Review Article

A Novel Perception on the Genetic and Epigenetic Aspects of Endometriosis

Lenika .A, Ramakrishnan .V, Akram Husain RS*

Human Cytogenetics and Genomics Laboratory, Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Kelambakkam, Chennai ,Tamilnadu.

Ms. Lenika is pursuing her final year of undergraduate in Medical Genetics, Faculty of Allied Health Sciences, Chettinad Hospital and Research Institute, Chettinad Academy of Research and Education, Chennai, Tamil Nadu. Her research interest is genetic and epigenetic aspects of gynecological disorders.

Corresponding author - Dr. Akram Husain RS – (akramhusain87@gmail.com)

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Abstract

Endometriosis is a complex gynaecological disease mostly affecting women of reproductive age (25 to 35 years) in 10% of the world population. Various theories have described the pathogenesis of endometriosis. Amongst them, the genetic/epigenetic theory explains nearly all observations of endometriosis. So-far several genetic loci were analyzed for their potential role in the pathogenesis of endometriosis, and some were proven to be pathologically significant. Other than the genes, the epigenetic modifications such as mRNA levels, miRNA expression, methylation and acetylation profiles were also being analyzed for their potent role in endometriosis. This review is aimed at discussing the recent developments in the genetic and epigenetic aspects of endometriosis as a disease condition.

Keywords: Genetic disorders; Epigenetics; Gynaecological disease; Endometriosis.

Introduction

Endometriosis is a complex gynaecological disease that affects more than 10% of the women of reproductive age worldwide and is characterized by ectopic endometrial and stromal cell growth. Symptoms experienced by women with endometriosis extend from pelvic pain, dysmenorrhoeal, dyspareunia, irregular bladder and bowel functioning to infertility.[1] Endometriosis can be classified based on the site of the tissue growth: peritoneal (in the peritoneum), ovarian (on the ovary) and deep infiltrating endometriosis (in the recto-vaginal region). The precise pathogenic cause of endometriosis is yet to be discovered, but several theories summarize the possibilities of the pathogenicity. One among the theories, the retrograde menstruation is widely accepted, and it states that the endometrial tissue fragments flow to the ectopic parts where they continue to settle and proliferate by establishing its blood supply. Altered immune actions, coelomic metaplasia and metastatic spread, stem cells, genetics and epigenetics were also included in explaining the pathogenesis of endometriosis.[2]

Genetic studies estimate that 50% of the endometriosis is accounted for by the hereditary factors, and the first-degree relatives are at a 6%-9% higher risk of developing endometriosis. The occurrence of endometriosis is occasional in men and women with the absence of endometrium. The comorbidity of this condition with several other conditions makes the etiology estimation harder and studies estimate that 21%-41% of the women with subfertility encounter endometriosis.[3] Although its relationship with adenomyosis is not explained, women encountering adenomyosis were observed with the existence of endometriosis2. The co-existence of autoimmune diseases, allergies, asthma, fibromyalgia, and allergies were also confirmed.[4]

Endometriosis might increase the risk of preterm pregnancies, abnormal placentation, and changes in the contradictory patterns of the endometrium, higher risk of vaginal and ovarian infections, increased chances of getting cancers. Several biochemical changes were observed in endometriosis affected women, which includes the immunological compounds, altered levels of prostaglandins, ILGF-1, NK cells, and growth factors. The severity of the condition, age, medical comorbidity and history, and several other factors are considered while availing the treatment options. Treatment options in the case of the diagnosed endometriosis are oral hormonal pills, hormonal agonists, and hormonal replacement therapy. The

genetic and epigenetic causes of this condition are continuously being searched for, and as of now, several studies have reported variations in methylation profiles, in the RNA expressions and histone modifications. Researchers believe that genetic and epigenetic modifications can be causal to the pathogenesis of this disease condition and they form the targets for a better treatment option.

Pathogenesis

Several theories have explained the pathogenesis of this condition including Sampson's retrograde menstruation theory, coelomic metaplasia, mullerianosis, the genetic and epigenetic theory, and also some studies have recommended the role of oxidative stress in the pathogenesis of endometriosis (Fig.1). Retrograde menstruation theory is the most accepted theory among all the proposed theories, and this explains that the endometrial tissue is transported to other ectopic parts (especially the cavity of the peritoneum and the fallopian tube) by the Reflex throughout the menstrual cycle blood and they establish a blood supply and start proliferating1. The proposed theory can be concluded to be true through several observations: First, the menstrual fluid contains living cells with growth and implantation potential and thus can implant and grow in the ectopic parts. Second, the most observed endometriotic growth part is the left side of the pelvis which also proves the reliability of this thesis.[2] Third, all women experience some degree of retrograde menstruation. Fourthly, experimentally endometrium can be grown in the peritoneum.[5] Yet, this theory cannot explain the endometriosis in men and in women without a uterus, the survival of the endometrial tissues outside the uterus. Endometrial stem cell implantation is the extended theory of retrograde menstruation which explains that the endometrium and cells like mesenchymal stem cells are shed into the peritoneum by the retrograde menstruation and establishing ectopic implants.[6]

The metaplasia theory states that the peritoneum contains a considerable amount of undifferentiated cells, and those undifferentiated cells develop into endometrial cells and the formation of ectopic endometrial-like tissue.[1] Although the metaplasia theory cannot explain the factors that result in the transformation of peritoneal cells into endometrial cells, the inductive theory which extends the coelomic metaplasia theory states that several factors including hormonal, immunological factors are behind the scenes of the transformation process. The Mullerianosis theory suggests that estrogen-responsive migration of embryological Mullerian duct remnants and their development into endometrial lesions in the ovary. This theory is supported by epidemiological studies that report

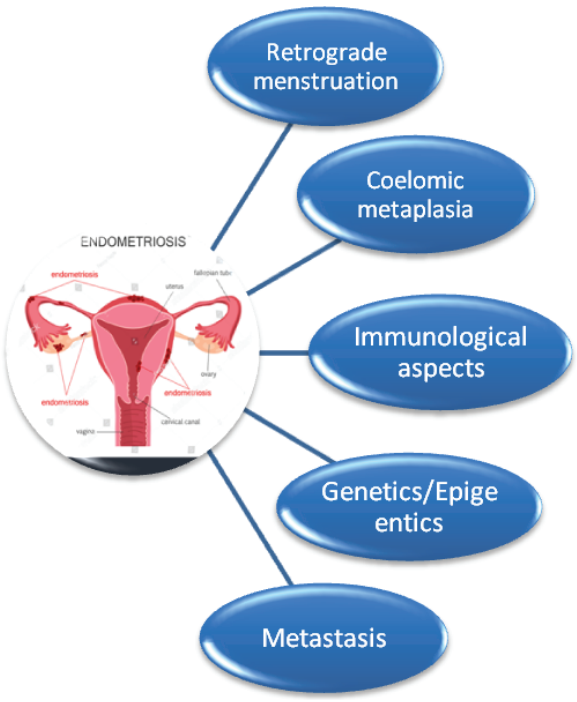

Figure 1: The pathogenesis of endometriosis.

that exposure to diethylstilbestrol will increase the risk of endometriosis.[7] Although this is proven by studies, this theory only explains the development of ovarian endometriosis.[5]

Immunological aspects of endometriosis

The immunological aspects were also found to play a role in the etiology of endometriosis. Woman with endometriosis is observed with poor Cell-mediated immunity profile especially the natural killer (NK) cell activity is poor and thus the endometrial tissues are not assumed as superfluous tissues. Endometriosis affected women are observed with decreased cytotoxicity, increased leukocytes, macrophages and their secretions such as cytokines, growth factors specifically, vascular endothelial growth factor (VEGF). Thus make the endometrial tissue proliferate with greater vascular supply1. The eutopic endometrial cells of those with endometriosis were proven to be resistant to the action of NK cells and this is accounted to the ICAM-1 (intercellular adhesion molecule-1) secreted by the eutopic cells. In support of this immunological aspect, the co-existence of several autoimmune diseases such as rheumatoid arthritis, lupus erythematosus are observed. The overproduction of the cytokines, chemokines and the increased iron concentrations (due to local bleeding at the sites of endometrial tissue growth) result in inflammations. The inflammatory responses are also accounted by the increased reactive oxidative species (ROS) because of tissue injury in the ectopic site with endometrial tissue growth. The genetic and epigenetic factors of

endometriosis are discussed in the following part here in this review.

Genetic basis for endometriosis

Over the past few years, several genetic studies were carried out and estimated the hereditary of endometriosis. The estimated prevalence of endometriosis in the first-degree relatives of women with endometriosis is 6.9% whereas that of the controls was less than 1%. Twin studies also estimate higher concordance rates of endometriosis, and also a 50% inheritability of the same.[8] Significant linkage was observed in two chromosome locations, 10q25 and 7q13-15 however the linkage scores were above the value of 3, and therefore the genes in those locations (CYP2C19, INHBA, SFRP4, HOXA10) were not confirmed to be the major genes in endometriosis.[9,10] Several other genes such as WNT4, VEZT, FN1, IL1A, CDKN2B, SERP4, NR2F2, NR5A, HDAC3, COL1A1, COL1A2, CDH1, ICAM1, HLA alleles were also investigated by several studies for their functional involvement in the pathology of endometriosis.[8-11.12,13]

Endometriosis and single nucleotide polymorphisms

ESR1 and ESR2

Estrogen is proven to have an essential role in the development of endometriosis. Estrogen usually works through ERα (estrogen receptor alpha) and ERβ (estrogen receptor beta), and in mouse models prove their role in infertility.[14] Meyer et al. (2014) tested the DNA methylation profiles of various types of endometrial tissues and the eutopic endometrium by MS-PCR (Methylation Specific Polymerase Chain Reaction). This study observed no difference in the methylation profiles of the ESR1 and ESR2 genes. A Chines-Han population study aimed at discovering the gene variants correlating with the risk of endometriosis and related infertility. The polymorphism rs3798573 (ESR1) is found to be significantly associated with endometriosis and related infertility in the Han Chinese women. Whereas, no relation between the rs1159327 (ESR1), rs3020348 (ESR1), and rs17179740 (ESR2) and endometriosis-related infertility or endometriosis was observed in the study.[17]

PR

Progesterone plays a vital role in the endometrium where it regulates the expression of progesterone receptor genes, alters miRNA levels and several other epigenetic modifications. The inflammation preceding the lesion formation leads to severe endometriosis and provokes progesterone resistance in the endometrial tissue and therefore studying the progesterone receptors, their genetic/epigenetic modifications were included in the study of endometriosis.[18] The PGR variation rs10895068 and Alu insertion in the 306th position do not contribute to the risk of endometriosis and also the fertility issues related to endometriosis.[15] The PGRB (Progesterone Receptor beta) and PGRA (Progesterone Receptor alpha) genes were observed to be methylated in 39% and 19% of the endometriosis cases, respectively. Therefore, the epigenetic changes in the PGR promoter regions in the intestinal endometriosis were observed to be significant.[20]

VEGF

VEGF gene located in chromosome 6 and encodes for VEGF, an activator of angiogenesis. A case-control study involved 480 cases and 600 controls, genotyped VEGF polymorphisms -460 (T>C) and +405 (G>C) by PCR-RFLP (polymerase chain reaction-restricted fragment polymorphism) in northern Iran. The study observed that the risk of endometriosis is high in +405 (G>C) CC individuals than the carriers of CC or CG ($p<0.0001$) and therefore endometriosis risk was associated with the C allele ($p=0.002$). But, the genotypes of -460 (T>C) do not significantly differ ($p=0.63$) between the two groups (cases and controls).[22] An Iranian population study observed no significant genotypic and allelic phenotypic differences were observed for the +450 (G>C) VEGF polymorphism and therefore according to the mentioned study the +450 (G>C) polymorphism of the VEGF gene was not related with the endometriosis risk[25] (Table. 1).

Epigenetic aspects of endometriosis

Several epigenetic modifications were observed to be involved in predisposing an individual to endometriosis. Methylation in the HOX-A10, although appears to be an important mechanism in endometriosis, doesn't correlate with the gene expression profiles. Borghese et al., in 2012, proved that the DNMT3L hypermethylation has a critical function. The methylation aspect of DNMT3L affected by the DNMT3L (rs8129776) is associated with cancer, where they affect the genes involved in endometriosis.[27] The levels of acetylation of H4 in endometriosis patients were observed to be lower when compared with those in the controls. Whereas the H3 acetylation levels do not differ significantly between the two groups and in eutopic endometriosis, the HDAC1 mRNA levels were decreased ($p=0.006$), the HDAC2 mRNA levels were higher ($p<0.001$), decreased levels of SIRT1 mRNA in the eutopic group were observed.[28] Li et al., in 2016 observed that the methylation profile of the cadherin gene (CDH1) promoter does has a relationship with the development of ovarian endometriosis and whereby the aberrant methylation thus increases the risk of the

Gene	Location	Description	Mutation /Polymorphism	Risk of endometriosis	Study cohorts	References
ESR1	Chromosome 6 (6q25.1)	ESR1 corresponds to the estrogen receptor alpha that controls the estrogen expression levels in all reproductive cells.	*rs2234693*	Not associated	European	Lamp *et al.,* 2011
			rs3853250; rs3853251	Not associated	American	Trabert *et al.,* 2011
			rs3798573	Associated	Han-Chinese	Wang *et al.,* 2013
			rs1159327, rs3020348	Not associated	Han-Chinese	Wang *et al.,* 2013
ESR2	Chromosome 14 (14q23.2)	ESR2 encodes for estrogen receptor beta which posses anti-proliferative effects.	*rs17179740*	Not associated	Han-Chinese	Wang *et al.,* 2013
			shorter CA repeats	Associated	European	Lamp *et al.,* 2011
PR	Chromosome 11 (11q22.1)	It is a steroid hormome receptor that affects the cell proliferation and differentiation. The aberrant expression of PRA and PRB in endometriosis	*rs10895068*	Associated	Australian, European	Near *et al.,* 2011
			rs10895068	Not associated	European	Lamp et al., 2011
			rs1042838	Not associated	American	Trabert et al., 2011
VEGF	Chromosome 6 (6q21.1)	The growth factor is important for the cell proliferation, migration of endothelial cells and angiogenesis. Their potent role in the formation of ectopic lesions was also postulated in several studies.	*+405 (G>C)*	Associated	Iran	Emamifar *et al.,* 2011
			-460 (T>C)	Not associated		
			-936 T>C	Associated	Meta-analysis; no specific population reported	Liang *et al.,* 2012
			-2578A>C, -460C>T, +405C>G, and -1154G>A	Not associated		
CDH1	Chromosome 16 (16q22.1)	The CDH1 gene encodes glycoprotein important for the epithelial development, cell integrity. The expression of CDH1 in endometrium lesions was inconsistent whereas that of the normal endometrium is consistent throughout the menstrual cycle.	*+54C/T*	Associated	India	Govatati *et al.,* 2011
			-347GA/2160A/+54C	Associated		
			rs4783689	Associated	Japan	Yoshida *et al.,* 2012
			3'-UTR C --> T; -160 A/-347 GA	Associated	China	Shan *et al.,* 2007

Table 1: List of genes associated with endometriosis risk

condition.[29] The methylation profile of the promoter region of matrix metalloproteinase-2 (MMP2) was related to the differential expression of MMP2 in the ectopic endometrium of the endometriosis patients.[30] A Chinese study also found two and five CpGs in the COMT and HOXA10 genes, respectively, that were differentially expressed between the eutopic and ectopic endometrium and therefore their linkage in endometriosis was thus confirmed.[31]

A GWAS study of DNA methylation patterns in endometriosis by Wang and his/her colleagues in 2019 observed significant differences in the expression of DNMT1, DNMT3A, DNMT3B, and MBD2 in eutopic and endometriotic lesions vs. control endometrium. They reported that these genes with differential methylation profiles between the controls and the patients with endometriosis are involved in the defense, immunological responses, regulation of MAP kinase and its activity, inflammatory responses, hormonal responses,

cytokine regulation and other important responses involved in the pathology of endometriosis.[32] The hyper/hypomethylation of ESR2, CYPI9A1, PRB, NR5A1, GATA2, STAR, RUNX3, H3K4, ID2, RBBP7, TNFRSFIB, and IGF21 was already investigated for their effects in the development of endometriosis.[33]

Conclusion

Endometriosis is the growth of endometrial tissues in the ectopic sites. Genetics and epigenetic theory explain every aspect of endometriosis. Genomic studies were carried out to explore the genetic basis of this disease and to understand the biology of the disease. This review provides an update on the epigenetic and genetics of endometriosis which will improvise the non-invasive diagnostic methods, understanding the comorbid conditions and the possibility for the development of better-personalized treatment options for endometriosis.

Conflicts of interest

All the authors declare that they have no conflict of interest

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