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Bioengineering approaches for the endometrial research and application

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ABSTRACT

The endometrium undergoes a series of precise monthly changes under the regulation of dynamic levels of ovarian hormones that are characterized by repeated shedding and subsequent regeneration without scarring. This provides the potential for wound healing during endometrial injuries. Bioengineering materials highlight the faithful replication of constitutive cells and the extracellular matrix that simulates the physical and biomechanical properties of the endometrium to a larger extent. Significant progress has been made in this field, and functional endometrial tissue bioengineering allows an in-depth investigation of regulatory factors for endometrial and myometrial defects in vitro and provides highly therapeutic methods to alleviate obstetric and gynecological complications. However, much remains to be learned about the latest progress in the application of bioengineering technologies to the human endometrium. Here, we summarize the existing developments in biomaterials and bioengineering models for endometrial regeneration and improving the female reproductive potential.

1. Introduction

The endometrium is a sensitive and complicated tissue that responds precisely to circulating hormone levels and is strongly associated with other parts of the female reproductive system [1,2]. The structural and functional integrity of the endometrium largely dominates female reproductive potential [3]. However, primary endometrial lesions and related injuries caused by operations may interrupt common crosstalk responsible for hormone-regulated endometrial repair or partial replacement, leading to severe obstetric and gynecological complications [4,5]. Therefore, exploring novel research models of the endometrium and repair methods for pathological conditions of the endometrium is crucial.

In recent years, efforts have been made to develop platforms aimed at rebuilding or simulating the endometrial tissue, including two-dimensional (2D) cell culture systems and explant models to illustrate the histological and molecular characteristics of the endometrium [6–8]. Additionally, developing more dynamic and adjustable methods based

Abbreviations: 2D, two-dimensional; AKR1C1, aldo-keto reductase family 1 member C1; BADS99, B cell lymphoma-2-associated death promoter Ser99; ECM, extracellular matrix; HA, hyaluronic acid; HAECM, human amniotic membrane extracellular matrix; HIF, hypoxia-inducible factor; IUA, intrauterine adhesion; IGF-1, insulin-like growth factor 1; KGF, keratinocyte growth factor; MI, menin-MLL inhibitor; NHC, N-heterocyclic carbene; Nrf2, nuclear factor-erythroid 2-related factor 2; PARPis, poly ADP-ribose polymerase inhibitors; PEG, polyethylene glycol; PIC, polyisocyanide; PNIPAM, poly-N-isopropylacrylamide; PTEN, phosphatase and tensin homolog; PVA, polyvinyl alcohol; TET1, ten-eleven translocation 1; TrxR, thioredoxin reductase; SC, stem cell.

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on bioengineering technologies by taking advantage of replicating tissue structures and functions is essential to narrowing physiological gaps between tissues or organs in vivo and culture models in vitro [9]. Importantly, bioengineering appliances and tools have multiple advantages compared to animal models used in previous endometrial studies, especially in the establishment of menstrual models, as well as financial and ethical considerations. Therefore, attention should be paid to the application of bioengineering appliances and tools in the field of the endometrium [9,10].

Over the past few decades, bioengineering materials for endometrial studies, including organoids, microfluidics, hydrogels, and various bioscaffold systems, have been intensively studied in clinics or laboratories and have shown potent potential in partial regeneration or reconstruction of the endometrium. Currently, bioengineering methods and tissue engineering technologies exhibit enormous potential for endometrial modeling and the development of therapeutic alternatives. However, comprehensive reviews illustrating the latest progress in the application of bioengineering technologies in the human endometrium are lacking. Therefore, this review aims to summarize the current efforts in the development of bioengineering materials and highlight the updated modeling and therapeutic strategies for endometrial diseases. This review begins with a brief overview of the human endometrium under normal and pathological conditions, followed by a comprehensive description of the development and applications of bioengineered materials in endometrial diseases. In addition, the existing limitations and major challenges encountered in the field of endometrial bioengineering are mentioned. Finally, we provide new insights into future perspectives to meet the needs for further clinical use. We hope that the review can serve as a reference for future discoveries.

2. Structure and composition of the endometrium

The endometrium is a precisely controlled tissue that comprises a simple columnar epithelium overlying a multicellular stroma (Fig. 1) [11]. The epithelial layer mainly consists of luminal and glandular epithelial cells that line the intact uterine cavity and cover the pits extending into the myometrium [12]. Abundant cellular components, including connective tissue composed of fibroblast-like stromal cells, spiral arteries composed of perivascular cells, tubular glands for endocrine functions, and innate immune cells, have been identified in the stroma, all of which are of great significance in cell communication. Stromal cells and the scattered extracellular matrix (ECM) play a vital role in providing structural and functional support, whereas recruited perivascular and immune cells play a crucial role in the dynamic process of blood vessel remodeling [13,14]. Furthermore, several cell populations in the basal layer of the endometrium have self-renewing ability and differentiate into stromal and epithelial cells, which ensures endometrial integrity during menstruation [15]. The number and proportions of various cell groups actively vary according to the menstrual cycle, which provides evidence of crosstalk among cells via endocrine and

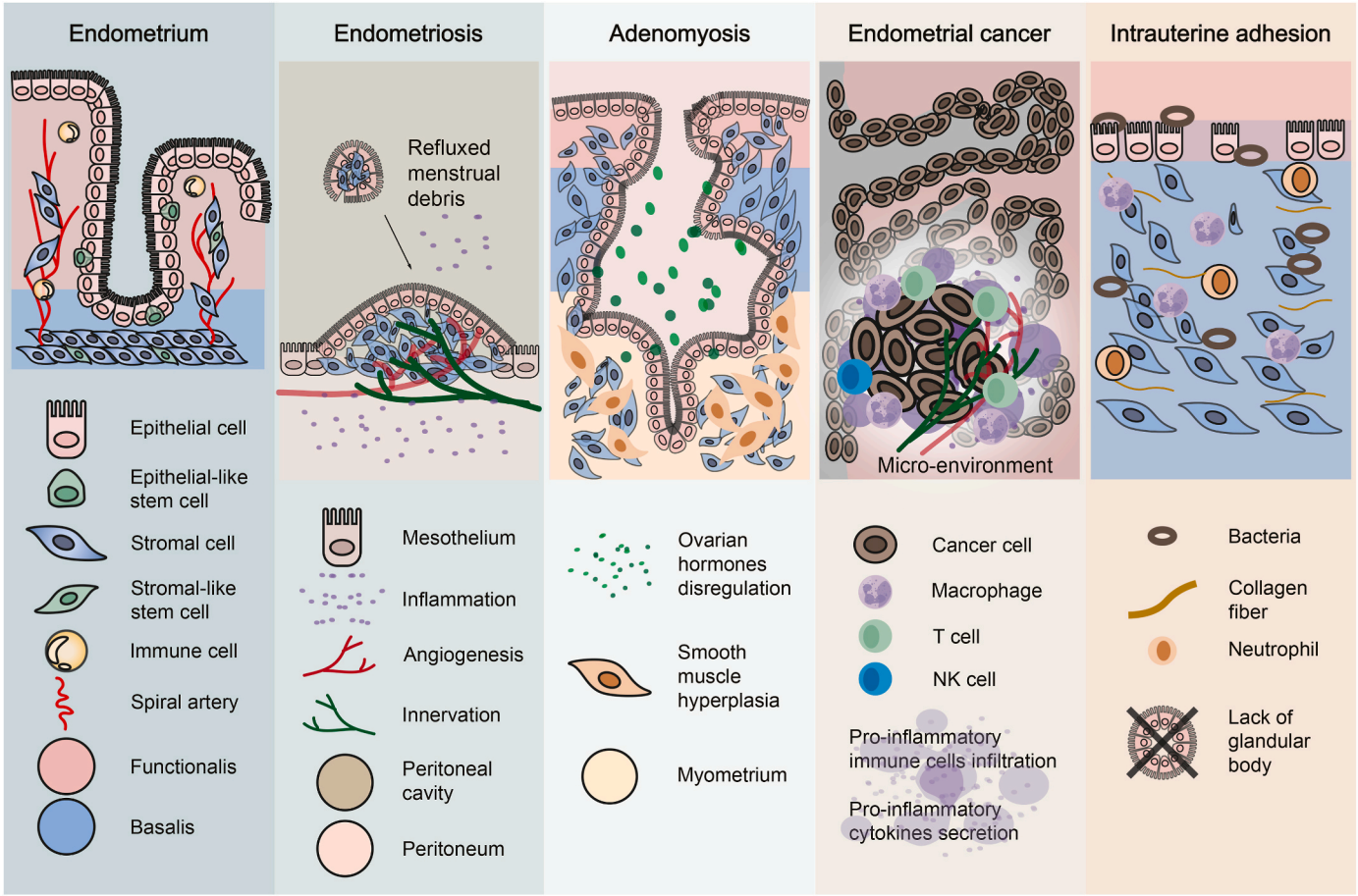

Fig. 1. Schematic diagrams of human endometrium in both physiological and pathological status.
The endometrium, consisting of a simple columnar epithelium and multicellular stroma, can be divided into the functionalis and basalis according to its response to ovarian hormones. Endometriosis and adenomyosis are diseases wherein the endometrium-like tissues are located outside the endometrium. In the former, lesions grow within the peritoneal cavity and mostly invade the ovaries, whereas in the latter, the ectopic endometrium grows in the myometrial layer. Endometrial cancer is defined as a state of atypical hyperplasia of the endometrial epithelia and glands with proinflammatory responses. The functional epithelium in intrauterine adhesions is displaced by adhesive and fibrotic layers that lack normal vascularization or glands.

immune features and provides endometrial shedding and subsequent re-epithelialization with high possibility and efficiency [16,17].

The endometrium is the innermost layer of the uterine wall that grows and differentiates in response to fluctuations in the steroid hormones estrogen and progesterone produced by the ovaries, which play an indispensable role in the maintenance of female reproductive potential [18]. The highly regulated process, consisting of periods of "wounded" and "refreshment," undergoing pro-inflammation responses, blood vessel remodeling, and the formation of new layers, paves the theoretical foundation to study tissue repair in endometrial diseases and allows opportunities to remove these abnormal conditions [19]. However, the regenerative abilities of the endometrium may be lost because of impaired hormonal response caused by serious pathological alterations or physiological aging. Steroid-dependent events in the endometrium are altered in endometriosis and adenomyosis, possibly owing to chronic inflammation [20,21]. The hormonal response and endometrial regeneration also disappear in cases of Asherman's syndrome and a thin endometrium due to disruptions of endometrial cell composition [22]. Additionally, during the development of endometrial cancer, an imbalance in hormone sensitivity results in excessive endometrial proliferation, which subsequently leads to uncontrolled endometrial hyperplasia [23]. Therefore, studies focusing on the injured endometrium are needed to provide insights into the mechanisms involved in the development and survival of diseased tissues.

3. Engineering technologies focusing on the endometrium

The current understanding of bioengineering allows for the improvement and treatment of many endometrial diseases, such as endometriosis, Asherman's syndrome, and female infertility. Compared with traditional methods, in vitro models based on bioengineering tools offer safer, more efficient, and more ethically sound approaches for pharmacological experiments and drug screening [24,25]. Furthermore, by means of accurate precise mimicking, bioengineering applications can unravel the cellular communication and molecular mechanisms that govern the intricate processes of endometrial regeneration.

3.1. Organoids

Organoids are promising three-dimensional (3D) cellular models that emphasize the architectural and functional features of organs and tissues, making full use in rebuilding structures and restoring functions in in vitro biomedical systems [26]. Endometrial organoids derived from progenitor cells and stem cells (SCs) of human tissues or animal models are capable of self-renewal and differentiation, extensively retaining the polarity of constitutive cells and gland-like tissue structures [27].

In the 21st century, several laboratories have reported the generation of human endometrial organoids by enzymatically dissociating endometrial tissue, which subsequently matures and grows into hollow spherical structures in specific media [28]. Compared with endometrial organoids derived from animal models, specific nutrients added into the human endometrial organoid culture system are different, including growth factors, hormones, and key regulators involved in signaling pathways [29]. These organoids show potent stability in retaining genetic traits during cell division and differentiation, and their ability to restore secretory characteristics under thawing conditions after cryopreservation has been fully tested [30]. Additionally, positive responses to estrogen and progesterone have been observed in epithelial cells of endometrial organoids, paving the way for studies on endometrial-related diseases [31,32]. Notably, endometrial stromal, angiogenic, and immune cells that have been identified in the human endometrium can be cultured along with epithelial SCs in vitro. This approach is beneficial for precisely simulating in vivo tissues and allows for the investigation of the roles played by different types of cells [33,34]. Endometrial organoids are expected to reveal crucial intracellular signaling pathways and depict the entire morphological characteristics of the tissue, greatly enhancing our understanding of the physiological and pathological traits of the human endometrium at the cellular level [35,36]. Controversies regarding the cellular sources of endometrial regeneration exist owing to the existence of a hierarchical network of SC differentiation; therefore, more efforts are needed to build an accessible and ideal research model that allows the analysis of gene expression patterns [15,37].

Organoids have gradually taken a dominant position in research on the organs of the female reproductive system. Apart from the application of the human endometrium, efforts have also highlighted progress in terms of the ovary, vagina, and cervix, allowing the generation of unprecedented insights into preclinical modeling for normal and impaired reproductive potentials [38]. Furthermore, combining these models with other microtechnologies (including single-cell analysis and gene editing) makes them suitable for individual therapies and personalized medicine [39,40].

3.2. Microfluidics

Microfluidics are also regarded as microphysiological systems that simulate physiological states at the tissue or organ levels by controlling trace water flow, including interactions among tissues, microvascular perfusion, and physicochemical traits of microenvironments [41]. They can be used to illustrate cellular interactions by studying the mechanisms that produce these microscopic properties, particularly the shear forces and concentration gradients in the surroundings. To date, the design of microfluidic technologies has been developed from simple chip platforms with only the cell types to multicellular chambers representing the entire organ system [42,43].

Endometrial microfluidic systems show potent potential to recreate controllable endocrine signaling and real-time feedback from cells compared with traditional static cultures [44]. Moreover, multi-chamber orthogonal microfluidics offers distinct advantages for accurately replicating the hemodynamic properties of the endometrium in vitro, allowing for full interaction of the uterine vasculature with human endometrial stromal cells [45]. These advantages have led to the development of in vitro pathological models and pharmaceutical applications. Additionally, endometrial microfluidics have been extensively studied in the context of endometrial receptivity. Ahn et al. [46] designed an in vitro endometrial model with a multichannel microfluidic cell culture system consisting of five microchannels that induce the formation of three cellular layers of the human endometrium from epithelial cells and stromal fibroblasts to endothelial cells. This technique faithfully displays the process of vascular angiogenesis involved in the proliferative and secretory characteristics of the endometrium and sheds light on dynamic traits during embryo implantation in terms of morphological and biochemical aspects [46]. Additionally, microfluidic systems underscore the crucial role that ECM rearrangement plays in endometrial decidualization. This process depends on the altered mechanical forces between the endometrial cells and the feedback system of the hypothalamic–pituitary–gonadal axis [47–49]. However, the limitations of endometrial microfluidic chips that focus on the human endometrium fail to reveal their interactions with other organs. Data from microfluidic systems are limited, in terms of highlighting potential endocrine loops in the female reproductive system and studying these organs as a whole [50]. Considering the interactive culture of multiple organ systems, more efforts should be made in microfluidics for female reproductive medicine, considering the interactive culture of multiple organ systems.

Briefly, the microenvironment portrayed by endometrial microfluidics largely depends on unique experimental designs, which endow research platforms with more flexibility and possibilities for innovation. Microfluidic culture systems emphasize the endocrine and paracrine effects within cellular and stromal components owing to variable physical and mechanical qualities, overcoming challenging obstacles in reproductive science, especially looking at how sex hormones act and

the monthly repair of the human endometrium.

3.3. Hydrogels

Hydrogels derived from natural and synthetic materials are cross-linked polymers that form the ECM for in vivo injection and in vitro models (Table 1) [51]. It is an available material based on dynamic covalent bonds and ionic interactions and possesses elevated levels of controllable response properties. Physical, chemical, and enzymatic cross-linking is applied to improve thermal stability and mechanical ductility [52]. Moreover, the addition of bioactive molecules in hydrogel systems allows for a more precise regulatory paradigm [53,54]. According to the above modifications, hydrogels become popular materials to mimic natural living tissues and organs.

Hydrogels with a unique composition and topology function as a physical scaffold for cell behavior and cytoskeletal movement and play a vital role in providing biochemical and mechanical signals that modulate tissue or organ development and micro-environmental homeostasis owing to their low immunogenicity and potent cytocompatibility [86]. Importantly, different types of hydrogels have distinct effects on cell behavior, including cell migration, proliferation, and differentiation owing to the diverse molecular skeletons of hydrogels. Therefore, adding hydrogels to the in vitro culture system is conducive to simulating the physiological state of cells or tissues, and for in vivo experiments. Besides, hydrogels can be used as a delivery system targeting drugs into the lesion location and exerting the inherent capability of polymers, including mechanical strength and the surrounding environment, to facilitate tissue repair or regeneration [87,88]. Injectable hydrogels undergo a biodegradable process with released active ingredients, achieving positive therapeutic efficacy in the absence of injectable exogenous hormones and constituent cells [89]. Subsequently, the disappearance of in vivo hydrogels decreases the risk of secondary infections related to surgery or pathological conditions [90]. Furthermore, efforts are underway to optimize hydrogels and address their existing drawbacks, such as poor cell adhesion, low mechanical strength with specific environmental stimuli, and underlying toxicity to cells [91]. For instance, nanoarchitecture-integrated hydrogel systems have been designed to achieve efficient encapsulation and well-organized cargo [92]. Additionally, advancements in 3D bioprinting have helped in understanding the spatial recapitulation of hydrogels in detail, which is in turn advantageous for developing and promoting low-cost, nontoxic, and biocompatible hydrogels [93].

In conclusion, hydrogel culture systems exert a potent effect on monitoring cell behavior in response to microenvironments owing to their adjusted mechanical, physical, and chemical properties. These advantages make hydrogels excellent research tools and promising platforms for studying hormone-sensitive endometrial activity [94,95].

3.4. Bio-scaffolds

Traditional opinions on promoting injured endometrial repair and regeneration highlight the importance and therapeutic potential of the transplantation of originally inhabiting cells, especially multifunctional SCs. However, a minimal increase in fertility rates secondary to the application of SCs has been reported owing to poor cell viability after transplantation [96,97]. To address this issue, biomaterial-based scaffolds have been designed to act as fertilizers that provide a proper structure for cell adhesion and modulation of cell behavior, promoting the recruitment of therapeutic cells at the site of injury to ensure and maintain the survival of transplanted SCs [98,99].

Table 1
Summary of different hydrogels and their potential biomedical applications.

Hydrogel	Source	Origin	Function	Drawback	References
Collagen	Protein-based hydrogel	ECM of connective tissue	Replace the entire ECM	Poor thermal stability, mechanical strength, and enzymatic resistance	[55,56]
HA	Protein-based hydrogel	Diverse animal tissues and bacteria	Regulate blood vessel permeability and protein function during tissue repair	Degrade rapidly	[57,58,59]
Gelatin	Protein-based hydrogel	Collagen	Facilitate cell remodeling and adhesion	Functioning depends on the appropriate temperature	[57,60,61]
Fibrin	Protein-based hydrogel	Thrombus	Direct related cells involved in tissue repair and regeneration	Risks for pathogen transmission	[56,62]
Elastin	Protein-based hydrogel	Diverse animal tissues	Induce tissue regeneration, hybrid hydrogels based on elastin gain extraordinary mechanical and antimicrobial properties	Cost high	[63–65]
Alginate	Polysaccharide-based hydrogel	Complexes such as proteoglycans	FDA-approved medical materials in clinical translation	Barriers in the diffusion of substances	[66,67]
Agarose	Polysaccharide-based hydrogel	Agar or seaweed containing agar	FDA-approved adoptable biomaterial for 3D cell culture and 3D bioprinting	Gel performance highly depends on hydrogen bonds	[68,69]
Chitosan	Polysaccharide-based hydrogel	Polysaccharide chitin	Promote cell attachment, differentiation, and morphogenesis	Insufficient mechanical properties	[70–72]
Cellulose (nanocellulose hydrogel)	Polysaccharide-based hydrogel	Structural polysaccharide in plants	Responsible for metabolic activity and proliferative capacity of the cells	Poor surface energy and intermolecular interactions	[73–75]
PEG	Artificially synthesized	Ethylene oxide, water or ethylene glycol	Regulate the number of adherent cells, hybrid hydrogels based on PEG show the potential to promote organoid formation and xenotransplantation	Easy hyperexpansion, insufficient cell scale	[55,76,77]
Poloxamer (Pluronic, Lutrol, and Synperonic)	Artificially synthesized	Ethylene oxide, propylene oxide, ethylene oxide	Assign thermal sensitivity to hybrid hydrogels derived from poloxamer	Low mechanical strength, fast erosion	[78,79]
PIC	Artificially synthesized	Oligoglycol	Study the effect of matrix stiffness on cell behavior	Unknown long-term degradability	[56,80]
PVA	Artificially synthesized	PVA	Instructive for cell-matrix remodeling and multicellular morphogenesis	Poor cell adhesion	[81,82]
PNIPAM	Artificially synthesized	PNIPAM	Crucial materials for hybrid hydrogels, useful for the analysis of cell mechanobiology	Low molecular weight polymers are inherently toxic to cells	[83–85]

Abbreviations: ECM, extracellular matrix; HA, hyaluronic acid; PEG, polyethylene glycol; PIC, polyisocyanide; PNIPAM, poly-N-isopropylacrylamide; PVA, polyvinyl alcohol.

Decellularized ECM is prepared by the decellularization of human tissues or animal samples, and numerous methods have been proposed to improve its quality [100]. Decellularized scaffolds contain nutrients and favor the growth of initial members [101,102]. Oriented differentiation toward endometrial epithelial and stromal cells is allowed when mesenchymal cells are cultured in a decellularized endometrium, giving rise to human endometrial-like tissues in vitro [103]. Additionally, the decellularized ECM retains the native specificity and function of the original tissue [104]. Campo et al. [104] reported that only the acellular scaffold systems extracted from the synchronous endometrial coating exerted a beneficial role in improving the development of the endometrium, whereas a similar effect of nonsynchronous materials was not apparent. More importantly, natural crosslinking materials including decellularized scaffolds, instead of traditional chemical materials, are beneficial in suppressing over-activated inflammatory responses or transplant rejection of natural bio-scaffold systems making them competitive materials to shorten the healing time of the pathological endometrium [105].

Human amniotic membrane ECM (HAECM)-derived, uterus-derived, and urinary-derived decellularized scaffolds are well-studied endometrial bioengineering techniques endowed with different advantages [106,107]. Decellularized scaffolds such as human endometrium and the urinary, ECM collected from the placental amniotic membrane improve the sensitivity of endometrial stromal cells to estradiol [106]. Estradiol-loaded HAECM scaffolds upregulate a series of growth factors, including epidermal growth factor, insulin-like growth factor 1 (IGF-1), and vascular endothelial growth factor, which are conducive to the growth of endometrial cells [108]. Decellularized scaffolds based on the human endometrium or uterus are beneficial for personalized regenerative medicine in patients with infertility because they specifically inherit diverse pathological characteristics from different patients [109]. Moreover, the therapeutic potential of the uterus-derived decellularized scaffolds is also attributed to altering the frequency of natural killer (NK) cells located in the endometrium, a crucial immune cell group responsible for a favorable environment for endometrial decidualization [109]. Besides, these typical scaffolds are reported to protect the body from the potential immunogenicity of the materials, making them practical and safer alternatives for clinical applications [101].

However, some issues must be addressed before the larger-scale application of acellular scaffolds. First, studies have proposed that the mechanical properties of decellularized scaffolds should be carefully optimized to provide solid support for tissue rebuilding [101]. Second, the simple and fixed design of physical frameworks with inherent ECM components is often disadvantageous, which makes them fail to fit the specific pathological states with abnormal metabolic levels in each patient. Therefore, the transition from traditional scaffold-based bioengineering methods to extensive scaffolded systems comprising several tissue modules in response to distinct cellular heterogeneity and physiological properties should be highlighted [98]. Furthermore, based on animal experiments, some researchers have reported that transplanted decellularized endometrial scaffolds lose their ability to induce epithelization within one month [110]. Extending the length of the effective

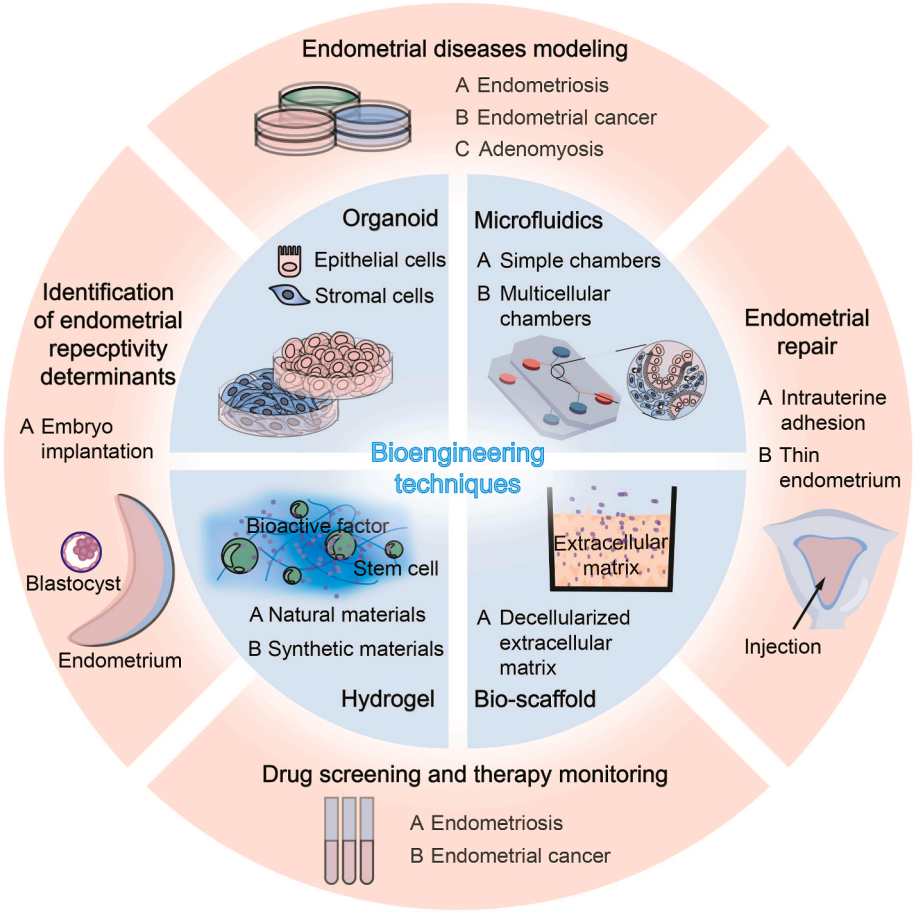

Fig. 2. Endometrial bioengineering technologies and their potential applications.
Endometrial bioengineering studies highlight the promising prospects of endometrial organoids, microfluidics, hydrogels, and bio-scaffolds. They can be used for endometrial disease modeling, endometrial repair, and pharmacological experiments, and have great potential in targeted therapeutic design for endometrial receptivity improvement, playing a vital role in realizing the combination of a general understanding of healthy and diseased human endometrium and personalized medicine.

treatment windows for decellularized endometrial scaffolds is important for further clinical applications.

4. Application of bioengineering technology in endometrial diseases

Based on the pathological characteristics of human endometrial diseases and the differences in treatment priorities, we summarize and classify the existing application achievements of the above bioengineering technologies into four platforms: i) building endometrial models under physiological and pathological conditions, ii) repair or regeneration for severe adhesion or weakness of the endometrium, iii) pharmacological experiments and drug screening, and iv) deepening the comprehensive understanding of female infertility (Fig. 2).

4.1. Endometrial diseases modeling

In addition to modeling the physiological state of the human endometrium as described above, the application of bioengineering technologies has deepened the current understanding of the pathogenesis and progression of endometrial diseases.

4.1.1. Endometriosis

Endometriosis refers to the ectopic growth of the endometrium in the peritoneal cavity or ovaries, which is illustrated by Sampson's retrograde menstruation theory, closely related to aberrant responses of the endometrial tissue to sexual hormones [111]. In vitro models based on bioengineering have great advantages according to the particularity of spontaneous menstruation, compared to animal models or cell culture systems [112].

In vitro culture systems based on organoids have successfully replicated responses to the regulatory hormones estrogen and progesterone during endometriosis [113]. First, epigenetic changes, including histone modification and DNA methylation, are tightly involved in aberrant hormonal sensitivity during the development of the lesion. Variations in the number and function of steroid hormone receptors affected by gene modifications lead to an attenuation of hormonal sensitivity in endometriosis [114,115]. Second, based on organoids at different clinical stages of endometriosis, overactivation of related genes and alterations in signaling pathways related to intercellular interactions such as adhesion and invasion are observed [116]. Evidence from current studies suggests that Notch signaling is overactivated in endometriosis, contributing to abnormal estrogen sensitivity and hyperproliferation of glandular epithelial cells [117]. Third, organoids derived from endometriotic biopsies from different lesions also exhibit differences in cellular composition. In 2022, Tan et al. [118] identified a perivascular mural cell found in peritoneal lesions instead of ovarian lesions in endometriosis, which plays a vital role in angiogenesis promotion and immune cell recruitment. The discovery of lesion heterogeneity further plays a crucial role in drug screening and personalized treatment. Besides, more recently, researchers noticed that the pathological characteristics of endometriosis are linked to the diseased condition of endometrial cells and to the microenvironment where the lesion occurs [20]. Such an understanding promotes the addition of microfluidics to endometriosis organoid modeling systems, providing well-controlled platforms by regulating nutrient supply and waste removal. The mechanical signatures of the endometrial stroma in eutopic lesions can be precisely illustrated using adjustable parameters [119]. The novel design is also beneficial for screening biomarker candidates and testing promising drugs using tiny microfluidic chips [120].

4.1.2. Endometrial cancer

Organoids are used as in vitro culture models for studying endometrial cancer [121]. Endometrial cancer organoids have successfully recapitulated tumor histology and morphology [122]. In these organoid culture systems, the characteristics of the tumor genome from patients are fully preserved, which allows for long-term stability and precise fidelity of in vivo transplantation experiments [123]. Additionally, this approach enables capturing the heterogeneity in endometrial cancer growth, which is considered a key factor in the failure of previously targeted therapies [122]. In addition to subsequent research on endometrial cancer organoids derived from patients, Geurts et al. [39] proposed an endometrial cancer model originating from the insertion of nonsense mutations in phosphatase and tensin homolog (PTEN) into endometrial organoids. This discovery has provided new insights into the mechanisms underlying the initial stages of endometrial tumorigenesis. Further studies have suggested that the concurrent deletion of PTEN, forkhead box protein A2, and p53 in endometrial epithelial cells plays a key role in triggering mesenchymal transition [39,124,125]. Aberrations in the phosphatidylinositol 3-kinase pathway and Kirsten rat sarcoma viral oncogene mutations may exert synergistic effects [126]. Moreover, the high reliability of endometrial cancer organoids for recreating patient tumors makes them promising tools for drug screening and individualized therapies [126,127]. Inhibition of signaling pathways involved in tumorigenicity, improvement of progestin metabolism, and blocking autophagy with targeted drugs may help in overcoming endometrial cancer cell resistance and represent promising therapeutic approaches [128–130].

In addition to organoid-based culture systems that highlight cancer cells, hydrogels can mimic the tumor microenvironment in vitro. They provide a more intuitive and safer method for illustrating the role of tumor microenvironment, compared with subcutaneous injections or orthotopic engraftment into the uterus of mice [94,131]. Recently, researchers proposed that the application of hydrogels may be beneficial for demonstrating the underlying mechanisms of endometrial tumor metastasis [132]. The considerable potential for the applicability of this concept relies on logical extrapolation of the outcomes of hydrogels in various reproductive system tumors, such as breast and ovarian cancers. However, a gap exists in the form of insufficient evidence associated with endometrial cancer, necessitating further research and investigation [133,134].

4.1.3. Adenomyosis

Invasion of the endometrial tissue into the myometrium is a typical trait of adenomyosis [135]. According to current knowledge, notable differences in the invasive ability of adenomyotic and healthy tissues lead to the development of adenomyosis [136]. Existing bioengineering technologies for adenomyosis in vitro models highlight reconstruction of the dominant microenvironment as a key factor that induces transport of the endometrial layer into the myometrium [137,138]. The application of microfluidic chips has revealed the indispensable role of mechanical stress due to peristaltic flow within the uterus in the pathogenesis of adenomyosis [138,139]. Further studies are required to mimic other possible elements involved in the pathogenesis and development of adenomyosis, such as the invasion and survival of endometrial cells in the myometrium of the uterus, the creation of a microvascular network and intercellular communications, mechanical stimulation of the ECM, and potential interactions with the nervous and immune systems. Moreover, since the clinical characteristics of adenomyosis are complicated, and the symptoms of the disease vary and overlap with those of other diseases, there is a lack of consensus on the diagnosis and etiology [140]. Realizing as many pathological alterations as possible and relating them to clinical practice is an existing challenge in adenomyosis modeling.

4.2. Endometrial repair

Impairment of the endometrium makes it more vulnerable to lesion deterioration, subsequently leading to intrauterine adhesion, irregular fibrosis, a thin endometrium, and high susceptibility to infectious diseases, even damage to reproductive capacity. Bioengineering platforms fully harness the effects of loaded inherent mediators and build

interactions between exogenous systems and endogenous components through immunomodulation and endocrine regulation to improve recovery from endometrial impairment.

4.2.1. Intrauterine adhesion

Asherman's syndrome or intrauterine adhesion (IUA) is characterized by poor repair and fibrosis of the endometrium, which is mainly caused by postoperative adhesion of the endometrial basal layer [141]. Traditional strategies, such as surgical treatment, SC transplantation, estrogen treatment, and assisted reproductive technology, remain the primary options used for treating IUA. However, a growing number of studies have proposed several limitations such as secondary destruction, recurrence of IUA, and the possibility of SC carcinogenesis in vivo, which restrict their clinical application [142–144].

The application of various bio-scaffolds has shown great advantages for the treatment of IUA. Bio-scaffolds based on hyaluronic acid (HA) gels act as physical barriers to prevent adhesion [145]. Based on animal models, HA gels have been shown to alleviate excessive fibrosis and improve natural fertility [146]. Meanwhile, the therapeutic effects of HA gels and their safety and efficacy have been fully evaluated in several well-designed clinical trials [147,148]. However, there remain limitations to the application of HA gels in restricting the recurrence of IUAs and increasing pregnancy rates [149]. The advantages of scaffold platforms that function as delivery systems have also been reported [150]. Drug-loaded hydrogels and porous microfluidics allow for the combination of multiple therapeutics owing to their potent encapsulation capability, alleviating postoperative IUAs and improving endometrial repair [151,152]. Embedded active proteins and estrogen in bio-scaffolds endow them with antioxidant properties that protect against fibrosis within the uterine cavity and encourage the self-repair of the remaining endometrial cells by downregulating excessive oxidative stress and fibrosis-related mediators [153–157]. Administration of both SCs and their derivatives, such as human umbilical cord mesenchymal SCs (UCMSCs), mesenchymal SCs (MSCs), apoptotic bodies, and secretomes, in hydrogels and acellular scaffolds also potentially contribute to satisfactory endothelial regeneration after IUA [57,158,159]. Collagen, a practical framework for promoting wound healing and tissue repair, has been applied to acellular scaffolds [160]. Collagen scaffolds loaded with SCs and multiple growth factors show great potential for improving the regeneration of injured endometrium, among which UCMSC-based collagen delivery systems have reached phase I clinical trials [161,162]. Additionally, hydrogels can prolong the short biological half-life of growth factors in vivo, resulting in endometrial recovery in IUA rats [163].

In addition to scaffold systems, endometrial organoids are clinically feasible to overcome the limitations of traditional SC-oriented therapies for IUA. In 2022, Zhang et al. [164] created a murine IUA model based on endometrial organoids that overcame the limitations of SCs, and their transplantation promoted endometrial repair in IUA mice. Applying proper stimulation such as low-level laser therapy positively affects endometrial regeneration in animals and induces an active response to ovarian hormones [165].

4.2.2. Thin endometrium

A thin endometrium has an average thickness of below 7–8 mm, which may be caused by physical and biochemical factors such as frequent intrauterine operations, radiotherapy, infectious diseases, and endocrine-disrupting drugs [166]. Recently, hormonal treatments, including sex hormones and growth hormones, cell therapies involving the transportation of human amniotic cells or SCs, and administration of growth factors, vascular endothelial factors, and platelet-rich plasma were extensively investigated, and positive outcomes are reported [167]. However, there are still limitations that need to be improved owing to the complicated endometrial microenvironment and immunogenic risks of exogenous regulators. Current studies have proposed the possibility and efficacy of bioengineering-based vector systems that are injectable and loaded with SCs and other nutritional factors in response to the need [168,169].

Specially designed drug-loaded hydrogel scaffolds and microfluidic technologies with different characteristics are gradually being applied in animal models, allowing for a prolonged retention time of loaded drugs in vivo to exert related effects. Notably, the combination of microfluidic electrospray technology with drug-loaded HA gels enables well-controlled drug release [169]. In 2021, an artificial endometrium with the mechanical characteristics and biological traits of the human endometrium greatly preserved was constructed using a scaffold consisting of HA, collagen, agarose, and diverse constitutive cells, including endometrial epithelial, stromal, and vessel cells [170]. Subsequent experiments in animal models have demonstrated the significant effects of artificial endometrial transplantation on relieving thin or damaged endometrial linings [170]. Other molecules added to bio-scaffolds, such as growth factors and microRNAs, also play a vital role in endometrial regeneration in thin endometria [169,171]. Similar to treatment with IUA, the injection of HA gels loaded with SCs and their exosomes helps in improving the thickness of the thin endometrium and increases fertility rates [172,173]. Additionally, the administration of SC-derived exosomes instead of SCs potentially lowers the prevalence of adverse events caused by the immunogenicity and tumorigenicity of SCs [174,175]. Recent studies have revealed that HA gels mixed with exosomes derived from UCMSCs and adipose SCs significantly promote the proliferation of endometrial stromal and endothelial cells, leading to an increase in the endometrium and prevention of endometrial fibrosis [176,177]. Therefore, bioengineered materials loaded with these exosomes may provide new directions for the treatment of thin endometrium [178].

4.3. Drug screening and therapy monitoring

Bioengineering technologies are used in several pharmacological experiments, such as drug evaluation and screening, especially in terms of malignant tumors, musculoskeletal disorders, and the nervous system, whereas related studies focused on the human endometrium remain finite [179–182]. Endometrial organoids derived from patients and microfluidic materials are feasible for drug sensitivity testing of the endometrium (Table 2).

In vitro culture systems based on bioengineering technologies are an ideal method to study the pathogenesis of endometrial diseases, depending on the precise simulation of human endometrium under diverse pathological statuses. Bioengineering plays a crucial role in exploring the underlying therapeutic targets of potential drugs by monitoring changes in gene expression and cell behavior under disease conditions [126,127]. Meanwhile, results from these platforms are more reliable than those from traditional 2D cell/tissue culture and animal models based on the observation of the therapeutic effects of drugs on the bioengineered human endometrium in vitro [26,116]. Additionally, the complexity and variability of microfluidics and hydrogels allow culture models to be precisely regulated by the administration of external chemicals or biological stimulation. Their adjustable properties make these materials exhibit great potential for pharmacological experiments, offering vital opportunities for therapeutic monitoring and drug screening [190,191]. Microscopy and fluorescence technologies could be used to detect the distribution and concentration of drugs loaded in these bioengineering technologies, promoting the evaluation of cell responsiveness and minor alterations between cells and the microenvironment [192,193]. Undoubtedly, the application and clinical promotion of bioengineering materials used for endometrial diseases for drug screening and testing will eventuate based on the profound understanding of the advanced progress in the field of endometrial bioengineering platforms within recent years [55,194]. Therefore, by studying the existing experimental results, we can conclude that bioengineering platforms are promising tools for pharmacological experiments on endometrial diseases.

Table 2
Endometrial bioengineering materials applied in the drug sensitivity test.

Bioengineering technique	Endometrial disease	Drugs	Potential mechanism	References
Organoid	Endometrial cancer	56 drugs	–	[126]
Organoid	Endometrial cancer	10 drugs	–	[127]
Organoid	Endometrial cancer	Brusatol	Suppress Nrf2-TET1-AKR1C1-mediated progestin metabolism	[128]
Organoid	Endometrial cancer	PARPis (Olaparib, Rucaparib and Talazoparib)	Combined inhibition of BADS99 phosphorylation and PARP	[129]
Organoid	Endometrial cancer	Ixazomib and romidepsin	Overcome drug resistance by inhibiting the autophagy pathway	[130]
Organoid	Endometrial cancer	Gold(I)–NHC complex	Suppress the expression of TrxR and Nrf2	[183]
Organoid	Endometrial cancer	MI 136	Downregulate the HIF pathway	[184]
Organoid	Endometrial cancer	Napabucasin	–	[185]
Organoid	Endometrial cancer	Paclitaxel and cisplatin	–	[186,187]
Organoid	Endometriosis	Urolithin A, urolithin B	–	[188]
Microfluidics	–	Levonorgestrel	Increase endometrial permeability and suppress angiogenesis in a dose-dependent manner for emergency contraception	[46]
Microfluidics	–	19 drugs	Inhibit angiogenesis for contraception	[189]

Abbreviations: AKR1C1, aldo-keto reductase family 1 member C1; BADS99, B cell lymphoma-2-associated death promoter Ser99; HIF, hypoxia-inducible factor; MI, menin-MLL inhibitor; NHC, N-heterocyclic carbene; Nrf2, nuclear factor-erythroid 2-related factor 2; PARPis, poly ADP-ribose polymerase inhibitors; TET1, ten-eleven translocation 1; TrxR, thioredoxin reductase.

4.4. Identification of endometrial receptivity determinants

Embryo implantation is the most important process for a successful pregnancy, depending on the secretory profiles of endometrial epithelial cells during the receptive phase [195]. There is only a short period when a competent blastocyst can burrow into the prepared endometrium owing to the menstrual cycle and monthly repair of the human endometrium [196]. Moreover, this physiological process is difficult to simulate in vitro and has not been fully studied owing to ethical issues and the complexity of animal model manufacturing, resulting in an incomplete understanding of primary infertility and the failure of infertility treatment. The emergence of in vitro endometrial culture systems based on bioengineering technologies has focused on resolving these issues. The application of a bioengineering-centered endometrium provides vital advantages for recapitulating and interpreting cellular interactions and tissue organization in vivo [197].

Organoids have been successfully established from the human endometrium and present promising characteristics that better mimic the receptive phase and explain endometrial receptivity [198]. These culture systems can incorporate endometrial cells, including stromal cells, immune cells, and small blood vessels, with microenvironmental substances to obtain the basic conditions for communication with blastoids in vitro [198]. Precise organization observed in structures like the uterine glands of the human endometrium is successfully preserved in endometrial organoids. This preservation ensures a structural foundation for simulating decidualization in vitro [199]. Additionally, endometrial organoids have been tested to demonstrate their ability to respond to ovarian hormones [200]. Transcriptome and proteome analyses have indicated that steroid hormones and prostaglandin E_2 precisely regulate the secretory ability of uterine glands in human endometrial organoids [201,202]. These apical secretions derived from endometrial glandular epithelial cells are closely related to endometrial receptivity and exert a crucial effect on stromal cell decidualization and trophoblast cell adhesiveness relative to alterations during female fertility [203]. Endometrial organs have great potential for simulating mechanical signals during embryo implantation in addition to mimicking biochemical signals. Hennes et al. [204] demonstrated the existence of a mechanosensitive ion channel, piezo-type mechanosensitive ion channel component 1 (Piezo1), in human endometrial organoids to support the role of current density and differential transmembrane calcium concentration. Therefore, endometrial organoids offer a long-term and sustainable approach for assembling the human endometrium in vitro. These organoids are especially valuable for studying cellular composition, tissue organization, and responses to regulatory signals in vivo, which allows for an in-depth study of decidualization and endometrial receptivity.

5. Challenges and future perspectives

Currently, new insights into bioengineering technologies greatly contribute to recent advantages in studies on female reproduction and effective interventions for endometrial diseases and provide platforms for improving culture systems and promising clinical therapies. Novel materials with the potential to replicate the human endometrium in vitro, including organoids, microfluidic systems, hydrogels, and acellularized ECM scaffolds, have been used to illustrate the basic mechanisms of reproductive biology, pathogenesis, and drug identification of endometrial diseases. They show great potential for restoring reproductive function and female fertility.

Although indispensable progress has been made, the challenge for more in-depth analyses now lies in how to recapitulate significant genetic, epigenetic, and molecular relationships related to endometrial modeling and repair, to highlight the advantages compared with traditional study methods that concentrate on the cellular and organotypic levels. First, existing data from human endometrial models have not fully revealed the intricacies of endometrial biology and related diseases. One of the challenges that must be resolved is the use of a standardized substrate in in vitro culture systems. As summarized previously, bio-scaffold systems, including hydrogels, decellularized scaffolds, and microfluidics, display potent tailorable properties that make them versatile and attractive substrates for organoid preparation [28]. Different types of scaffold systems have been designed to fit specific cell groups, which allow for customization based on individual culture requirements and eliminate the use of a universal ECM surrogate. Seeding molecule-loaded hydrogel microspheres onto human organoid precursors narrows the gap between the in vitro culture systems and in vivo tissues, providing more tunable properties and better therapeutic effects in regenerative medicine [205,206]. To date, a

combination of endometrial organoids and hydrogels has been used to study endometriosis [55], endometrial cancer [94], IUA [164], and the decidualization process [207], which indicates the expanding applicability of organoids to study various endometrial pathologies and their underlying biological mechanisms. Similarly, decellularized scaffolds derived from the endometrium and HAECM provide a more bioactive environment for organoids by taking advantage of their proliferative properties and chromosomal stability [208,209]. The incorporation of the above-mentioned bio-scaffolds into endometrial organoids helps to mimic the biochemical signals that are regulated in vivo. In contrast, the application of microfluidics focuses on mechanical alterations, which govern junctional adhesion and cytoskeletal rearrangement in cellular activities and play an indispensable role in affecting the migration of endometrial stromal cells [44]. Thus, the combined use of endometrial organoids and microfluidic chips has great potential for developing models for endometriosis and embryo implantation [49,112,210]. Therefore, endometrial organoids and co-culture systems with bioengineered scaffolds are expected to be used for studying specific niches of the functional and basal layers, thus deepening our understanding of the endometrium. Second, further efforts should be made to update the design of endometrial bioengineering materials to meet the needs of the multicellular groups in the endometrium. For instance, different cellular components, such as epithelial, perivascular, and immune cells from the human endometrium, can be added to organoids derived from SCs for a full simulation of the human endometrium under physiological and pathological conditions. Assembling simple hydrogels or microfluidic chips loaded with different cell types is also a vital method. Each component of the scaffold systems can be altered in response to diverse endometrial biology conditions, which may also be crucial to promoting personalized medicine and targeted therapies. Finally, ethical standards and safety evaluations of applied bioengineering should be considered regarding the possibility of promoting clinical applications. Many studies focusing on therapeutic strategies for thin endometrium or intrauterine adhesion proved the feasibility of hydrogels loaded with drugs or bioactive factors; however, most achievements are still in the animal experimental stage. Currently, only two types of collagen-based hydrogels have entered the clinical trial stage; however, the risks of allergic reactions and pathogen transmission still exist. Therefore, investing more effort in identifying the potential side effects and optimizing bioengineering-based therapeutic methods is essential.

Collectively, bioengineering strategies for treating endometrial diseases require long-term scientific research before large-scale clinical application. Further efforts are still needed to overcome the following aspects: the difficulty of existing bioengineering models to mimic the complex network of molecular, endocrine, and tissue/organ interactions of the endometrium in vivo; poor evidence for clinical safety; and difficulties in building relationships between in vitro endometrial bioengineering materials and other organs in the female reproductive system. We believe that advances in bioengineering technology will gradually overcome these problems and redefine the therapeutic strategies and protocols for endometrial diseases.

6. Conclusions

In conclusion, we comprehensively reviewed the development of bioengineering in the context of the human endometrium and highlighted frontier research in modeling and therapeutic strategies for endometrial diseases. Bioengineering technologies hold a promising perspective for deepening current knowledge related to the etiology and growth of endometrial diseases owing to their adjustable mechanical and biochemical properties. These endometrial bioengineering materials used as endometrial in vitro culture platforms and feasibly loaded systems for drugs are expected to play an important role in early diagnosis, effective treatment, and prognosis throughout the disease. In summary, we believe that the translation of these bioengineering technologies will greatly facilitate the treatment of endometrial disease.

CRediT authorship contribution statement

Wanlin Dai: Writing – original draft, Visualization. **Junzhi Liang:** Writing – original draft, Visualization. **Renhao Guo:** Writing – review & editing. **Zhongyu Zhao:** Visualization. **Zhijing Na:** Supervision, Funding acquisition. **Dake Xu:** Supervision. **Da Li:** Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

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

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