Journal of Assisted Reproduction and Genetics (2023) 40:955–967
https://doi.org/10.1007/s10815-023-02772-5

REVIEW

The prospects of cell therapy for endometriosis

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Published online: 25 March 2023

Abstract
Endometriosis is a chronic inflammatory estrogen-dependent disease characterized by the growth of endometrial-like tissue outside the physiological region. Despite the fact that this disease is common, laparoscopic surgery is currently the gold standard in the treatment of endometriosis. In this regard, it is necessary to develop new effective methods of minimally invasive therapy for endometriosis. One of the promising areas in the treatment of endometriosis is cell therapy. Cellular therapy is a vast branch of therapeutic methods with various agents. Potential cell therapies for endometriosis may be based on the principle of targeting aspects of the pathogenesis of the disease: suppression of estrogen receptor activity, angiogenesis, fibrosis, and a decrease in the content of stem cells in endometriosis foci. In addition, immune cells such as NK cells and macrophages may be promising agents for cell therapy of endometriosis. Standing apart in the methods of cell therapy is the replacement therapy of endometriosis. Thus, many studies in the field of the pathogenesis of endometriosis can shed light not only on the causes of the disease and may contribute to the development of new methods for personalized cell therapy of endometriosis.

Keywords Endometriosis · Cell therapy · Pathogenesis of endometriosis · Replacement therapy · Macrophages · Fibrosis

Introduction

Endometriosis as severe gynecological condition

Endometriosis (EM) is defined as an estrogen-dependent chronic proliferative disorder characterized by ectopic presence of endometrial-like tissue with the stroma and distinctive endometrial glands outside the endometrium [1, 2]. The manifestations include severe pelvic pains, dysmenorrhea, dyspareunia, and infertility [3, 4] which adversely affect the quality of life in its various aspects — job-related, social, sexual, etc. An international multicenter study covering 10 countries revealed decreased working efficiency in more than a half of patients with EM [5].

The disease affects up to 10% of reproductive-age women — a rough estimate given the high incidence of delayed and erroneous diagnostics for this condition [6]. Apart from the symptomatic diversity, the disease presents with high etiological and pathogenetic diversities which hamper its early diagnosis.

EM often shows focal patterns confined to the uterus, the fallopian tubes, and/or the ovaries — this form is termed "genital EM." In other cases, the lesions spread across abdominal wall and may reach distant heterotopic locations including the intestines, the urinary bladder, ureters and navel, the diaphragm, peripheral nerves, the lungs, the skin, the eyeball, the liver, and the brain [7–9]. Such extragenital forms of the disease are further classified as pelvic and extrapelvic [7]. The broad and variative symptomatic spectrum of extragenital EM complicates its differential diagnosis [10].

Clinical algorithms for EM

The primary diagnostic procedures include physical examination and biochemical tests for CA-125 and CA-72 [10], followed

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by ultrasound scans and magnetic resonance imaging (MRI). This sequence affords accurate diagnosis in the majority of cases, with estimated sensitivity and specificity of ≥ 90%; still, the accuracy can be undermined by morphological diversity of lesions, particularly with endometrioid cysts and small foci. In this regard, biochemical tests, ultrasound scans, and MRI are not the actual standard in the diagnosis of EM. Accordingly, laparoscopic intervention followed by histopathological examination of the putative foci remains the gold standard diagnostic option for this pathology [10].

Surgical elimination of the foci restoring the normal topography of anatomical structures is a moderately conservative treatment for EM — by contrast with radical resections of pelvic organs. Although the "conservative" surgeries bring pain relief and improve the quality of life, 25% of the patients report residual post-laparoscopic pains associated with EM; furthermore, 15% of the patients experience recurrent pains and 20% receive repeated surgical interventions [11]. Across the sources, recurrence rates and expected need for repeated intervention may reach as high as 54% [12].

Hormonal therapies for EM are aimed at suppression of the ectopic endometrial growth [13]. Such protocols with a backbone of gonadotropin-releasing hormone (GnRH), danazol, or gestagens are used either on their own or as adjuvant to laparoscopic surgery [14]. Despite the anti-relapse efficacy of hormones, especially GnRH agonists [15], they have been shown to increase the risks of neoplastic transformation within the lesions [14]. Takagi and colleagues reported clinical case of malignant transformation of ovarian endometrioma after 8 years of GnRH agonist and dienogest therapy [16]. Mechsner and co-authors revealed the case of a 35-year-old patient with endometriosis and adenomyosis that was treated with GnRH analogues [17]. Five months later, endometrial carcinoma was diagnosed. Thus, the search for new effective methods of minimally invasive therapy for EM is required [18].

The goal of this article is to review the literature material on aspects of the pathogenesis of endometriosis, as well as on potential methods of cell therapy of endometriosis aimed at suppressing aspects of the pathogenesis.

Methods

Search strategy

A search was made of the literature on the pathogenesis of endometriosis and potential therapeutic strategies based on targeting suppression of aspects of the pathogenesis. Articles were searched through Google Scholar and the ClinicalTrials.gov database, where the search keywords were "endometriosis," "endometriosis pathogenesis," "endometriosis cell therapy," and "macrophages in endometriosis." All analyzed articles were published.

Search criteria

Inclusion criteria: clinical trials, reviews, original article, guidelines, case report. We analyzed articles in any language.

Exclusion criteria: abstracts.

Results

Pathogenetic factors and components of EM

EM results from ectopic presence of endometrial-like tissue with stroma and glands outside the inner lining of the uterus. A host of theories concerning EM onset has been put forward, focusing on how cells presumably originating in the endometrium can survive and thrive in non-habitual microenvironments. Known survival factors for endometrial cells at ectopic locations include genetic alterations endowing the cells with ability to evade apoptosis and invade surrounding tissues, permissive hormonal status, and local immunity failure [19]. As the lesions grow and become progressively vascularized, the disease develops its prominent inflammatory component eventually resolving into fibrosis. We shall now consider these factors and components individually.

Abnormal hormone levels

Hyperestrogenism and progesterone resistance are characteristic of EM and facilitate its progression [19].

The increased content of estrogens in EM foci has long been known, with 17β-estradiol being the main hormone implicated in survival and growth of the foci [19]. Although 17β-estradiol is chiefly produced by the ovaries and spreads with circulation, its synthesis can also proceed within EM lesions through enzymatic activities of aromatase and steroidogenic acute regulatory protein. Of note, these activities are not detected in eutopic endometrium [20, 21]. In addition, the lesions present with elevated expression of estrogen receptors α and β (respectively, ERa and ERb) as compared with eutopic endometrium [22].

Estradiol, ERa, and ERb have been implicated as key factors required for the ectopic lesion growth. Knockout of ERa inhibited ectopic endometrial proliferation, cell adhesion, and neoangiogenesis in mouse model. Although ERb deficiency has a less pronounced impact on the estrogen-dependent growth [23], ERb has been shown to specifically mitigate the tumor necrosis factor α (TNFα)-induced apoptosis in the foci [1].

Apart from the elevated levels of estrogens and their receptors, the lesions show progesterone resistance — a consequence of low expression of progesterone receptor

B (PGR-B) and null expression of progesterone receptor A (PGR-A). In healthy uterus, progesterone inhibits endometrial cell proliferation while inducing decidualization. Accordingly, progesterone resistance of the ectopic endometrial grafts supports their uncontrolled growth through non-activation of progesterone-dependent genes including the 17β-hydroxysteroid dehydrogenase 2-encoding *HSD17B2* responsible for conversion of estradiol into the less active estrone [24].

Thus, endometrial-like heterotopias present with high levels of estradiol and its receptors aggravated by local failure of progesterone-dependent estradiol inactivation. Under these conditions, the grafts tend to grow in a poorly controllable manner by means of cell proliferation and apoptosis evasion [22, 24].

Inflammatory component

Independently of their much disputed origin (the variants include retrograde dissemination of menstrual discharge and focal trans-differentiation of mesothelium), EM foci invariably challenge the local immunity [25] promoting a decline in the cytotoxic T cell and natural killer (NK) cell activities and a parallel increase in the peritoneal macrophage counts [26] and neutrophils [27, 28]. It was noted that neutrophils are found in large numbers in the foci of endometriosis, while the number of neutrophils also increases in the blood and peritoneal fluid [29]. Chemoattraction of neutrophils to endometriosis foci occurs mainly due to increased synthesis of IL8 and VEGF in the foci, which contributes to the implantation of endometrial cells and the growth of a vascular network [30, 31]. IL8 is able to stimulate an increase of FasL expression, which leads to the death of T-cytotoxic lymphocytes and the formation of an immunotolerant microenvironment [32]. In addition, it has been shown that neutrophils are able to secrete IL17a, which also has angiogenic activity [33], and to produce more ROS, ARG1, prostaglandins, etc., which could cause local immune suppression [34].

Among immune cells involved in the pathogenesis of endometriosis, T-regulatory (Treg) cells are found in large numbers in endometrioid lesions [35, 36]. The role of Treg in the progression of endometriosis remains poorly understood, and the data are often contradictory. According to some data, the complete elimination of Treg in mice leads to an increase in the volume of foci in endometriosis modeling [37], and in other studies, the opposite effect was observed when Treg's CD25 molecule was blocked with antibodies [38].

As the pro-inflammatory microenvironments tend to favor the engraftment and growth of heterotopias [25, 26, 39], the chronic nature of EM-associated inflammation facilitates fibrotic changes — a prominent complication of EM [40].

Fibrosis

Tissue repair can take several alternative routes, which include regeneration per se defined as recovery of authentic functional units and fibrosis defined as replacement of the damaged units with connective tissue [41, 42]. EM has been associated with progressive fibrotic changes often supported by pseudo-menstrual bleedings with concomitant platelet activation. The activated platelets release high amounts of transforming growth factor β (TGFβ) known to induce the fibroblast and myofibroblast differentiation [43]. By contrast with the acute inflammatory reactions smoothly succeeded by regeneration, chronic inflammation favors fibrotic changes. EM provides a striking example of this tendency: under conditions of cyclic tissue damage, pro-inflammatory stimulation, and hormonal imbalance, myofibroblasts are constantly producing extracellular matrix. Accumulation of this matrix without sufficient means for its degradation and clearance eventually results in fibrosis [41, 42].

Moreover, despite the accepted definition of EM foci as composed of characteristic stromal and glandular elements, advanced stages of the disease often present with purely fibrotic lesions. For instance, rectovaginal EM foci are typically fibromuscular, without any signs of the loose endometrial-like stroma. Other forms of EM can also be difficult to recognize for the same reason: in about 40% of ovarian endometriomas, the cyst is overgrown by fibrous tissue without epithelium, whereas pelvic adhesions most commonly found in EM and causing characteristic symptoms contain no endometrial tissue at all [44].

Angiogenesis

Angiogenesis is crucial for the expansion of ectopic foci into distinctive EM lesions. Vascularization of the ectopic tissue is supported by a variety of factors including pro-inflammatory mediators, notably interleukin 1β (IL1β) produced by activated macrophages at the site of engraftment. This strong signaling molecule triggers production of interleukin 6 (IL6) and vascular endothelial growth factor (VEGF) by the grafts, facilitating the blood vessel ingrowth [45, 46]. Stromal cells of the ectopic lesions have also been shown to produce interleukin 8 (IL8) — another pro-inflammatory cytokine with pro-angiogenic properties [47].

Apart from the chronic inflammatory conditions, vascularization of the foci is supported by estradiol and hypoxia. Serum and local levels of the hypoxia-induced factor 1 subunit α (HIF1α) in EM are known to be high [48] and positively correlate with those of VEGF [49]. Estrogens additionally support angiogenesis by stimulating *VEGF* expression in endometrial stromal cells [3] and promoting the endothelial progenitor cell recruitment from the bone marrow [50].

Adult stem cells (aSCs)

Endometrial aSCs ensure regenerative potential of the endometrium: these low-differentiated cells give rise to tissue-specific differentiated progeny while retaining their capacity of self-renewal [51]. On a par with in situ sources, endometrial SCs can be physiologically delivered from the bone marrow: considerable chimerism within the endometrium (0.2–48% for epithelial cells and 0.3–52% for stromal cells) was demonstrated in a study enrolling female recipients of bone marrow transplants with non-matched HLA. The percentage of transplant-derived cells correlated with the length of follow-up post-transplantation. The data indicate that bone marrow-derived SCs are capable of repopulating the endometrium [52].

Detection of aSCs in both the endometrium and menstrual discharge [53] supports the so-called retrograde menstruation theory of EM [51]. The presence of aSCs in EM foci has been confirmed as well; moreover, expression of the SC pluripotency genes *SOX2*, *NANOG*, and *OCT4* within EM lesions is higher compared with eutopic endometrium [54]. Another marker of SCs, proto-oncogene c-Kit, was also locally over-expressed within the lesions as compared with eutopic endometrium both in patients with EM and in healthy individuals [55]. These findings confirm the role of low-differentiated endometrial cells in the ectopic engraftment [51].

At that, maintenance and growth of advanced EM foci involve SCs from extra-uterine sources, notably the bone marrow lineages [56]. In hysterectomized LacZ-transgenic mice with wild-type endometrium implants in the abdominal cavity (validated as a model for endometriosis), LacZ-expressing non-uterine SCs appeared within EM lesions showing the capacity to differentiate into epidermal and stromal progenies with detectable frequencies of 0.04% and 0.1%, respectively [56].

Thus, hormonal imbalances, inflammation, apoptosis evasion, SC involvement, angiogenesis, and fibrosis jointly support the growth and development of endometrial heterotopias [19, 47, 51]. Despite the importance of considering these factors in combination, each of them may provide links to particular therapeutic targets.

For instance, apoptosis levels in eutopic endometrium of patients with EM are lower compared with matched healthy women; hence, the chances of stray endometrial fragments survival in atypical microenvironments (e.g., abdominal wall) are higher, consistently with their presumed role during the onset of EM [57]. The effect appears to be persistent, given higher expression levels of anti-apoptotic proteins BCL-2 and BCL-XL within the foci [58, 59], and probably targetable as one of likely causations of the pathogenic process.

Cell therapies: an overview

Cell therapies are technologically advanced modalities based on parenteral administration ("transplantation") of cell products — living cell suspensions or their equivalents [60], either autologous (derived from patient's own tissues) or allogeneic [61].

Despite the enormous clinical interest, these techniques are still in their infancy — mostly at preclinical phases, some existing as purely fundamental concepts [61]. Cell therapies can be roughly classified into "regenerative" and "immunotherapies" [62].

Regenerative medicine aims at recovery of damaged structures — possibly through the use of resources (cellular, enzymatic, paracrine, etc.) provided by a transplant [61]. For instance, mesenchymal stem cells (MSCs) have been extensively featured in clinical trials for diabetes, osteoarthritis, kidney diseases, spinal injuries, bone and cartilage defects, and Parkinson's and Alzheimer's diseases, autoimmune diseases, etc. [63].

Immunotherapy can be broadly defined as harnessing the immunity or its mechanisms [64, 65], although the term is often used in a narrow sense, synonymously with "immunoediting" and "adoptive T cell therapy." This group of methods involves selective isolation of immune cells, their modification conferring curative properties, ex vivo expansion, and transplantation to the patient [64, 65]. The approach is epitomized by the chimeric antigen receptor (CAR) T cells genetically modified to bind and destroy cells that express tumor antigens [66]. An alternative cell-based principle considered for cancer treatment involves transplantations of NK cells and macrophages [67, 68].

Cell therapeutic strategies for EM

Cell suspensions and related products hold promise for EM, as indicated by 11 registered clinical trials currently under way [69]. The ultimate success will depend on correct understanding of the disease biology [70]. We shall now consider, one by one, the biologically justified treatment strategies for EM.

Inhibition of estrogen signaling

High local production of estradiol and high expression of ERs in EM lesions facilitate disease progression [20] and should be targeted. Systemic suppression of estrogen levels may show adverse side effects including emotional lability, weight gain, bone resorption, and infertility [71, 72], which can be avoided by using selective modulation of ERs with specific inhibitors at particular locations. Bazedoxifene,

known to counteract the estrogen-induced endometrial growth, is a prospective anti-EM drug. Intraperitoneal administration of bazedoxifene to mice with experimentally induced EM afforded a decrease in the ectopic lesion size, proliferation rates, and gland density compared to sham-treated animals. The apparently local action of bazedoxifene, confined to endometrial-like milieus, strengthens its therapeutic prospects as selective ER modulator in EM [72].

Alleviation of fibrosis

Fibrosis, a major component of EM, can be also regarded as its severe complication [73]. The resolution/alleviation of fibrosis can be achieved by targeting particular cells and their derivatives implicated in its origin.

For instance, EM progression continually challenges the platelet pools with periodic bleedings and vasodilation [4]. Adhesion and aggregation of platelets within the lesions are supported by local release of thrombin and thromboxane A [74]. The activated platelets, in turn, initiate fibrosis and promote expansion of the lesions through upregulation of pro-angiogenic VEGF and COX2, matrix-remodeling MMP9, and anti-apoptotic Bcl-2 [4]. Accordingly, platelet depletion in EM can be therapeutically justified.

Indeed, a platelet depletion procedure involving intravenous administration of rat anti-mouse GPIba polyclonal IgG into mice with modeled endometriosis caused a 60% decrease in the size of the foci in mouse model, accompanied by significantly reduced expression of proliferation marker PCNA, pro-angiogenic VEGF and COX2, endothelial marker CD31 and pro-fibrotic factors FGFR2, fibronectin, collagen type I, and smooth muscle actin α (aSMA) compared with other groups of animals. Namely, research of the effects of platelet depletion was performed in comparison with mice with endometriosis, which were intravenously administered either anti-mouse non-immune polyclonal IgG or platelets obtained from male mice. Platelet depletion also alleviated the infiltration of EM foci with the anti-inflammatory M2-polarized macrophages characteristic of pro-EM microenvironments [4].

Apart from activated platelets, a major pro-fibrotic effect is exerted by TGFβ-triggered cellular cascades potentially targetable in EM, notably the TGFβ/Smad pathway [75]. Indeed, TGFβ levels in the foci are significantly higher compared with the eutopic endometrium [76]. TGFβ has been shown to stimulate cell invasion, proliferation, and survival in the foci, suppress NK activities, and ultimately promote fibrosis [77–79]. In vitro exposure of endometrial MSCs to a TGFβ receptor 1 kinase inhibitor A83-01 induced profound transcriptomic changes. The treated cells exhibited enhanced pro-angiogenic, anti-fibrotic, and immunomodulatory properties compared with non-treated control cultures [80]. These data, however, expose angiogenesis and fibrosis as competitive processes, both contributing to EM progression, so that inhibition of one may favor the other, and their relationship within the framework of particular therapy should be carefully balanced and regulatable.

Exosomes are membrane-bound vesicles capable of delivering biologically active cargo to specific sites of the body. Exosomes are immunologically tolerable, capable of crossing physiological barriers, and particularly suitable for microRNA transportation [81]. MiR-214 was shown to inhibit the TGFβ-induced transcription of pro-fibrotic *Col1a1*, *aSma*, and *Ctgf* in endometrial cells, whereas in vivo exosomal delivery of miR-214 to Nude mice with induced EM significantly inhibited *Ctgf* and *Col1a1* in the xenografts compared with non-treated control animals [73].

The pro-fibrotic effects of TGFβ signaling heavily rely on myofibroblasts and their implication in fibrosis. Myofibroblasts are non-muscle contractile cells activated in response to injury [44, 82]. They are chiefly derived from resident fibroblasts, but can also differentiate from pericytes, epithelial and endothelial cells, vascular smooth muscle cells, and bone marrow lineages [44, 83]. Myofibroblasts are known to be major producers of extracellular matrix in fibrosis [83]. Apart from the collagen synthesis, myofibroblasts ensure contraction of the wound as a part of normal healing process; however, under chronic inflammatory conditions, the mechanical strain may promote microfractures and thus aggravate the damage [82].

TGFβ signaling triggers myofibroblast differentiation; accordingly, TGFβ signaling inhibition counteracts fibrosis in a myofibroblast-dependent manner [84]. Natural agonists of myofibroblast differentiation include Notch, NF-κB, ARID1A, TP53, PTEN, HIF1α, BRAF, PI3K/Akt, KRAS, and CDKN2A cellular proteins. Targeted suppression of these molecules may interfere with myofibroblast differentiation and thereby alleviate fibrosis in EM [85].

Inhibition of stem cell capacities

Stem cells (SCs) participate in the onset and progression of the foci and can be recruited to them from both the "retrograde" menstrual fluid and the bone marrow. SC recruitment, therefore, represents an apparent target in EM, elimination of which may significantly inhibit the progression [86]. Bazedoxifene, shown to inhibit the ectopic endometrial growth by selective modulation of ERs [72], can also interfere with SC recruitment to the foci. Combined administration of bazedoxifene and conjugated estrogens to experimental animals significantly inhibited SC recruitment from the uterus and assimilation in the lesions, thereby promoting significant

reduction of the lesions. Of note, bazedoxifene had no effect on SC recruitment to the uterus in control animals [87].

Endothelial progenitor cells (EPCs) make a prominent contribution to EM. Recruited from the bone marrow, these cells ensure neovasculogenesis within the foci [88]. The CXCR4-positive EPCs are attracted to the foci by SDF1 — a factor produced by stromal cells and activated by hypoxia. Subcutaneous injections of CXCR4 inhibitor AMD 3100 interfered with EPC recruitment, promoting a decrease in capillary density within the lesions [88].

Another receptor-ligand axis involving CXCR4, with chemokine CXCL12 as a binding partner, has been implicated as well. Estradiol has been shown to induce both the release of CXCL12 by endometrial stromal cells and the release of CXCR4 by bone marrow SCs. The AMD 3100-mediated inhibition reduced the immigration of bone marrow SCs by 50% [89]. Progestins used as a conventional treatment for endometriosis may trigger a similar mechanism; at least, they have been shown to inhibit the production of CXCL12 [90].

Thus, the inhibition of SC recruitment to the foci, potentially safe and efficacious, represents a relevant strategy in EM [86, 90].

Inhibition of angiogenesis

Focal angiogenesis has been identified as key to EM progression and its targeted inhibition can be therapeutically relevant [86, 91].

Systemic administration of anti-angiogenic agents was tested in EM models. Injections of flt-1, a competitive inhibitor of VEGF-A, to Nude mice with human endometrial xenografts dramatically reduced the number of active foci, causing regression of the lesions to thin-walled cysts filled with necrotic masses. The compromised expression of vascular markers within residual lesions was indicative of failed angiogenesis [92].

The macrophage migration inhibitory factor (MIF) is known to be strongly pro-angiogenic. The increased production of MIF in endometrial heterotopias facilitates their growth. Accordingly, MIF inhibition may prove beneficial in EM. Indeed, administration of MIF antagonist (S,R)-3-(4-hydroxyphenyl)-4,5-dihydro-5-isoxazole acetic acid (ISO-1) to Nude mice with modeled EM afforded a decrease in lesion size and degradation of their architecture compared with control animals [93].

Other anti-angiogenic small molecules can also promote regression of EM. These include bevacizumab (a humanized anti-VEGF monoclonal antibody), sorafenib (multikinase inhibitor), parecoxib (COX2 selective inhibitor), epigallocatechin-3-gallate (a prominent bioactive component of green tea), progestins, and retinoic acid [47, 94]. Apart from anti-angiogenic effects, these agents can also stimulate apoptosis within ectopic lesions [47, 94].

Inhibition of cell survival

Apoptosis is a physiological process, vital to normal functioning of living tissues. Endometrial heterotopias show reduced rates of apoptosis compared with eutopic endometrium, which favors growth of the foci and is potentially targetable for its prevention [57].

Telomeric DNA consists of tandem repeats that protect the chromosomal termini. In somatic cell lineages, telomeres undergo eventual shortening associated with the loss of both proliferative capacity and genomic stability; the length of telomeres is therefore regarded as an inverse measure of cell senescence. Telomerase is a ribonucleoprotein complex responsible for telomere maintenance through addition of tandem repeats. The abnormally high expression of telomerase components, as if continuously rejuvenating the cells, is characteristic of many tumors [95]. Noteworthy, patients with EM have higher telomerase activity in eutopic endometrium compared with conditionally healthy women [96], although the ectopic foci are telomerase-negative [97]. Targeting telomerase activity may therefore prevent the primary exodus of endometrial cells in predisposed individuals, but is not likely to prevent the growth of the foci once established at ectopic locations.

The mitogen-activated protein kinase (MAPK) signaling cascade can contribute to combined activation of telomerase and the apoptosis inhibitor surviving [98]. Abnormal activation of this cascade enhances both proliferation and survival of endometrial cells in patients with EM compared to conditionally healthy controls [99]. Accordingly, MAPK cascade can be regarded as a candidate therapeutic target in EM [98]. Indeed, in vivo administration of p38 MAPK inhibitor adezmapimod (SB203580) significantly reduced the size of ectopic lesions and mitigated the levels of IL1β, TNFα, MMP2, and MMP9 markers in peritoneal fluid [100].

MicroRNAs are heavily involved in apoptosis regulation. MiR-141-3p has been attributed with apoptosis-related protective effects in EM, its levels significantly decreased in ectopic lesions compared with eutopic endometrium. In functional tests, miR-141-3p inhibited proliferation and migration, while enhancing expression of pro-apoptotic Bax and reducing expression of anti-apoptotic Bcl-2 in cells of the foci [101]. These observations position miR-141-3p as a candidate pro-apoptotic biological drug for EM. Another study identified miR-141 as a TGFβ1/Smad2 signaling inhibitor in human endometrial adenocarcinoma cell line Ishikawa and an inhibitor of the TGFβ1-induced epithelial-mesenchymal transition [102]. This finding substantiates the idea of microRNA-based precision treatments for EM.

Cell therapies for EM

Immunotherapy

EM is characteristically accompanied by dysregulation of peritoneal immunity. The retrograde contamination of the pelvic and abdominal cavities with menstrual discharge may occur physiologically, but not the engraftment: under proper immune surveillance, the endometrial fragments are quickly eliminated by peritoneal macrophages and NK cells [103]. The endometrial graft survival, adhesion, and invasion are indicative of compromised local immunity.

NK cells

Human NK cells are functionally diverse and consist of several subpopulaitons: cytotoxic, interferon-producing, etc. Cytotoxic NK cells contain specific granules with granzymes, perforin, etc., ensuring their strong cytolytic capacity [104]. Decreased counts of cytotoxic NK cells in peritoneal fluid and peripheral blood of patients with EM have been demonstrated in several studies [105]. Replenishment of these counts, possibly by infusions of cell product, may rescue the compromised peritoneal immunity with an overall curative effect in EM.

In tumors, cytotoxic NK cells are capable of distinguishing between normal and transformed cells to specifically eliminate the latter on their own or in cooperation with dendritic cells [106, 107]. The antibody-mediated depletion of NK cells facilitated colorectal cancer progression in mouse model and the lytic activity of NK cells towards cancerous and pre-cancerous cells of colon carcinoma has been demonstrated [108].

The cytotoxic activity of NK cells is negatively regulated by activated platelets which promote fibrosis; the effect can be reversed or mitigated by TGFβ signaling inhibition [109]. Accordingly, combined suppression of platelet activation and TGFβ signaling represents a plausible strategy in EM. One clinical trial focused on the efficacy of autologous NK cells in EM is already close to completion [110].

Neutrophils

Neutrophils, along with other leukocytes, are involved in the regulation of many processes both in normal and pathological conditions, including inflammation and repair. EM is no exception [28]. In addition to the production of interleukins and growth factors, mentioned above, the neutrophils of patients with EM are characterized by a number of other features. It has been noted that neutrophils in endometriosis produce more Neutrophil Extracellular Traps, which leads to an increase in their concentration in blood plasma and peritoneal fluid [111]. However, the role of Neutrophil Extracellular Traps in the development of EM remains unexplored. At the same time, the ability to phagocytosis of neutrophils in EM is significantly reduced, while it is restored after the removal of foci [112]. Due to the significant role of neutrophils in the progression of EM, they can be considered as possible therapeutic agents. In this case, the cellular mechanisms of degranulation suppression should become the point of application [113]. In this regard, in addition to degranulation, it is possible to influence on the factors that contribute to the migration of neutrophils, their activation, and maturation [34].

Macrophages

Apart from NK cells and neutrophils, a major influence on EM onset and expansion comes from macrophages [105]. The foci are dominated by the anti-inflammatory M2-polarized macrophages shown to support the engraftment, proliferation, angiogenesis, and neurogenesis [68, 114].

Accordingly, EM-associated M2-polarized macrophages can be regarded as a putative target, while their functional opponents, the pro-inflammatory M1-polarized macrophages, will probably exert a curative effect in EM [68]. Infusions of M1-polarized macrophages to mice with experimental EM facilitated significant regression of the lesions [115].

The resident M2-polarized macrophages within the foci suppress the inflammatory reaction without eradicating it completely, and thereby support the transition of the initial acute phase to chronic inflammation and fibrosis [41, 116]. A TLR7-dependent stimulation of the pro-fibrotic M2-polarized macrophages (human or murine) promoted their reprogramming thereby alleviating fibrosis. Specific delivery of TLR7 agonist to the anatomical sites of fibrosis was achieved through conjugation with folate capable of high-affinity binding with receptors expressed by activated pro-fibrotic macrophages [117].

Incidentally, depletion of EM-associated macrophages may provide comparable benefits. For instance, the F4/80 antibody-mediated depletion of macrophages afforded a 40% reduction in the size of EM foci in mouse model [4, 104, 110, 115].

Cell replacement therapies

Such therapies involve delivery of cell product to affected sites of the body in order to replace a compromised or irrelevant cell population with its normal or curative equivalents [118]. The prospects/examples include transplantations of pancreatic β-cells in insulin-dependent diabetes [119] and

Table 1 A summary of prospective biology-based therapies for EM

Option	Strategy	Validation setup	Effect	Reference
Inhibition of estrogen-dependent growth	Selective modulation of estrogen receptors	Intraperitoneal administration of bazedoxifene in CD1 allograft model	Decrease in the endometrial cell proliferation, gland counts, and size of the foci	[72]
Resolution of fibrosis	Platelet depletion	Intravenous administration of rat polyclonal anti-mouse GPIbα IgG in BALB/c allograft model	Reduced expression of PCNA, pro-fibrotic, and pro-angiogenic factors; decrease in both the size of the foci and their infiltration with M2-polarized macrophages	[4]
	TGFβ signaling inhibition	Treatment of endometrial MSCs with TGFβ receptor 1 kinase inhibitor A83-01	Enhancement of pro-angiogenic, anti-fibrotic, anti-inflammatory, and immunomodulatory properties	[80]
		Transfection of Ishikawa endometrial carcinoma cell line with miR-141	Inhibition of TGF-b1/Smad2 signaling cascade, suppression of epithelial-mesenchymal transition	[102]
		Intraperitoneal injections of miR-214-enriched ectopic endometrial stromal cell-derived exosomes in Nude xenograft model	Reduced expression of pro-fibrotic genes, e.g., CTGF and collagen A1	[73]
	Myofibroblast differentiation inhibition	Speculative; possible targets include TGFβ1, Notch, NF-κB, ARID1A, TP53, PTEN, HIF-1α, BRAF, PI3K/Akt, KRAS, and CDKN2A	Expected to interfere with myofibroblast differentiation	[85]
Ectopic SC crackdown	Inhibition of stem cell migration from the uterus to the foci	Intraperitoneal injections of bazedoxifene combined to oral estrogen in C57BL/6 allograft model	Inhibited recruitment of stem cells from the uterus to the foci; decrease in the size of the foci	[87]
	Inhibition of endothelial progenitor cell migration from bone marrow to the foci	Subcutaneous injections of SDF1/CXCR4 + antagonist AMD 3100 in C57BL/6 allograft model	Inhibited endothelial progenitor cell recruitment with consequent reduction in capillary density in the foci	[88]
Inhibition of angiogenesis within the foci	Anti-angiogenic drug administration	Subcutaneous injections of VEGF-A inhibitor flt-1 in Nude xenograft model	Reduced expression of vascular markers within the foci; numerical and architectural regression of the foci	[92]
		Miscellaneous, with bevacizumab, sorafenib, parecoxib, epigallocatechin-3-gallate, progestins, retinoic acid, etc	Inhibited vasculogenesis, reduction of microvascular density within the foci	[47]
	Inhibition of pro-angiogenic factors	Intraperitoneal injections of MIF antagonist ISO-1 in Nude xenograft model	Reduction in the size of the foci and deterioration of their architecture	[93]
Stimulation of apoptosis and suppression of telomerase activity in the foci	Inhibition of MAPK signaling	Intraperitoneal injections of p38 MAPK inhibitor SB203580 in BALB/c allograft model	Reduction in the size of the foci, decreased content of IL1β, TNFα, MMP2, and MMP9 markers in peritoneal fluid	[100]
	Apoptosis stimulation, microRNA-dependent	Transfection of ectopic endometrial stromal cells with miR-141-3p mimic	Suppression of proliferative and migratory capacities and survival enhancement (Bcl-2↓, Bax↑) in the endometrial stromal cells	[101]

Table 1 (continued)

Option	Strategy	Validation setup	Effect	Reference
Immunotherapy	Promotion of NK cell-mediated cytotoxicity	Replenishment of cytotoxic NK cell counts	Expected to promote regression of the foci	[104]
	M1 macrophage administration	Intraperitoneal injections of M1-polarized macrophages in BALB/c allograft model	Reduction in the size of the foci and deterioration of their architecture	[115]
	Macrophage reprogramming in situ	Targeted delivery of folate-conjugated TLR7 in C57BL/6 model of idiopathic lung fibrosis	Macrophage reprogramming towards anti-fibrotic phenotypes	[117]
	Macrophage depletion	Intraperitoneal injections of F4/80-specific antibodies in BALB/c allograft model	Reduction in the size of the foci	[4]
Cell replacement therapy	Replacement of endometrial stromal cells with progesterone-sensitive equivalents	Directed differentiation of hiPSC into endometrial stromal cells	Differentiated cells responded to hormonal stimuli and expressed characteristic signatures of primary endometrial stromal cells	[122]

embryonic SCs in cardiovascular and neurodegenerative disorders [120, 121].

In EM, cell replacement has been considered for stromal fibroblasts of the ectopic lesions, regarded as progesterone resistant [122]. The defect can be corrected through replacement with autologous equivalents differentiated from induced pluripotent cells (iPSCs) of the patient. A protocol for iPSC differentiation into endometrial stromal fibroblasts afforded cells with authentic phenotypes, capable of decidual-like reaction in response to specific hormonal stimuli characteristic of secretory phase of the menstrual cycle. The cells expressed a similar transcriptomic signature with primary fibroblasts of the eutopic endometrium. The proposed replacement therapy with such cells is a tantalizing prospect, as their supply is virtually unlimited and transplantations are unburdened both ethically and immunologically [122].

Possible side effects of potential cell therapy for endometriosis

Despite the prospect of using cellular agents in the treatment of EM, these methods may have possible side effects. For instance, as already mentioned, the activation of cytotoxic NK cells may be a potential strategy in the treatment of EM. It has been shown that administration of monalizumab, an antibody blocking the NK cell receptor NKG2A, activates cytotoxic NK cells against tumor cells. So, in a clinical study on the administration of the drug to patients with gynecological malignant neoplasms, it was revealed that headache, fatigue, and vomiting were more frequent side effects [123]. In this regard, despite the great potential for the use of cellular agents in the treatment of endometriosis, this area is still developing and requires additional preclinical studies aimed, in particular, at identifying possible side effects of therapy.

Conclusion

The choice of management strategy for EM should be highly personalized and depend on severity and clinical priorities (infertility therapy, pain relief, etc.) [87]. Due to multifactorial nature of the disease, its treatment may cause unwanted enhancement of some factors at the expense of others. Favorable cases, however, may present with a joint synergistic improvement in clinical and morphological parameters — suppression of fibrosis during immunological recovery, a decrease in SC recruitment during anti-estrogen treatment, apoptosis stimulation by anti-angiogenic drugs, etc. [47, 72, 94, 117, 124]. The scope of prospective methods of cell therapy for EM (Table 1) isconstantly expanding.

Author contributions Daria Artemova, Polina Vishnyakova, Elena Gantsova, Andrey Elchaninov, Timur Fatkhudinov, Gennady Sukhikh had the idea for the article. Daria Artemova, Polina Vishnyakova performed the literature search and data analysis. Daria Artemova, Polina Vishnyakova, Elena Gantsova, Andrey Elchaninov drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

Funding Part of the work concerning endometriosis was supported by a grant for young Russian scientists MK-1573.2022.3. This paper has been supported by the PFUR University Strategic Academic Leadership Program. Part of the work concerning macrophages was supported by Russian Science Foundation [grant number 22-14-00152].

Declarations

Conflict of interest The all authors claim no conflict of interest. The authors have no relevant financial or non-financial interests to disclose.

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