writing – review & editing, Formal analysis, Data curation. **Yuxin He:** Writing – review & editing, Formal analysis. **Wei Zhao:** Writing – review & editing, Visualization, Supervision, Resources. **Wen Li:** Writing – review & editing, Writing – original draft, Methodology, Investigation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e37573.

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