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NEW PERSPECTIVES IN THE PATHOGENESIS OF ENDOMETRIOSIS – POTENTIAL TREATMENT STRATEGIES TARGETING THE SMART ADULT STEM CELLS

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ABSTRACT:
POPULATIONS OF CLONOGENIC EPITHELIAL AND STROMAL CELLS WERE FIRST REPORTED IN 2004 AND SINCE THEN, DIFFERENT POPULATIONS OF STEM/PROGENITOR CELLS HAVE BEEN IDENTIFIED. THIS REVIEW IS AIMED AT BRINGING NEW PERSPECITVES FOR ENDOMETRIOSIS DEVELOPMENT, TO PROVIDE A BETTER UNDERSTANDING OF PATHOGENIC THEORIES, ALONG WITH POTENTIAL TREATMENT TARGETS. STUDIES SHOW THAT ENDOMETRIUM IS RICH IN STEM CELL POPULATIONS, SUCH AS ENDOMETRIAL MESENCHYMAL STEM CELLS (EMSC), ENDOMETRIAL EPITHELIAL PROGENITOR CELLS (EEP) AND SIDE POPULATIONS (SP). THEIR ROLE IS IMPORTANT IN PHYSIOLOGY, REGENERATION AND REPAIR, BUT ALSO IN THE GENERATION OF ENDOMETRIOSIS. ENDOMETRIOSIS MAY ARISE FROM DISLOCATED OR ABERRANT STEM CELLS, FROM THE ENDOMETRIUM OR EXOGENOUS SOURCES, SUCH AS BONE-MARROW. MORE FINDINGS SUPPORT THE BIDIRECTIONAL MOVEMENT OF CELLS BETWEEN EUTOPIC AND ECTOPIC ENDOMETRIAL TISSUE THROUGH SIGNALING PATHWAYS. EMSC RESIDE IN A

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PERIVASCULAR NICHE AND ARE LIKELY TO MEDIATE ANGIOGENESIS AND STROMAL REGENERATION. TREATMENT OPTIONS FOCUSE ON THE INHIBITION OF THE ECTOPIC EMSC MIGRATION, PROLIFERATION AND ANGIOGENESIS. THE MAIN PURPOSE FOR THE FUTURE CLINICAL PRACTICE IS TO ESTABLISH ACCURATELY THE DIAGNOSIS OF ENDOMETRIOSIS AND POTENTIAL THERAPEUTIC TARGETS. THE ADVANCEMENTS IN OUR KNOWLEDGE ABOUT DIFFERENT TYPES OF ENDOMETRIAL STEM/PROGENITOR CELLS PROVIDE THE BASIS FOR A BETTER UNDERSTANDING OF ENDOMETRIOSIS PATHOGENESIS.

KEYWORDS: STEM CELLS, ENDOMETRIOSIS, PATHOGENESIS, MESENCHYMAL STEM CELLS

INTRODUCTION

Endometriosisis a pathological condition defined by the presence of endometrial glands and stroma in extrauterine locations[9]. The most common location for the ectopic endometrial tissue is the pelvic peritoneum, but there is not impossible to also find extrapelvic involvement, because endometriosis has been described in almost every area of the female body[10]. The prevalence varies between 6%-12% in asymptomatic women and 35%-50% in women with pelvic pain or infertility[11]. The variety of molecular differences between endometriosic lesions and the eutopic endometrium creates difficulties in developing new targets and therapeutic regimens[12]. In this regard, multiple researches have been made regarding the presence of progenitor stem cells in the endometrium and the correlation of this phenomenon with endometrial regeneration and the menstrual cycle[13]. The endometrium has a huge proliferation potential, quantified by the tissue growth of more than 14 days, being able to cycle through cellular proliferation, differentiation, shedding and regeneration of the functional layer by approximately 300-400 times during the

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[13] Abreu, Jaqueline Pedroso; Rebelatto, Carmen Lucia Kuniyoshi, Savari, CA; Capriglione, LGA; Miyague, Lye; Noronha, L; Amaral, VF; *The effect of mesenchymal stem cells on fertility in experimental retrocervical endometriosis.* Rev Bras Ginecol Obstet, 2017, 39(5): 217-223. doi: 10.1055/s-0037-1601484.

reproductive life of a woman[14]. The first evidence of endometrial stem cell survival was provided by Padykula et al., who demonstrated that primates possess a germ cell compartment located in the deep basal layer where intense mitotic activity of the epithelial cells persists after ovulation and menstruation[15]. Chan et al. (2004) was the first to demonstrate the clonogenicity in the human endometrium, defined as the ability of a single endometrial cell to produce a colony, harvesting small populations of endometrial cells (0,22%) and stromal cells (1,25%) which possessed clonogenic activity[16]. Since then, more and more stem cells/progenitor cell populations have been identified and consistent with this aspect, mesenchymal cells derived from the hematogenous bone marrow that could participate in the endometrial regenerative process. and progression of endometriosis, have been studied[17]. The initial theories of endometriosis pathogenesis are the retrograde menstrual theory, neonatal uterine bleeding, coelomic metaplasia, Mullerian ducts and immune and could support new hypothesis of endometrial stem cells. Moreover, the origin of endometrial stem cells is continuously debated, being believed that they originate either from fetal stem cells or by periodically sowing with the source of the hematogenous bone marrow in response to injuries[18]. This review focuses on the characteristics of endometrial stem/progenitor cells and examines their role in the pathogenesis of endometriosis.

STEM CELLS

Adult stem cells are non-differentiated cells that have the ability to generate multiple differentiated cell types identical to those from the tissue they reside while maintaining their ability to renew[19]. Unlike embryonic stem cells, which have the ability to generate cells from all the three layers (endoderm, mezoderm, exoderm), adult stem cells are either unipotent (capable of generating a single cell type) or multipotent (capable of generating several cell types in a particular tissue)[20]. Adult stem cells resides in niches, anatomical structures that constitute a suitable microclimate that favors signaling between the side cells and the stem cell population and the maintenance of the local homeostasis[21]. The involvement of the stem cells in the pathogenesis of endometriosis has been studied especially *in vitro* by harvesting tissue samples collected from women with histopathologically confirmed endometriosis by surgical approach or by experimental models with endometriosis. Thus, the clonogenic, renewal, multipotential properties ande valuation of the gene profiles expressed by them, together with the markers and the transcription factors, were tested. Originally, the genes that determined the stem cell character were identified in embryonic stem cells, while adult stem cells not expressing the same „stem" genes. By

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[18] Dhesi, AS; Morelli, SS; *Endometriosis: a role for stem cells.* Women`s Health, 2015, 11(1): 35-49.
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comparison between endometriosic lesions and endometrial tissues, it was found that the UTF1, TCL1 and ZFP42 genes express more intense activity in endometriotic implants ($p<0,005$ for UTF1) and GDF3 expresses more intense activity in the endometrium[22]. By immunohistochemical analysis, SALL4 showed increased expression in the stromal cells from the periglandular areas of the endometriosic lesions, although the expression of the corresponding mRNA from both types of samples suggested the post-transcriptional involvement of this factor in the pathogenesis of endometriosis[23]. Regarding Oct-4, it was highlighted both in the endometrial stromal cells and in ectopic lesions, even stimlating cell migration[24]. Pacchiarotti et al. demonstrated that Oct-4 has significantly greater expression in endometriosic tissues (32.3%), unlike the endometriotic tissue of women without endometriosic disease, supporting the ability of endometriosic cells to renew, maintain, and survive[25]. Another transcription factor associated with the Notch1 transmembrane receptor is the RNA-binding protein, Musashi-1, a factor associated with the maintenance and asymmetric division of neural and epithelial progenitor cells. Its expression is significantly increased both during the proliferative phase of the endometrium and in the endometriotic lesions[26]. Other transcription factors have been shown to have increased expression in endometrioti clesions, such as: SOX2, c-kit, NANNOG and SALL4[27].

HUMAN STEM/PROGENITOR ENDOMETRIAL CELLS

a. ENDOMETRIAL MESENCHYMAL STEM CELLS (EMSC)

They are non-haematopoietic stem cells that can be found in the haematogenous bone marrow and many other tissues and can differentiate into cells derived from mesodermal lines (eg. cartilage, bone, muscle, adipose tissue). They can be found in both basal and functional endometrium layers. Their isolation can be accomplished using dual specific markers, either CD146 + and PDGFRβ (CD140b) cells, or Sushi Domain containing 2-SUSD2 positive cells (formerly W5C5), identifying the mesenchymal cells as pericytes or perivascular cells from the basal and functional endometrium *layers*[28]. eMSC have also been found to some extent in the

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menstrual blood, justifying a wider membership in the endometrial layers than limitation to the endometrial basal layer. In contrast, the analyzed gene profiles were similar between the premenopausal and postmenopausal basal cell layers, suggesting that the stem/progenitor cells would rather originate from the endometrial basal layer, playing an important role in the cyclic regeneration of the epithelium and the endometrial stroma that occurs after each menstruation[29]. eMSC, which are located in the microclimate of ectopic lesions determine a selection process that leads to the survival of the clones with pronounced migratory, proliferative and angiogenic activities. It is considered that extrauterine microclimate found in ectopic lesions could modulate epigenetic eMSC by changing their characteristics[30]. Moreover, the ectopic eMSC from endometriomas express higher levels of IL-1β and COX-2 in comparison with eMSCs from eutopic endometrium[31]. The properties of eMSC from endometriotic lesions appear to be enhanced against eutopic eMSC, with higher proliferative capacity with significantly longer doubling time and significantly higher proliferative cumulative proliferation, with much enhanced invasiveness and migratory ability, as well as stimulation of angiogenesis. It is considered that extrauterine microclimate found in ectopic lesions could modulate epigenetic eMSCs by changing their characteristics[32]. The properties of CSMs from endometriotic lesions appear to be potentiated against eutopic CSMs, with higher proliferative capacity with significantly longer doubling time and significantly higher proliferative cumulative proliferation, with much enhanced invasive and migratory ability as well as stimulation of angiogenesis[33]. The CSM-e may be identified by the following markers: CD146, PDGFRβ, CD29, CD44, CD73, CD90, CD31, CD34, CD45[34]. Bone marrow mesenchymal stem cells (CSM-mo) are considered to have the ability in vivo to form a single cell, a bone heterotopic tissue or organs derived from the bone marrow (auditory bones: malleus, incus, stapes). The analogy definition for CSM-e would be the generation of the vascularized stroma with the ability to differentiate into a deciduous stroma when transplanted. This has not yet been demonstrated, but when CSF-2 SUSD-2 + clonal derived cells and were incorporated into subcapsular renal parenchymal vessels in immunocompromised mice, they produced endometrial stroma[35]. Schwaband Gargett argued that the eMSC CD149 + PDGFRβ +

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subpopulation represents 1.5% of stromal endometrial cells[36]. A single specific marker for endometrial tissue was identified for isolation of CSM-e clonogenic cells, namely SUSD2 + 2, with perivascular location, which are mainly characterized as Side Population cells (SP cells), which will be disscused in detail.

MESENCHYMAL-EPITHELIAL TRANSITION AND STEM CELL MIGRATION BETWEEN ENDOMETRIOTIC AND ENDOMETRIAL LESIONS

There is clear evidence from many studies that have shown that stem cells are capable of massive trafficking from endometrial lesions to the endometrium. These cells produce factors that are able to alter the uterine receptivity. Studies were conducted on models of mice transplanted with green fluorescent protein (PVF) tagged tissue. The protein chain reaction (PCR) has denied the presence of PVF in the control group and confirmed the presence of PVF in the group of endometriotic mice. Immunofluorescence was used to locate cells in the endometrium[37]. Cells that expressed PVF in the tissues of the experimental group were mainly located in the basal endometrium layer and were never identified in the luminal epithelial layer or in the glandular cell consistency. Uterine cells that originated in ectopic lesions expressed a distinct genetic profile compared to the eutopic endometrium, such as Snail1, Snail3, Goosecoid and downregulation of the Zeb2 gene. This is the exact gene profile that is associated with epithelial-to-mesenchymal transition[38]. The proccess implies the loss of the epithelial cells polarity and the conversion to the mesenchymal phenotype. The migration is realised as mesenchymal stem cells. The cells that engraft into the uterine stroma display the activation of Wnt signaling pathway, which is an absolute indicator for epithelial identity, even though these cells were not located in the epithelium[39]. Wnt signalling is essential for the development of many tissues including the endometrium and is required for the maintenance of stem populations in adult organs. Wnt7a is envolved in postmenstrual endometrial regeneration, while Wnt4 is observed in normal development of the endometrial glands and also in the stromal decidualization when embryo implanting[40]. These endometriosis-derived cells were found in the stroma despite secreting signaling molecules of epithelial cells. All this abnonmalities lead to a disruption with decreased endometrial receptivity with further consequences, in endometriosis patients. The ectopic Wnt signaling distorts the optimal endometrial developing[41].

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ENDOMETRIOSIS-DERIVED CELLS CIRCULATION WITH EMSC MARKERS AND THEIR IMPLANTATION

There are studies that demonstrated cells with endometriosic lesions provenience express MSC markers and enter the circulation with subsequent ability to differentiate into type II alveolar cells in vivo. Li et al. identified cells from circulation that expressed endometrial stem cell markers CD140b and CD146 in subjects with donor tissue that comprised the endometriosis. This suggest that populations of MSC scan spread over large distances [26]. Similarly, Becker et al. showed that endothelial progenitor cells (eEPCs) were found elevated in the circulating blood after disease induction[42]. The presence of both types of stem/progenitor cells are highly suggestive for active disease and may serve as biomarkers for detecting the pathology in cause[43].

b. ENDOMETRIAL EPITHELIAL PROGENITOR CELLS (EEPCS)

These clonogenic epithelial cells reside in the basalis endometrium layer. The specific marker for the endometrial basalis epithelium is the stage-specific embryonic antigen-1 (SSEA-1 or CD15). When examining in vitro, the cultured cells expressed increased telomerase activity and longer telomers than SSEA-1- cells, which represents a characteristic of the stem/progenitor cells. There were also found larger spheroids and fewer ER-α and progesterone receptors, which might suggest that *in vivo*, SSEA-1+ cells may be found close to the junction between the functionalis and basalis[44].

Recently, N-cadherin was identified as a specific marker for humane EPCs using gene profiling to differentiate between premenopausal and postmenopausal endometrial epithelial cells. There were found 11 upregulated genes in postmenopausal endometrial epithelium, including CDH2 and CDH3, which encode for the N-cadherin and P-cadherin respectively. The expression of the N-cadherin gene was found to be associated with greater self-renewal and more population doublings than N-cadherin- endometrial epithelial cells[45]. Changing the cell phenotypes within endometriotic lesions may be responsible for the invasiveness of endometriotic cells. A well-differentiated CK+E-Cadherin-N-Cadherin+ population is found in the epithelial population, similar to carcinoma micrometastasis[46]. In line with the early carcinoma, endometriosic lesions regress during estrogen depletion therapy but reoccur when cessationing the therapy, suggesting that stem/progenitor cells in the lesion remain dormant and then reactivate under estogen exposure[47].

The relationship between vasculogenesis in endometriosis and endothelial progenitor cells is not well established. There are some studies though that showed the recruitment of eEPCs are

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highly important in the process of creation of blood vessels. The origins of eEPCs are from hematopoietic stem cells, myeloid cells and multipotent bone marrow progenitors. The first step represents the mobilization of EPCs from the bone marrow through VEGF (vascular endothelial growth factor), FGF-2 (fibroblast growth factor) and estradiol[48]. VEGF expression by endometrial cells varies with the menstrual cycle, with higher levels in the proliferative phase than in the secretory phase, in the peritoneum[49]. It is well-known that endometriosis is associated with high-levels of VEGF and FGF-2 and that it is an estrogen-dependent condition. In return, mobilized EPCs secrete angiogenic factors, such as VEGF and IL-8 which promote recruitment of further EPCs and involve them into forming *de novo* microvessels[50].

c. SIDE POPULATION CELLS (SPC)

SPC is represented by a mixed population of epithelial, stromal and endothelial cells, with a predominance of endothelial cells. It represents a specific phenotype that results from high expression of plasma membrane transporters (e.g. ABCG2), which transport organic molecules out of cells, including DNA-binding dye Hoechst 33342, which allows them to be identified through flowcytometry[51]. The endometrial SPC were described using specific markers as it follows: 27% EpCAM+ epithelial, 51% endothelial, 15% CD10+ stromal and 25% CD146+ endothelial/eMSC[52]. The presence of thee MSCs and endothelial phenotypes (CD146+PDGFRβ+) suggest that the SPC play an important role in vasculogenesis during endometrial regeneration[53]. The studies expressed some important differences regarding the type of isolating the cells, showing different stem cell functions *in vivo* and *in vitro*. *In vitro*, epithelial and stromal SPC express typical MSC characteristics, evolving to decidualization, with an enhanced capacity to undergo osteogenic and adipogenic differentiation, similarly to MSCs and to clonogenic endometrial stromal cells[54]. While *in vivo*, when transplanted under the kidney capsule or skin of immunocompromised mice, the SP

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cells from human produce endothelial tissue (46%), epithelial tissue (00.02-8%) and stromal structures (13%)[55].

HOMING AND MOBILIZATION OF STEM CELLS

The traffic of the stem cells is mediated and regulated by low molecular weight cytokines that attract different cells through chemotactic mechanisms. The most investigated pathway in this regard is CXCR4-CXCL12, which was first investigated from the pathogenesis of cancer, when promoting invasion and cellular migration, as well as angiogenesis in the tissue samples that express CXCL12 and communicate in a paracrine manner. CXCL12 is mostlye xpressed in sites where there is injury and inflammation and can be found in the stroma and the epithelium of the endometrium[56]. CXCR4 is the receptor of CXCL12. The difference between serum CXCL12 in women with and without endometriosis is less than observed in the murine models; this thing may be due to the more importance of the microenvironment of the endometriosis lesions, that abund from CXCL12[57]. The CXCR4/CXCL12 axis in involved in stem cell metastasis as well and represent a multistep process as CXCR4 positive cells first leave their stem cell niche, then are transported to the tissues which express high concentrations of CXCL12 via peripheral blood or the lymphatic system[58]. The levels of CXCL12 mRNA are in concordance with the endometriosis derived stem cells in animals with and without endometriosis. Serum CXCL12 is elevated in active disease, independent from estrogen regulation and endometriosis can develop from CXCL12 which mediate the ectopic endometriosis-derived stem cell mobilization. There is strong evidence that CXCR4-CXCL12 may contribute to the endometriosis and angiogenesis in ectopic lesions and that circulating endometriosis stem cells would propagate the disease through lymphatic or vascular dissemination, which may also serve as markers for active lesion establishment[59]. Also, as a therapy tool, the CXCR4-CXCL12 axis, as a primary pathway involved in the recruitment of the bone marrow-derived cells, may represent a novel approach to control the spread of this common disease, inhibiting the abnormal pathways of cell migration between the uterus and the ectopic foci[60].

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POTENTIAL ANGIOGENIC MANAGEMENT ON ENDOMETRIOSIS AND STEM CELL TARGETED THERAPY

The antiangiogenic drugs have been tested in many diseases that include the angiogenesis mechanism and this could also be incriminated in endometriosis. Sorafenibis a protein tyrosine kinase inhibitor that target Raf kinases and growth factors that include PDGFRβ, c-Kit and eMSC markers. In endometriosis, Sorafenib induces regression in lesion volume in heterologous mouse model of endometriosis and autologus rat model[61]. The results showed that however the target therapy, the lesions still persisted in the endometriosis foci and the pain was not alleviated[62]. On the other hand, studies demonstrated that *in vitro*, the angiogenetic properties, as well as migration and proliferation of ectopic eMSCs were reduced through HIF-1αand VEGF inhibition[63]. Another approach was described by inhibiting the delivery of the miRNA when targeting VEGF. This method was used *in vitro* showing the decrease in motility and proliferation when expressing miR-199a-5p downregulated VEGFa of eMSCs, with promising results in both heterologous and homologous mouse models of endometriosis, with lesion suppresion[64]. The mechanism of action of the Sorafenib is by inhibiting the phosphorylation of ezrin in ectopic MSCs, with consequent limitation of the ectopic MSCs migration, proliferation and VEGF release[65].

Another promising tool for endometriosis are SERMs (selective estrogen receptor modulator), which have an agonistic/antagonistic activity over ER (estrogen receptors), depending on the type of SERMs. Bazedoxifene (BZA) is a new type of SERM therapy which does not stimulate the endometrium in postmenopausal women and is best able to counteract the effect of estrogens on the proliferation. The mechanism of action is related to the suppresion of the ER expression of estrogen-mediated cell proliferation. There are studies that show BZA treatment

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leads to decreased stem cell engraftment and recruitement in endometriosis, as well as decreasing the lesion size[66].

CONCLUSION

Several different populations of the endometrial stem/progenitor cells, including CD140+, CD146+, or SUSD2 eMSCs, N-cadherin+ eEPs and SP cells may be used to establish the diagnosis of endometriosis or as therapeutiuc targets.There are hypothesis that support the idea that early onset endometriosis may be due to endometrial stem/ progenitors cells impairment. Some studies show that aberrant or dislocated stem cells, either from ectopic or eutopic endometrial tissue, may play an important role in the endometriosis onset and genesis. After both *in vivo* and *in vitro* studies, the endometrial stem cells represent the new targets in the pharmacologic arsenal and promise potential therapeutic methods. Further research is required in order to evolve and develop new strategies over endometriosis pathology.

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