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Review

# Systems genetics view of endometriosis: a common complex disorder

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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 [illegible] 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.

## 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], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [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.

## Section snippets

### 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 …

### Epigenetic mechanisms

Impairment of gene function may occur at any stages of gene expression with mutations leading just to genetic polymorphisms at one end of the scale or really deleterous mutations on the other. Epigenetic mechanisms such as DNA methylation, specific micro-RNA or DNA spreading provide basic regulation of gene activity. The establishment in embryogenesis and further maintenance of cell type-specific epigenetic patterns are essential to form adequate gene expression profiles for normal cell…

### Environmental factors

Besides genetics and epigenetics, environmental factors seem to play a role in endometriosis susceptibility. Experimentally, endometriosis can be induced by low doses of dioxine treatment in monkeys, which gives some credit to an exogenic impact into endometriosis origin [7], [29]. In line with these findings, our earlier studies suggested involvement of null alleles of detoxification gene *GSTM1* in the development of endometriosis [34], [35], [36]. The association of detoxification gene…

## Genetic and epigenetic interactions leading to endometriosis

As we have seen, endometriosis as a common disease should be considered as an outcome of the complex interactions between abnormal genetic and epigenetic factors augmented by some environmental toxins. Meanwhile, each factor alone is not sufficient to launch and support the disease. Not all women subjected to toxic environmental pollutants suffer from immunological or hormonal imbalances or even develop endometriosis. It seems most likely that endometriosis predominantly affects women with some …

## Systems genetics of endometriosis

Gene interactions through their RNA and protein moieties, functional epistasis, contributing to suppression and induction of the genes participating in the relevant gene-networks, their

protein products and related metabolic pathways should be addressed by systems genetics. This is a novel integrative genome approach directed to determine genetic architecture of complex traits, including common diseases [40].

Taking into account the partially epigenetic nature of endometriosis, the following…

## Condensation

A systems genetics approach to endometriosis is reviewed, and an epigenetic landscape two-step hypothesis of endometriosis development is suggested.…

## Conflict of interest statement

The authors declare that they have no conflict of interests.…

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