Medical Hypotheses 103 (2017) 10–20

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

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

Antonio Simone Laganà [a,*], Salvatore Giovanni Vitale [a], Francesca Maria Salmeri [b], Onofrio Triolo [a], Helena Ban Frangež [c], Eda Vrtačnik-Bokal [c], Lily Stojanovska [d], Vasso Apostolopoulos [d], Roberta Granese [a], Vincenza Sofo [b]

[a] Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Messina, Italy
[b] Department of Biomedical Sciences, Dentistry and Morphological and Functional Imaging, University of Messina, Messina, Italy
[c] Department of Reproduction, University Medical Center Ljubljana, Ljubljana, Slovenia
[d] Centre for Chronic Disease, College of Health and Biomedicine, Victoria University, Melbourne, VIC, Australia

ARTICLE INFO

Article history:
Received 4 September 2016
Accepted 21 March 2017

Keywords:
Endometriosis
Embryology
Body patterning
Embryonic stem cells
Proteins homeodomain
Wingless type proteins

ABSTRACT

The theory of retrograde menstruation as aetiopathogenesis of endometriosis formulated by John 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 ectopic müllerian remnants of the endometrium, endocervix and endosalpinx 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 ectopic. There is 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 metalloproteinase and pro-inflammatory cytokines activate/alter peritoneal microenvironment, creating the conditions for differentiation, adhesion, proliferation and survival of ectopic endometrial cells.

Background

Endometriosis is characterized by the presence of functionally active endometrial tissue, stroma and glands outside the urine cavity [1]. Numerous theories have been proposed for the pathogenesis of endometriosis, such as retrograde menstruation, coelomic metaplasia and Müllerian remnants [2], as well as it was defined as hormonal disease, autoimmune disease, (epi)genetic disorder or due to environmental stimuli [3,4] or nutritional deficiency [5–7]. Among the various hypotheses, the one that has 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 [8]. The prevalence of endometriosis is estimated to be 10% [9,10], with a further 11% of women whose disease is not clinically diagnosed [11]. 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) [12,13], of which 84% are located within the bladder [14]; other organs of involvement include pancreas, spleen [15], liver, intestinal tract [16], gallbladder [17], abdominal wall and umbilicus [18], brain [19]. The most common symptoms and signs of endometriosis are chronic pelvic pain, dysmenorrhea

* Corresponding author at: Unit of Gynecology and Obstetrics, Department of Human Pathology in Adulthood and Childhood "G. Barresi", University of Messina, Via C. Valeria 1, 98125 Messina, Italy.
E-mail address: antlagana@unime.it (A.S. Laganà).

http://dx.doi.org/10.1016/j.mehy.2017.03.032
0306-9877/

[20] and infertility [21], which may cause severe impact on patient's psychological wellbeing and quality of life [22,23]. 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 [24], whilst disease occurs in 10% of cases. Apparently, the hypothesis of retrograde menstruation as the pathogenesis of endometriosis does not explain this gap. Interestingly, Ebert et al. [25] found endometriotic foci in the cul-de-sac and uterosacral ligaments of a 9-years-old patient undergoing pre-menarche. In any case, even if the presence of ectopic endometrium in human female fetuses at different gestational ages was already demonstrated [26–28], the presence of endometriosis in male individuals with normal karyotype (46, XY) [29–34] still remains controversial. Such cases can only be explained by the incomplete differentiation of the müllerian ducts.

The 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 [35], many advances have been made in the direction of understanding the effects but not the causes of the disease. We hypothesize that, during organogenesis, a deregulation of genes and the Wingless-related integration site (Wnt)/β-catenin signaling pathway would produce an aberration and the axial extension of the identity of the anterior-posterior patterning, whilst a deregulation of Hox genes and cofactor Pre-B-Cell Leukemia Homeobox 1 (Pbx1) produces an aberration in the segmentation of the mesoderm (Figs. 1 and 2). This may cause aberrant placement of stem cells with endometrial phenotype and maintain them in quiescent niches. In post-pubertal age, the estrogenic activity recruit and stimulate Peritoneal Fluid Mononuclear Cells (PFMCs) with consequent induction of pro-inflammatory microenvironment [high levels of Tumor Necrosis Factor (TNF)-α and Interleukin (IL)-1β] which, in turn, activate the transcription factor NFκB. On one hand, transcriptional activity induces the expression of Vascular Endothelial Growth Factor (VEGF) that stimulates the vascular endothelial cell; on the other hand, Müllerian Inhibiting Factor (MIF) induces endometrial cell mitosis, whose survival is supported by the activation of anti-apoptotic gene B-cell lymphoma 2 (Bcl-2), by the degradation of the extracellular matrix by metalloproteinases (MMPs) via Intercellular Adhesion Molecule 1 (ICAM-1) and Vascular Cell Adhesion Molecule 1 (VCAM-1), creating the conditions for differentiation, adhesion, proliferation and survival of ectopic endometrial cells. Understanding of the biological, genetic and epigenetic mechanisms, which regulate the differentiation and development of the urogenital tract during the fetal stage, might be a priority for researching the aetiopathogenesis of endometriosis.

Evaluation of the hypothesis

Embryogenesis

The primordial germ cells are derived from the primitive streak (from epiblast to caudal area): they remain in the extra-embryonic mesenchyme to complete gastrulation and subsequently migrate along the allantois endoderm, conserving 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 embryonic epithelial cells have similar morphological characteristics of differentiated epithelia, whilst mesenchymal cells contribute to the basal membrane, form later in time the *lamina propria* and smooth muscle, and differentiate into

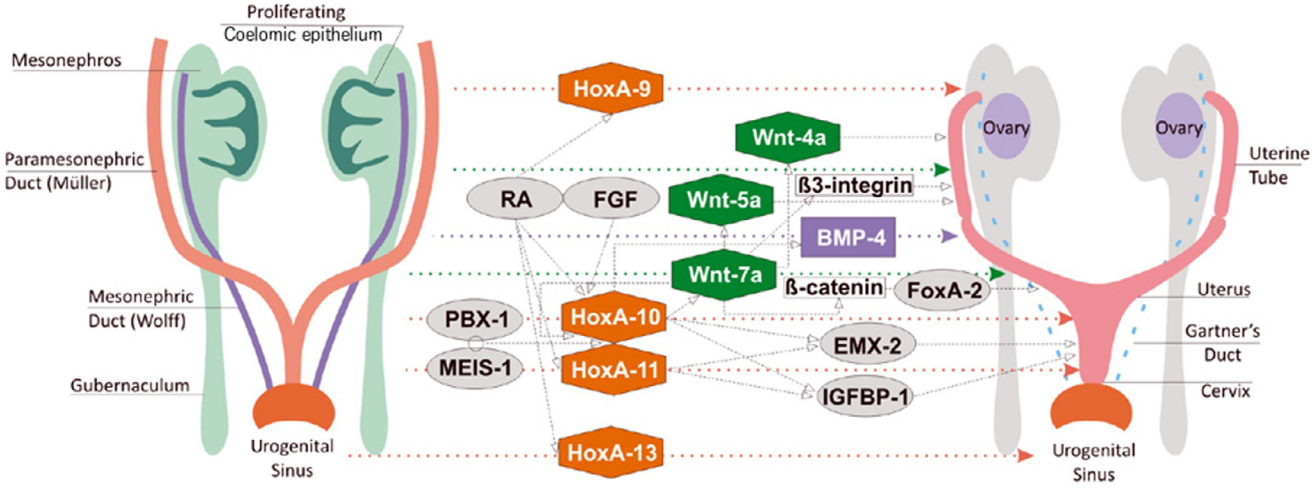

Fig. 1. The epithelial cell populations of the embryo have similar morphological characteristics of differentiated epithelia, whilst mesenchymal cells contribute to the basal membrane, forming the *lamina propria*, smooth muscle and connective tissue. During the early stages of organogenesis, the mesoderm emerges from the primitive streak and gives rise to coelomic epithelium. The Müllerian ducts arise from invagination of the coelomic epithelium during fetal development, which further differentiates to form the oviduct, uterus and upper part of the vagina. The clusters of Hox genes undergo transcriptional control by cofactors such as retinoic acid (RA), Fibroblast Growth Factor (FGF) and Wnt signaling: HOXA-9 is expressed in the oviduct, HoxA-10 (via BMP-4, Wnt7a and β3-integrin) and HoxA-11 (via EMX-2 and IGFB1) are expressed in the uterus, HoxA-11 and HoxA-13 in the cervix and vagina. The Wingless genes are implicated in endometrial glandular and stromal morphology: Wnt7 has been shown to be involved in the regulation of HoxA-10 and HoxA-11, while Wnt5 in the development of 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. 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 canonical signaling pathway of 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 hEmSC (human Embryonic Stem Cell) in a state of self-renewal.