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Medical Hypotheses

Unus pro omnibus, omnes pro uno: a novel, evidence-based, unifying theory for the pathogenesis of endometriosis.

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ABSTRACT

The theory of retrograde menstruation as aetiopathogenesis of endometriosis formulated by John A Sampson in 1927, shows clear shortcomings: this does not explain why retrograde menstruation is a physiological process that affects 90 % of women, while endometriosis occurs in only 10 % of cases; it also does not explain the endometriotic foci distant from the pelvis, nor explains the cases of endometriosis in male patients. The immunological alterations of the peritoneal fluid explains the effects of disease, such as the inhibition of the physiological processes of cytolysis, but does not explain the cause. There is evidence to support the hypothesis that müllerian remnants of the endometrium, and endocervix endosalpinx, ectopic, are items from the genital ridge leaked during organogenesis. It is known that tissues derived from coelomatic epithelial and mesenchymal cells have the potential to metaplastically differentiate into epithelium and stroma. In addition, the phenotype of the ectopic endometrial cells is significantly different from those eutopics. There is no scientific evidence that, during organogenesis, the genes of the Homeobox and Wingless family play a fundamental role in the differentiation of the ducts of Muller and development of the anatomical structure of the urogenital tract. We present here a hypothesis that deregulation of genes and the Wnt signaling pathway Wnt/β-catenin leads to aberrations and deregulation within the mesoderm, thus, may cause aberrant placement of stem cells. In addition, immune cells, adhesion molecules, extracellular matrix metalloptroeinases and pro-inflammatory cytokines activate/alter cells, creating the conditions for differentiation, adhesion, proliferation and survival of ectopic endometrial cells.

Keywords: Endometriosis, Embryology, Body Patterning, Embryonic Stem Cells, Proteins homeodomain, Wingless Type Proteins.

Background

Endometriosis is characterized by the presence, in the anomalous endometrial tissue, functionally active, with the presence of stroma and glands [1]. Numerous theories have been proposed for the pathogenesis of endometriosis, such as, retrograde menstruation, coelomic metaplasia and müllerian remnants [2], a hormonal disease, autoimmune disease, genetic disorder or due to an environmental stimuli [3]. Amongst the various hypotheses, the one that enjoys the greatest consensus is retrograde menstruation. Retrograde menstruation is when endometrial cells and fragments desquamate during menstruation and are transported via the fallopian tubes into the peritoneal cavity, instead of flowing out the body, and implant and proliferate onto peritoneal surfaces or pelvic organs [1]. The prevalence of endometriosis is estimated to be 10 % [4], with a further 11 % of women whose disease is not clinically diagnosed [5]. Endometriosis predominantly affects the ovaries (up to 88 %), the ligaments of the uterus, fallopian tubes, the cervical-vaginal area, urinary tract and the rectum; the involvement of the urinary tract is rare (1-2 % of all cases) [6,7], of which 84 % are located within the bladder [8]; other organs of involvement include, pancreas, spleen [9], liver, intestinal tract, gallbladder [10], wall of the abdomen and the umbilicus [11]; with brain endometriosis also being reported [12]. The foci of endometriosis distant from the pelvis can be explained as being derived from buds of the embryonic genital ridge and originate within the müllerian ducts which, during organogenesis, are located at the top. Retrograde menstruation is a physiological phenomenon which occurs in 76-90 % of women [13], whilst disease occurs in 10 % of cases. The hypothesis of retrograde menstruation as the pathogenesis of endometriosis does not explain the gap between physiological prevalence (76-90 %) and the pathological (10 %). Interestingly, a case of endometriosis in the cul-de-sac and uterosacral ligaments was histologically confirmed in a patient undergoing pre-menarche

at 9 years of age [14]. However, this does not explain the cases of endometriosis in male individuals with normal phenotype (46, XY), such as: endometrioma in the abdominal wall [15]; endometriosis of the bladder [16]; a case histologically indistinguishable from endometrial tissue [17]; cystic endometriosis of the epididymis [18]; paratesticular endometriosis [19]; a mass located laterally to the spermatic cord, removed surgically, whose histology showed tissue similar to the endometrium, a proliferation of smooth muscle, endometrial glands and stroma [20]. Such cases of male patients can only be explained by the incomplete differentiation of the müllerian ducts.

Hypothesis

The theory of "retrograde menstruation", as a "cause" of endometriosis, does not correlate with the incidence among physiological events, and prevalence of the disease does not correlate with the endometriotic foci distant from the pelvis in the reported cases in male patients. Since 1927, the year of Sampson's theory, many advances have been made in the direction of the effects but not the causes. We hypothesize that, during organogenesis, a deregulation of genes and the Wnt signaling pathway Wnt/β-catenin would produce an aberration and the axial extension of the identity of the anterior-posterior patterning, whilst a deregulation of Hox genes and cofactor Pbx1 produces an aberration in the segmentation of the mesoderm (Fig. 1, Fig. 2). This may cause aberrant placement of stem cells with endometrial phenotype, ectopic, and maintain them in quiscent niche. In post-pubertal, the estrogenic activity activate peritoneal macrophages with consequent induction of pro-inflammatory cytokines TNF-α and IL-1β which, in turn, activate the binding to DNA through the transcription factors of NFκB; transcriptional activity, through the inflammatory cytokines IL-6 and IL-8, induces the expression of VEGF that activates the vascular endothelial cell,

while MIF induces cell endometrial, mitosis, and the survival is supported by the activation of anti-apoptotic gene Bcl-2, from the degradation of the extracellular matrix by MMPs and the entry phone via ICAM and VCAM, creating the conditions for differentiation, adhesion, proliferation and survival of ectopic endometrial cells. Understanding of the biological mechanisms, genetic and epigenetic, which regulate the differentiation and development of the urogenital tract during the fetal stage, might be a priority for researching the aetiopathogenesis of endometriosis and understanding of our hypothesis.

Evaluation of the hypothesis

Embryogenesis

The primordial germ cells are derived from the primitive streak (from epiblast to caudal area); remaining in the extra-embryonic mesenchyme to complete gastrulation and subsequently migrate along the allantois endoderm; maintaining the feature of cell division throughout the development of the embryo and preserving all the characteristics of stem cells. Following gastrulation, the embryonic germ cells contribute to the formation of the epithelial and mesenchymal tissues. The epithelial cells population of the embryo have similar morphological characteristics of differentiated epithelia, whilst mesenchymal cells contribute to the basal membrane, forming the lamina and smooth muscle of tubules and differentiation into connective tissue. The space beneath the epithelium and between the mesenchymal cells is filled with extracellular matrix molecules and their receptors [21-23]. During the early stages of organogenesis, the mesoderm arises from the primitive streak and gives rise to the epithelial coelomatic. The müllerian ducts born by invagination of coelomatic epithelium, during fetal development results in the female reproductive tract, which is further differentiated to form the uterus, oviduct and vaginal canal higher. Animal studies have

demonstrated that the coelomic epithelium forms the müllerian ducts [21]. The coelom is derived from the same lateral plate mesoderm that, in turn, are derived from the primitive streak [22]. The anatomy of the female urogenital tract arising from the müllerian ducts is completed at the time of birth with the exception of the uterus; the histological architecture and the tissue specificity reach full development in the post-natal period with the full radial patterning of 3 basic histological structures: (i) endometrium, (ii) myometrium and (iii) perimetrium. This results in the structured development of endometrial glands luminal epithelium, the organization and stratification of the endometrial stroma, and, the differentiation and growth of the myometrium [23-27].

Hox - Homeobox genes

In mammals, the Hox genes are well known for their crucial role during embryogenesis, and in particular the axial development of the skeleton, the hind brain, and, the limbs. Their involvement in organogenesis has been shown, in particular, during urogenital differentiation [28]. The Hox genes control the fate of cells and the segmental embryonic formatting. The sequential arrangement of the Hox genes on its chromosome associates with the spatial distribution and protein expression along the antero-posterior axis of the embryo [29]. The biological specificity of Hox proteins derives from cooperation with specific cofactors that contribute to modulate the binding to DNA for the control of the expression of target genes [30]. The protein cofactors include, pre-B-cell leukemia homeobox (PBX) and myeloid ecotropic viral integration site (MEIS) [31,32]. The sub-cellular localization of proteins PBX is highly regulated in different cellular contexts; it has been hypothesized that the binding of PBX with MEIS induces translocation to the nucleus where it associates with Hox proteins which regulate target genes; Pbx is necessary to allow the formation of heterotrimeric complex DNA binding involving Meis proteins [33, 34]. Pbx has

been shown to act as a direct regulator of expression of the target gene, and this adjustment takes place via interactions that require the cooperation of other members of the family homeobox as Meis and Hox [35]. These have been shown to be involved in malformations of the urogenital tract and its inactivation which leads to complete absence of müllerian structures [36,37]. This plays a critical role as a regulator of the development and the absence of which leads to embryonic lethality and multiple system abnormalities of tissues and organs. Pbx1 is extensively expressed in the mesenchymal tissues during differentiation of the urogenital organs, and inadequate cell proliferation leads to total absence of the adrenal glands, whilst the formation of the gonads shows a rudimentary sexual differentiation. The lack of expression of Pbx1 greatly reduces the evolution of the urogenital ridge which translates into reduced differentiation of the mesonephros and kidneys and in the absence of the müllerian ducts [38-40]. Pbx1 has been proven to be expressed in the ductus Müller but absent in the Wolff ductus during the differentiation of both sexes [40]. The clusters of Hox genes during development, are subject to transcriptional control by cofactors such as RA (Retinoic Acid) [40], FGF (Fibroblast Growth Factor) [41,42] and the genes of the Wnt signaling [43]; this loop of self-induction and/or repression of Hox genes occurs within the same cluster [44-46], as well as the post-transcriptional regulation [47,48]. During organogenesis patterning of female genital tract is regulated by homeobox transcription factors [49]: HoxA9 is expressed in the oviduct, HoxA10 (via BMP-4 Bone Morphogenetic Protein, Wnt7a and β3-integrin) and Hoxa-11 (by Emx-2 Empty spiracles homeobox gene and IGFB1 Insulin-like Growth Factor Binding protein) are expressed in the uterus [50]. HoxA11 and 13 in the cervix and vagina [51]. HoxA genes play a role in regulating temporal and spatial expression in the formation and differentiation of the müllerian ducts [52].

Wnt - Wingless genes

Wnt4 is essential for the formation of the müllerian ducts. [53] In fact it is involved in numerous anomalies and female genital morphology in endometrial glandular and stromal breakdown. Wnt7 is involved in the maintenance of HoxA10 and HoxA11 genes whilst Wnt5 in the development of the genital anterior-posterior axis [54,55]. Wnt5a and Wnt7a are necessary for proper glandular genesis and are expressed, respectively, in the stroma of the uterine and uterine epithelium [56]. Downstream of Wnt genes, β-catenin [57] is associated with the Foxa2 forkhead family [58]. There are 3 types of signaling pathways: Wnt/β-catenin, Wnt/JNK (c-Jun N-terminal kinases) and Wnt/$Ca2^{+}$. Wnt binds via cell surface receptors, to disable the Axin complex, consequently inhibiting the phosphorylation of β-catenin from the complex by Axin [59]. β-catenin enters the nucleus in cooperation with factors Lymphoid Enhancer Factor / Transcription Factor (LEF / TCP), which by binding to DNA activates gene transcription [60]; the absence of stimulation by Wnt causes the phosphorylation of β-catenin from the Axin complex, which is phosphorylated and then targeted for ubiquitination and degradation in the proteasome [61]. It was shown that an estrogenic compound may interfere with Wnt expression and/or β-catenin target genes with a consequent alteration of the development of the female reproductive tract [62, 63]. The signaling pathway of canonical Wnt genes and Wnt/β-catenin, are associated in the control of different types of stem cells and can act as a factor niche to keep the embryonic stem cells (EmSC) in a state of self-renewal [64-66].

Müllerian derivatives and remains

Congenital anomalies of the urogenital tract: During organogenesis differentiation between male and female urogenital systems takes place. Between the eighth week and the fourth month the male urogenital tract initially develops from embryological structures which are

resolved with female-specific activation of the male genome. A missing or incomplete differentiation results in disorders of sex development, chromosonic abnormalities (such as, Turner syndrome and Klinefelter's syndrome), Müllerian agenesis, Rokitansky syndrome, developmental disorders or testicular androgen insensitivity syndrome (or Morris syndrome).

Remains and Müllerian derivatives: Sexual differentiation is, in some congenital diseases, absent or incomplete, thus, it is plausible to assume that they can co-exist in the development of müllerian remnants in asymptomatic individuals. Many müllerian events suggest that tissues derived from the epithelium and mesenchymal cells coelomate (Secondary Müllerian System) and have the potential to differentiate directly into epithelial cells and stromal cell; possibly a metaplastic hypothesis for the pathogenesis of endometriosis [67]. The peritoneal cavity is a matrix for the benign and malignant proliferation of the secondary müllerian system where it can develop endometriosis, endosalpingiosis and endocervicosis [68]. Under immunologically "normal" conditions, the peritoneal cavity has the ability to prevent the evolution towards endometriosis, however, failure to remove fragments of endometrial tissue from the peritoneal cavity induces local inflammation, activation of macrophages which secrete cytokines and chemokines some of which can cause metaplasia of the peritoneum or the development of müllerian residues [69]. Pelvic masses and congenital malformations associated with müllerian have been reported at the time of diagnosis of endometriosis, comprising of smooth muscle tissue within the uterine cavity, but, pose diagnostic uncertainty between smooth muscle metaplasia or müllerian remnant of the system [70,71]. It is speculated that in males with normal male phenotype who develop endometriosis, have prostatic utricle as a remnant of the uterus embryo [15].

Müllerianosis: There are considerable difficulties in the differential diagnosis between endometriosis and müllerianosis. The main difference is that, in endometriosis, ectopic endometrial tissue cyclically executes outside of the uterine cavity invading the outer surface of other organs, whilst, in müllerianosis, there is tissue present in the endosalpinx, endometrium and endocervix, whose most common form is found in peritoneal pockets. Batt RE et al. have laid down 3 conditions for the diagnosis of müllerianosis: 1) no evidence of pelvic endometriosis, 2) no direct communication with endocervix, endometrium or endosalpinx, and, 3) no surgery to the reproductive organs. Given the presence of the 3 components, endometrium, endocervix and endosalpinx, supports the hypothesis that müllerian remnants generated from the genital ridge leaked during organogenesis [72]. In the presence of defects in the genesis of the genital tract, differentiation and cell migration can be incomplete or aberrant. Any cells with aberrant gene expression in the migratory path through the rear pelvic floor can be implanted abnormally. Pluripotent cells can cause endometrial metaplasia or endometriosis in post puberty. Studies on the coelomic cavity and müllerian duct, both in the fetal period and in adulthood, suggests that the epithelium coelomatic, fabrics and related adult epithelia müllerian derivatives, have common embryological origin [73]. In fact, in peritoneal biopsies of the cul-de-sac in female infants who had died from sudden infant death syndrome (SIDS), had a small whitish plaque, (~200μm in diameter), which showed glandular epithelium with well-defined structures surrounding the stroma [74]. In addition, in fetal autopsies, the incidence of ectopic endometrium in 5 different locations identified in the recto-vaginal septum close to the cable Douglas near the mesenchymal tissues of the wall rear of the uterus in the cannula at the level of the muscular wall of the uterus. Thus, one possible reason of endometriosis, is the dislodgement of primitive endometrial tissue outside the uterine cavity during organogenesis [75,76].

Müllerian cyst remains in cavitated: Accessory and Cavitated Uterine Masses (ACUM) is a sporadic condition seen in young females, which has significant clinical manifestations, in particular severe dysmenorrhea and recurring pelvic pain. The diagnosis presents considerable difficulties, so as to be placed in the differential with uterine malformations such as bicornuate uterus and segmental atresia, cystic areas or degenerate with adenomyosis, leiomyomas and degenerated primary dysmenorrhea essential [77]. ACUM is diagnosed more frequently in women aged less than 30 years and in nulliparous women (although sporadic cases are reported of women over the age of 30 years and multiparous) [78]. The term Asian juvenile cystic adenomyoma was used for the diagnosis of cases with clinical and histopathological features similar to ACUM [77,78]. The ACUM are generally located at the level of insertion of the round ligament and is likely associated to a dysfunction of the female gubernaculum. The aetiopatogenic hypothesis classifies this as a new variety of Müllerian anomalies [79] which may be caused by duplication or from ectopia and the persistence of müllerian duct, whose fabric is to be placed in an ectopic position at the level of the attack of the round ligament and could be related to a dysfunction of the gubernaculum [79,80].

Stems cells

Human embryonic stem cells (hEmSC): hEmSC are pluripotent cells derived from various stages of embryonic development and represent the only form of stem cells able to proliferate indefinitely and to differentiate into all types of tissue-specific cells. The hEmSC are generally derived from the inner cell mass of the blastocyst to the stage of pre-implantation embryo. hEmSC cell lines are well characterised in regards to genomic integrity and pluripotency and express high levels of telomerase activity. Telomerase (or terminal transferase) is a ribonucleoprotein that adds telomere repeats to the chromosomal ends and

thus, maintains telomere length, and is crucial in the replication life span [81]. The expression of telomerase correlates with immortality of cell lines, and, the reintroduction of telomerase activity in some cell lines extends their replication activity [82]. The hEmSC, being pluripotent possess the characteristics to differentiate into the 3 germ layers which form all tissues of the embryo - (i) ectoderm, (ii) mesoderm, and, (iii) endoderm. They have specific morphological and molecular properties, they possess specific properties that epigenetic chromatin structure is open-ended to allow the entry of transcription factors, and, regulates gene expression [83]. In the promoter regions of pluripotency genes OCT4 (octamer-binding transcription factor 4) and Nanog (homeobox transcription factor - regulator involved-in inner cell mass and embryonic stem) it denotes a marked reduction in methylation of CpG nucleoids (cytosine-phosphate-guanine nucleotide) [84]. These properties are necessary to characterize the epigenetic hEmSC in a pluripotent state and distinctive, undifferentiated stem cell hEmSCs derived from cell lines that form both the endoderm and mesoderm. For endoderm differentiation Activin-A ligand activates transforming growth factor beta (TGF-β) [85], bone morphogenetic protein (BMP),, fibroblast growth factor (FGF) and the Wnt family of genes, which are typical modulators of the mesoderm [86].

Endometrial stem progenitor cells (hESP): Adult stem cells are found in an undifferentiated form and have the characteristics of self-renewal through cell division dependent microenvironment or niche. They are important for the regeneration and recovery of organs and tissues by ensuring regular functional maintenance. The human endometrium is composed of epithelium, glands and stroma, which during the menstrual cycle are subject to profound changes in tissue structure and function; the recovery is ensured by the presence of the endometrial progenitor stem cells that are assumed to reside within the basal layer [87]. Several lines of endometrial stem cells and progenitor cells have been characterized that show

large plastic capacity with high availability differentiation [23,88-90]. Endometrial stem progenitor cells (hESP), differ for patterns of expression of cell surface markers for clonal efficiency, to the microenvironment of the niche, and endometrial localization [91,92]. In fact, in a study of clonal analysis of endometrial epithelial cells and stromal cells derived temporally on the phases of the cycle, non-clonogenicity ranged from proliferative to secretory phase endometrium and between cycling and inactive, for both epithelial stromal cells, showing that the inactive endometrium contains clonogenic epithelial cells and stromal cells [93]. Some studies have suggested the origin of hESP from bone marrow as a source of exogenous [94,95]. Endometriotic lesions are detectable in a functionally pathological stage, and it is extremely rare to detect microscopically the phases of attachment and proliferation of endometrial tissue in the peritoneum, which is an area with high incidence of injury [96]. The origin of the cells within ovarian endometriomas are monoclonal, whilst peritoneal lesions are polyclonal [97-99]. The cells that give rise to ectopic endometrial implantation must necessarily possess the ability to migrate, the angiogenic potential for proliferation and pluripotency to form glandular tissue and the hESP cells demonstrate all the requirements [87]. Inded a hypothesis was formulated in that repeated physical and biochemical injuries caused by inflammatory cytokines and reactive oxygen species are able to trigger the cell cycle of quiescent stem cells that may be involved in the development of benign and malignant endometrial aberrations as endometrial hyperplasia, endometriosis and endometrial cancer [100].

Stem/progenitor cells residing in adult uterus (SP): The mucosal lining of the uterus remarkably regenerates during the reproductive years of a woman and this plasticity of the endometrium has been attributed to a small population of stem/progenitor cells, known as side population (SP). In fact, SP cells reside in the adult basal endometrium and is assumed to be

the remains of the original epithelial cells, the Müller Duct (MD) [101]. The SP has all the features that define poorly differentiated stem cells that are able to divide asymmetrically and quiescently [102]. The stem cells, to maintain the pool of progenitors from which arise the differentiated cells, are programmed to have a long lifespan; in order to activate the mechanisms of protection from senescence and stress of DNA, including the activation of several signaling pathways such as Shh (Sonic hedgehog), Wnt/β-catenin, Bmi-1 (B lymphoma Mo-MLV insertion region 1 homolog) the expression of Bcl-2 anti-apoptotic and the increased capacity of the repair of DNA damage [103-108]. The SP are characterized by high expression of stem cell markers and low levels of differentiation markers, high expression of genes that are part of some of the signal transduction pathways such as the Wnt/β-catenin [109] and of genes involved in regulation of cell cycle [110]. Compared with other stem cells, the SP are small, even smaller than those from non SP [111,112] and have endoplasmic reticulums with ribosomes which indicates a lack of metabolic activity [113]. The SP are generated in the embryo, and, persist in specific niches, where they can remain mitotically quiescent for long periods of time maintaining the capacity for self-renewal,symmetric division and the ability to rapidly produce progenitors for asymmetric division [114]. The microenvironment surrounding stem cells contribute to a number of functions, such as, physical anchorage for stem cells as well as cell-cell communiation mediated by direct contact and/or indirect extracellular factors. In as such, Wnt ligands are secreted by both stem cells and niche cells, BMPs are released from the cells and niche Shh epithelial cells, which interact between neighboring cells through the Notch signal transmembrane. This microenvironment also provides signaling through the cellular receptor integrin [115] and its co-expression with CD133 (prominin-1) in basal cell lysophospholipids [116] as well as through signaling mediated by metalloproteinases [117]. The identification and characterization of SP cells will further aid in our understanding of normal human

endometrial regenerative cyclic processes and the pathophysiology of human endometrial proliferative diseases, including endometriosis, endometrial hyperplasia and cancer [118,119].

Mesenchymal stem cells from bone marrow: Mesenchymal stem cells (MSC) are multipotent stromal cells which have the ability to differentiate into a variety of specialized cell types. Cells derived from bone marrow, known as bone marrow stromal cells (BMSC) have been used in a number of studies. It has been hypothesized that endometrial stem cells may originate from mesenchymal stem cells of the bone marrow. Stem cells derived from bone marrow are able to differentiate into hematopoietic cells and contribute to the maintenance of different tissues; cells of the bone marrow donor-derived have been identified in the uterine human endometrium [120]. In fact, $CD45^+$ hematopoietic progenitor cells colonize within the epithelial layer of the uterus, and. during pregnancy over 80 % of epithelial cells are derived from these cells [121]. In addition, in intravenous transplantation of bone marrow stem cells, the epithelial (0.02÷48 %) and stromal (0.03÷52 %) compartments arose from the donor [122]. Furthermore, endometrial regenerative cells (ERC) compared to BMSC cells are similar but not identical in regards to, their morphology, the production of cytokines, the inhibition of mixed leukocyte reactions, the expression micro RNA (miRNA) and global gene expression. However, ERC are affected by over-expression of gene immune path, whilst BMSC are affected by over-expression of gene path stem/tumor; ERC also show greater inhibition of proliferation [123]. In other studies, ERC have been isolated from menstrual blood, which are distinct from the MSC as they do not express the BMSC marker STRO-1 (cell surface protein expressed by bone marrow stromal cells and erythroid precursors) [124,125]. It is not known whether the transplanted cells retain all the characteristics of stem cells, and whether they behave like those for the physiological endometrial cyclicity; the

mechanism of physiological recruitment of stem cells from the bone marrow into the uterus is not clear.

Stem cell niche: In adults, stem cells reside in a physiologically limited and specialized microenvironment, called a niche, which supports stem cells but changes in nature and position according to the type of fabric [126,127]. The niche is a collection of cells in a specific anatomic location which together aid in the maintainance (number, proliferation and fate) of stem cells via secretion of extrinsic factors [128-130]. The morphological configuration of the dimensional niche can define the number of stem cells within a tissue. The asymmetric cell division of stem cells allows the self-renewal and differentiation of the cell produced by providing a simple method for tissue homeostasis; divisions are dependent on cell polarity within the cell and are influenced by cell niche. Most of the asymmetric divisions determine a stem cell, and a cell differentiation in which the daughter cell is placed outside of the niche. The self-preservation given to the daughter cell allows it to keep features such as stem cell proliferation and maintenance of undifferentiated state [131]. The ability of cells to divide asymmetrically to produce 2 different cell types provides the cellular diversity proper to each multicellular organism. The asymmetric localization of cell-cell junctions and/or the intrinsic cells is crucial to the fate and position within the niche and is used to specify cell polarity and asymmetric divisions that determine the polarity of the cell fate; the asymmetric divisions are directly regulated by genes that control the process of division and determine different fates for the two daughter cells [132]. The molecular signaling Shh, BMP, FGF and Notch are implicated in the control of stem-cell self-renewal and regulation of the fate of the lineage in different systems [128-130]. Reactive oxygen species (ROS), a natural byproduct of metabolism of oxygen plays an important role homeostastis. However, during stress, the levels of ROS increases as well as the number of free radicals, such as, superoxide

radical anion, hydrogen peroxide and hydroxyl radical, which cause DNA damage. The levels of intracellular ROS plays a crucial role in the control of self-renewal capacity of stem cells in the long term as they may involve signaling of JNK (c-Jun N-terminal kinases) and FoxO (trigger for apoptosis through up-regulation of genes) and sub-regulation of Polycomb (protein Able to remodel chromatin and Hox gene silencing) [133].

Marking of endometrial cells

The phenotype of SP cells is similar to that of adult stem cells and is detected with fluoro-cytometric analysis using Hoechst 33342 dye (H33342 Bisbenzimide trihydrochloride), through the expression of ABC transporters, Brand gene expression Bcrp1 (ABCG2) that characterizes the phenotype of SP [134]. It was shown that the upper fraction is composed mainly of epithelial cells while the lower fraction contains both the epithelial and stromal cells; populations expressing epithelial $CD9^+$ and E-cadherin while the portion stromal express $CD13^+$ demonstrated the presence of endometrial progenitor stem cells [135]. Cunha GR et al. obtained the differentiation of hEmSC into mesodermal cells; the line of hESCs with genetic characterization of Forkhead protein- green fluorescent protein that regulates cell regionalization, placed under the control of MIXL1 (Mix paired-like), homeobox protein that acts as a transcription factor for the regulation of cell fate, demonstrating that FRT (female reproductive tract) arises from embryonic bodies characterized by $MIXL^+$; have also observed the expression of Hoxa-10 and Pax2 during development of hESCs epithelial FRT [136]. The use of cell surface markers was used for the isolation of endodermal progeny of hESCs. SOX17, FOXA1, FOXA2, HNF1β, HNF4α, KITL, SHH and HB9 were used as markers expressed in cells $CD49e^+$ $CD141^+$ $CD238^+$;

OCT4, NANOG, and MEOX1 SOX7 were used to mark the pluripotency expressed in cells CD49e-/low CD141-CD238 [137].

Consequences and discussion

John A Sampson, publication in 1921, reported observations in 14 patients with cysts in that the coating was similar to that in hematomas in the uterine lining with both having content similar to the phase of the menstrual cycle [138]; whilst the study of 1927, of 293 cases in a period of 5 years, presented at the "American Gynecological Society", adopted the theory of retrograde menstruation as the aetiopathology of endometriosis [139]. The problem-related histogenesis of endometriosis does not accept or reject the theory of Sampson JA, but provided a direction for research. The basic question is why retrograde menstruation is a physiological process that affects 90 % of women and endometriosis occurs only in 10 % of cases? How do we explain the endometriotic foci away from the pelvis? How are we to explain the cases of endometriosis in male patients? The theory of endometriosis, such as endometrial cells from functional retrograde menstruation, since its formulation, has shown gaps. Endometriotic lesions are detectable at a pathological stage, and it is extremely rare to be able to detect microscopically the phases of attachment and proliferation of endometrial tissue in the peritoneum [96]. Numerous studies have attempted with rigorous methods, to give answers as to why the eutopic plant develops resistance to the elimination by the immune system, demonstrating the altered function of macrophages and natural killer cells: that in the early stages of the disease there is a prevalence of pro-inflammatory cytokines (Th1 profile), whilst in late stages this changes to a Th2 profile [140]; that alterations of immune peritoneal exert an immunosuppressive effect on the activity of phagocytic and cytotoxic immune cells infiltrating the endometrial tissue, promoting immunoescaping, survival and growth of

endometrial cells [141-144]. Therapeutic strategies can be improved through the use of non-steroidal anti-inflammatory drugs [145], combination oral contraceptives [146,147], progestin [148], selective progesterone receptor modulators [149], GnRH agonists [150], and, aromatase inhibitors [151,152]. Ultimately we are able to demonstrate the pathophysiological mechanisms that allow grafting of endometriotic cells and the inhibition of the physiological processes of cytolysis, but the origin of these cells remains unknown. In 1987, Redwine and colleagues examined peritoneal biopsies of the cul-de-sac of female infants who died from SIDS, reported a case with well-defined structure glandular epithelium surrounded by stroma [74]. Fujii S in 1991, suggested that the tissues derived from epithelial and mesenchymal cells coelomatic accompaniment, called "Secondary Müllerian System" have the potential to differentiate into epithelium and stroma, metaplastic, and that this potential is a basic concept in the pathogenesis endometriosis [153]. Batt RE et al. in 2007, concluded that the presence of endometrium and endocervix endosalpinx, which supports the hypothesis of müllerian remnants generated from the genital ridge leaked during organogenesis [72]. Master PG et al. in 2012, investigated fetal autopsies and noted the presence of ectopic endometrium, assuming that one possible cause of endometriosis was the dislocation of primitive endometrial tissue outside the uterine cavity during organogenesis [76]. Bouquet de Jolinière J et al. in 2012, demonstrated that reproductive organs derived from autopsies of female fetuses (via immunohistochemical analysis) were identified ectopic, and, concluded that endometriosis may develop from misplaced endometrial glands and/or residues of embryonic cells [154]. hESCs, identified in the basal layer of the endometrium, appear to possess the phenotype that contains all the characteristics of self-renewal and differentiation that occurs in the context of the niche in which they exist, or in those in which they migrate. hESCs possess a potential immunomodulatory triggered by hypoxic stimuli, proteolytic, inflammatory, in order to induce angiogenesis, intercellular communication, migration, and capacity to

differentiate into cells of the same lineage (Fig. 1, Fig. 2) [155]. It was also hypothesized that the hESCs may have originated from mesenchymal stem cells of the bone marrow; studies on the expression of miRNA and global gene expression, showed that they could be considered similar but not identical, and that the endometrial regenerative cells were affected by over-expression of gene immune path, whilst bone marrow stromal were characterized by over-expression of gene path stem/tumor. In addition, the regenerative cells showed a greater inhibition of endometrial proliferation (Fig. 1, Fig. 2) [123]. It has not been demonstrated whether the transplanted cells retain the characteristics of stem cell, if they behave as physiological ones for endometrial cyclicity, but, above all, mechanism of physiological recruitment in the uterus has not been shown. Moreover, Delbandi and colleagues evaluated characteristics of the cells and ectopic endometrial stromal eutopics in women with respect to controls eutopics of healthy women and noted that ectopic endometrial stem cells differ from eutopics, with a greater capacity for proliferation, greater adhesion to the extracellular matrix, increased invasiveness and higher levels of pro-inflammatory cytokines, IL-6 and IL-8 [156]. The Hox genes control cell fate and segmental embryonic patterning along the antero-posterior axis of the embryo [29] in cooperation with specific cofactors and in particular, through the Notch signaling pathway, determining positional identity and the activities of the genetic cascade of somitogenesis [157]. The morphogenetic processes axial extension, the segmentation of the mesoderm and anterior-posterior patterning are regulated by the interaction between Hox genes and Wnt: while Wnt, RA and FGF regulate the axial extension and the identity of the anterior-posterior patterning, Hox, Cdx (paraHox genes) and Notch are involved in the segmentation of the mesoderm [158]. PBX and MEIS contribute to modulate the binding to DNA for the control of the expression of target genes and Pbx1, in particular, is widely expressed in mesenchymal tissues during the differentiation of the urogenital organs [38-40]. Wnt7 has been shown to be involved in the maintenance of the genes HoxA10 and

11, and Wnt5 in the development of the genital anterior-posterior axis [54,55]. Three members of the family Wnt (Wnt4, Wnt5a and Wnt7a) have proved to be fundamental for uterine development: inactivation of Wnt4 causes sex reversal; Wnt7 causes inactivation of stratified epithelium, stroma and the absence of thin gland; inactivation of Wnt5 inhibits the development of the correct anatomy of the uterus [119]. In the presence of defects of adjustment, on the part of the genes responsible, during organogenesis differentiation of the urogenital tract and/or the migration of the cells may be aberrant or incomplete, and any cells with aberrant gene expression during the migratory path may implant themselves in the anomalous [73]. Tissues derived from the epithelium and mesenchymal cells accompanying coelomatic have the potential to differentiate directly into epithelium and stroma and [67]. Hoang Ngoc and colleagues studied embryonic finds, and came to the conclusion that the myometrium is derived from the primitive mesenchyme, and the endometrium is derived from mesoltelio coelomatic [159]. The signaling pathway of canonical Wnt, the Wnt/β-catenin, is implicated in the control of various types of stem cells and can act as a factor to maintain the niche hESP in a state of self-renewal [64-67]. Targeted research on the coelomic cavity and the müllerian duct epithelium suggest that coelomatic and associated tissues, epithelia adults and müllerian derivatives have a common embryological origin, and that pluripotent cells can cause endometrial metaplasia or endometriosis in post pubertal stage [73]. The estrogenic activity active peritoneal macrophages with consequent induction of pro-inflammatory cytokines TNF-α and IL-1β which, in their turn, activate the binding to DNA through the transcription factors of NFκB; through inflammatory cytokines IL-6 and IL-8, induces the expression of VEGF that activates the vasculature endothelial cell, while MIF induces cell mitosis endometrial, and survival is supported by the activation of anti-apoptotic gene Bcl-2, from the degradation of the extracellular matrix by MMPs and the entry phone via ICAM and VCAM (Fig. 1, Fig. 2) [160].

Conclusion

It is ncessary to understand the biological and genetic mechanisms that regulate the differentiation of the urogenital tract during the phase of embryonic organogenesis, in the period of completion of development of the urogenital tract, and in post-puberty. It is important to study the signaling pathways of Hox genes and cofactors Pbx and Meis genes and Wnt signaling pathway Wnt/β-catenin. It is necessary to deepen the knowledge on embryonic stem cells, niches and the functioning of the regulatory mechanisms of the states of quiscenze, self-renewal, proliferation and functional specialization. The research on immuno-phenotype, proliferation capacity, invasiveness and adhesion to the extracellular matrix of the endometrial stem cells (hESCs) eutopic and ectopic should be implemented. The study of the causal mechanisms of endometriosis involves in-depth knowledge of embryology, genetics, biology, histology, immunology and specific expertise in medical research with multidisciplinary teams which together, will lead to understanding our hypothesis and etiology of endometriosis..

References

[1] Vinatier D, Dufour P, Leroy JL. The mechanisms of endometriosis. Rev Prat. 1999; 49(3):254-7.

[2] Uğur M, Turan C, Mungan T, Kuşçu E, Senöz S, Ağiş HT, Gökmen O. Endometriosis in association with müllerian anomalies. Gynecol Obstet Invest. 1995;40(4):261-4.

[3] Guo SW. Epigenetics of endometriosis. Mol Hum Reprod. 2009;15(10):587-607.

[4] Eskenazi B, Warner ML. Epidemiology of endometriosis. Obstet Gynecol Clin North Am. 1997; 24(2):235-58.

[5] Buck Louis GM, Hediger ML, Peterson CM, Croughan M, Sundaram R, Stanford J, Chen Z, Fujimoto VY, Varner MW, Trumble A, Giudice LC; ENDO Study Working Group. Incidence of endometriosis by study population and diagnostic method: the ENDO study. Fertil Steril. 2011; 96(2):360-5.

[6] Westney OL, Amundsen CL, McGuire EJ, Bladder endometriosis: conservative management, J Urol, 2000; 163(6):1814-1817.

[7] Traşcă ET, Traşcă E, Tiţu A, Riza ML, Busuioc I. Ureteral stenosis due to endometriosis. Rom J Morphol Embryol. 2012;53(2):433-7.

[8] Shook TE, Nyberg LM, Endometriosis of the urinary tract, Urology, 1988; 31(1):1-6.

[9] Sinder C, Dochat GR, Wentsler NE, Splenoendometriosis, Am J Obstet Gynecol, 1965; 92:883-884.

[10] Saadat-Gilani K, Bechmann L, Frilling A, Gerken G, Canbay A, Gallbladder endometriosis as a cause of occult bleeding, World J Gastroenterol, 2007; 13(33):4517-4519.

[11] Kyamidis K, Lora V, Kanitakis J, Spontaneous cutaneous umbilical endometriosis: report of a new case with immunohistochemical study and literature review, Dermatol Online J, 2011; 17(7):5.

[12] Thibodeau LL, Prioleau RG, et al. "Cerebral endometriosis." Journal of neurosurgery 1987; 66(4):609-610.

[13] Seli E, Berkkanoglu M, Arici A. Pathogenesis of endometriosis. Obstet Gynecol Clin North Am. 2003; 30(1):41-61.

[14] Ebert AD, Fuhr N, David M, Schneppel L, Papadopoulos T: Histological confirmation of endometriosis in a 9-year-old girl suffering from unexplained cyclic pelvic pain since her eighth year of life. Gynecol Obstet Invest 2009; 67:158.

[15] Martin Jr JD, Hauck AE. Endometriosis in the male. Am Surg. 1985; 51 (7):426-30.

[16] Pinkert TC, Catlow CE, Straus R. Endometriosis of the urinary bladder in a man with prostatic carcinoma. Cancer. 1979; 43(4):1562-7.

[17] Schrodt GR, Alcorn MO, Ibanez J. Endometriosis of the male urinary system: a case report. J Urol. 1980; 124 (5):722-3.

[18] Giannarini G, Scott CA, Moro M, Grossetti B, Pomara G, Selli C. Cystic endometriosis of the epididymis. Urology. 2006;68 (1):203.e1-3.

[19] Fukunaga M. Paratesticular endometriosis in a man with a prolonged hormonal therapy for prostatic carcinoma. Pathol Res Pract. 2012; 208(1):59-61.

[20] Simsek G, Bulus H, Tas A, Koklu S, Yilmaz BS, Coskun A. An Unusual Cause of Inguinal Hernia in a Male Patient: Endometriosis. Gut and Liver 2012; 6(2):284-285.

[21] Orvis GD, Behringer RR. Cellular mechanisms of Mullerian duct formation in the mouse. Dev Biol. 2007; 306:493-504.

[22] Funayama N, Sato Y, Matsumoto K, Ogura T, Takahashi Y. Coelom formation: binary decision of the lateral plate mesoderm is controlled by the ectoderm. Development 1999; 126:4129-4138.

[23] Ye L, Mayberry R, Lo CY, Britt KL, Stanley EG, et al. Generation of Human Female Reproductive Tract Epithelium from Human Embryonic Stem Cells. PLoS ONE 2011; 6(6): e21136.

[24] Schatten G, Spencer TE, Hayashi K, Hu J, Carpenter KD. Comparative developmental biology of the mammalian uterus. Burlington, MA: Elsevier;2005: 85-122.

[25] Gray CA, Bartol FF, Tarleton BJ, Wiley AA, Johnson GA, Bazer FW, Spencer TE. Developmental biology of uterine glands. Biol Reprod 2001; 65:1311-1323.

[26] Bartol FF, Wiley AA, Floyd JG, Ott TL, Bazer FW, Gray CA, Spencer TE. Uterine differentiation as a foundation for subsequent fertility. J Reprod Fertil Suppl 1999;54: 287-302.

[27] Bartol FF, Wiley AA, Spencer TE, Vallet JL, Christenson RK. Early uterine development in pigs. J Reprod Fertil Suppl 1993; 48:99-116.

[28] Burel A, Mouchel T, Odent S, Tiker F, Knebelmann B, Pellerin I, Guerrier D. Role of HOXA7 to HOXA13 and PBX1 genes in various forms of MRKH syndrome (congenital absence of uterus and vagina). J Negat Results Biomed 2006; 5:4.

[29] LaRonde-LeBlanc NA, Wolberger C. Structure of HoxA9 and Pbx1 bound to DNA: Hox hexapeptide and DNA recognition anterior to posterior. Genes Dev. 2003; 15;17(16):2060-72.

[30] McGinnis W, Krumlauf R: Homeobox genes and axial patterning. Cell 1992; 68:283-302.

[31] Burglin TR. Analysis of TALE superclass homeobox genes (MEIS, PBC, KNOX, Iroquois, TGIF) reveals a novel domain conserved between plants and animals. Nucleic Acids Res 1997; 25:4173-4180.

[32] Berthelsen J, Kilstrup-Nielsen C, Blasi F, Mavilio F, Zappavigna V. The subcellular localization of PBX1 and EXD proteins depends on nuclear import and export signals and is modulated by association with PREP1 and HTH. Genes Dev 1999; 13:946-953.

[33] Shen WF, Rozenfeld S, Kwong A, Kom ves LG, Lawrence HJ, Largman C. HOXA9 forms triple complexes with PBX2 and MEIS1 in myeloid cells. Mol. Cell. Biol. 1999; 19:3051-3061.

[34] Shen WF, Montgomery JC, Rozenfeld D, Moskow JJ, Lawrence HJ, Buchberg AM, Largman C. AbdB-like Hox proteins stabilize DNA binding by the Meis1 homeodomain proteins. Mol. Cell. Biol. 1997; 17:6448-6458

[35] Capellini TD, Zewdu R, Di Giacomo G, Asciutti S, Kugler JE, Di Gregorio A, Selleri L. Pbx1/Pbx2 govern axial skeletal development by controlling Polycomb and Hox in mesoderm and Pax1/Pax9 in sclerotome. Dev Biol. 2008; 321(2):500-14.

[36] Ferretti E, Schulz H, Talarico D, Blasi F, Berthelsen J. The PBX-regulating protein PREP1 is present in different PBX-complexed forms in mouse. Mech Dev 1999; 83:53-64.

[37] Selleri L, Depew MJ, Jacobs Y, Chanda SK, Tsang KY, Cheah KS, Rubenstein JL, O'Gorman S, Cleary ML. Requirement for Pbx1 in skeletal patterning and programming chondrocyte proliferation and differentiation. Development 2001; 128:3543-3557.

[38] Schnabel CA, Godin RE, Cleary ML. Pbx1 regulates nephrogenesis and ureteric branching in the developing kidney. Dev Biol 2003; 254:262-276.

[39] Schnabel CA, Selleri L, Cleary ML. Pbx1 is essential for adrenal development and urogenital differentiation. Genesis 2003; 37:123-130.

[40] Schnabel CA, Selleri L, Jacobs Y, Warnke R, Cleary ML. Expression of Pbx1b during mammalian organogenesis. Mech Dev 2001; 100:131-135.

[41] Marshall H, Nonchev S, Sham MH, Muchamore I, Lumsden A, Krumlauf R. Retinoic acid alters hindbrain Hox code and induces transformation of rhombomeres 2/3 into a 4/5 identity. Nature 1992; 360:737-741.

[42] Dubrulle J, McGrew MJ, Pourquie O. FGF signaling controls somite boundary position and regulates segmentation clock control of spatiotemporal Hox gene activation. Cell 2001; 106:219-232.

[43] Miller C, Pavlova A, Sassoon DA. Differential expression patterns of Wnt genes in the murine female reproductive tract during development and the estrous cycle. Mech Dev 1998, 76:91-99.

[44] Gould A, Morrison A, Sproat G, White RA, Krumlauf R. Positive cross-regulation and enhancer sharing: two mechanisms for specifying overlapping Hox expression patterns. Genes Dev 1997; 11:900-913.

[45] Nonchev S, Maconochie M, Gould A, Morrison A, Krumlauf R. Cross-regulatory interactions between Hox genes and the control of segmental expression in the vertebrate central nervous system. Cold Spring Harb Symp Quant Biol. 1997; 62:313-23.

[46] Hooiveld MH, Morgan R, in der Rieden P, Houtzager E, Pannese M, Damen K, Boncinelli E, Durston AJ. Novel interactions between vertebrate Hox genes. Int J Dev Biol 1999; 43:665-674.

[47] Sham MH, Hunt P, Nonchev S, Papalopulu N, Graham A, Boncinelli E, Krumlauf R. Analysis of the murine Hox-2.7 gene: conserved alternative transcripts with differential distributions in the nervous system and the potential for shared regulatory regions. EMBO J. 1992;11(5):1825-36.

[48] Benson GV, Nguyen TH, Maas RL. The expression pattern of the murine Hoxa-10 gene and the sequence recognition of its homeodomain reveal specific properties of Abdominal Blike genes. Mol Cell Biol 1995; 15:1591-1601.

[49] Cunha GR. Stromal induction and specification of morphogenesis and cytodifferentiation of the epithelia of the Mullerian ducts and urogenital sinus during development of the uterus and vagina in mice. J Exp Zool 1996; 196:361-370.

[50] Taylor HS, Vanden Heuvel GB, Igarashi P. A conserved Hox axis in the mouse and human female reproductive system: late establishment and persistent adult expression of the Hoxa cluster genes. Biol Reprod 1997; 57:1338-1345.

[51] Branford WW, Benson GV, Ma L, Maas RL, Potter SS. Characterization of Hoxa-10/Hoxa-11 transheterozygotes reveals functional redundancy and regulatory interactions. Dev Biol 2000; 224: 373-387.

[52] Warot X, Fromental-Ramain C, Fraulob V, Chambon P, Dollé P. Gene dosage-dependent effects of the Hoxa-13 and Hoxd-13 mutations on morphogenesis of the terminal parts of the digestive and urogenital tracts. Development 1997; 124:4781-4791.

[53] Vainio S, Heikkila M, Kispert A, Chin N, McMahon A P. Female development in mammals is regulated by Wnt-4 signalling. Nature 1999; 397,405-409.

[54] Miller C, Sassoon DA. Wnt-7a maintains appropriate uterine patterning during the development of the mouse female reproductive tract. Development 1998; 125:3201-3211.

[55] Mericskay M, Kitajewski J, Sassoon D. Wnt5a is required for proper epithelial-mesenchymal interactions in the uterus. Development 2004; 131:2061-2072.

[56] Hayashi K, Yoshioka S, Reardon SN, Rucker EB 3rd, Spencer TE, DeMayo FJ, Lydon JP, MacLean JA 2nd. WNTs in the neonatal mouse uterus: potential regulation of endometrial gland development. Biol Reprod. 2011; 84(2):308-19.

[57] Jeong JW, Lee HS, Franco HL, Broaddus RR, Taketo MM, Tsai SY, Lydon JP, DeMayo FJ. Betacatenin mediates glandular formation and dysregulation of beta-catenin induces hyperplasia formation in the murine uterus. Oncogene 2009; 28:31-40.

[58] Dunlap KA, Filant J, Hayashi K, Rucker EB 3rd, Song G, Deng JM, Behringer RR, DeMayo FJ, Lydon J, Jeong JW, Spencer TE. Postnatal deletion of Wnt7a inhibits uterine gland morphogenesis and compromises adult fertility in mice. Biol Reprod 2011; 85:386-396.

[59] Lee E, Salic A, Krüger R, Heinrich R, Kirschner MW. The roles of APC and Axin derived from experimental and theoretical analysis of the Wnt pathway. PLoS Biol. 2003;1(1):E10.

[60] MacDonald BT, Tamai K, He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. Dev Cell. 2009;17(1):9-26.

[61] Liu C, Li Y, Semenov M, Han C, Baeg GH, Tan Y, Zhang Z, Lin X, He X. Control of beta-catenin phosphorylation/degradation by a dual-kinase mechanism. Cell. 2002;108(6):837-47.

[62] Veeman M.T, Axelrod J D, Moon R T. A second canon. Functions and mechanisms of b-catenin-independent Wnt signaling. Dev. Cell 2003; 5,367-377.

[63] Kuhl M, Sheldahl L C, Park M, Miller J R, Moon R T. The Wnt/Ca2þ pathway: A new vertebrate Wnt signaling pathway takes shape. Trends Genet. 2000; 16,279-283.

[64] Reya T, Clevers H. Wnt signalling in stem cells and cancer. Nature 2000; 434,843-50, ISSN:0028-0836

[65] Valkenburg K, Graveel G, Zylstra-Diegel C, Zhong Z, Williams B. Wnt/β-catenin Signaling in Normal and Cancer Stem Cells. Cancers 2011; 3,2050-2079, ISSN: 2072-6694.

[66] Nusse R. Wnt signaling and stem cell control. Cell Res 2008; 18,523-7, ISSN: 1001-0602.

[67] Fujii S. Secondary müllerian system and endometriosis. Am J Obstet Gynecol. 1991 Jul;165(1):219-25.

[68] Lauchlan SC. The secondary müllerian system revisited. Int J Gynecol Pathol. 1994; 13(1):73-9.

[69] Vinatier D, Dufour P, Leroy JL. The mechanisms of endometriosis. Rev Prat. 1999; 49(3):254-7.

[70] Kaufman Y, Lam A. The pelvic uterus-like mass--a primary or secondary Müllerian system anomaly? J Minim Invasive Gynecol. 2008; 15(4):494-7.

[71] Mueller F, Kuehn K, Neudeck H, Siedentopf N, Ulrich U. Disseminated peritoneal leiomyomatosis with endometriosis. J Minim Invasive Gynecol. 2012; 19(3):380-2.

[72] Batt RE, Smith RA, Buck Louis GM, Martin DC, Chapron C, Koninckx PR, Yeh J. Müllerianosis. Histol Histopathol. 2007; 22(10):1161-6.

[73] Suginami H. A reappraisal of the coelomic metaplasia theory by reviewing endometriosis occurring in unusual sites and instances. Am J Obstet Gynecol. 1991; 165(1):214-8.

[74] Redwine DB. The distribution of endometriosis in the pelvis by age groups and fertility. Fertil Steril 1987; 47:173.

[75] Signorile PG, Baldi F, Bussani R, D'Armiento M, De Falco M, Baldi A. Ectopic endometrium in human foetuses is a common event and sustains the theory of müllerianosis in the pathogenesis of endometriosis, a disease that predisposes to cancer. J Exp Clin Cancer Res. 2009; 28:49.

[76] Signorile PG, Baldia A. Endometriosis: New concepts in the pathogenesis The International Journal of Biochemistry & Cell Biology 2010; 42:778-780

[77] Acién P, Bataller A, Fernández M, Acién MI, Rodríguez JM, Mayol MJ. New cases of accessory and cavitated uterine masses (ACUM): a significant cause of severe dysmenorrhea and recurrent pelvic pain in young women. Hum Reprod. 2012; 27(3):683-694.

[78] Acién P, Acién M, Fernández F, Mayol MJ, Aranda I. The cavitated accessory uterine mass. A Mullerian anomaly in women with an otherwise normal uterus. Obstet Gynecol 2010; 116:1101-1109.

[79] Acién P, Sánchez del Campo F, Mayol MJ, Acién M. The female gubernaculum: role in the embryology and development of the genital tract and in the possible genesis of malformations. Eur J Obstet Gynecol Reprod Biol 2011; 159:426-432.

[80] Acién P, Acién MI. The history of female genital tract malformation classifications and proposal of an updated system. Hum Reprod Update 2011; 17:693-705.

[81] Harley CB. Telomere loss: mitotic clock or genetic time bomb? Mutat Res. 1991;256(2-6):271-82.

[82] Bodnar AG, Ouellette M, Frolkis M, Holt SE, Chiu CP, Morin GB, Harley CB, Shay JW, Lichtsteiner S, Wright WE. Extension of life-span by introduction of telomerase into normal human cells. Science. 1998;279(5349):349-52.

[83] Gan Q, Yoshida T, McDonald OG, Owens GK. Concise review: Epigenetic mechanisms contribute to pluripotency and cell lineage determination of embryonic stem cells. Stem Cells. 2007; 25: 2-9.

[84] Lagarkova MA, Volchkov PY, Lyakisheva AV, Philonenko ES, Kiselev SL. Diverse epigenetic profile of novel human embryonic stem cell lines. Cell Cycle. 2006; 5: 416-20.

[85] D'Amour KA, Bang AG, Eliazer S, Kelly OG, Agulnick AD, Smart NG, Moorman MA, Kroon E, Carpenter MK, Baetge EE. Production of pancreatic hormone-expressing endocrine cells from human embryonic stem cells. Nat Biotechnol. 2006; 24:1392-401.

[86] Evseenko D, Zhu Y, Schenke-Layland K, Kuo J, Latour B, Ge S, Scholes J, Dravid G, Li X, MacLellan WR, Crooks GM. Mapping the first stages of mesoderm commitment during differentiation of human embryonic stem cells. Proc Natl Acad Sci U S A. 2010; 107: 13742-7.

[87] Maruyama T, Masuda H, Ono M, Kajitani T, Yoshimura Y. Human uterine stem/progenitor cells: their possible role in uterine physiology and pathology. Reproduction. 2010;140(1):11-22.

[88] Cervelló I, Gil-Sanchis C, Mas A, Delgado-Rosas F, Martínez-Conejero JA, Galán A, Martínez-Romero A, Martínez S, Navarro I, Ferro J, Horcajadas JA, Esteban FJ, O'Connor JE, Pellicer A, Simón C. Human endometrial side population cells exhibit genotypic, phenotypic and functional features of somatic stem cells. PLoS One. 2010; 5(6):e10964.

[89] Bratincsák A, Brownstein MJ, Cassiani-Ingoni R, Pastorino S, Szalayova I, Tóth ZE, Key S, Németh K, Pickel J, Mezey E. CD45-positive blood cells give rise to uterine epithelial cells in mice. Stem Cells. 2007; 25(11):2820-6.

[90] Masuda H, Matsuzaki Y, Hiratsu E, Ono M, Nagashima T, Kajitani T, Arase T, Oda H, Uchida H, Asada H, Ito M, Yoshimura Y, Maruyama T, Okano H. Stem cell-like properties of the endometrial side population: implication in endometrial regeneration. PLoS One. 2010; 5(4):e10387.

[91] Tsuji S, Yoshimoto M, Takahashi K, Noda Y, Nakahata T, Heike T. Side population cells contribute to the genesis of human endometrium. Fertil Steril. 2008; 90(4 Suppl):1528-37.

[92] Schwab KE, Chan RW, Gargett CE. Putative stem cell activity of human endometrial epithelial and stromal cells during the menstrual cycle. Fertil Steril. 2005; 84 Suppl 2:1124-30.

[93] Ikoma T, Kyo S, Maida Y, Ozaki S, Takakura M, Nakao S, Inoue M. Bone marrow-derived cells from male donors can compose endometrial glands in female transplant recipients. Am J Obstet Gynecol. 2009; 201(6):608.e1-8.

[94] Taylor HS. Endometrial cells derived from donor stem cells in bone marrow transplant recipients. JAMA. 2004; 292(1):81-5.

[95] Gargett CE, Masuda H. Adult stem cells in the endometrium. Mol Hum Reprod. 2010; 16(11):818-34.

[96] Redwine DB. Was Sampson wrong? Fertil Steril. 2002;78(4):686-93.

[97] Wu Y, Basir Z, Kajdacsy-Balla A, Strawn E, Macias V, Montgomery K, Guo SW. Resolution of clonal origins for endometriotic lesions using laser capture microdissection and the human androgen receptor (HUMARA) assay. Fertil Steril. 2003;79 Suppl 1:710-7.

[98] Nabeshima H, Murakami T, Yoshinaga K, Sato K, Terada Y, Okamura K. Analysis of the clonality of ectopic glands in peritoneal endometriosis using laser microdissection. Fertil Steril. 2003; 80(5):1144-50.

[99] Mayr D, Amann G, Siefert C, Diebold J, Anderegg B. Does endometriosis really have premalignant potential? A clonal analysis of laser-microdissected tissue. FASEB J. 2003; 17(6):693-5.

[100] Wang Y, Sacchetti A, van Dijk MR, van der Zee M, van der Horst PH, Joosten R, Burger CW, Grootegoed JA, Blok LJ, Fodde R. Identification of quiescent, stem-like cells in the distal female reproductive tract. PLoS One. 2012; 7(7):e40691.

[101] Gargett CE. Uterine stem cells: what is the evidence? Hum Reprod Update 2007; 13: 87-101.

[102] Ho MM, Ng AV, Lam S and Hung JY: Side population in human lung cancer cell lines and tumors is enriched with stem-like cancer cells. Cancer Res 2007; 67,4827-4833.

[103] Jordan CT. Cancer stem cell biology: from leukemia to solid tumors. Curr Opin Cell Biol 2004; 16: 708-712.

[104] Massard C, Deutsch E, Soria JC. Tumour stem cell-targeted treatment: elimination or differentiation. Ann Oncol 2006; 17:1620-1624

[105] Park IK, Qian D, Clarke MF. Bmi-1 is required for maintenance of adult selfrenewing haematopoietic stem cells. Nature 2003; 423:302-305.

[106] Liu S, Dontu G, Mantle ID, et al. Hedgehog signaling and Bmi-1 regulate self-renewal of normal and malignant human mammary stem cells. Cancer Res. 2006; 66:6063-6071.

[107] Brown JM, Wilson G. Apoptosis genes and resistance to cancer therapy: what does the experimental and clinical data tell us? Cancer Biol Ther 2003; 2: 477-490.

[108] Bao S, Wu Q, McLendon RE, Hao Y, Shi Q, Hjelmeland AB, et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature. 2006; 444(7120):756-60.

[109] Reya T. Regulation of hematopoietic stem cell self-renewal. Recent Prog Horm Res. 2003; 58:283-95.

[110] Wu C and Alman BA: Side Population cells in human cancers. Cancer Letters 2008; Vol. 268, 1-9.

[111] Benchaouir R, Rameau P, Decraene C, Dreyfus P, Israeli D, Pietu G, Danos O, Garcia L. Evidence for a resident subset of cells with SP phenotype in the C2C12 myogenic line: a tool to explore muscle stem cell biology. Exp Cell Res 2004; 294, 254-268.

[112] Paiva CS, Pflugfelder SC, Li DQ. Cell size correlates with phenotype and proliferative capacity in human corneal epithelial cells. Stem Cells 2006; Vol. 24, 368-375.

[113] Hirschmann-Jax C, Foster AE, Wulf GG, Nuchtern JG, Jax TW, Gobel U, Goodell MA, Brenner MK. A distinct “side population” of cells with high drug efflux capacity in human tumor cells. Proc Natl Acad Sci USA 2004; 101,14228-14233.

[114] Martinez-Agosto JA, Mikkola HK, Hartenstein V, Banerjee U. The hematopoietic stem cell and its niche: a comparative view. Genes Dev. 2007; 21(23):3044-60.

[115] Collins AT, Berry PA, Hyde C, Stower MJ, Maitland NJ. Prospective identification of tumorigenic prostate cancer stem cells. Cancer Res 2005; 65, 10946-10951.

[116] Yu Y, Flint A, Dvorin EL, Bischoff J. AC133-2, a novel isoform of human AC133 stem cell antigen. J Biol Chem 2002; 277,20711-20716.

[117] Annabi B, Lachambre MP, Plouffe K, Sartelet H, Béliveau R. Modulation of invasive properties of CD133(+) glioblastoma stem cells: a role for MT1-MMP in bioactive lysophospholipid signaling. Mol Carcinog 2009; 48,910-919.

[118] Gargett CE, Chan RW, Schwab KE. Hormone and growth factor signaling in endometrial renewal: role of stem/progenitor cells. Mol Cell Endocrinol 2008; 288: 22-29.

[119] Hubbard SA, Gargett CE. A cancer stem cell origin for human endometrial carcinoma? Reproduction 2010; 140:23-32.

[120] Du H, Taylor HS. Contribution of bone marrow-derived stem cells to endometrium and endometriosis. Stem Cells. 2007; 25:2082–2086.

[121] Bratincsak A, Brownstein MJ, Cassiani-Ingoni R, Pastorino S, Szalayova I, Toth ZE, Key S, Nemeth K, Pickel J, Mezey E. CD45-positive blood cells give rise to uterine epithelial cells in mice. Stem Cells. 2007; 25:2820–2826.

[122] Taylor HS. Endometrial cells derived from donor stem cells in bone marrow transplant recipients. Jama. 2004;292:81–85.

[123] Wang H, Jin P, Sabatino M, Ren J, Civini S, Bogin V, Ichim TE, Stroncek DF. Comparison of endometrial regenerative cells and bone marrow stromal cells. J Transl Med. 2012; 10:207.

[124] Meng X, Ichim TE, Zhong J, Rogers A, Yin Z, Jackson J, Wang H, Ge W, Bogin V, Chan KW, Thebaud B, Riordan NH. Endometrial regenerative cells: a novel stem cell population. J Transl Med 2007; 5:57.

[125] Murphy MP, Wang H, Patel AN, Kambhampati S, Angle N, Chan K, Marleau AM, Pyszniak A, Carrier E, Ichim TE, Riordan NH. Allogeneic endometrial regenerative cells: an "Off the shelf solution" for critical limb ischemia? J Transl Med 2008; 6:45.

[126] Schofield R. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. Blood Cells. 1978;4(1-2):7-25.

[127] Li L, Xie T. Stem cell niche: structure and function. Annu Rev Cell Dev Biol. 2005;21:605-31.

[128] Spradling A, Drummond-Barbosa D, Kai T. Stem cells find their niche. Nature. 2001;414(6859):98-104.

[129] Lin H. The stem-cell niche theory: lessons from flies. Nat Rev Genet. 2002 Dec;3(12):931-40.

[130] Tumbar T, Guasch G, Greco V, Blanpain C, Lowry WE, Rendl M, Fuchs E. Defining the epithelial stem cell niche in skin. Science. 2004;303(5656):359-63.

[131] Yamashita YM, Yuan H, Cheng J, Hunt AJ. Polarity in stem cell division: asymmetric stem cell division in tissue homeostasis. Cold Spring Harb Perspect Biol. 2010;2(1):a001313.

[132] Toledano H, Jones DL. Mechanisms regulating stem cell polarity and the specification of asymmetric divisions. StemBook, ed. The Stem Cell Research Community 2009.

[133] Owusu-Ansah E, Banerjee U. Reactive oxygen species prime Drosophila haematopoietic progenitors for differentiation. Nature 2009; 461:537-541.

[134] Kato K, Yoshimoto M, Kato K, Adachi S, Yamayoshi A, Arima T, Asanoma K, Kyo S, Nakahata T, Wake N. Characterization of side-population cells in human normal endometrium. Hum Reprod. 2007; 22(5):1214-23.

[135] Maruyama T, Masuda H, Ono M, Kajitani T, Yoshimura Y. Human uterine stem/progenitor cells: their possible role in uterine physiology and pathology. Reproduction. 2010; 140(1):11-22.

[136] Cunha GR. Epithelial-stromal interactions in development of the urogenital tract. Int Rev Cytol 1976; 47:137-194.

[137] Wang P, Rodriguez RT, Wang J, Ghodasara A, Kim SK. Targeting SOX17 in human embryonic stem cells creates unique strategies for isolating and analyzing developing endoderm. Cell Stem Cell. 201; 8(3):335-46.

[138] Sampson JA. Perforating hemorrhagic (chocolate) cysts of the ovary. Am J Obstet Gynecol 1921; 2:526-528.

[139] Sampson JA. Peritoneal endometriosis due to the menstrual dissemination of endometrial tissue into the peritoneal cavity. Am J Obstet Gynecol 1927; 14:422-469.

[140] Pizzo A, Salmeri FM, Ardita FV, Sofo V, Tripepi M, Marsico S. Behaviour of cytokine levels in serum and peritoneal fluid of women with endometriosis. Gynecol Obstet Invest. 2002; 54(2):82-7.

[141] Sturlese E, Salmeri FM, Retto G, Pizzo A, De Dominici R, Ardita FV, Borrielli I, Licata N, Laganà AS, Sofo V. Dysregulation of the Fas/FasL system in mononuclear cells recovered from peritoneal fluid of women with endometriosis. J Reprod Immunol. 2011; 92(1-2):74-81.

[142] Laganà AS, Salmeri FM, Retto G, Sturlese E, Pizzo A, De Dominici R, Sofo V. Stage-related changes of peritoneal soluble TNFα and TNFR1 and TNFR2 in cells recovered from peritoneal fluid of women with endometriosis. J Reprod Immunol. 2012; 94(1): 94-95.

[143] Laganà AS, D'Ascola A, Salmeri FM, Sofo V, Pizzo A, Retto G, Sturlese E, De Dominici R, Campo S. mRNA expression of Foxp3 and RORc transcription factors and of IL-10 and IL-17A cytokines in ovarian endometrioma of women with endometriosis. Journal of Endometriosis. 2012; 4(4):227-228.

[144] Laganà AS, Pizzo A, D'Ascola A, Salmeri FM, Sofo V, Retto G, Sturlese E, De Dominici R, Borrielli I, Campo S. mRNA expression of transcription factors and cytokines in immune cells of ovarian endometrioma from women with endometriosis. Reproductive Sciences. 2013; 20(3, Supplement):146-147.

[145] Jones SC. Relative thromboembolic risks associated with COX-2 inhibitors. Ann Pharmacother 2005; 39:1249.

[146] Vercellini P, Frontino G, De Giorgi O, Pietropaolo G, Pasin R, Crosignani PG. Continuous use of an oral contraceptive for endometriosis-associated recurrent dysmenorrhea that does not respond to a cyclic pill regimen. Fertil Steril 2003; 80:560.

[147] Wiegratz I, Kuhl H. Long-cycle treatment with oral contraceptives. Drugs 2004; 64:2447.

[149] Petta CA, Ferriani RA, Abrao MS, Hassan D, Rosa E Silva JC, Podgaec S, Bahamondes L. Randomized clinical trial of a levonorgestrel- releasing intrauterine system and a depot GnRH

analogue for the treatment of chronic pelvic pain in women with endometriosis. Hum Reprod 2005; 20:1993.

[149] Chwalisz K, Perez MC, Demanno D, Winkel C, Schubert G, Elger W. Selective progesterone receptor modulator development and use in the treatment of leiomyomata and endometriosis. Endocr Rev 2005; 26:423.

[150] Rabin D, McNeil LW. Pituitary and gonadal desensitization after continuous luteinizing hormone-releasing hormone infusion in normal females. J Clin Endocrinol Metab 1980; 51:873.

[151] Bulun SE, Yang S, Fang Z, Gurates B, Tamura M, Zhou J, Sebastian S. Role of aromatase in endometrial disease. J Steroid Biochem Mol Biol. 2001; 79(1-5):19-25.

[152] Amsterdam LL, Gentry W, Jobanputra S, Wolf M, Rubin SD, Bulun SE. Anastrazole and oral contraceptives: a novel treatment for endometriosis. Fertil Steril 2005; 84:300.

[153] Fujii S. Secondary müllerian system and endometriosis. Am J Obstet Gynecol. 1991; 165(1):219-25.

[154] Bouquet de Jolinière J, Ayoubi JM, Lesec G, Validire P, Goguin A, Gianaroli L, Dubuisson JB, Feki A, Gogusev J. Identification of displaced endometrial glands and embryonic duct remnants in female fetal reproductive tract: possible pathogenetic role in endometriotic and pelvic neoplastic processes. Front Physiol. 2012; 3:444.

[155] Spitzer TL, Rojas A, Zelenko Z, Aghajanova L, Erikson DW, Barragan F, Meyer M, Tamaresis JS, Hamilton AE, Irwin JC, Giudice LC. Perivascular human endometrial mesenchymal stem cells express pathways relevant to self-renewal, lineage specification, and functional phenotype. Biol Reprod. 2012;86(2):58

[156] Delbandi AA, Mahmoudi M, Shervin A, Akbari E, Jeddi-Tehrani M, Sankian M, Kazemnejad S, Zarnani AH. Eutopic and ectopic stromal cells from patients with endometriosis exhibit differential invasive, adhesive, and proliferative behavior. Fertil Steril. 2013.

[157] Dubrulle J, Pourquié O. Coupling segmentation to axis formation. Development. 2004;131(23):5783-93.

[158] Deschamps J, van Nes J. Developmental regulation of the Hox genes during axial morphogenesis in the mouse. Development. 2005; 132(13):2931-42.

[159] Hoang-Ngoc M, Smadja A, Hervé de Sigalony JP. A classification of uterine tumors based on embryogenesis. Arch Anat Cytol Pathol. 1991; 39(3):94-102.

[160] Soares SR, Martínez-Varea A, Hidalgo-Mora JJ, Pellicer A. Pharmacologic therapies in endometriosis: a systematic review. Fertil Steril. 2012; 98(3):529-55.

Figure legends

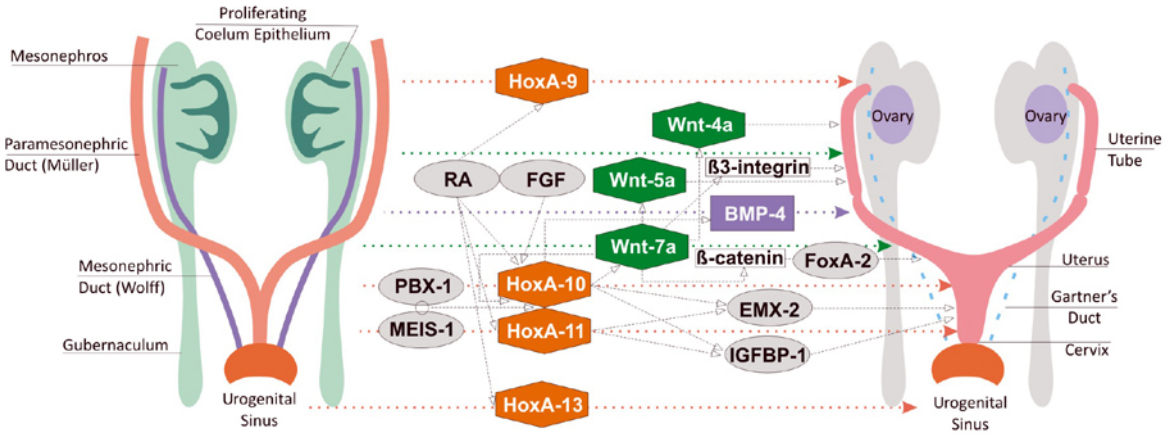
Fig. 1.

The epithelial cell populations of the embryo have similar morphological characteristics of differentiated epithelia, whilst mesenchymal cells contribute to the basal membrane, forming the lamina and smooth muscle of tubules and differentiation into connective tissue. During the early stages of organogenesis, the mesoderm emerges from the primitive streak and gives rise to coelomic epithelium. The müllerian ducts (Wnt4 is essential) arise from invagination of the coelomic epithelium during fetal development resulting in the female reproductive tract, which further differentiates to form the oviduct, uterus and vaginal canal higher. The clusters of Hox genes during development, undergo the transcriptional control by cofactors such as retinoic acid RA [40], FGF and Wnt signaling; during organogenesis patterning of the female genital tract is regulated by homeobox transcription factors: HOXA9 is expressed in the oviduct , Hoxa-10 (by BMP-4, Wnt7a and β3-integrin) and Hoxa-11 (via Emx-2 and IGFB1) are expressed in the uterus, Hoxa-11 and 13 cervix and vagina. The Wingless genes are implicated in endometrial glandular and stromal morphology: Wnt7 has been shown to be involved in the maintenance of the genes HoxA10 and HoxA11, while in the development Wnt5 genital anteroposterior axis: Wnt5a and Wnt7a are both necessary for proper glandular genesis , and Wnt5a, in particular, is a critical element in the endometrial glandular formation which entails the role of epithelial-mesenchymal interaction required for uterine development. As a downstream effector of the Wnt genes, it has been demonstrated that the involvement of β -catenin and FoxA2, in the absence of stimulation by Wnt, causes the phosphorylation of β-catenin which is phosphorylated and then targeted for ubiquitination and degradation in the proteasome. In the signaling pathway of the canonical Wnt genes, Wnt/β-catenin, is

implicated in the control of various types of stem cells and can act as a niche factor to keep the EmSC (Embryonic Stem Cell) in a state of self-renewal.

Fig. 2.

Fetal development: the morphogenetic processes of the axial extension, of the segmentation of mesoderm and anterior-posterior patterning are regulated by the interaction between Hox genes and Wnt signaling network in a gene that involves Wnt/β-catenin, in the extension and axial the identity of the anterior-posterior patterning, while the cofactors of Hox gene, Pbx1 and Meis1 are involved in the segmentation of the mesoderm; Wnt7 has been shown to be involved in the maintenance of the genes HoxA10 and HoxA11, while in the development Wnt5 genital anterior-posterior axis; Wnt4 is involved in the sexual way, Wnt7 in the epithelium, stroma and glands, Wnt5 in the anatomy of the uterus. Postnatal development: molecular signaling of Shh, BMP, FGF and Notch are implicated in the control of stem cell self-renewal and in regulating the fate of the lineage; the estrogenic activity active peritoneal macrophages with consequent induction of pro-inflammatory cytokines TNF-α and IL-1β which, in turn, activate the binding to the DNA through the transcription factors of NFκB; the transcriptional activity through inflammatory cytokines IL-6 and IL-8, induces the expression of VEGF that activates the vasculature endothelial cell, while MIF induces cell mitosis endometrial and survival is supported by the activation of the anti-apoptotic gene Bcl-2 , from the degradation of the extracellular matrix by MMPs and the entry phone via ICAM and VCAM. Post-pubertal development: the eutopic plant develops resistance to elimination by the immune system, demonstrating altered function of macrophages and natural killer peritoneal cells; in the early stages of the disease there is a prevalence of proinflammatory cytokines (Th1 profile), while in the late stages cytokines predominantly fibrogenic and angiogenic action (Th2 profile) prevails.


Proliferating
Coelum Epithelium
Mesonephros
Paramesonephric
Duct (Müller)
Mesonephric
Duct (Wolff)
Gubernaculum
Urogenital
Sinus
HoxA-9
Wnt-4a
RA
FGF
Wnt-5a
ß3-integrin
BMP-4
Wnt-7a
ß-catenin
FoxA-2
PBX-1
HoxA-10
EMX-2
MEIS-1
HoxA-11
IGFBP-1
HoxA-13
Ovary
Ovary
Uterine
Tube
Uterus
Gartner's
Duct
Cervix
Urogenital
Sinus