EDITORIAL   **OPEN ACCESS**

Current theories on endometriosis pathogenesis

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Editorial,

Endometriosis is a common chronic gynecological disorder affecting more than 10% of women of reproductive age. It is characterized by the presence of endometrial glands and stroma outside the uterine cavity. Despite the fact that our knowledge of this disease is older than 150 years, our knowledge of the pathogenesis of endometriosis is far from complete. In this short review, we summarize the current theories on possible causes of endometriosis.

Our knowledge of endometriosis extends back to 1860, when von Rokitansky first described this disease [1]. This disease is characterized by the presence of ectopic endometrium resulting in pain, infertility and/or lesion progression. Between 5 and 10% of women of reproductive age are affected. Despite the long research, the definite cause(s) of endometriosis is still unsolved and this disorder remains among the most enigmatic women diseases. Endometriosis is not only connected with infertility, but also with several types of cancer, most of all ovarian. Based on histopathological studies, it was suggested that atypical endometriosis is in fact a premalignant condition [2]. This hypothesis is nothing new, as the relation between endometrial tissue and ovarian cancer was described almost 100 years ago [3].

Studies evaluating ovarian cancer patients showed 10% occurrence of transformed endometriomas [4], this incidence in patients with clear cell ovarian cancer is elevated to 36% [5]. On one hand, there are no doubts about the fact that endometriosis increases the risk of ovarian cancer but on the other hand, it seems that the progression of disease is not affected [6]. However, despite decades of intensive research, exact mechanisms responsible for the malignant transformation of endometrial tissue are not elucidated. One of the reasons might be the rather long period of time between the appearance of benign ovarian masses and cancer diagnosis [7].

Pathogenesis

The pathogenesis of endometriosis has been the focus of attention of active investigations for decades, resulting in numerous hypotheses. The most probable hypothesis of the pathogenesis suggests that the adhesion and subsequent growth of endometrial fragments occurring in the peritoneum is caused by the retrograde menstruation phenomenon [8]. This hypothesis suggests that a pressure gradient resulting from dyssynergic uterine contractions drives endometrial fragments through the fallopian tubes. Subsequently, these fragments implant peritoneal cavity and slowly invade pelvic structures. Several factors such as early age at menarche, long duration of menstruation or reproductive or personal factors will influence the occurrence pelvic contamination by regurgitated endometrium [9, 10]. Constitutional and personal factors might include family history, nevi, alcohol abuse or exercise.

Additional molecular and/or cellular alterations might be involved. The most common is altered steroid biosynthesis and receptor responses that favor the slow processes of cell implantation and growth. These alterations involve increased estrogen recaptor beta (ERβ) expression, which might be a reason why hormone therapy, particularly estrogen therapy, is often supposed to stimulate the growth of endometriosis, with additional increase in the risk of ovarian cancer development [11]. Additional molecular alterations include increased aromatase expression, perturbation in progesterone signaling (such as involvement of HOXA10, FOXO1, NF-κB, Hic-5 or NCoR2). Faster invasion can also

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be influenced by increased vascularization caused by increased production of peritoneal VEGF and influx of Tie-2 expressing macrophages.

Probably the most widely accepted hypothesis is the retrograde menstruation hypothesis, based on the possibility that the endometriotic implants arise from retrograde menstruation of endometrial tissue through the fallopian tubes [12], which was observed as early as 1938 [13]. The finding that women with endometriosis have larger volumes of retrograde material than healthy women might be another stone in the mosaic, but it does not represent a direct indication, similarly studies showing that women with cervical or vaginal outlet obstructions have a higher risk of endometriosis [14].

Three main theories supporting the concept of in situ development have been suggested including a Mullerian and Wolffian rest theory, coelomic metaplasia theory and metaplasia following endometrial stimulation theory. Mullerian remnant abnormalities are mainly suggested for endometriosis infiltrating the cul-de-sac and uterosacral ligaments. Aberrant migration or differentiation of the Mullerian ducts might influence spreading of cells in the migratory pathways of normal organogenesis into the posterior pelvic floor [10, 15]. There is no higher frequency of endometriosis in patients with Mullerian abnormalities, but outflow obstruction probably represents an important contributing factor.

Similarly, coelomic metaplasia theory suggests that the coelomic epithelium covering the serosa of the peritoneum and the ovary may undergo a metaplastic change into endometrium. The problem with this theory is the lack of knowledge about the responsible stimulus, with both hormonal and environmental factors being suggested, but not clearly established. The main support is based on the fact that embryologically, thoracic, abdominal and pelvic peritoneum are derived from the same cell lineage as mullerian ducts.

The endometrial stimulation theory is based on suggestions that at a local level, endometriotic and adenomyotic tissues produce estrogens, which may be involved in the tissue growth through interacting with the estrogen receptor [16]. Estrogens support ectopic endometrium growth. The ectopic tissue has been repeatedly shown to be ER positive, with ERβ being the prominent receptor [17, 18]. This is further supported by the fact that despite the rarity of postmenopausal endometrioisis, there is a risk in patients taking hormone therapy [19]. Hormone therapy, in general, and estrogen therapy in particular, is often supposed to stimulate the growth of endometriosis, with additional increase in the risk of ovarian cancer development. This risk is particularly high in postmenopausal endometriosis. The situation complicates the fact that implants of endometrosis contain estrogen, progesterone and androgen receptors, but the effects of these hormones on tissue are the opposite – estrogen stimulates proliferation and androgens cause atrophy and regression.

Additional hypothesis, which recently gained interests, is focused on stem cells and suggests that endometriotic lesions arise from ectopic endometrial stem cell progenitors [20]. It is possible that new implants of persistent fetal stem cells might be involved in tissue regeneration and growth. A finding that several HOX genes controlling lineage infidelity in ovarian cancer [21] are expressed in primitive hematopoietic cells suggested a role in early hematopoietic differentiation. Additional studies supported the idea that HOX genes expressed in ovarian epithelial cells might regulate cancer stem cells.

Endometrial-derived cells from hysterectomy samples showed a significant level of clonogenicity, with two types of colonies generated. The authors of this study speculated that the larger colonies derived from endometrial stem/progenitor cells [22]. A later study found no differences in clonogenic potential among cells derived from proliferative, secretory, or inactive endometrium [23]. As inactive endometrium contains no endometrium functionalis, it is possible that these putative stem cells reside in the basalis layer and do not disappear after menopause.

The theory of importance of endometrial stem cells was further supported by numerous findings that endometrial-derived cells can establish endometriotic implants [24]. A study evaluating the expression patterns of estrogen and progesterone receptor in normal endometrium and in endometriotic implants showed that the expression patterns of implants mimicked the patterns of the basalis layer [25]. When we add the fact that the women suffering from endometriosis have larger volumes of retrograde menstrual flow, one can speculate that these implants progress from the retrograde menstruation of endometrial progenitor cells [26]. Bone marrow transplantation experiments showed the presence of bone marrow-derived cells in stroma and endometrial glands [27].

Another possibility is focused on the fallopian tubes, which were revealed as a carrier of the menstrual endometrium into the peritoneal cavity and/or on the surface of ovary. Tubal epithelia shed living cells on ovarian epithelial inclusions [28] and the majority of the ovarian epithelial inclusions in the ovarian serous carcinoma derived from tubal epithelia [29]. Subsequent studies found FMO3 and DMBT1 genes to be important biomarkers. By testing the expression levels of these genes in the fallopian tube and the endometrium from the same patients using real-time PCR, western blotting and immunohistochemistry, the authors found that in 56% of cases, DMBT1 was highly expressed in the endometrium, but minimally in the fallopian tube. The expression of FMO3 was exactly opposite. These experiments suggested that a high proportion of ovarian endometriosis might be derived from the fallopian tubes [30].

Based on the short survey of current hypothesis about the pathology and development of endometriosis, it is clear that despite decades of intensive research, no single

theory can perfectly account for the manifestation of all cases of endometriosis. Clearly, more research including better animal models is necessary.

How to cite this article
Vetvicka V, Kralickova M. Current theories on endometriosis pathogenesis. Edorium J Mol Pathol 2015;1:1–4.

Article ID: 100001M12VV2015

doi:10.5348/M12-2015-1-ED-1

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Author Contributions

Vaclav Vetvicka – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Milena Kralickova – Acquisition of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

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