Chapter

The Role of the Molecular Genetic Approach in the Pathogenesis of Endometriosis

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Abstract

Advances in cytogenetic, molecular genetic, and molecular cytogenetic techniques have provided convincing evidence in favor of a genetic basis for endometriosis and corroborating the higher prevalence of the disease in first-degree relatives of affected women. The regulatory mechanisms involved in the morphological and biochemical differentiation of the uterine endometrium are obviously complex, but consistent somatic genetic alterations have been identified. A higher percentage of aberrant metaphases showing aneuploidy, dicentric chromosomes, endomitosis, and chromosomal spraying have been detected in several trials. These results were further amplified by multicolored fluorescent in situ hybridization (FISH) analysis demonstrating the presence of alterations, where at least chromosomes 1, 16, 17, and 22 show structural aberrations containing genes that could play a role in the development and/or progression of endometriosis. Overall, the non-random distribution along with the subchromosomal location of the genetic alterations strongly supports the idea that these anomalies are relevant and are associated with the endometriotic process.

Keywords: molecular genetic, endometriosis, chromosome, hybridization

1. Introduction

Endometriosis is a systemic, multisymptomatic, and disabling condition for women. Even when endometriosis originates from pelvic implantation, it can spread to other bodily surfaces outside of it.

These endometriosis cells do not shed and migrate like endometrial cells. They remain in situ, causing hemorrhage and an inflammatory response during each hormonal cycle, conditioning the different symptoms and complications in each affected organ.

Although the pathophysiological mechanism has been well studied, the cause of endometriosis remains uncertain. This fact has motivated the development of multiple and diverse theories that have tried to explain this pathology. The biggest problem is that they have been exclusionary theories, so they have not been able to define a cause that fits different scenarios.

It is under this concept and with the advent of new techniques of genetic and molecular study that new theories have been developed based on genetic changes and molecular alterations, which, being inclusive, provide a better vision of the origin of endometriosis and of the way it manages to develop much more effective therapeutic strategies.

In this chapter, we will discuss some aspects of the molecular genetic approach, with relevant findings on the definition and pathogenesis of endometriosis

2. Understanding endometriosis

2.1 Theories of endometriosis

Endometriosis is an estrogen-dependent chronic inflammatory disease that primarily affects women of reproductive age and is defined as the presence of endometrial glands and stroma outside the uterine cavity [1].

The first reference of endometriosis appeared in 1690, when Daniel Shroen described the presence of "ulcers" disseminated in the pelvic cavity and that appeared only in women of reproductive age. From that date, different theories have been developed in an attempt to explain its origin; however, even today, endometriosis remains an enigmatic disease.

The pathogenesis of endometriosis can be included in six theories, which in turn can be subdivided into two groups depending on whether the implants come from the uterine or extrauterine endometrium [2].

2.1.1 Origin of uterine endometriosis

2.1.1.1 Theory of retrograde menstruation

It is the most widely accepted theory about the etiopathogenesis of endometriosis. It was proposed in 1920 by Sampson. Menstruation ascends from the ostium, passes through the tubes and empties into the peritoneal cavity, with the subsequent implantation and growth of the endometrial fragments deposited in the peritoneal cavity. They represent an autotransplant, in which normal endometrial tissue is transplanted to an ectopic location in the body. This theory explains the higher frequency of endometriosis and the anatomical distribution of the lesions. However, it is not able to demonstrate the presence of endometriosis outside the peritoneal cavity, the appearance in early puberty, newborns, women affected by the Mayer-Rokitansky-Küster-Hauser syndrome or in the male [2, 3].

2.1.1.2 Theory of hematogenous or lymphatic dissemination of endometrial tissue (Halban theory)

It is based on the demonstration of ectopic endometrial tissue in locations distant from the uterus such as brain, lung, inguinal region, etc. However, on its own it is not capable of resolving its adhesion and progression capacity [2].

2.1.2 Origin of extrauterine endometrial endometriosis

2.1.2.1 The theory of coelomic metaplasia (Meyer's theory)

The peritoneum and endometrium appear to have a common embryological precursor that is the coelomic epithelium. Dioxins are proposed as a possible external chemical agent that acts as an endocrine disruptor. This theory could explain why although most women have some degree of retrograde menstruation only a small percentage have endometriosis, as well as the presence of the disease in the absence of menstruation [3–5].

2.1.2.2 Theory of endometrial stem cells

Stem cells in the circulation from bone marrow or from the basal layer of the endometrium could differentiate into endometrial tissue at different locations even from a distance. This theory would explain why women without endometriosis can have endometriosis, men with prostate cancer or after treatments can have high doses of estrogen [3, 4].

2.1.2.3 Theory of the Müllerian remains

Residual cells during embryonic development maintain the ability to develop endometriotic lesions influenced by estrogen stimulation [7].

2.1.3 Genetic predisposition

Endometriosis has a hereditary component. Susceptibility loci of the disease have been established in the 10q26 and 7p15 chromosomal regions. The endometrial cells need to adhere to each other and to the peritoneum, and integrins and cadherins participate in this process. Likewise, there is an upregulation of the antiapoptosis gene BCL-2 [5–7].

2.1.4 Hormone dependence

Endometriosis is an epigenetic disease in which the steroidogenesis factor 1, the estrogen, and progesterone receptors are hypomethylated in the ectopic endometrium causing a greater estrogenic effect locally. The endometriotic implants express aromatase and dehydrogenase of 17B-hydroxysteroid type 1, which are the enzymes responsible for converting androstenedione to estrone and estrone to estradiol. At the same time, there is a deficit of 17B-hydroxysteroid type 2, an enzyme responsible for deactivating estrogen (passes estradiol to estrone), and estrogen receptors α and β are expressed differently, with a marked increase in β receptors, favoring all this a greater estrogenic environment [8–10].

2.1.5 Resistance to progesterone

Normal endometrial tissue does not express aromatase and produces abundant dehydrogenase and 17B-hydroxysteroid type 2 in response to progesterone, ensuring the attenuation of estrogenic effects at the endometrial level during the luteal phase. In endometriosis, there is a relative resistance to progesterone that prevents the attenuation of the estrogenic stimulus. Prostaglandin E2 is the most potent inducer of aromatase activity in endometrial stromal cells and acts through the PGE2 receptor. The estradiol produced by the increased activity of aromatase increases the production of PGE2 for the stimulation of cyclooxygenase 2 in the endometrial cells of the uterus, causing a positive feedback that accentuates the estrogenic effects on the production of endometriosis [9].

2.1.6 Immunological factors

Different studies have shown the possibility that alterations in the immune system are responsible for the persistence of the ectopic endometrium, preventing immune mechanisms from eliminating endometrial cells within the peritoneal cavity [2].

These studies have shown a greater number of macrophages with altered function and alterations in the function of the natural killer cells, with a lower cytotoxic

activity, in turn an alteration in the humoral immunity to observe an increase in the concentration of IgG endometrial antibodies as well as IgG and IgA antibodies against endometrial and ovarian tissue.

2.2 Pathogenesis of endometriosis

Regardless of the mechanism that promotes endometriosis, it is a fact the presence of endometrial cells with the potential to be implanted in the receptors tissues, especially in the mesothelium of the pelvic cavity.

In the pathological process of endometriosis in the pelvic organs such as the ovary, the clinical consequence is the formation of chocolate cysts, which can be explained in different ways: (i) during each hormonal cycle, bleeding occurs in the endometriosis accumulation, with an inversion and invagination of the epithelium. At the same time, a cellular inflammatory process begins with adhesions to the surrounding peritoneum. (ii) Chocolate or endometriosis cysts affect the follicular cyst of the ovarian epithelium. (iii) A process of celomic/endometriosis metaplasia of the ovarian epithelium.

At the peritoneal level, especially in the rectovaginal septum, a natural evolution of the peritoneal endometriosis of the Douglas pouch may be caused by secondary infiltration of endometriosis emboli or metaplasia of embryonic/müllerian remains located in the rectovaginal septum [10].

A permissive peritoneal environment for the initiation and progression of endometriotic lesions may also be associated with the altered function of immune cells, together with local pelvic inflammatory processes that aid in the evasion of clearance by the immune system. In addition to the amount of menstrual endometrium reflux present in the peritoneal cavity, the altered secretion of immune factors, the formation of autoantibodies, impaired immune recognition, and the elimination of ectopic endometrial cells facilitate the initiation and progression of endometriosis. Laschke and Menger suggest that the "gut microbiome" or "microenvironment" could be crucial in the pathogenesis of endometriosis through the aberrant priming of immune responses [11].

2.3 Local microenvironment, exosomes

The endometrial lesions are composed of the same structural units as the lining of the uterus, the endometrium. This glandular epithelium is positive for cytokeratin and is apparently composed of two cell types, namely, positive E-cadherin and very few negative E-cadherin cells. The endometriotic stromal cells express mesenchymal markers such as vimentin and THY-1 and can be distinguished from the surrounding fibroblasts by, for example, expression of the CD10 metallo-endopeptidase membrane (common acute lymphocytic leukemia antigen).

The adhesive, proliferative, and invasive properties of the endometriosis conjunctive tissue, as well as the cellular functions of this epithelium can be related to the components of its extracellular matrix [13, 14].

Thus, in the pathogenesis and progression of endometriosis, the local microenvironment is vital to understand how endometriosis cells adapt to the control mechanisms of their host, escaping from immunological detections. The cell-stromal intercommunication through paracrine, hormonal, and angiogenic messengers is vital for the perpetuity of endometriosis tissue [15–17].

In a model by Hull et al., comparing the microarray data obtained from a xenotransplant model and eutopic versus ectopic endometrial paired samples, they identified alterations in four pathways: cell injury (ubiquitin/proteasome), inflammation (NFκB), tissue remodeling (TGF-β), and cell proliferation (KRAS). There is

thus an extensive metabolic reprogramming and the acquisition of changes similar to cancer that are reflected in an increase in the capacity of penetration and cellular penetration, a reduced apoptotic potential and an altered immune function [16].

The local microenvironment could also influence by altering gene expression through, for example, epigenetic changes (DNA methylation), histone modifications, and miRNA. The molecular networks associated with endometriosis are regulated by miRNA at the posttranscriptional level. In fact, 22 miRNAs aberrantly expressed in endometriotic lesions have been identified. In addition to differentially expressed miRNAs, the altered DNA methylation pattern occurs during the onset and/or progression of endometriosis. Since endometriosis is an estrogen-dependent but progesterone-resistant condition, it is not surprising that its respective promoter regions are affected accordingly [17].

In addition to the epigenetic modifications, endometriotic cells also present chromosomal abnormalities and instability that could alter gene expression by loss or mutations of DNA sequences expressed as alterations in the signaling pathways in endometriotic cells (regulatory proteins) [8, 12, 13].

Endometriosis cells release extracellular vesicles, such as exosomes and microvesicles, composed of various types of plasma membranes and origin of endosomal membrane, which are an alternative source for intercellular communication as they contain, for example, miRNAs with target genes in signaling pathways connected to the embryo-endometrial interface or enzymes and are capable of modulating cellular responses, for example, survival, differentiation, or modulation of immunogenic responses, important for endometriosis during implantation [18–23].

Exosomes containing ectonucleotidase could contribute to the progression of endometriosis and the local suppression of immune responses by regulating extracellular ATP and increasing extracellular adenosine levels [17].

They can also exert enhanced angiogenic effects. It is likely that the endometrial exosomes can be directed retrogradely in the pelvic cavity or can be detached by the menstrual cells and influence the fate of the ectopic cells. Thus, in the control of the local microenvironment, exosomes could be an important factor in allowing a temporary endometriotic lesion to establish a sufficient blood supply to grow and survive in the ectopic site. The endometrial exosomes of women with endometriosis act in an autocrine, paracrine, and endocrine fashion but in turn may play a role in the manifestation of endometriosis as a disease.

Diaphonia within the local microenvironments through the exosomes can represent the union intersection where the different theories about the pathogenesis of this entity converge. They could, through their ability to send information between tissue strains, to induce changes such as metaplasias, tissue remodeling, and even represent a mechanism of regulation/alteration in signal transduction [18].

2.4 Phenotype and cytogenetics of endometriosis

Ectopic endometrial cells have been little investigated, mainly due to the rare availability of endometriotic tissue required for cell culture and the limited number of cells, particularly those of epithelial phenotype. The proposed in vitro cell models have their limitations since the endometriotic lesions are histologically complex and contain both glandular and stromal elements. Therefore, cell lines immortalized with a cell type, which normally exhibit characteristics of undifferentiated cells, do not accurately represent the situation in vivo. Thus, to evaluate the endometriosis phenotype, the cultures are prepared in general from biopsies of the various lesions [22, 23].

Among epithelial markers, cytokeratin expression remains one of the most specific characteristics of endometriosis cells. More than 40% of the cells were

immunoreactive with the anti-progesterone receptor (PR) antibody which shows a brown nuclear stain produced by the diaminobenzidine colorimetric reaction. Less than 15% are immunoreactive with the anti-androgen receptor antibody. Cytokeratins such as vimentin were expressed in endometriotic stromal cells. Therefore, most of the phenotypic characteristics of the normal endometrium are conserved in the endometriosis cells.

The existence of genomic aberrations in the tissues of endometriosis is probably related to genes involved in the development of the disease. Most genetic changes occur as germ line defects that can result in a hereditary predisposition to the development of endometriosis with a genetic basis for endometriosis. The prevalence of the disease is higher in first-degree relatives of affected women than in the general population [21–23].

2.4.1 Chromosomal abnormalities observed in endometriotic cells, loss of heterozygosity

For decades, it has been a challenge to obtain consistent results on genetic abnormalities in endometriosis cells. The information produced by conventional cytogenetic and karyotypic studies is limited. The culture of pure endometriotic cells is hampered by the mixture of epithelial and stromal cells in addition to the inflammatory infiltrate containing fibroblasts and histiocytic cells; in addition, there may be excessive growth of normal cells [24].

Despite the difficulties, cytogenetic analysis plays an important role in the understanding of endometriosis, being the only technique that has the capacity to identify new chromosomal translocations, monosomies, and trisomies in chromosomes 11, 16, and 17.

Somatic genetic changes have been detected, distributed along several chromosomes, including chromosome 9p, 11q, and 22q. There have been allelic imbalances in 82% of endometriotic lesions diagnosed simultaneously with ovarian carcinoma.

These genetic studies have the limitation of having an adequate amount of endometriosis tissue from the patient and a simile of normal tissue to be used as control tissue, and in turn they have been limited to evaluating specific areas of the genome (detect loss of part of a chromosomal arm). But even so, they have been sufficiently useful to define the importance, in the development of endometriosis, of the inactivation of one or more suppressor genes [24–28].

2.4.2 Genetic aberrations by FISH: fluorescent in situ and hybridization comparative genomic hybridization

FISH is a technology that uses DNA probes labeled with a fluorophore to detect or confirm gene or chromosomal abnormalities that are generally beyond the resolution capability of routine cytogenetics. First, the DNA sample (metaphase chromosomes or interphase nuclei) is denatured, a process that separates the complementary strands of the double-stranded structure in the DNA double helix. To the denatured sample is then added the probe of interest, which will be associated to the DNA of the sample at the target site, in the process called hybridization, where a double helix is re-formed. The probe is covalently linked (labeled) with a fluorophore, which emits an observable signal through a fluorescence microscope; thus the DNA sample can be classified according to the presence or absence of the signal, which reveals the presence or absence of the target sequence in the chromosomal DNA.

Comparing the genetic analysis with the FISH analysis, we can see that the FISH, by not requiring endometriosis cell culture and avoiding the inconveniences of cellular heterogeneity, has been more effective in revealing clonal aberrations such as

monosomy for chromosomes 16 and 17 and an increase in the number of cells with trisomy 11 [29–33].

The comparative genomic hybridization by arrays (CGH-a) allows to realize a molecular karyotype and detect alterations inferior to 10 Mb throughout the genome. The genomic DNA of the sample and a control sample are differentially labeled with fluorescent dyes and hybridized with the oligonucleotides. The results are analyzed using quantitative methods with analysis software to determine the number of copies. It will not detect low-level mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype.

This microarray analysis uses approximately 180,000 oligonucleotides that cover the entire genome at an average resolution of 30 KB, 1714 genes with all the exons covered, 700 microRNAs, and the entire mitochondrial genome [38, 39].

Through CGH-a, primary endometriotic lesions have been examined for gains and/or chromosomal losses. The losses that predominated over the gains showed a grouping in certain chromosomal regions that suggests a recurrent non-random pattern of chromosomal alterations.

The average number of alterations of the copy in our series of endometriotic tissues was 3.1 per injury, which is low compared to malignant tissues [21].

The most common regions of loss of genomic material have been located in 1p involving at least 1p32–36 (50%), 5p (33%), 6q (27%), 7p14-p22ter (22%), 16qter (22%), and 22q12.3-qter (50%) segments. The other less common changes in the number of copies included the loss involving the arms of chromosomes 9q (22%), 16q (22%), and 17q [21, 22, 24–29, 33].

Chromosome 1 deletions were particularly common in all types and stages of endometriosis tissues, including peritoneal implants, endometriomas, and umbilical nodules. The gains were found less frequently and were located on chromosomes 6q and 17q. Several novel regions located on chromosomes 1p, 6q, and 22q that could harbor single or multiple tumor suppressor genes involved in the pathogenesis of endometriosis have been identified [38, 39].

2.4.3 Chromosomal instability in endometrial lesions

Chromosomal instability in endometrial lesions is the alteration of the chromosomal constitution that takes place in diverse pathological conditions: fundamental characteristic of the neoplasic cells (the majority of the malignant and benign tumors), precancerous lesions (dysplasia, leukoplakia, and cystically altered tissues), chronic inflammatory conditions, infectious diseases, and diseases induced by viruses (herpes, HPV, EBV, etc.).

Genomic instability is mainly caused by chromosomal alterations in non-neoplastic precursor lesions and mutation of the P53 gene, and in errors in DNA replication detected by the instability of microsatellites (deficiency in the repair mechanism of DNA mismatch) [34, 35].

Endometriosis tissues present this instability, through the presence of chromosomal copies, numerical changes, chromosomal deletions, translocations, the presence of endomitosis, premature centromeric dislocations, and the presence of micronuclei.

The loss of essential genes or even of whole chromosomes explains the high invasive potential of endometriotic cells. The genomic alterations (rearrangements) initiated can be a primary event that facilitates the initiation and dissemination of endometriosis. It is the alteration of the chromosomal constitution that takes place in diverse pathological conditions: fundamental characteristic of the neoplasic cells (the majority of the malignant and benign tumors), precancerous lesions (dysplasia, leukoplakia, and cystically altered tissues), chronic inflammatory conditions, infectious diseases, and diseases induced by viruses (herpes, HPV, EBV, etc.) [34–37].

3. Conclusions

Endometriosis, even when in essence it is not a mortal disease, is a major health problem in general due to the disability it causes in young and fertile women, in full reproductive stage.

Genetic factors play a predominant role in approximately one-third of chronic disorders in adulthood; so, it is logical to think that endometriosis in turn presents a genetic etiology. Genetic diseases in general can be chromosomal, monogenic, or multifactorial. Currently, epigenetics attempts to explain genetic and environmental interactions and studies changes in gene expression mediated by mechanisms other than the sequence changes of their nucleotides. These epigenetic changes include DNA methylation, histone modification, and interfering RNA. Epigenetic alterations are associated with inflammation and persistence of the lesions. The results of research on the role of these changes in endometriosis are very valuable in the design of future therapeutic strategies.

Currently, epigenetic studies based on FISH technology and comparative genomic hybridization have shown important chromosomal alterations, especially in chromosomes 1, 16, 17, and 22, and it is believed with greater certainty that they are the loci involved in the persistence and progression of chromosomes. Endometriosis cells.

It is in these locations where there has been an instability of DNA information through mechanisms of deletions, translocations, which have led on the one hand to the loss of important genomic information (loss of heterogizity) in endometrial diploid cells, fundamental alterations in the self-regulation, and apoptosis of these aberrant endometrial cells, by mutations as occurs with the P53 gene. These alterations not only occur in the endometriosis cell but are capable of being transmitted to other cells either in an autosomal manner when replicated, or through shared information through a microenvironment mediated by exosomes.

For the researchers, the process of analyzing cultured cells that reproduce the epigenetic changes of an endometriosis cell in vivo has been a feat, but the results of the investigation of the role of these changes in endometriosis have been very valuable and will be useful in the design of future therapeutic strategies (**Figures 1–3**).

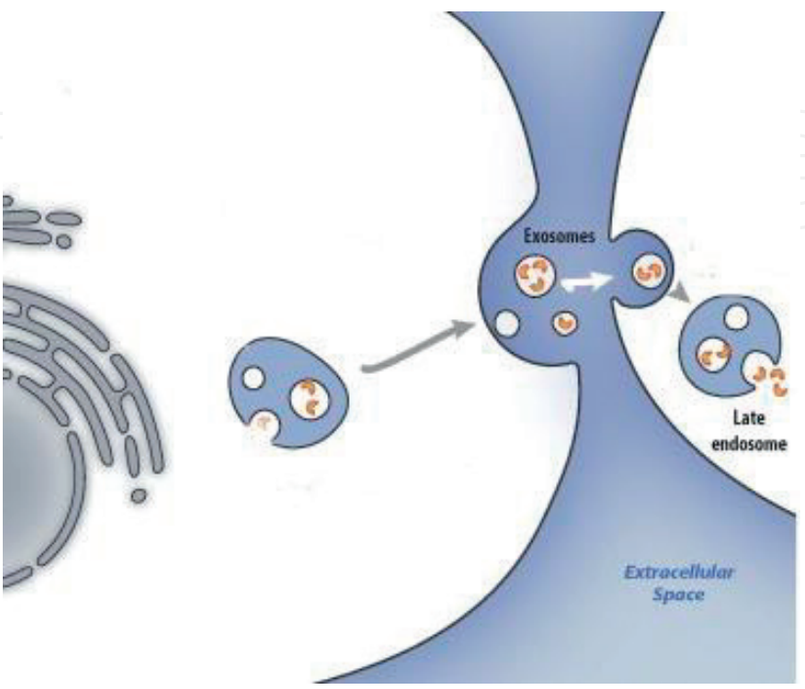

Figure 1.
Exosomes containing ectonucleotidase could contribute to progression of endometriosis.

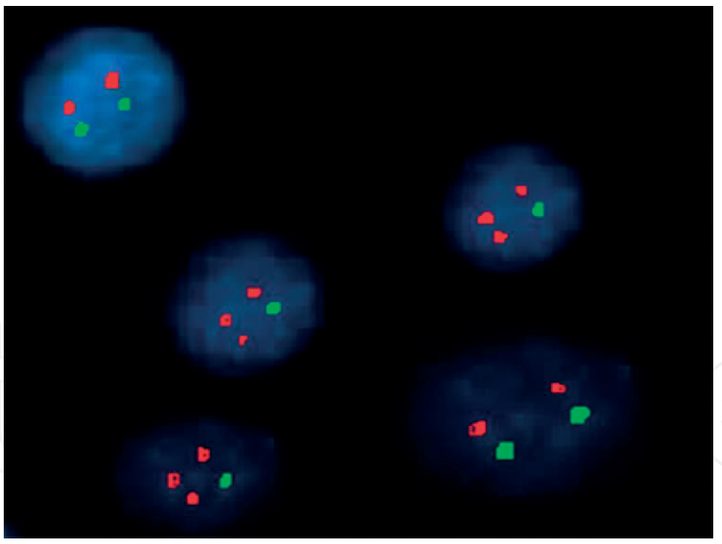

Figure 2.
Clonal aberrations detected by FISH.

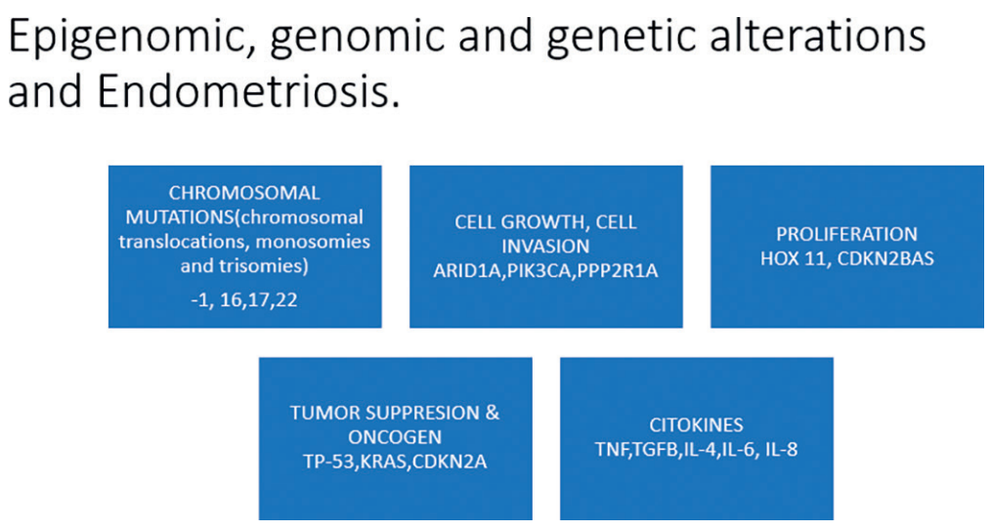

Figure 3.
Summary of alterations in endometriosis.

Conflict of interest

I certify that I do not have an actual or potential conflict of interest in relation to this article.

Appendices and nomenclature

Exosomes: are cell-derived vesicles that are present in many and perhaps all eukaryotic fluids, including blood, urine, and cultured medium of cell cultures.

Cadherin: is a group of cellular adhesive (membrane glycoprotein) that keeps cells tightly bound in time, favoring the organization of tissues and organs, facilitating the mobility of heterogeneous groups of cells.

Phenotype: A phenotype is the composite of an organism's observable characteristics or traits, such as its morphology, development, biochemical or physiological properties, behavior, and products of behavior.

Cytokeratin: are keratin proteins found in the intracytoplasmic cytoskeleton of epithelial tissue. They are an important component of intermediate filaments, which help cells resist mechanical stress.

Heterozigosity: A heterozygote is an organism that has different alleles in a gene. This organism carries different forms of a gene, where those forms produce different phenotypic results. In each case, the same gene has slight variations.

Hybridization: is the process of interbreeding individuals from genetically distinct populations to produce a hybrid. A genetic hybrid would therefore carry two different alleles of the same gene.

Monosomy: the condition of having a diploid chromosome complement in which one (usually the X) chromosome lacks its homologous partner.

Trisomy: is a type of polysomy in which there are three instances of a particular chromosome, instead of the normal two. A trisomy is a type of aneuploidy (an abnormal number of chromosomes).

Deletion: is a mutation (a genetic aberration) in which a part of a chromosome or a sequence of DNA is lost during DNA replication. Any number of nucleotides can be deleted, from a single base to an entire piece of chromosome.

Translocation: is a chromosome abnormality caused by rearrangement of parts between nonhomologous chromosomes. A gene fusion may be created when the translocation joins two otherwise-separated genes.

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