Placenta and Reproductive Medicine

REVIEW ARTICLE

Extracellular matrix and extracellular matrix-derived materials in reproductive medicine

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Abstract

Infertility has become a worldwide issue, and many patients cannot benefit from assisted reproductive technologies (ART). The extracellular matrix (ECM) is critical in tissue organization and remodeling. The female reproductive system plays an important role in menstruation, pregnancy, and ovulation and may influence fertility. In addition, ECM has a wide variety of components, good biological properties, and extensive application experience as a biomaterial. In-depth research on the ECM in the female reproductive system and the development and application of ECM-derived materials may provide new ideas for solving infertility problems. This review aimed to summarize the regulation and changes of ECM in the uterus and ovary, and to discuss the progress of research on ECM-derived materials in reproductive tissue engineering. An extensive search in PubMed and Embase was conducted using keywords including extracellular matrix, uterus, ovary, tissue engineering, and material. We are devoted to combining research on ECM-derived materials with clinical practice and intend to provide ideas for solving clinical problems in reproductive medicine.

Key words: extracellular matrix, reproductive medicine, tissue engineering

Introduction

With 8%–12% of couples of reproductive age worldwide currently suffering from infertility,[1] treatment of infertility has become a real challenge. In the past few decades, reproductive medicine has developed rapidly, with repeated breakthroughs in research in assisted reproductive technologies (ART).[2,3] However, patients with uterine infertility may not benefit from ART, which remains difficult to solve. Patients with damaged ovaries also cannot regain their fertility through ART alone.

Recently, the physiological role played by the extracellular matrix (ECM) in the process of implantation and pregnancy has been increasingly evidenced. ECM is a 3-dimensional (3D) polymeric network structure widely distributed in the body, providing structural and functional support to cells and tissues. It is critical in regulating cell processes, including proliferation, survival, differentiation, migration, angiogenesis, and immune response.[4] In the reproductive system, the ECM is dynamically regulated during the menstrual cycle, peri-implantation, pregnancy, and delivery, and its dysregulation is related to various diseases.[5] Therefore, research focused on ECM in the female reproductive system and infertility is becoming more prevalent.

Moreover, ECM provides another way of thinking about the treatment of infertility. Patients suffering uterine infertility or ovarian damage may benefit from other

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technologies, such as oocyte cryopreservation[6] and organ transplantation.[7] The further development of these technologies is closely related to tissue engineering and biomaterial science. Biological scaffolds derived from ECM have been shown to promote tissue repair and reconstruction in animal experiments and clinical studies. Due to its biodegradability and biocompatibility, ECM has already been applicated in tissue engineering and regenerative medicine.[8]

The components of ECM include collagen, proteoglycans (PGs) or glycosaminoglycans (GAGs), elastin, elastic fibers, laminin, and fibronectin.[4] Collagen has the mechanical function of providing many critical biomechanical properties in the body and the biological function to help tissue anchor and adhere.[9] Collagen has been applicated in biomaterial science and clinical medicine for years as an important natural renewable resource. Hyaluronic acid (HA) is an important type of GAG in ECM which has special functions in embryogenesis and tissue repair[10] and is a biomaterial with promising applications. Elastin is an insoluble protein component of ECM conferring elasticity to organs, whose mechanical properties may regulate cell properties, implying a positive effect on cell growth. It is the major constituent of elastic fibers, whose alignment influences cell phenotype, adhesion, and proliferation.[11,12] The application of elastin-based materials also has been reported.[13] Laminins are essential glycoproteins in the specialized ECM, basement membrane. They play a role in attaching ECM to the cell surface and serve as a platform for other ECM components to stably attach to, during which they regulate multiple cellular activities and signaling pathways.[14,15] Fibronectin is a protein that controls cell adhesion, spreading, migration, proliferation, and apoptosis.[16]

In summary, ECM is made up of a wide variety of components, has good biological properties and application experience. Furthermore, its regulation and physiological roles within the reproductive system are increasingly studied. Therefore, ECM may provide new ideas for developing reproductive medicine and facilitating material science research in reproductive medicine. This review aims to summarize the regulation and changes of ECM in the uterus and ovary, and to discuss the progress of research on ECM-derived materials in reproductive tissue engineering. We are devoted to combining research on ECM-derived materials with clinical practice, intending to provide ideas for solving clinical problems.

METHODOLOGY

An extensive literature search in PubMed and Embase was conducted using the keywords and their permutations shown in Table 1. Original articles and reviews in English were scanned, and conference proceedings were checked through Embase.

Table 1: Keywords used for literature searching

Section	Keywords
Full text	extracellular matrix; collagen; fibronectin; laminin; elastin; hyaluronic acid
Roles of ECM	uterus; endometrium; ovary; pregnancy; ovulation
ECM-derived materials	material
Application	tissue engineering; ovary; uterus

ECM: extracellular matrix.

ROLES OF THE ECM IN THE FEMALE REPRODUCTIVE SYSTEM

Metabolism of ECM

Proteolysis of ECM components during physiological and pathological processes is accomplished by the assembly, structural remodeling, correction of overexpression, and release of bioactive fragments and growth factors.[17] In the process of ECM degradation, matrix metalloproteinases (MMPs), a disintegrin and metalloproteinase (ADAM), and a disintegrin and metalloprotease with thrombospondin motifs (ADAMTS) play important roles,[18–20] all of which belong to the superfamily of metzincin proteases, a family of multidomain zinc-dependent endo-proteases. Among them, the main enzymes to degrade ECM are MMPs,[21] which can degrade most of the important protein components of ECM, including collagen, fibronectin, elastin, and laminin.[22,23]

MMPs, ADAM and ADAMTS are regulated to maintain the homeostasis of ECM. Endogenous tissue inhibitors of matrix metalloproteinases (TIMPs) can selectively inhibit different subtypes of MMPs, ADAMs, and ADAMTS, therefore playing a role in matrix accumulation and proteolysis.[24] Multiple factors and pathways tightly regulate the expression level and activity of MMPs/TIMPs *in vivo*, and the MMPs/TIMPs balance will further affect ECM. For instance, tumor necrosis factor (TNF)-α may enhance the collagenolytic activity of MMP-1 *via* up-regulating the expression of MMP-3, and down-regulate the expression of TIMP-1 to degenerate collagen.[25,26] When the extracellular-signal-regulated protein kinase 1/2 (ERK1/2) pathway is blocked, the expression of MMP-1 is decreased, and collagen III accumulation is promoted,[27] while ERK1/2 may also mediate up-regulation of MMP-2 and MMP-9.[28] In the female reproductive system, the composition of ECM is similar but with some tissue specificity. The regulation of MMPs also varies due to distinct environments.

ECM in the uterus

Regulation ECM in the uterus

In the endometrium, MMPs are secreted by endometrial cells. In physiological processes such as menstruation,

endometrial remodeling, decidualization, and embryo implantation, MMPs play a significant role and are regulated by various factors.[29] MMP-1, -3, and -9 were specifically related to tissue degradation in menstrual endometrium and activated by interleukin-1 (IL-1) and TNF-α.[30] MMP-7, MMP-11, and TIMP-1 are related to the remodeling of the endometrium in the normal menstrual cycle.[31] MMPs have been proven to be regulated by sex steroid hormones during the menstrual cycle. For example, progesterone can inhibit the secretion and release of MMP-11 and -14. Estrogen can enhance this process *via* the up-regulation of progesterone receptors.[32] Besides, MMP-2 and MMP-9 are indispensable for embryo implantation. They are the key rate-limiting enzymes in ECM remodeling during implantation, while correction of the overactivity of MMP-2 and MMP-9 is associated with a higher rate of successful implantation.[33]

In the placenta, MMP-2 and MMP-9 are expressed in a cell-specific manner. It has been reported that a significant correlation between TNF-α and MMP-9 in the second trimester may contribute to a successful pregnancy outcome.[34] Increased expression of MMP-9 contributes to ECM degradation, thus promoting rupture of fetal membrane and separation of the placenta during delivery.[35]

Changes of ECM during pregnancy

Decidualization occurs during the implantation window, and stromal fibroblast-like cells differentiate into epithelial-like decidua cells.[36] To better receive the embryo, the endometrial epithelial cells lose polarity, and the intercellular space becomes wider and is inserted by the ECM.[37] The ECM composition has undergone overall changes, especially collagen type IV, laminin, and fibronectin.[37,38] According to staining results, collagen type IV appears earlier around the spiral arteries of the decidualized sheath and may be involved in arterial remodeling.[39] For successful trophoblast invasion, the arrangement of collagens in the decidua is uneven, with collagen fibrils thicker around the trophoblast.[40] Laminin undergoes a transient reduction in the secretory phase but increases to an abundant level during decidualization and after the invasion. As well as collagen IV, laminin may play an essential role in decidualization and invasion and has a remarkable effect on the enhancement of endometrial ECM stiffness.[37,41,42] Fibronectin can be secreted by decidual stromal cells and trophoblasts and is regarded to mediate the migration of trophoblasts.[39]

Pathological states in the uterus

The causes of uterine infertility include intrauterine adhesions, thin endometrium, uterine septa, uterine myomas, and endometrial polyps.[43,44] Among others, intrauterine adhesions and thin endometrium are usually related to damage to the endometrium caused by traumatic uterine cavity procedures.[45,46] When the endometrium is injured, the native cells are replaced by fibroblasts and myofibroblasts and produce a large amount of ECM, including collagen, leading to the formation of uterine scar, which may cause infertility.[47]

Recurrent implantation failure (RIF) is a definition that applies to women undergoing ART. It is suggested that a case of RIF can be diagnosed when > 3 failed embryo transfers with high-quality embryos or the failed transfers of ≥ 10 embryos in multiple transfers happen.[48] RIF due to endometrial factors has been a challenge in reproductive medicine. Some studies have suggested that dysregulation of the endometrial ECM may limit trophoblast invasion, leading to RIF.[49] HA may have a two-sided effect on pregnancy and play a role as a sticky matrix for embryos to attach, therefore reducing implantation failure. However, the accumulation of HA may be related to early embryo loss.[50] Laminin, fibronectin, integrin, and other ECM components may influence embryo implantation directly or indirectly.[51,52]

Recurrent pregnancy loss (RPL) is the failure of two or more clinically recognized pregnancies.[53] The exact mechanism of ECM involvement in RPL is unclear. However, studies have shown that the increased adhesion between ECM and T cells may be part of the immunological mechanism of RPL.[54] Besides, the staining of MMP-2, MMP-9, TIMP-1, and TIMP-2 was observed in the ECM of decidual tissue from RPL patients. Moreover, it was reported that the expression of MMP-2 was significantly lower and MMP-9 were significantly higher in patients with normal fetal chromosome than in abnormal.[55]

ECM in the ovary

Regulation of ECM in the ovary

In the ovary, collagen degradation is important in the process of ovulation. During luteal involution, activation of MMPs is crucial for protein depletion. MMP-2 may degrade collagen type IV, while membrane-type 1 MMP (MMP-14) may activate MMP-2 and degrade collagen type I, III, and IV.[56] MMP-14 and MMP-2 are also expressed in developing human ovarian follicles, and MMP-2 is present in the follicular fluid.[57] MMP-9 was also detected in the follicular fluid with a lower amount of activity than MMP-2, and a decrease of MMP-9 was observed during the change in follicle shape prior to ovulation.[58] A significant increase of MMP-10 expression in human granulosa cells between the pre and late-ovulatory phases was also reported.[59] Besides, HA is of great importance in ovarian ECM, which plays a role in regulating ovarian stiffness along with collagen. The content of HA in ovarian ECM is regulated by hyaluronidase (Hyal1) and hyaluronate synthase (Has3) and decreases with age.[60]

Change of ECM during ovulation

The composition of follicular basal lamina (mainly composed of collagen type IV and laminin) dynamically

changes during ovulation. As the oocyte grows and the granulosa cells proliferate, the basal lamina expands, and the zona pellucida matrix develops around the oocyte.[61] The basal lamina is degraded on ovulation but preserved if atresia occurs.[62] Besides, an HA-abundant matrix forms within the oocyte complex during ovulation and is critical for fertility.[61]

Pathological states in the ovary

In patients with ovarian dysfunction, such as premature ovarian failure (POF) and polycystic ovarian syndrome (PCOS), their ovarian ECM may also change. POF refers to the loss of ovarian functions before the age of 40,[63] and is the outcome of ovarian fibrosis, which can be caused by surgery, inflammation, and abnormal immune reaction and undergoes ECM deposition.[64] PCOS results from an imbalance in female sex hormones, leading to cysts in the ovarian antral follicles.[65] Studies have shown that the circulating levels of MMP-2 and -9 increase in women with PCOS, which may be associated with abnormal basement membrane rupture or follicular atresia.[66]

ECM-DERIVED MATERIALS

Components of ECM

Inspired by the properties of ECM, including its composition, function, and metabolism, research on ECM-derived materials is flourishing. A summary of the main applications of ECM-derived materials in reproductive medicine is presented in Table 2. Among others, the components of ECM are the simplest ECM-derived materials, such as collagen and HA.

Collagen is a protein characterized by a distinctive triple helix super-secondary structure of three polypeptide chains.[9] As part of the ECM, collagen supports cell growth and contributes to mechanical resilience. Despite the advantages of being renewable, biocompatible, and biodegradable, collagen has limitations as a biomaterial that prevent its application, such as relatively weak mechanical strength and biological stability. Crosslinking is the joining of two or more molecules by a covalent bond, either intramolecularly or intermolecularly, and the reagents used for crosslinking are called crosslinkers.[81] Crosslinking is an approach to overcome these limitations for collagens and other biomaterials.[82,83] However, cross-linking can make polymeric materials less biodegradable and increase toxicity.[84] Therefore, it is suggested that more suitable crosslinking methods be developed.[85]

HA is an anionic, non-sulfated GAG composed of a stable oligosaccharide that consists of D-glucuronide and N-acetylglucosamine groups through glycosidic bonds.[10] HA's properties, including cellular communication, healing and scar-forming, mediation of inflammation, connection, and hydration capacity, can be improved by crosslinking for tissue engineering.[10,86,87] HA is also a common crosslinker.[88] Besides, a high concentration of HA has been used in embryo transfer as an adherence compound, which may improve the outcomes of IVF/ICSI.[71]

Decellularized ECM

The decellularized ECM (dECM) is obtained by removing the cellular components of different tissues and organs from their ECM scaffold using mechanical, chemical, and enzymatic treatments.[89] The purpose of ECM decellularization is to preserve the components and structure of ECM while removing xenogeneic cells to avoid immune reactions.[90] The mechanical strength and stability of dECM scaffolds can be improved through crosslinking to produce more material products, such

Table 2: Summary of applications of common ECM-derived materials

Materials	Introduction	Main applications
Components of ECM	Basic ECM-derived materials	
Collagen	The most important protein of ECM	Endometrial scaffold[67–69] Coating for 2D follicle culture[70]
Fibronectin	A protein of ECM	Coating for 2D follicle culture[70]
Laminin	A protein of ECM	Coating for 2D follicle culture[70]
HA	The most important GAG of ECM	Adherence compound for ET[71]
Decellularized ECM	A scaffold obtained by removing all the cells of tissues from their ECM	Coating for MSCs culture[72]
		Uterine scaffold[73–75]
		Ovarian scaffold[76,77]
ECM-derived hydrogel	An appropriate 3D culture media	
Matrigel	Composed of various ECM components	3D follicle culture[70]
		Transplantable artificial ovary[78]
Collagen hydrogel	Hydrogel mainly composed of collagen	3D follicle culture[79]
HA hydrogel	Hydrogel mainly composed of HA	3D follicle culture[80]

ECM: extracellular matrix; HA: hyaluronic acid; GAG: glycosaminoglycan; ET: embryo transfer; 3D: 3-dimensional; 2D: 2-dimensional.

as hydrogels.[91] The dECM can be recellularized for *in vivo* and *in vitro* studies. Mesenchymal stem cells (MSCs) are a heterogeneous population of stromal stem cells with regeneration properties and immunomodulation properties.[92] However, their poor viability at the transplantation site limits their clinical application.[93] The dECM can provide a better environment for the MSCs, promotes their proliferation, and preserve stem cell properties.[94,95] This combination may overcome a series of challenges.[96]

ECM-derived Hydrogel

Hydrogels are a class of 3D water-swollen networks of polymers that are assembled by physical or chemical crosslinking processes. Among the components of ECM, collagen is commonly used as a natural material for hydrogel. Hyaluronic acid is also a common material for hydrogels, but most of the hyaluronic acid used in hydrogels is semi-synthetic.[97] Hydrogels have special physiochemical properties, including water-swelling, porous structures, and self-healing. Naturally, derived hydrogels usually have good biocompatibility and biodegradability but poor mechanical properties, including rigidity and stretchability. Therefore, crosslinking mediated by glycation and enzyme are typically used to increase these mechanical properties.[98]

Hydrogel is an appropriate 3D culture media to explore the migration and proliferation of stem cells instead of using ECM directly.[99] It also has been applied in treating diseases, such as intrauterine adhesions, as physical barriers or delivery systems, therefore playing a role in promoting tissue repair, reducing infection, and delivering therapeutic drugs.[100]

APPLICATION OF ECM-DERIVED MATERIALS IN REPRODUCTIVE TISSUE ENGINEERING

Uterine tissue engineering

Uterine tissue engineering offers hope for patients with uterine infertility. The development of scaffolds is always the first and vital step, and scaffolds for reproductive tissue engineering have been explored.[101,102] ECM-derived materials, including natural, synthetic, and decellularized ECM materials, have been used.[103]

Tissue engineering dominated by a single natural or synthetic material usually focuses on the endometrium. In a study,[104] collagen type I obtained from bovine was used to construct a scaffold with thermal dehydration crosslinking. This scaffold was then loaded with human umbilical cord-derived MSCs (UC-MSCs) and used in an induced murine uterine defect model. So far, clinical trials on humans also have been conducted.[68,69] A phase I clinical trial using allogeneic UC-MSCs on collagen scaffolds for patients with uterine adhesion reported benefits to patients' endometrial condition, as well as successful pregnancy and delivery.[68]

The design and application of dECM scaffolds, which usually involve the full-thickness uterine tissue, is a different strategy. In one study,[73] rat uteri were decellularized using detergents (including sodium dodecyl sulfate, Triton X 100, and sterile phosphate buffered saline) to produce dECM scaffolds, which were then placed onto a partially excised uterus, realizing recellularization and regeneration *in vivo* and even successful pregnancy. Studies have shown that the sampling site of ECM, the methods to decellularize, and the transplanting orientation of the scaffold are all critical to the outcome.[74,75]

Ovarian tissue engineering

In recent years, due to health and social factors, the demand for fertility preservation has increased dramatically.[105] In such cases, the construction of an artificial ovary is an idea that demands a higher level of material science.

ECM coating has been used for follicle culture, but it has been found that the structure of follicles is better preserved in the 3D matrix.[70] One study[79] used a collagen hydrogel core (softer) and a degradable alginate hydrogel shell (harder) to encapsulate follicles of deer mice, mimicking the medulla and cortex of the ovary respectively, and successfully created a 3D culture environment. Another study[80] reported an HA-alginate hydrogel as a promising material for *in vitro* mouse follicle culture. For *in vivo* experimentation, an alginate-Matrigel matrix containing isolated ovarian cells has been designed to construct a transplantable artificial ovary. Seven days after being grafted into the mouse model, degradation of the matrix scaffold and angiogenesis around the follicles were observed.[78] However, finding a matrix to cultivate and transplant isolated human follicles is still challenging. The dECM seems to be a promising material for the scaffold of the transplantable artificial ovary. In a recent study,[76] donated cryopreserved ovarian tissues were decellularized and reseeded with human ovarian stromal cells and preantral follicles. These artificial ovaries were grafted into immunodeficient mice, with 5 out of 20 follicles managing to be recovered. It is worth mentioning that the donors of ovarian tissue include patients with malignant tumors, while no malignant cells were found in the grafted tissues. Another study[77] reported clinical cases that used dECM scaffold to help transplant frozen-banked ovarian tissue back into patients. Follicular development was observed and both of the patients were able to conceive through IVF-ET, with one having already successfully delivered.

CONCLUSIONS AND PERSPECTIVES

This review focuses on the regulation of ECM in the uterus and ovary, and discusses the progress of ECM-derived materials in uterine and ovarian tissue engineering. ECM is involved in and plays an important role in pregnancy and ovulation. However, most current studies on ECM and infertility seem to focus on mechanistic hypotheses,

while no clear pathways have been investigated yet. However, the importance of ECM as a tissue scaffold and an environment for cellular activity is undeniable. Therefore, ECM-derived materials are critical in uterine and ovarian tissue engineering, providing new ideas for solving reproductive medicine clinical problems from materials science and regenerative medicine perspectives.

On the one hand, ECM-derived materials can be used for organ repair and reconstruction, which are novel therapeutic strategies for infertility. We follow the progress of such research and are inspired by several clinical trials. These translational medicine results bridge tissue engineering and clinical medicine, providing experience to solve clinical problems. On the other hand, the mechanical and biological stability of ECM-derived materials is not satisfactory enough, for ECM has a complex structure and can be regulated by multiple factors *in vivo*. This is also a challenge in the translation from *in vitro* to *in vivo* and from basic to clinical research. Therefore, modifying strategies to improve the properties of ECM-derived materials while preserving their advantages deserve further investigation—for example, the crosslinking and decellularization methods for dECM. Recently, 3D-printing technology has greatly broadened the horizon of tissue engineering and regenerative medicine. Developing bio-ink of ECM-derived materials with better performance for reproductive medicine is also a promising research direction.

In future research, a deeper understanding of the role played by ECM in infertility, leading to targeted modification of ECM-derived materials to enable better applications in reproductive medicine, would be a bright perspective to promote the combination and co-development of reproductive medicine and materials science.

Author Contributions

Zhengyan Hu: Conceptualization, Methodology, Investigation, Writing—Original draft preparation. Rui Gao: Investigation. Hanxiao Chen: Writing—Reviewing and Editing. Minqi Chen: Investigation. Lang Qin: Conceptualization, Supervision.

Conflict of Interest

None declared.

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