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Advanced Biomaterials for Promoting Endometrial Regeneration

Zhe Yin, Juan Wang, Wenguo Cui, and Chao Tong**

The endometrium, as the innermost structure of the uterine cavity, plays a direct role in the implantation of the fertilized egg, its conception, and the formation of normal menstruation. In recent years, with the increasing rate of uterus-related surgeries, the damaged endometrium often fails to repair itself to its original state, resulting in a high incidence of menstrual disorders and reduced fertility in women in their reproductive years. Therefore, it is essential to repair the damaged endometrium to reduce menstrual disorders, pregnancy difficulties, and other adverse events. Biomaterials have become an important medical tool for tissue repair due to their excellent biocompatibility, shape plasticity, and functional versatility. Functional biomedical materials play an important role in endometrial repair through rational design, which is expected to fundamentally address the current shortcomings of endometrial repair to maximize repair, maintain female fertility, and solve the problem of medically induced endometrial destruction. This review describes the potential and several aspects of the design, function, and application of different biomedical materials capable of repairing endometrium. In brief, this review provides a comprehensive summary and outlook of biomaterials for endometrial repair.

1. Introduction

The endometrium (mucosal layer), located at the body and base of the uterus, is the innermost structure of the uterus and plays an irreplaceable role in embryo implantation and menstruation formation. Its structure and thickness alter depending on the age and functional status of a woman. The endometrium comprises a single layer of columnar epithelium and the lamina propria. The epithelium is similar to the tubal epithelium and consists of ciliated and secretory cells, while the lamina propria consists of connective tissue and uterine glands and vessels. In the connective tissue, there are many less differentiated spindle or astrocytes called stromal cells with large round nuclei and less cytoplasm that synthesize and secrete collagen and proliferate and differentiate with the cyclic changes of the endometrium. The glandular epithelium mainly comprises secretory cells, with fewer ciliated cells. The branches of uterine arteries enter the endometrium through the myometrium in a spiral alignment and become spiral arteries, which are highly sensitive to sex hormones stimuli. The endometrium can also be divided into shallow and deep layers according to its structural and functional characteristics. The shallow layer, located near the uterine cavity, is the functional layer; it comprises two layers (spongy and dense) and accounts for two-thirds of the thickness of the entire endometrium. The functional layer sheds at each menstrual cycle, and embryo implantation occurs in this layer. The deep layer is the basal layer, which accounts for one-third of the thickness of the entire endometrium. The basal layer does not shed during menstruation or delivery and can proliferate and repair, generating a new functional layer. Therefore, the damage to the basal layer of the endometrium impairs the ability of the endometrium to repair itself, even if the hormones are secreted normally.

In recent years, the increasing rate of uterine surgery has resulted in adverse outcomes due to damage to the endometrium (**Figure 1**). In this type of surgery, the original anatomy of the uterus is disrupted to a greater or lesser extent, leaving the endometrium thin or absent, the submucosal vessels and interstitium exposed, and the muscles defective, which usually makes the patients more prone to abnormal uterine bleeding symptoms. Currently, hormone-containing drugs and birth control devices are often used clinically to repair the endometrium.[1] However, the effectiveness of the treatment is mediocre and does not fully restore the endometrium to its pre-damaged state. Another promising treatment is stem cell therapy, which utilizes the potential of cell differentiation. Studies have shown that using stem cells from bone marrow, endometrium, menstrual blood, fat, embryo, and umbilical cord blood can promote the recovery

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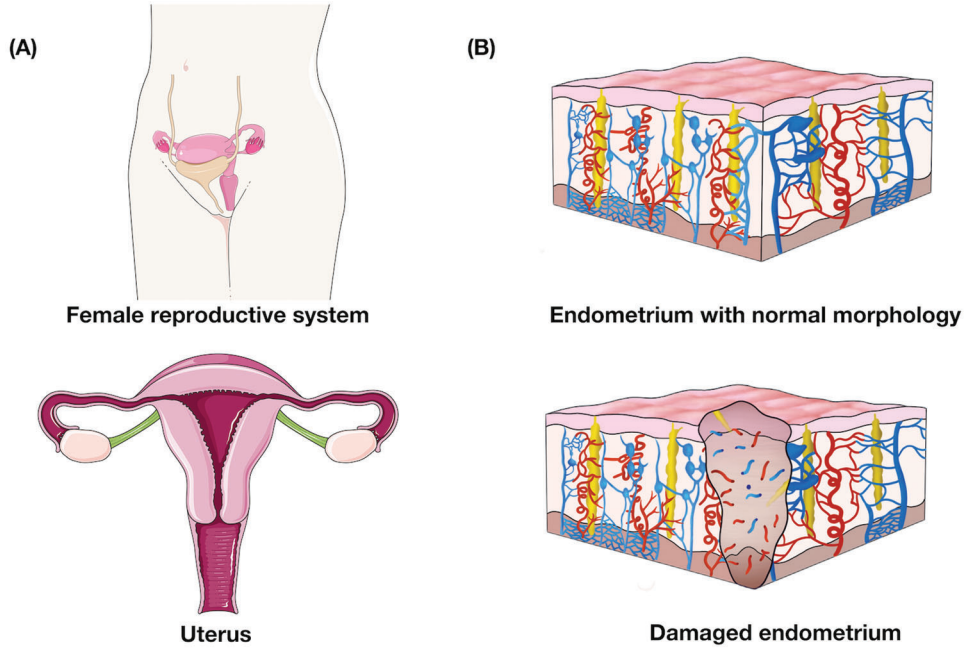

Figure 1. Diagram of the uterus and the structure of the endometrium. The endometrium includes veins, arteries, and many glands that, if damaged, can affect fertility-related functions. A) Normal morphology of the uterus; B) Schematic diagram of the structural stratification and damage of the endometrium.

of uterine structure and function. Stem cell therapy can promote the regeneration and repair of the endometrium through paracrine and immune regulation, destroy fibrosis formation and promote the regeneration of blood vessels.[2] Although stem cell therapy is the most effective treatment method, it exerts tumorigenic and immunogenic properties to a certain extent.[4–6] Furthermore, it is challenging to obtain stem cells, especially for adults and the elderly, who have less available stem cell material, low purity, and rapid aging. It is also challenging to preserve the obtained stem cells.[3] Stem cells can also cause immune rejection of the host, significantly reducing the effect of stem cell therapy. Therefore, better therapeutic approaches to repair endometrial damage and avoid all the shortcomings of drug-based and stem cell therapies is of immense practical importance.

Tissue regeneration is a promising treatment modality for broken finger reimplantation[7] and muscle defect repair,[8] in which biocompatible scaffold materials have shown favorable results. Biomaterials, also known as biomedical materials, are natural or synthetic unique functional materials that can diagnose, treat, replace, repair, or induce the regeneration of cells, tissues, and organs. Given the high water content and excellent biocompatibility and biodegradability of hydrogels, combining these materials with drugs, stem cells, and stem cell derivatives has been speculated to have promising therapeutic applications.[9] Considering that the endometrial tissue is fragile and undergoes cyclic shedding along with estrogen and progesterone changes, suitable biomedical materials should have the following characteristics: 1) softer texture to avoid damaging the normal endometrial area; 2) better compression and ductility to restore the standard shape in the uterine cavity after passing through the narrow cervical opening; 3) better antibacterial ability (good antimicrobial capacity to prevent the introduction of vaginal bacteria or fungi into the uterine cavity after delivery); 4) good biodegradability and biocompatibility; 5) ability to carry drugs or cytokines, etc. The biomedical materials that have been reported to promote endometrial repair are mainly classified as hydrogel, shape memory, and decellularized matrix biomaterials.[10–12]

Hydrogel materials are polymeric materials with high water content and have a highly flexible 3D network structure. Furthermore, hydrogels can absorb tens of times more water and swell in water without dissolving, as they contain many hydrophilic groups. Hydrogels facilitate cell growth and reproduction because of their similar physicochemical and mechanical properties to those of the native extracellular matrix (ECM); therefore, they impart a natural advantage for endometrial repair.[X] Some hydrogels are biodegradable and have good biocompatibility; therefore, well-suited as biomedical materials. Moreover, a hydrogel can be added or subtracted with different designs to achieve better antibacterial, compression, ductility, drug retardation, and repair functions (**Figure 2**A; **Table 1**).

Materials with shape memory effects are called shape memory materials and are usually divided into three categories: shape memory alloys, ceramics, and polymers. Compared with shape memory alloys and ceramics, shape memory polymers have low density, a high shape recovery rate, good biocompatibility, and biodegradability. Therefore, shape memory polymers have potential biomedical applications and have been used in several medical scenarios. For example, polyurethane shape-memory polymer foam as a 3D matrix has been used to support bone growth in vivo and in vitro; aliphatic polyester-based shape-memory polymers (SMPs) are used for internal fracture fixation (Figure 2B).

The ECM is a non-cellular component comprising proteoglycans and glycoproteins (the homogeneous state of the matrix) and fine filamentous collagen fibers (which play a role in

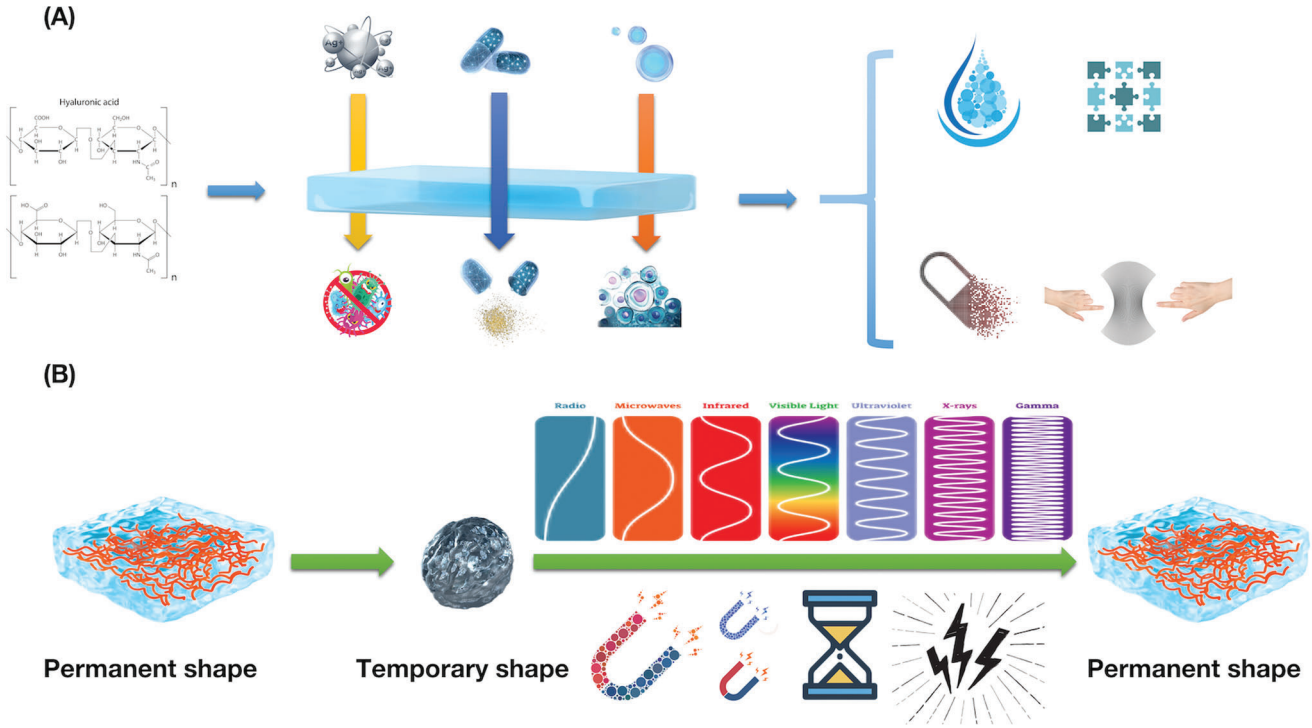

Figure 2. Common biomedical materials currently used to repair the endometrium. A) Function and characteristics of hydrogel (high water content, excellent biocompatibility, good decomposition ability, and deformability); B) Schematic diagram of shape memory material.

Table 1. Hydrogel materials to promote endometrial repair.

	Combination form	Advantages	Disadvantages	Other features	Effect	Literature
Micro-environmental protection type exosome hydrogel	Stem cell exosome + polyethylene glycol hydrogel	Avoids tumorigenicity and high immunogenicity in stem cell therapy	Insufficient stem cells collected from lighter people, the lower biological activity of stem cells from older people	①Tetra-armed cross-linked PEG hydrogel ②Ag^{+} Antibacterial effect	①Significantly promoted the proliferation of venous endothelial cells ②Significantly promotes angiogenesis and muscle production	Cui et al.[14] 2021
Bioengineered hydrogels containing apoptotic vesicles	Apoptotic vesicles + hyaluronic acid hydrogel	Avoids tumorigenicity and high immunogenicity in stem cell therapy	Apoptotic vesicles are not easily collected in large numbers	Apoptotic vesicles promote tissue regeneration	① Promote vascular regeneration of the endometrium, cell proliferation and ②Reducing endometrial fibrosis	Zhang et al.[16] 2021
Hyaluronic Acid Hydrogel with Mesenchymal Stem Cell Secretory Proteome	Mesenchymal stem cell secretory protein + hyaluronic acid hydrogel	①Avoid the tumorigenicity and high immunogenicity in stem cell therapy ②Cross-linked hyaluronic acid hydrogel with tight structure and slower slow release	Insufficient stem cells collected from lighter people, the lower biological activity of stem cells from older people	Cross-linked hyaluronic acid hydrogels are stronger and suitable for the slow release of drugs	Repair of the endometrium	Cheng et al.[17] 2019
Hydrogels loaded with small-molecule protein drugs	Estradiol decellularized matrix nanoparticles + Aloe/ Polysaccharide hydrogel	Avoids the potential toxic effects on cells from the use of poloxamer hydrogel alone	More complicated to make	Better use of estradiol hormone to promote endometrial growth locally and avoid systemic hormonal disorders.	Promotes endometrial repair	Zhao et al.[19] 2020

connecting and supporting cells) or the basic framework for cell attachment and metabolic sites. The ECM plays a crucial role in tissue morphogenesis, differentiation, and homeostasis. Its morphology and function directly affect the morphology and function of the constituted tissues. The decellularized matrix undergoes a series of chemical, physical, enzymatic digestion, and other decellularization processes to remove the antigenic components that can cause immune rejection while preserving the morphology, 3D spatial structure, and composition of the ECM and the functionality of some growth factors that are important for cell differentiation, such as transforming growth factor β, vascular endothelial growth factor, polysaccharides, and collagen.[13] The decellularization process provides a site for host cells to grow and metabolize, which can promote the growth of autologous fibroblasts and vascular endothelial cells in the allogeneic dermal scaffold, thus completing the repair and reconstruction of the defective tissue. The decellularized ECM material with good mechanical properties, histocompatibility, and no immune rejection in implantation can support and connect cells in vivo. Furthermore, its 3D spatial structure and cytokines are conducive to cell adhesion and growth. Therefore, biomedical materials based on decellularized matrix also have potential prospects in regenerative medicine.

2. Hydrogel-Based Biomaterials for Endometrial Repair

2.1. Exosome-Loaded Hydrogel

In the last decade, treatments involving the implantation of stem cells from different sources to repair endometrial damage have been considered the most promising treatment modalities.[2,5] However, the difficulty of obtaining stem cells, immunogenicity, and tumorigenicity limits stem cell therapy. Various stem cell-derived exosomes have recently been critical for cell regeneration. Therefore, stem cell exosomes help stem cell therapy breakthrough more limitations for better tissue regeneration treatment results.

Cui et al. from Shanghai Jiao Tong University have designed a novel polyethylene glycol hydrogel capable of loading exosomes.[14] The hydrogel was cross-linked in vitro using a mild ligand, which enabled it to have good self-healing properties and maintain its original stable structure during the cyclic shedding of endometrium under the effect of estrogen and progesterone. Ag^+ was also added to the hydrogel to ensure good antibacterial properties. This gel forms covalent bonds between the S^- and Ag^+ of polyethylene glycol (PEG). Although such a bond may break under powerful external shear force, the tight bond can be restored when the external force disappears, so this hydrogel can self-heal. Furthermore, this hydrogel has good drug-carrying properties; it can release drugs continuously and stably, which has a micro-environmental protection effect on the regeneration and functional recovery of the endometrium. The adipose stem cells (ADSCs) were extracted from adipose tissue, and then the ADSCs-exosomes were isolated and combined with the PEG hydrogel cross-linked with Ag^+ (**Figure 3**). This hydrogel (ADSCs-exos) with antibacterial and ADSC-exosomes loading functions could mediate the sustained release of exosomes with Ag^+ to promote endometrial regeneration, enhance endometrial tolerance, and exert anti-infective and anti-fibrotic effects. The authors demonstrated significant angiogenesis and an increase in the number of glands by injecting ADSCs-exos hydrogel into the damaged area of the uterine horn in a rat model of endometrial damage.[14] Related studies have shown that exosomes may reduce inflammation and enhance anti-inflammatory responses through macrophage polarization in vivo and in vitro.[15] Furthermore, α-SMA staining to assess the effects of ADSC-exosomes on muscle repairing has shown a significant increase in the number of muscle bundles in the animals of the ADSCs-exos hydrogel group compared with that in the — group.[x] In addition, Masson staining confirmed that ADSCs-exos hydrogel significantly alleviated the inflammation and fibrosis of the endometrium. [x] Because the volume of the uterine cavity in human mothers increases from 5 mL in early pregnancy to 5000 mL in late pregnancy, the myometrium of the uterus thins significantly in late pregnancy compared to early pregnancy. The thinning of the myometrium is closely related to uterine rupture, so when the damage in the uterine cavity reaches deep into the myometrium, the risk of uterine rupture in the subsequent pregnancy increases exponentially. Compared to the conventional oral antibiotic treatment for endometritis,[10] local drug therapy in the uterine cavity may be able to maintain the local drug concentration better, sustain anti-inflammatory, and repair the endometrium.[X] Ag^+ is a very effective antimicrobial agent, and is often used to prevent and treat infections and thus promote wound healing. [X] As mentioned earlier, the -SH of the four-armed PEG hydrogel and Ag-S are coordinated, forming a tight chemical bond. Therefore, during the gradual degradation of the hydrogel, Ag^+ can be gradually released to fight infection, and the powerful antibacterial ability of Ag^+ has been confirmed in relevant experiments. The test results showed that this hydrogel promotes the thickening of endometrium well, indicating that ADSC-exos hydrogel can promote the regeneration of functional endometrium and help restore fertility. Similarly, Zhang et al. from Zhejiang University have developed a hyaluronic acid (HA) hydrogel loaded with apoptotic vesicles.[16] The team developed a novel biomedical material by incorporating MSC-derived apoptotic vesicles into a HA hydrogel and demonstrated that apoptotic vesicles promoted endometrial vascular regeneration and cell proliferation and effectively reduced endometrial fibrosis in vitro, thereby repairing the endometrium and restoring impaired fertility (**Figure 4**).

Biomedical materials loaded with various stem cell exosomes have great potential in repairing the endometrium. First, this approach can avoid the direct use of stem cells for endometrial tissue repair, thus avoiding the limitations of stem cell therapy (tumorigenicity, difficulty in obtaining stem cells, immunogenicity, etc.). Furthermore, the combination of stem cell exosomes with biomedical materials, such as injectable and biocompatible hydrogels, increases the therapeutic efficiency of the exosomes. The hydrogel-based exosomes allow smooth entry into the uterine cavity without damaging the internal tissues of the uterine cavity and can also impart excellent antibacterial effects when Ag^+ is added. Nevertheless, this approach has some limitations. First, obtaining exosomes is complicated, requiring not only the isolation of suitable stem cell tissues but also the repeated purification of exosomes to meet the standards for use, which makes it difficult to produce them on a large scale. Second, the precise mechanism underlying the tissue repair effects of exosomes and

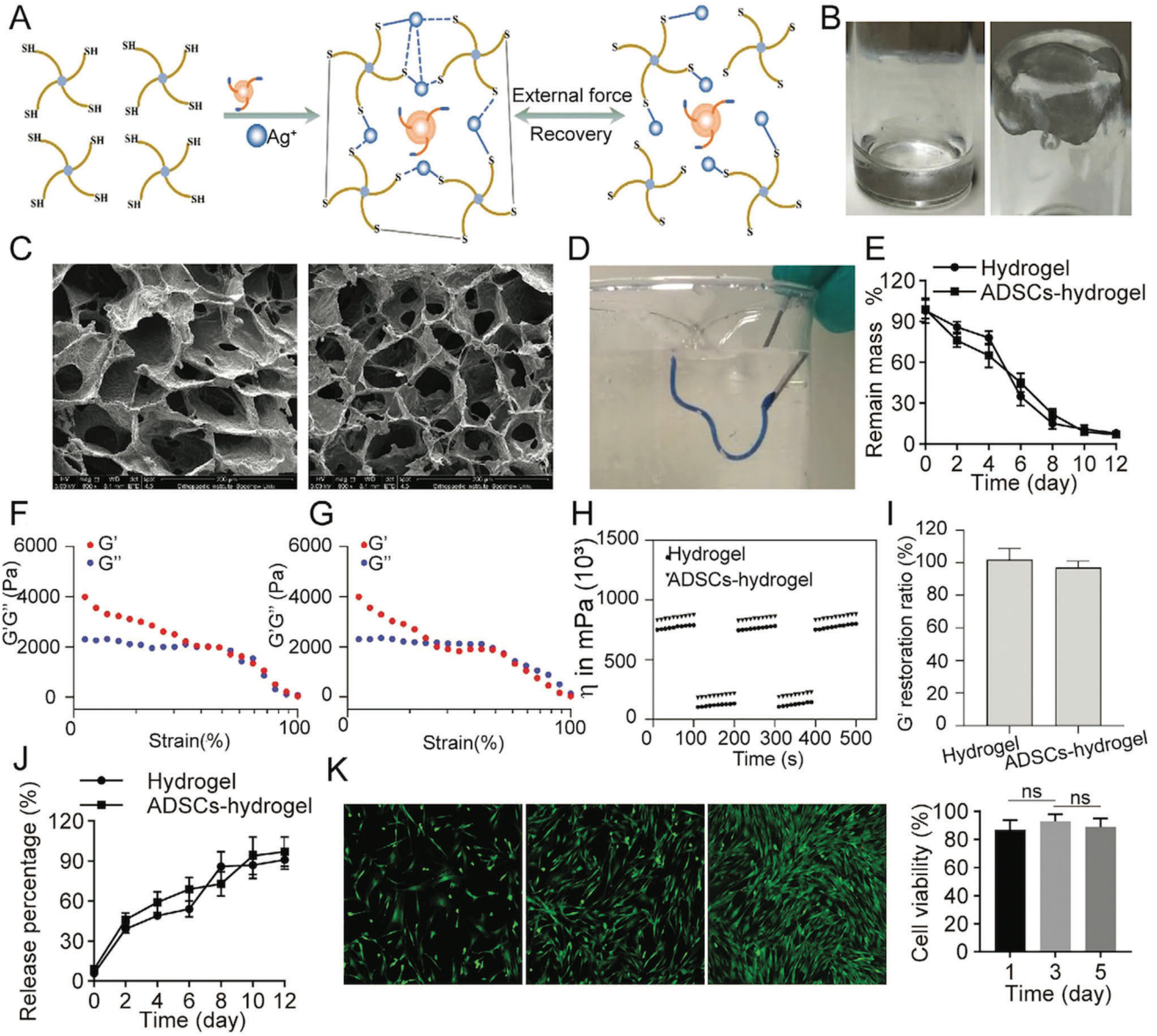

Figure 3. Adipose stem cell (ADSCs)-hydrogel characterization. A) Self-healing and injectability mechanisms. B) The mixture of four-arm PEG-thiol, AgNO3, and ADSC-derived exosomes. C) Scanning electron microscopy (SEM) images of hydrogel and ADSCs-hydrogel preparations. D) Images of hydrogel following into distilled water. E) The degradation curve of hydrogel and ADSCs-hydrogel in vitro. F) Strain sweep measurements of the storage moduli for PEG-Ag hydrogel (G′ and G″ correspond to the elastic modulus and the loss modulus, respectively), measured in kPa. G) Strain sweep measurements of the storage moduli for ADSCs-exo@hydrogel. H) The relationship between measured viscosity parameters and time (s). Strain shearing rates of 0.05% for the 100s and 500% for the 50s were measured. I) G′ recovery ratio of various hydrogels following two cycles of 1000% step strain. J) The release behavior of Ag^+ from the hydrogel and ADSCs-hydrogel. K) In vitro cytotoxicity of the ADSCs-exo hydrogel and quantitative analysis of live cells at 1, 3, and 5 days. Reproduced with permission.[14] Copyright 2021, Wiley-VCH GmbH.

other complications associated with the treatment process are not clear. Therefore, the safety of exosomes in tissue repair applications still needs more evaluation in the future. In the meantime, the selection of biomedical materials should consider the specific environment of the uterine cavity. First, the biomedical material selected should have good biocompatibility and suitable texture so as not to damage the fragile endometrium. Second, considering the slow treatment cycle, the degradation of biomaterials should not be too fast but preferably uniform over a certain period, which poses specific challenges to the chemical structure of the material.

2.2. Hydrogel Loaded with Secretory Proteome

Emerging evidence[17] demonstrates the application of HA hydrogels loaded with mesenchymal stem cells (MSCs) secretory proteome for endometrial repair. After identifying markers of MSCs by flow cytometry, the secretory proteome of MSCs (MSCs Sec)

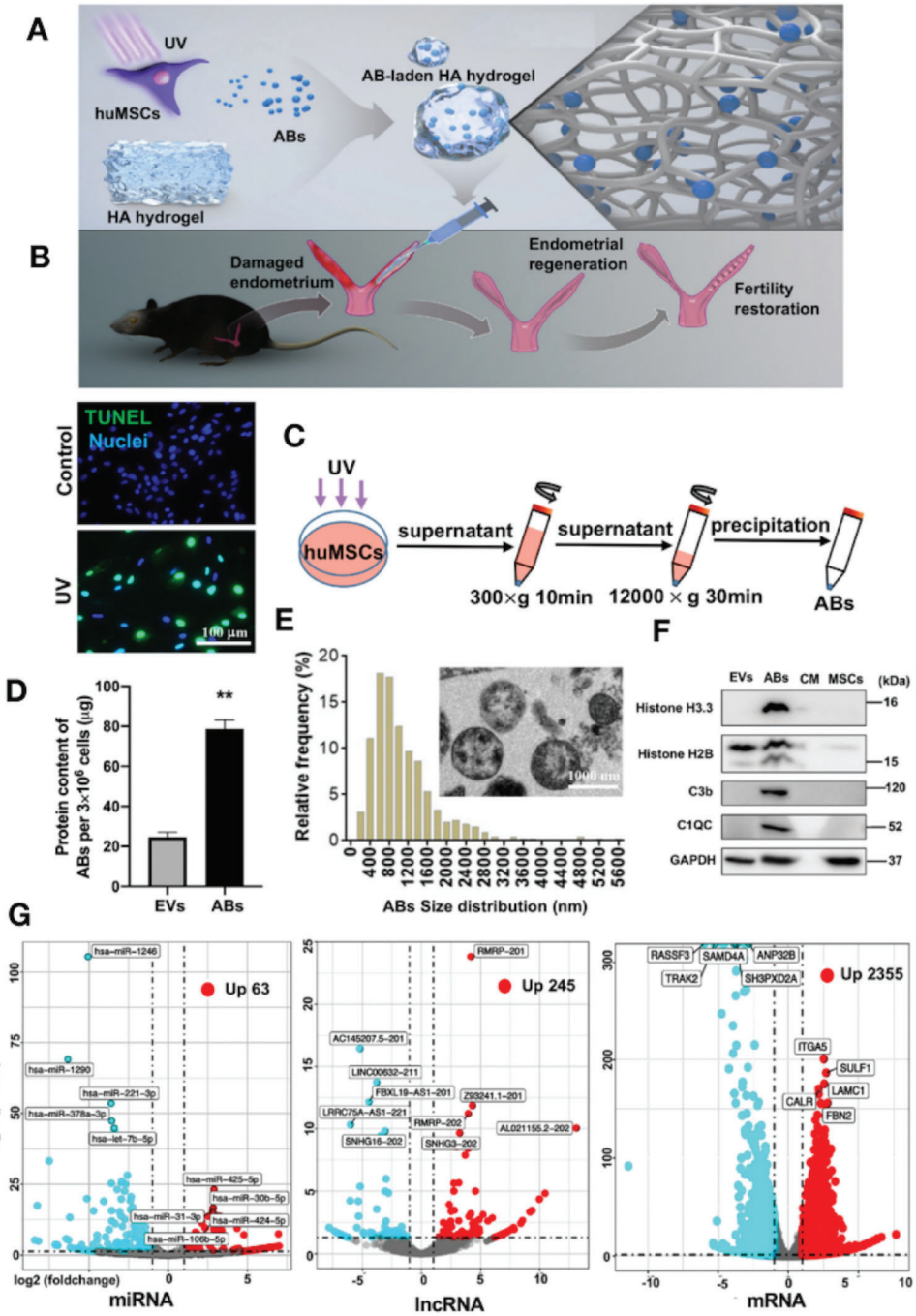

Figure 4. Schematic illustration of the design and application of the apoptotic body (AB)-laden hyaluronic acid (HA) hydrogel and the characterization of ABs derived from human umbilical cord-derived mesenchymal stem cells (huMSCs). (Print in color) A) Schematic illustration of the design and application of the AB-laden HA hydrogel, which comprises the production of ABs from apoptotic huMSCs for administration into the uterine cavity via a HA hydrogel in situ to promote endometrial regeneration and fertility restoration. B) Confocal images of the TUNEL-stained (green) huMSCs with UV treatment, those cells with no UV treatment served as the control, and all cells were labeled with DAPI (blue). C) Schematic of the procedure used for the isolation procedure of ABs via differential centrifugation. D) Relative protein content in ABs secreted from UV-treated huMSCs and extracellular vesicles (EVs) from no-UV-treated huMSCs. Data were normalized to the number of huMSCs in each plate ($n = 7$). E) Size distribution of ABs measured from transmission electron micrographs (TEM). Inset is a typical TEM image of ABs. F) Western blot analysis of ABs for H3.3, H2B, C1QC, C3b, and β-actin. G) Volcano plot showing significantly upregulated (red dots) and downregulated (blue dots) miRNAs, lncRNAs, and mRNAs in ABs, compared to EVs. $^{**}p < 0.01$. Reproduced with permission.[16] Copyright 2021, Elsevier.

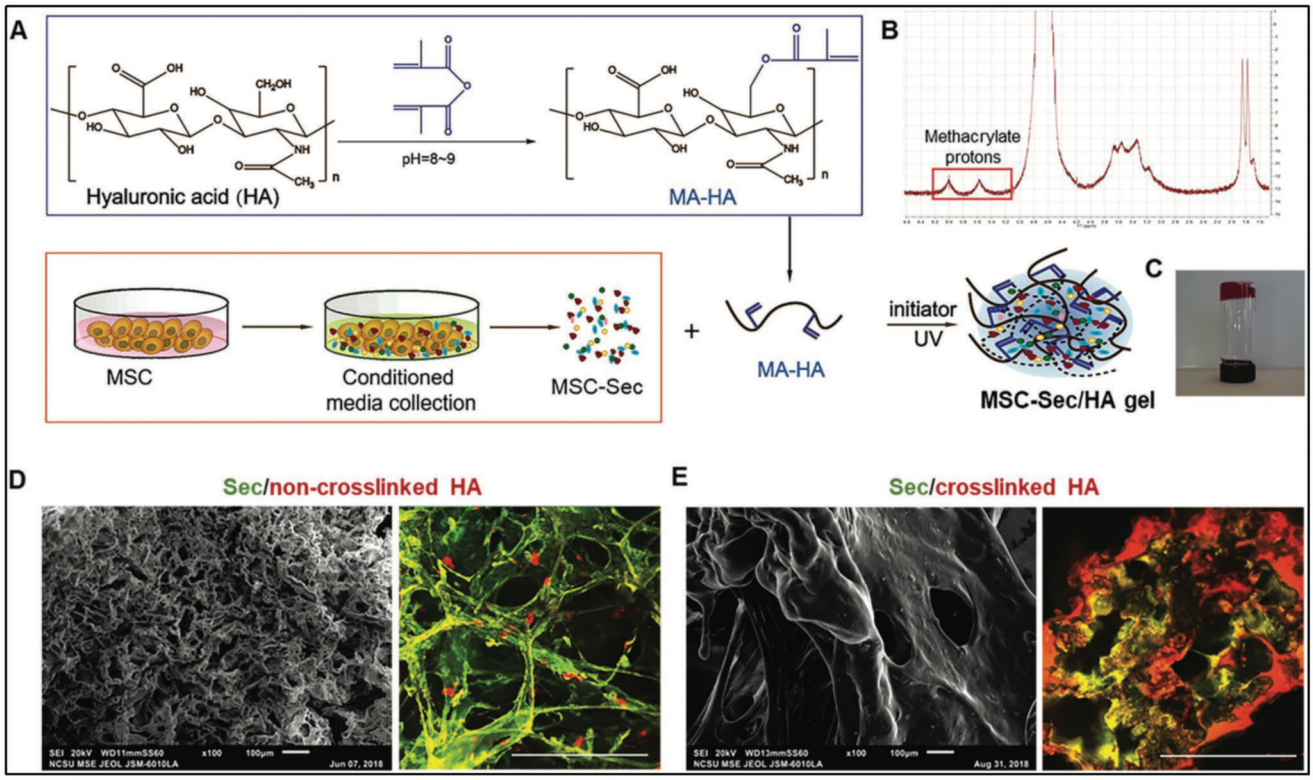

Figure 5. Fabrication and characterization of MSC-Sec-loaded crosslinked HA gel. A) Schematic showing the synthesis of MSC-Sec-loaded, crosslinked HA gel. B) MA-HA: 1H NMR (D_2O,300 MHz, δppm): 1.85–1.96 (m, 3H, CH_2=C(CH_3)CO), 1.99 (s, 3H, NHCOCH_3), 5.74 (s, 1H, CH^1H^2=C(CH_3) CO), 6.17 (s, 1H, CH^1H^2=C(CH_3)CO). C) State of HA gel at room temperature when the bottle is upside down (gelation). D) Representative SEM (scale bar: 100 μm) and color-depth projection confocal images of MSC-Sec/non-crosslinked HA; green represents MSC-Sec, and red represents HA. Scale bar in confocal image: 100 μm. E) Representative SEM (scale bar: 100 μm) and color-depth projection confocal images of MSC-Sec/crosslinked HA; green represents MSC-Sec, and red represents HA. Scale bar in confocal image: 100 μm. Reproduced with permission.[17] Copyright 2021, Wiley-VCH GmbH.

was identified and screened by cytokine arrays. MSCs Sec was analyzed for possible endometrial and endothelial cell proliferation and migration, including epidermal growth factor, insulin-like growth factor binding protein, insulin-like growth factor-1, and fibroblast growth factor.[18] These cytokines have been shown to contribute to endometrial proliferation and glandular reconstruction after trauma. Cross-linked HA hydrogels loaded with MSCs Sec were synthesized following the step shown in **Figure 5** as an effective vehicle for intrauterine drug delivery. The non-cross-linked HA hydrogel, approved for post-uterine surgery anti-adhesion, showed a more compact structure with smaller and fewer voids than the cross-linked HA hydrogel synthesized here, resulting in a more stable cross-linked HA hydrogel than the non-cross-linked HA hydrogel, thus achieving a slow release effect. The results demonstrated that the treatment of MSCs-Sec cross-linked HA gels contributed to the recovery of fertility in AS rats. Meanwhile, HE chromosome staining also suggested that the endometrial thickness and gland density were significantly increased in the MSCs Sec/HA treated group.

2.3. Hydrogel Loaded with Small-Molecule Protein Drugs

During the normal menstrual cycle of women, the hypothalamic-ovarian-gonadal axis influences the cyclic shedding and regeneration of the endometrium by cyclically regulating the release of estrogen and progesterone. Estrogen plays a more dominant role during the proliferative phase of the menstrual cycle. Therefore, hormone therapy is also an important treatment for endometrial damage. In clinical practice, for young women of childbearing age with fertility needs, oral estrogen or an intrauterine device with hormonal implants is often used to promote endometrial regeneration and vascularization. It has been shown that the concentration of estrogen in the uterine cavity is insufficient due to the lack of targeting and poor water solubility of estrogen. Such treatment is ineffective in repairing the endometrium and may cause systemic hormonal diseases such as breast cancer and thrombosis. Therefore, a treatment modality allowing intrauterine topical delivery with increased water solubility can provide better therapeutic results and avoid adverse side effects. Hydrogel retardation is a good delivery system, and Yao et al. have developed an aloe/paroxamer (AP) hybrid hydrogel.[19] This hybrid AP hydrogel overcomes the potentially toxic effects of simple poloxamer hydrogels on cells in direct contact while incorporating aloe vera extract, a plant-based material, resulting in a synthetic material with better repair capabilities, low immunogenicity, and temperature sensitivity. Zhao et al. also developed an estradiol (E2)-containing nanoparticle that could be embedded in an AP hybrid hydrogel. To prepare this hydrogel, the mouse uterus was first decellularized and subjected to DNA quantification

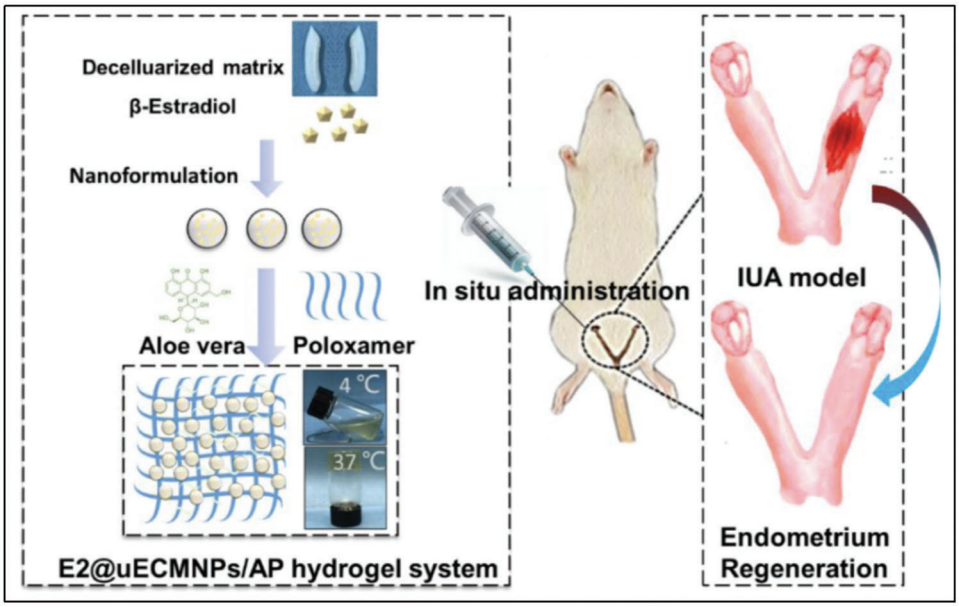

Figure 6. Schematic graphs of E2@uECMNPs/AP hydrogel system with multi-therapeutic effects to promote endometrial regeneration for the prevention of intrauterine adhesion. Reproduced with permission.[19] Copyright 2020, Elsevier B.V.

experiments to determine the removal of nuclei from the tissue. The decellularized tissue was then ground and centrifuged to collect the uterus-derived nanoparticles. E2 was then dissolved in acetone and added to the obtained mouse uterine decellularized tissue-derived nanoparticle solution to obtain an E2-loaded uterine decellularized nanoparticle solution (E2@uECMNPs). The aloe vera extract was added to the cold poloxamer solution, and the aloe vera poloxamer solution (AP hydrogel) was obtained after stirring. Then, the prepared E2@uECMNPs were added to the aloe vera pozzolanic solution to obtain the final hydrogel (E2@uECMNPs/AP hydrogel) (**Figure 6**). The experimental results showed that the AP hydrogel containing E2 decellularized nanoparticles could significantly repair the thickness and number of endometrial glands compared with other experimental groups, confirming the pro-healing effect of AP hydrogel and E2.

3. Nanosheets-Based Biomaterials for Endometrial Repair

3.1. Infrared Ultrasound-Based Shape Memory Biomaterials

SMPs are innovative materials that can pre-memorize a temporary shape and revert to the original shape when stimulated by appropriate conditions. Huang et al. developed near-infrared (NIR-II) light-responsive shape-memory composites[20] based on the combination of cuprorivaite ($CaCuSi_4O_{10}$) nanosheets (CUP NSs) as photothermal converters and polymers (d,l-propylene-*co*-trimethylene carbonate) (PT) as shape memory building blocks. The prepared CUP/PT composites exhibited excellent shape memory properties under NIR-II light and improved operational feasibility as an anti-adhesion barrier for IUA treatment. In addition, the released ions (silica and copper ions) stimulate endometrial regeneration due to the biological activity of angiogenesis. By physically combining PT with CUP NSs, NR-II near-infrared light-triggered shape memory composites were developed (**Figure 7**). Since the CUP NSs were embedded in the polymer network of PT, the surface of the composites was smooth, and no significant difference was observed between PT and CUP/PT composites. The incorporation of CUP NSs conferred excellent NIR-II photothermal properties to the CUP/PT material. A significant concentration-dependent temperature increase was observed under irradiation with NIR light at a power of 0.5 W/cm^{-2}. In addition, no significant temperature fluctuations were seen after several repetitions of cyclic switching of NIR-II NIR light, indicating the excellent photothermal stability of this composite. The analyses performed using dynamic mechanical analysis indicate that the CUP/PT-compliant material has good shape memory properties under direct heating as an external stimulus. According to previous studies, copper ions and specific concentrations of silica ions stimulate the proliferation of human venous vascular endothelial cells, so CUP/PT may be a potentially biodegradable material for repairing endometrial damage. Endometrial vascular endothelial cells (HEECs) have an important role in blastocyst implantation and are widely used to assess endometrial regeneration.[21] Human umbilical vein endothelial cells (HUVECs) have also been used to assess angiogenesis.[12] The evaluation of the effects of different ratios of CUP/PT composites on the proliferation of HEECs and HUVECs demonstrated the biocompatibility of these biomaterials. However, with an increase in time, a significant upward deceleration of 4-CUP/PT was observed compared to the other groups, which could be due to the high concentration of ions released by 4-CUP/PT, which had a negative effect on the cells. Furthermore, the study demonstrated that the cell proliferation in the 2-CUP/PT group increased significantly. Cell scratching experiments showed that the 2-CUP/PT group had more venous endothelial cell migration than that in the PT group. In the tubule formation assay, the number of tubes formed in the 2-CUP/PT

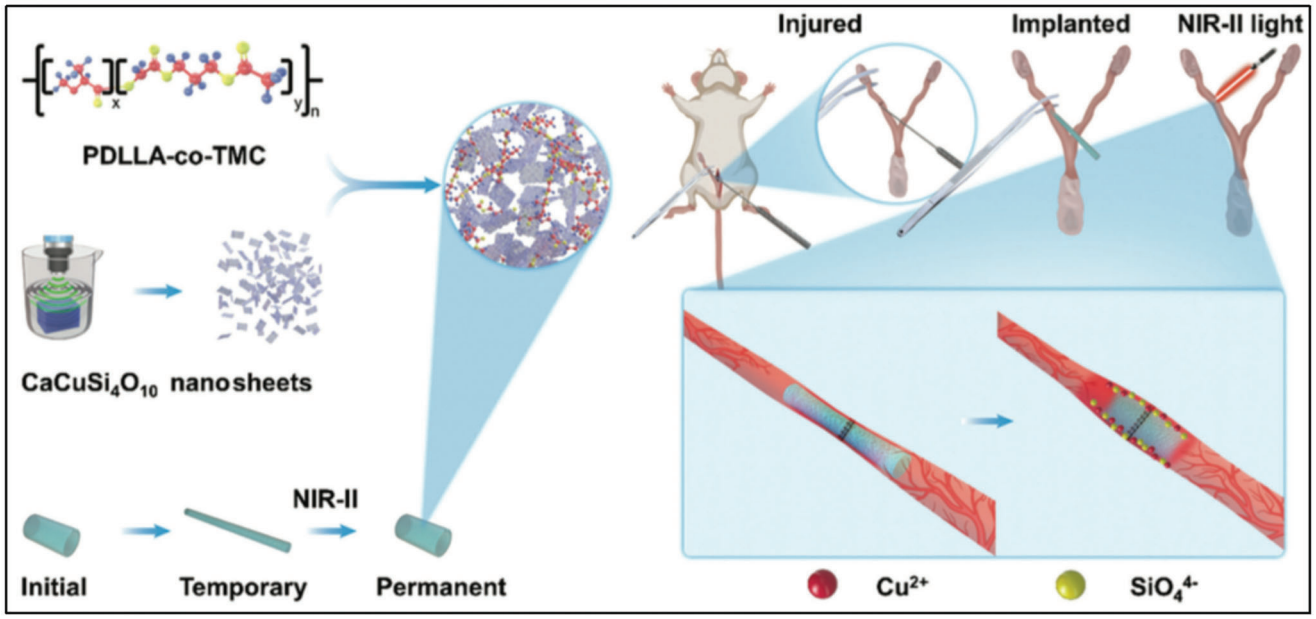

Figure 7. Schematic illustration of NIR-II light-responsive CUP/PT composites for IUA prevention and endometrial regeneration. Reproduced with permission.[20] Copyright 2021, Elsevier B.V.

group was significantly higher than that in the PT group when the composite was co-cultured with human umbilical vein endothelial cells in matrix gel. Two substances that promote cell proliferation. Biotoxicity tests showed normal blood parameters with no significant toxicity in the CUP/PT composite. HE staining showed that the 2-CUP/PT group had better resistance to uterine adhesions and better glandular repair than the PT group. In addition, the efficiency of this biomaterial was investigated in vivo, which showed that PT and CUP/PT degraded faster, probably due to the complex environment in the uterine cavity. This material has good photothermal and shape memory properties and is expected to be an intelligent anti-adhesion barrier for IUA. In contrast, the continuous release of bioactive ions (silica and copper ions) from this material promotes the proliferation of HEECs and HUVECs cells and the angiogenesis of HUVECs. In conclusion, this bioactive NIR-II responsive composite of CUP/PT was therapeutically effective in treating uterine adhesions and repairing the endometrium.

4. Decellularized Matrix Biomaterials for Endometrial Repair

4.1. Endometrial Cell-Based Decellularized Stromal Hydrogel

In the treatment of endometrial injury, common biomedical materials are usually synthesized from materials such as gelatin and HA. These synthetic materials lack tissue specificity and therefore do not fully mimic the endometrial ECM (EndoECM) structure in its natural state, making them poorly suited for clinical use. In the last few years, the bioengineering field has developed several materials that can replace damaged and diseased tissues, not only for therapeutic purposes and to host drugs or cells. Recent advances in decellularization technology can enable ECM to be obtained directly from tissues and organs.[22] Furthermore, it can be processed into ECM hydrogels with tissue-specific properties. This material combines the hydrophilic, slow-release, and shaping advantages of hydrogels with the highly bionic advantages of ECM and may become a biomedical material with great potential. In a previous study,[23] endometrial exfoliated ECM was obtained by decellularizing the tissue of the porcine uterine horn, which was then processed into a hydrogel, and growth factors were added to this hydrogel. After 2 weeks of treatment with the appropriate experimental groups, the mice were tracked in utero with EndoECM, and the area of the endometrium, the density of glands and collagen deposition were observed. The proliferation of endometrial cells and the formation of neo-vascularization in the endometrium were also measured. The comparison of the endometrial area between the groups demonstrated a slight increase in the area of the EndoECM and EndoECM + growth factors (EndoECM + GFs) groups compared to the saline group. In addition, the density of the endometrial glands was also slightly increased. However, no significant difference was observed in collagen deposition between the groups. The expression of the cell proliferation marker Ki67 was higher in the EndoECM and EndoECM + GFs groups compared to the saline group. Similarly, the number of immature vessels was upregulated in the EndoECM and EndoECM + GFs groups (**Figure 8**). Fertility assessment showed a significantly higher pregnancy rate in the EndoECM and EndoECM + GFs groups than that in the saline group; however, gestational sac weight did not differ significantly. In conclusion, this bioengineered hydrogel with added growth factors is a promising material to treat endometrial damage in AS or EA mouse models and help restore fertility.

4.2. Decellularized Matrix Hydrogel Based on Bladder Tissue

Bladder matrix (UBM) is a derived ECM biomaterial with an intact basement membrane that can be used to achieve complete

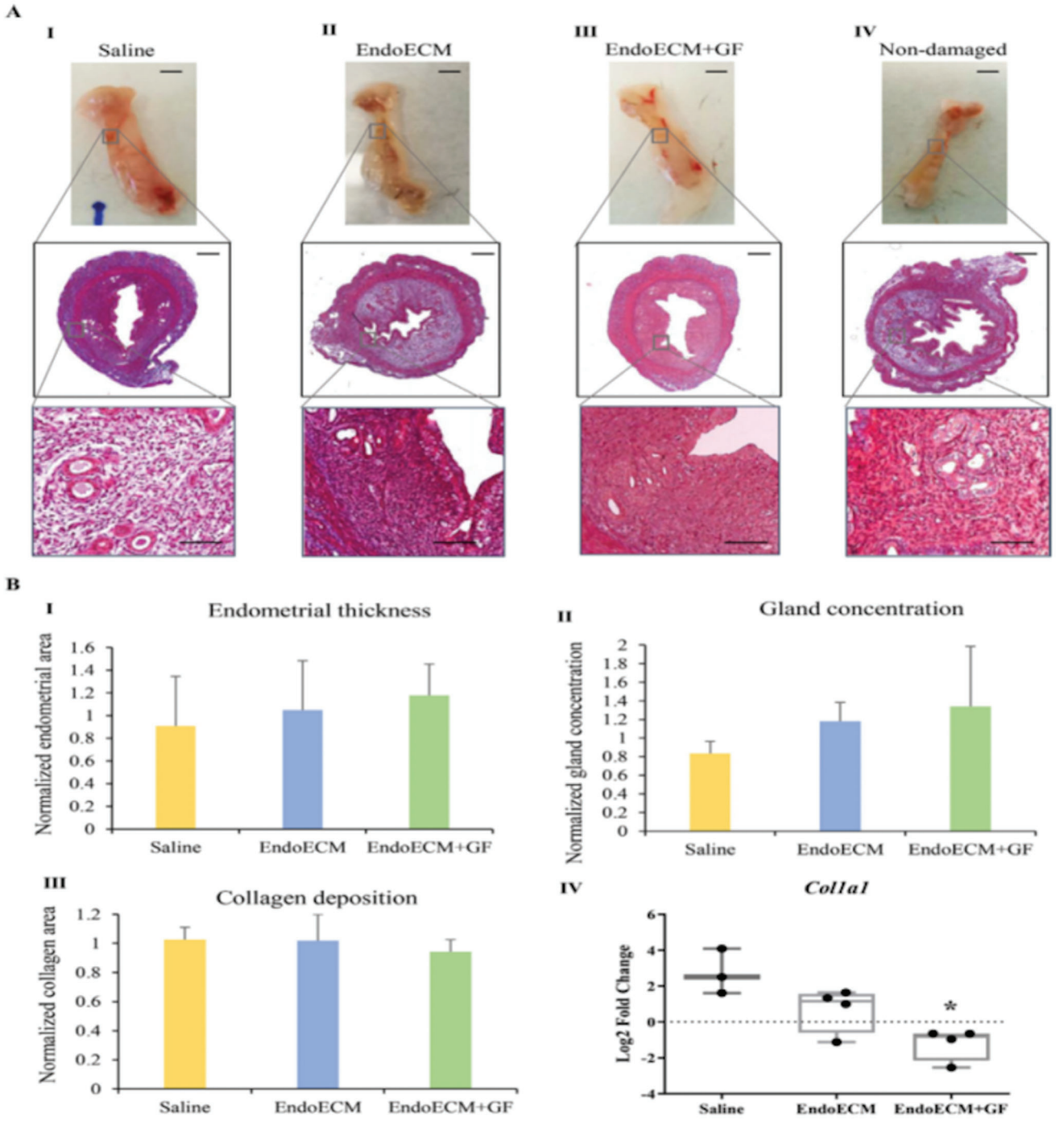

Figure 8. Uterine morphology, endometrial thickness/area, gland concentration, and collagen deposition 14 days post-treatment. A) Representative pictures and cross-sections of I) saline, II) EndoECM, III) EndoECM + GF, and IV) non-damaged uterine horns 14 days post-treatment. Scale bars = 5 mm (above), 500 µm (middle), and 100 µm (below). B) Representative image of I) endometrial thickness/area, II) gland concentration, and III) collagen deposition quantification. Scale bars = I) 500 µm and II,III) 100 µm. C) Quantification of I) endometrial thickness, II) gland concentration, III) collagen deposition, and IV) Col1a1 normalized quantitative expression in the saline, EndoECM, and EndoECM + GF groups by RT-qPCR, showing the normalized results with respect to non-damaged horns in all cases. Data are shown as average ± standard deviation for $n = 3–4$ per group. $* p < 0.05$. Reproduced with permission.[23] Copyright 2021, Elsevier.

self-healing. In a clinical study, UBM was shown to promote muscle repair,[8] which can also be applied to chronic non-self-repairing ulcers, allowing the ulcer to epithelialize and form limited scar tissue.[24] In addition, UBM promotes the reconstruction of soft tissue in trauma by creating neovascular soft tissue. UBM and ECM are closer to natural tissues and exhibit a natural resistance to infection, induce tissue regeneration, and have desirable mechanical properties and higher biological activity.[24]

Decellularizing intact tissues or organs usually prepare biological scaffolds comprising ECM. The resulting ECM scaffold material consists of structural and functional molecules that characterize the natural tissue ECM, such as collagen, laminin, fibronectin, growth factors, and glycoproteins.[11,13,25] UBM, a derivative of the ECM scaffold,[26] was prepared as follows: The bladder from 6 month old pigs was obtained immediately after euthanasia. Excess connective tissue and residual urine were removed. The plasma membrane, outer muscular layer, submucosa, and most of the mucosal muscular layer were mechanically removed. The uroepithelial cells of the mucosa were separated from the surface of the lumen by immersing the tissue in a 1.0 N saline solution. The resulting biomaterial was referred to as UBM, which consisted of the basement membrane of the uroepithelial cells and the underlying lamina propria. The surface characteristics of the UBM were observed using scanning electron microscopy; the UBM appeared loose and porous, with the 3D structure of the starting pores visible. The high porosity and large pore size of UBM facilitate cell colonization and proliferation. After the rat IUA model was established by mechanical injury, the endometrium was covered with a piece of UBM biomaterial at the corresponding location. All rats (n = 16) were injected with penicillin intramuscularly for three consecutive days to control infection. 1 month post-operation (open surgery), all 16 rats had different degrees of uterine adhesions in the operated area. HE staining revealed partial degradation of the UBM 2 weeks after surgery; however, the UBM material was completely degraded 4 weeks after surgery. In addition, the UBM group had more pronounced cellularization, thicker endometrial thickness, and more glands than those in the injury group. In contrast, these parameters did not differ from those in the normal and sham-operated groups. Masson staining also suggested that the area of fibrosis in the UBM group was lower than that in the injury group. Furthermore, ki67 was significantly higher in the UBM group than in the other groups. Immunohistochemistry revealed that the number of blood vessels in the UBM group was similar to that in the normal/sham-operated group. In conclusion, the authors demonstrated that UBM promotes functional endometrial repair by promoting the migration and proliferation of endometrial cells and the formation of new blood vessels, thus improving endometrial tolerance and increasing fertility. UBM implantation has the potential to be a new treatment for patients with IUAs; nevertheless, it warrants further investigation.

4.3. Amniotic Cell-Based Decellularized Matrix Hydrogel

Amniotic membrane is also a promising biomedical material that can secrete various growth factors that promote tissue regeneration and act as a mechanical barrier to protect damaged wounds. However, its immunogenic nature often limits its direct application to human tissues to avoid strong rejection reactions. Therefore, amniotic cells are removed using a decellularization technique, leaving only the ECM and extracellular components. Because of their excellent biocompatibility, biodegradability, and a high degree of bionic properties, decellularized amniotic cells are a promising material for human tissue repair and regeneration. Zheng et al. developed a human amniotic membrane ECM-based scaffold for hormone drug delivery and placed poly lactic-*co*-glycolic acid (PLGA) microspheres containing 17-βE2 into the scaffold.[27] This scaffold, comprising a decellularized matrix, can release estrogen-containing microspheres continuously for more than 20 days, which is highly consistent with the female menstrual cycle; in addition, the decellularized matrix allows better cell attachment and thus continuous drug delivery to the cells because of its innate close relationship with the cells (**Figure 9**). Cell proliferation experiments have also shown that the gradual release of E2 from this scaffold promotes the growth of endometrial cells more efficiently than free E2 (**Table 2**).

5. Biodegradable and Biocompatible Elastomer Biomaterials for Endometrial Repair

5.1. Bone Marrow-Derived Mesenchymal Stem Cells Loaded Elastic Poly(glycerol sebacate) Biomaterials

Uterine adhesions, usually caused by damage to the endometrium, can lead to infertility and recurrent miscarriages in women; however, no effective therapeutic strategies are known. Stem cells are an important therapeutic tool and are, in a sense, a material for tissue repair due to their high differentiation potential; however, the application of stem cells in repairing human tissues has some limitations. For example, they cannot remain in a specific site of an organ for a long time. Stem cells can be derived from allogeneic cells or autologous cells. The main limitations of allogeneic cells compared to autologous cells are the lack of safety, standardization, reproducibility, and the possibility of immune rejection (**Table 3**).

In contrast, autologous cells, such as bone marrow-derived MSCs (BMSCs), with good differentiation potential, are an essential source of cells for tissue repair. BMSCs are relatively easy to obtain and can be autologously transplanted without immune rejection, showing significant advantages in tissue and functional repair. Since direct injection of stem cells into the uterine cavity does not maintain the stem cells in their original location for a long time, the biomaterial used to host the stem cells is also very important. Traditional collagen/PLGA scaffolds are often used to host stem cells to promote endometrial and muscle cells, but the survival of implanted cells is still minimal. In addition, as a biomaterial, collagen has the potential risk of delayed hypersensitivity reactions, disease transmission, and immune reactions.

Sun et al. from Second Military Medical University designed and explored an elastic poly(glycerol sebacate) (PGS) scaffold capable of loading BMSCs,[28] which provides a 3D structure to aid in the attachment and growth differentiation of BMSCs. In vivo bioluminescence imaging showed that the PGS scaffold significantly prolonged the preservation time of BMSCs in a rat

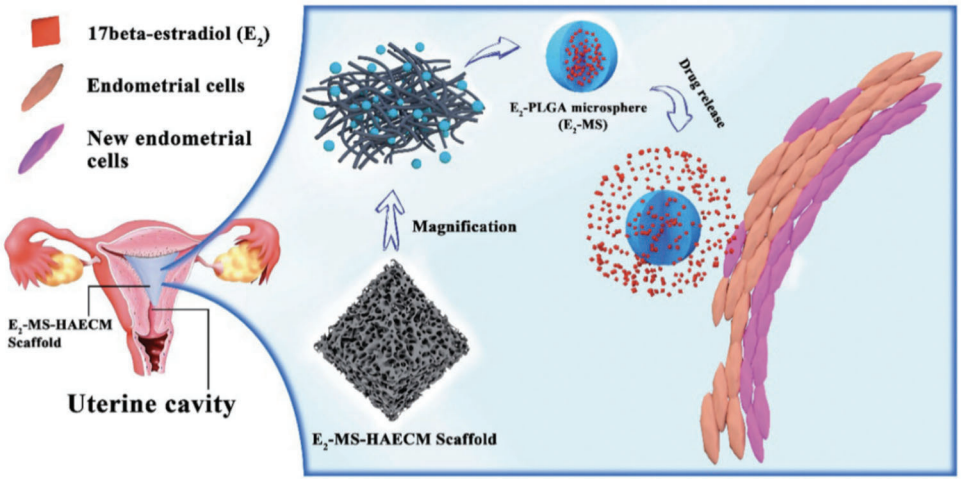

Figure 9. Schematic diagram of E2-MS-HAECM scaffold as the intrauterine controlled release system for endometrium regeneration. Reproduced with permission.[27] Copyright 2020, Taylor & Francis.

Table 2. Decellularized matrix materials to promote endometrial repair.

	Combination form	Advantages	Disadvantages	Effect	Literature
Bioengineered hydrogel with growth factors	Growth factor + extracellular matrix hydrogel	①Avoid the tumorigenicity and high immunogenicity in stem cell therapy ②The extracellular matrix is a natural material that can completely mimic the natural state and is highly bionic	Complex production, difficult to mass produce, few sources of amniotic membrane	Repair of the endometrium	Cervellóet al.[23] 2021
Biomaterials based on bladder matrix scaffolds	Bladder Matrix Stent	The bladder matrix is a natural material that can fully simulate the natural state and is highly bionic	Source of raw material is heterozygous animals may cause immune rejection	①Promote endometrial cell proliferation and migration ②Promote endometrial repair	Li et al.[24] 2019
Amniotic cell matrix-based hydrogel	Estradiol PLGA microspheres + amniotic cell matrix hydrogel	①Highly bionic amniotic cell matrix ②Able to release estrogen-containing microspheres continuously and slowly, coinciding with the menstrual cycle	Complex production, difficult to mass produce, few sources of amniotic membrane	Promotes endometrial repair with a sustained slow release of drug-containing microspheres	Zhao et al.[27] 2021

uterine injury model compared to direct injection of BMSCs or attachment of the stem cells to a conventional collagen/PLGA scaffold. Moreover, the constructed PGS/BMSCs complex promoted the differentiation of BMSCs into endometrial stromal cells, which was impossible when the BMSCs were attached to the conventional collagen/PLGA scaffold. PGS is a typical representative of synthetic bioelastomers with a wide range of biomedical applications, especially in soft tissue regeneration. The most important feature of PGS is its high elasticity, which allows it to maintain and restore various morphologies of soft tissues in a changing environment without adverse mechanical wear and tear to the cyclic environment due to its stiffness. Meanwhile, PGS porous scaffolds are promising carriers for various cells, such as human umbilical vein endothelial cells and MSCs.

Sun et al. designed PGS/BMSCs with PLGA/BMSCs and collagen/BMSCs constructs and recorded various parameters of endometrial environment repair in a rat model of uterine injury. The study revealed that the PGS scaffolds were more flexible and better adapted to uterine deformation than PLGA and collagen scaffolds. It also showed that PGS scaffolds significantly prolonged the in situ retention time of BMSCs in the uterine cavity compared with PLGA and collagen scaffolds, thus allowing the stem cells to have a longer duration of action. Finally, the PGS scaffold effectively promoted the transformation of BMSCs into endometrial stromal cells. In contrast, such differentiation could not be achieved when BMSCs were attached to the conventional collagen/PLGA scaffold. In addition, experiments showed that transplantation of PGS scaffolds alone could increase the probability of pregnancy in the rat uterus after injury. Therefore,

Table 3. Different approaches to repair endometrial damage.

	Advantages	Disadvantages	Examples	Literature
Hormonal therapy	①Significant therapeutic effect ②The source of hormones is more stable and can be produced on a large scale	①May lead to the recurrence of malignant tumors ②There are different side effects associated with hormone action, such as vaginal bleeding ③Non-linear hormone release	Mirena	Senturk and Erel,[1] 2008
Stem Cell Therapy	①Stem cells have excellent differentiation potential ②Stem cells promote tissue regeneration through paracrine and immune regulation	①Stem cells are more difficult to obtain, especially in adults and the elderly ②Stem cell therapy is potentially tumorigenic and immunogenic	Bone marrow-derived mesenchymal stem cells	①Song et al.[2] 2021 ②Azizi et al.[29] 2018
Advanced Biomaterials Therapy	①Avoid the tumorigenicity and high immunogenicity in stem cell therapy ②Able to release estrogen-containing microspheres continuously and slowly, coinciding with the menstrual cycle	Complex production, difficult to mass produce	Micro-environmental protection type exosome hydrogel	Cui et al.[14] 2021

PGS/BMSCs may be a promising therapeutic modality to promote endometrial injury repair.

6. Summary

In recent years, the endometrium is constantly being damaged with the increasing rate of uterine surgery. This damage may reach deep into the endometrial stroma, thus affecting the normal environment of the uterine cavity, which may affect the menstrual flow, cause amenorrhea, and even cause infertility, which can have a significant impact on women of childbearing age. Therefore, it is imperative to repair the damaged endometrium. Currently, the standard treatments for repairing damaged endometrium include hormone therapy and balloon stents, which do not repair the endometrium well and are prone to systemic hormone-related diseases. Pharmacological or hormonal treatments, for example, often do not act on the endometrium alone. In other words, the local concentration of drugs in the endometrium does not produce a satisfactory effect. It does not last long enough, which leads not only to a poor therapeutic effect of drugs or hormones on the endometrial repair but also to systemic hormonal disorders due to the systemic spread of drugs and hormones. Although stem cell therapy has excellent prospects for tissue regeneration, the lack of suitable stem cells and the immunogenicity and tumorigenicity of stem cells have prevented the direct application of stem cells for endometrial treatment. Emerging evidence demonstrates the potential benefits of stem cell-derived exosomes over parental stem cells in stem cell therapy. Therefore, we need a suitable carrier to confine drugs, hormones, exosomes, etc., to the endometrium and release them gradually, and new biomaterials are such a carrier. Biomedical materials are becoming an important medical tool for tissue repair, and rationally designed functional biomedical materials have gained increased clinical attention in endometrial repair. Biomedical materials have facilitated the development of endometrial treatment modalities by overcoming, to some extent, the shortcomings of traditional treatments. Among them, hydrogels have great potential due to their better biocompatibility and high water content. Furthermore, specific synthesis adds anti-inflammatory and antibacterial effects to such biomedical materials, making them more suitable for prolonged in vivo repair work. Another material is the shape memory material, which can be used for therapeutic purposes by pre-setting the shape of the material and restoring it to the pre-set shape after heating, ultrasound, and other conditions. Such materials are comparable to conventional biomedical materials in biocompatibility, degradability, and drug retardation. They also have more possibilities because of the controllability of their pre-set shapes and mechanics. Another material is the decellularized matrix biomedical material, which is more highly bionic than the two materials mentioned above. Since they are derived from tissues, their internal structure and interaction with cells are more similar to the physiological state. Compared with traditional treatment, these biomedical materials can better limit the local action of drugs or hormones and avoid systemic drug effects or systemic hormonal diseases, especially for people with high-risk factors for breast cancer. Biomedical materials have good biocompatibility, hypoallergenicity, and low immunogenicity, which are less likely to cause immune rejection by the body after entering the uterine cavity. Moreover, biomedical materials such as hydrogels, shape-memory materials, and decellularized matrix materials can add different functional groups to improve their functions according to the desired conditions. It has been demonstrated that these biomedical materials, when combined with drugs or hormones, can effectively promote the recovery of the endometrium: The thickness and density of the glands are significantly increased, and the vascularization among the endometrium is more pronounced, accompanied by less fibrosis. In conclusion, new biomedical materials are of great clinical value in the repair of the endometrium.

7. Challenges

Despite the great potential of biomaterials for endometrial repair, many mechanisms remain unclear, and there are still unresolved issues in the research and commercialization process: mass production and industrialization, raw material biocompatibility,

controllability, and material safety. Therefore, more research is needed to overcome these issues and to bring these biomedical materials to practical clinical applications. The key topics that need to be addressed and further developed are described below; these points also provide insights for future research.

(1) The drug release process from biomedical materials should correspond to the different tissue repair processes of the endometrium. Endometrial repair is a dynamic process in which the hormones or signaling substances, such as exosomes and secretory proteomes, needed for repair are dynamically changing at each stage. Therefore, a biomedical material that can more precisely regulate the release of drugs and hormones is needed to precisely regulate and repair endometrial damage in both space and time.
(2) Biomedical materials match the unique physiological environment of the uterine cavity and the endometrium. The material should take into account the normal menstrual cycle of women of childbearing age, so it should have better adhesion while not neglecting how to let the exfoliated endometrium discharge smoothly from the uterine cavity, not only to ensure that the material will not be discharged with menstrual blood but also to maintain good abrasion resistance and softness of the material to avoid damaging the normal endometrium. At the same time, due to the irregularity of the uterine cavity and the narrow cervical opening in infertile women, the material should have good deformability and passability, as well as the ability to be accurately positioned at the location where repair is needed after entering the uterine cavity. It also adapts itself to the shape of the uterine cavity and covers the wound to be repaired.
(3) The mechanism of immunology of biomedical materials in the uterine cavity is still not explicitly explained. Why are biomedical materials innately biocompatible, and how are they friendly to the immune system of an organism? Whether the material is also potentially damaging to the endometrium during mutual contact with endometrial cells needs to be explored in depth.
(4) Biomedical material body to construct an organoid of the endometrium. If it is determined that a potentially disruptive surgical procedure will be performed, perhaps a small amount of endometrial tissue containing stem cell tissue, such as the endometrial stroma, could be taken before the procedure. Then an artificial uterine organoid could be created from the new biomaterials. This creates a "private bank" of endometrial tissue and transplants the mature, healthy, homologous endometrium back into the uterine cavity of the patients when needed, thus avoiding the immune rejection that can occur with allogeneic transplants.
(5) Developmental biomaterials promote the natural regeneration of the endometrium. Every tree develops from a seed, and what kind of tree they eventually become is related to its species and environment. Therefore, developing a "seed-based" biomedical material that can "grow" over time could be helpful. When this new biomaterial is implanted in the uterine cavity, it can adapt to changes in the uterine cavity. When the uterine cavity is damaged, it will have more "land" to "grow" on its own, thus automatically filling and repairing the damaged endometrium.
(6) Silk fibroin is a kind of natural high molecular weight fibrin from mulberry silk, which contains various amino acids. Silk fibroin has become a promising biomedical raw material because of its good mechanical, physical, and chemical properties, flexibility, and tensile strength. After treatment, it can take different forms, such as fiber or solution. Therefore, this material, with good mechanical properties and excellent flexibility, can play a more significant role in endometrium repair.
(7) Stem cells, as a kind of customized ink, can be customized by special 3D printing devices according to the degree and shape of endometrial damage. The combination of 3D printing technology and stem cell therapy can benefit stem cell therapy by reducing the side effects. For example, the repair cells are different on different damaged surfaces; adding drugs and immunosuppressants to the "ink" can be advantageous to stem cells in promoting growth and avoiding tumorigenesis caused by immunogenicity.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords

endometrial repair, biomedical materials, endometrium, stem cells

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