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Review

Systems genetics view of endometriosis: a common complex disorder

Vladislav S. Baranov [a,b,*], Tatyana E. Ivaschenko [a], Thomas Liehr [c], Maria I. Yarmolinskaya [a]

[a] D.O Ott Research Institute of Obstetrics and Gynecology, Mendeleevskaya line, 3, 199034 St. Petersburg, Russia
[b] St Petersburg State University, Universitetskaya nab., 7/9, 199034 St. Petersburg, Russia
[c] Jena University Hospital, Friedrich Schiller University, Institute of Human Genetics, Kollegiengasse 10, D-07743 Jena, Germany

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ABSTRACT

Endometriosis is a condition in which cells derived from the endometrium grow outside the uterus, e.g. in the peritoneum (external genital endometriosis). As these cells are under the influence of female hormones, major symptoms of endometriosis are pain, especially during the cycle, and infertility. Numerous hypotheses for the formation of endometriosis can be found in the literature, but there is growing evidence of serious genetic contributions to endometriosis susceptibility. The involvement of genes, steroid hormone metabolism, immunological reactions, receptor formation, inflammation, proliferation, apoptosis, intercellular adhesion, cell invasion and angiogenesis as well as genes regulating the activity of aforementioned enzymes have been suggested. Some more recently suggested candidate genes picked up in genome-wide association studies are involved in oncogenesis, metaplasia of endometrium cells and pathways of embryonic development of the female reproductive system. However, gene mutations proven to be causative for endometriosis have not been identified so far, even though the abnormal expression of candidate genes for endometriosis could be provoked by different epigenetic modifications including DNA methylation, heterochromatization or introduction of regulatory miRNA. We hypothesize that endometriosis is induced by a combination of abnormal genetic and/or epigenetic mutations: the latter pave the way for pathological changes which become irreversible, and according to the "epigenetic landscape" theory, this proceeds to the typical clinical manifestations. Two stages in the endometriosis pathway are suggested: (1) induction of primary endometrial cells toward endometriosis, and (2) implantation and progression of these cells into endometriosis lesions. The model favors endometriosis as an outgrowth of primary cells different in their origin, canalization of pathological processes, manifestation diversity provoked by unique genetic background and epigenetic influences, which result in many different clinical forms of the disease.

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* Corresponding author at: D.O. Ott Research Institute of Obstetrics and Gynecology, Mendeleevskaya line, 3, 199034 St. Petersburg, Russia. Tel.: +7 812 328 04 87/+7 921 337 77 96; fax: +7 812 328 04 87.
E-mail addresses: baranov@vb2475.spb.edu, vsbar40@mail.ru (V.S. Baranov).

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Introduction

Endometriosis is a common disorder, affecting 10% of women of reproductive age. In endometriosis cells derived from endometrium grow outside the uterus, e.g. in the peritoneum. These cells are under the influence of female hormones, and thus, major symptoms arise during the woman's cycle as pain but it also causes infertility. Endometriosis as a complex disease is thought to arise from the interplay between multiple genetic and environmental factors [1,2].

The precise etiology of endometriosis remains unclear, and many different forms of endometriosis can be discriminated according to variable clinical and pathomorphological criteria. The most common classification of endometriosis relies on the number of endometriotic lesions (EL) and the depth of their outgrowths. The most common form of endometriosis is pelvic endometriosis with a number of disseminating EL invasions of the peritoneum (peritoneal endometriosis) and ovary (ovarian endometriosis). Distinct from peritoneal and ovarian endometriosis, rectovaginal septum adenomyotic nodules should be considered, originating from the Müllerian rests present in the rectovaginal septum [3]. Deep endometrial invasion in the uterine wall is treated as adenomyosis. In 0.5–1% of cases, endometriosis could give rise to tumor transformation [1,2].

Basic concepts of pathophysiology and pathogenesis of endometriosis were recently reviewed by Burney and Giudice [4]. Tentatively, endometriosis could be attributed to either (i) implantation of otherwise normal endometrial cells in the peritoneum, or (ii) metaplasia of preexisting undifferentiated epithelium or mesenchymal cells. Scenario (i) would implicate adhesion, angiogenesis and invasion of vital endometriosis-like tissue into the peritoneum and the organs of peritoneal cavity, while in scenario (ii) metaplasia could arise either from dedifferentiated coelomic cells of the peritoneum, from stem cells of native endometrium, from dormant embryonic cells embedded in pelvic lining or from mesenchymal progenitor cells of bone marrow. As might be inferred from Table 1, a dozen different theories and hypotheses are suggested to explain the origin and pathogenesis of this very common and still rather enigmatic disorder [5–17]. Each of these ideas from Table 1 could be addressed by solid clinical studies, and some by experimental data, though no single one is sufficient for understanding the molecular pathways of the disease. Thus, for endometriosis, one is still far from being able to offer early testing, reliable preclinical diagnostics and/or efficient personalized treatment.

Candidate genes

The genes and their variants potentially providing a hereditary contribution into endometriosis have been widely investigated [14]. Candidate gene association studies, whole genome linkage analysis as well as, more recently, genome-wide association studies (GWAS), have been applied and already yielded over 100 candidate genes [2,14]. The utility of the most of these genes for understanding the pathogenesis of endometriosis is still to be proven, but at least some of these genes identified by different methods, especially by the GWAS approach, could be already admitted as meaningful entities of endometriosis [18,20]. A recent meta-analysis narrowed down the earlier findings of GWAS to a total of seven single nucleotide polymorphisms (SNPs) that passed a genome-wide significance ($P < 5 \times 10 - 8$); also, at least six genes were recognized or suspected as the most plausible candidates of endometriosis (*WNT4*, *CDC42*, *HSPC157*, *HOX10*, *CDKN2BAS* and *FN1*) [19,20].

What is noteworthy is that a good correlation could be traced between the spectrum of endometriosis candidate genes and already postulated mechanisms of endometriosis origin [2,14,19]. Numerous genes responsible for hormonal imbalance, immunological impairments and neoplastic transformation of endometrium cells (metaplasia) have been implicated in endometriosis [2,21–23]. Major pathways and the genes thought to be involved in endometriosis due to the aforementioned observations are summarized in Fig. 1, and fall into seven principal groups. These include genes responsible for steroid sex hormones and their receptors, synthesis and metabolism (group 1), genes participating in endometrial cell proliferation and menstrual cycling (group 2), tumor suppressor genes and some oncogenes (group 3), the genes responsible for detoxification e.g. of industrial and agricultural pollutants, like benzopyrenes, pesticides, etc. (group 4), abundant and very polymorphic miRNA regulators (group 5), pre-inflammatory cytokines (group 6), and a cohort of other genes involved in angiogenesis and cell invasion (group 7).

Some other regions identified by GWAS also hold promise as candidate loci for endometriosis, but no major candidate genes specific for EL has been identified so far. However, it is presently assumed that any new endometriosis loci that contribute to the

Table 1
Basic theories/hypotheses of endometriosis origin.

No.	Theory/hypothesis	Pathophysiology	References
1	Transplantation	Retrograde menstruation	Sampson [5]
2	Immunologic	Failure to destroy endometrium cells in peritoneal cavity	Tariverdian et al. [6]
3	Toxicologic	Pro-inflammation cytokine stimulation	Foster et al. [7]
4	Metaplasia	Dormant stem-cells in peritoneum epithelium	Meyer [9]
5	Dormant embryonic cell	Dislocation of endometrium cells outside the uterine cavity	Signorile et al. [10]
6	Denervation–reinnervation	Abnormal contractility of uteri muscles	Quinn [11]
7	Hormonal	deregulation of sex hormones balances	Dizerega et al. [12]
8	Infection	Inflammation of pelvic epithelium caused by microbial infection	Chaudhury and Chakravarty [13]
9	Genetic	Candidate genes mutations and signaling pathway impairments	Rahmioglu et al. [14]; Kim and Yim [15]
10	Epigenetic	Impairment of gene regulation	Guo [16]