Review

Insight into the mechanisms of endometriosis associated ovarian cancers development

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Abstract

Women suffering from endometriosis face a higher risk for cancer development in ectopic endometrial tissue sites, especially in ovaries. Malignant transformation of endometriotic lesions represents a well know phenomenon, but mechanisms involved remain not entirely understood. However, novel evidences have emerged, improving our understanding of this entity. Genetic alterations, including but not limited to loss of heterozygosity, gene mutations, chromosome amplifications, overexpression of oncogenes, inactivation of tumor suppressor genes, variations in regulating genes and post transcriptional regulation of gene's expression, contribute to malignant transformation. Genetic instability is in linkage with multiple molecular processes, as production by heme and iron induced oxidative stress, local microenvironment with high concentrations of estrogens and recruitment of inflammation factors. This review summarizes the current knowledge of multileveled mechanisms potentially involved in the pathogenesis of endometriosis associated ovarian cancer.

Key Words: Endometriosis**;** Endometriosis associated ovarian cancer; Oxidative stress; estrogen

Introduction

Endometriosis represents a common, chronic gynecological disorder, affecting women of reproductive age. It's defined as the presence of functional endometrial glands and stroma in locations outside the uterus cavity (1). Prevalence of endometriosis among the general female population is 10% - 15%. However within women with infertility problems and dysmenorrhea or chronic pelvic pain it is as high as 65% (2). As endometriosis is an estrogen dependent disease, it's extremely rare after menopause, while following surgical excision of ectopic lesions, recurrences represent a common situation among younger women (3).

The etiology of endometriosis remain a difficult-to-solve puzzle, despite the fact that several hypothesis have been proposed and

Table 1.Studies on the prevalence of ovarian malignancy in patients with endometriosis.

AUTHOR	PREVALANCE	CASES
Aure et al. (8)	4%	35/831
Kurman and Craig (9)	7%	15/230
Russel P. (10)	11%	46/407
Vercellini et al.(11)	11%	63/556
Toki et al. (12)	21%	50/235
Jimbo et al. (13)	15%	25/172
Fukunaga et al. (14)	27%	50/182
Ogawa et al. (15)	29%	37/127
Vercellini et al.(16)	10%	22/209
Oral et al.(17)	8%	14/183
Machado-Linde et al. (18)	5,4%	27/496
Dzatic-Smiljkovic et al. (19)	9,1%	23/210

extensive research has been performed. The most known and accepted theory is Sampson's theory, while induction theory, celomic metaplasia proposal and embryonic cell rests hypothesis have been proposed in order to explain endometriosis development in cases that no retrograde menstruation exists. However, there is no universally accepted theory that could explain any presence of ectopic endometrial lesion and is generally considered that endometriosis development is of multifactorial etiology, including genetic, hormonal and immunological factors (4-6).

Despite the fact that endometriosis represents a benign gynecological disease, it contains features similar to those found in malignancies. Endometriotic cells as well as cancerous cells, can be both locally and distantly expanded to ectopic sites, can progressively invasively grow and can attach to other tissues and harm them (7). Endometriosis, however, does not have catabolic consequences and definitely does not represent a lethal entity.

Moreover, endometriosis is considered as a considerable risk factor for ovarian cancer development. Data demonstrate that women suffering by endometriosis have approximately 3 to 8 fold increased risk of developing ovarian cancer compared with general population (20, 21). In fact, the incidence of ovarian cancer in general population ranges between 5 and 9 new cases per 100 000 women per year and in contrast ovarian cancer is known to develop in 0.3–1.6% of women with endometriosis (22) (Table 1). Moreover, almost 40% of clear cell ovarian cancers and 10% -20% of endometrioid carcinomas are linked with ectopic endometriotic lesions (23) (Table 2). High variability among different histological types, suggest the possibility that endometriosis associated ovarian cancer may be developed through different mechanisms in comparison with non-endometriosis associated

Table 2. Relationship between endometriosis and ovarian cancer

AUTHOR	ENROLLED CASES	OR, SIR, RR, or HR	95% CI
Melin et al. (25)	64,492	1.43[2]	1.19–1.71
Kobayashi et al. (26)	6398	8.95[2]	4.12–15.3
Olson et al. (27)	1392	0.78[3]	0.25–2.44
Ness et al. (28)	12912	1.73[1]	1.10–2.71
Borgfeldt and Andolf (21)	112733	1.34[1]	1.03–1.75
Modugno et al. (29)	5051	1.32[1]	1.06–1.65
Brinton et al. (30)	104,561	1.69[3]	1.27–2.25
Rossing et al. (31)	2125	1.5[1]	1.1–2.1
Lee et al. (32)	239,385	1.90[4,a] to 18.57[4,b]	1.51 to 2.37 13.37 to 25.79
Pearce at al. (23)	21875	1.49[1]	1.34–1.65
Gemmill et al. (28)	4341	3.43[1]	1.74–6.54
Aris (33)	2562	1.6[3]	1.12–2.09
Stewart et al. (34)	3016	2.33[4]	1.02–5.35
Buis et al. (20)	3691	12.4[4]	2.8–54.2

Frequency of endometriosis in patients with ovarian malignancy.
Upper scripts: 1: OR, 2: SIR, 3: RR, 4: HR. a: recalled endometriosis, b: tissue-proved ovarian endometrioma
OR: odds ratio, SIR: standardized incidence ratio, RR: relative risk, HR; Hazard rates ratio, CI: confidence interval

ovarian malignancy. However, it should be highlighted that despite of noticed relationship between endometriosis and ovarian cancer, the overall risk in women suffering by endometriosis remains relative low, describing a relative rare entity. Nevertheless, endometriosis is still leisurely considered as a potential pre-invasive lesion and is currently classified as a tumor like lesion under the World Health Organization histologic classification of ovarian tumors (24).

Despite the doubtful potential association between those two entities, the field remains foggy, as little is known about the molecular pathways contributing to carcinogenesis and a firm causal association has not been established yet. Nevertheless, biotechnological advances over

the last decade, offered new insights of underlying mechanisms, which may be involved in malignant transformation. In this review, we aimed to highlight emerging novel data, contributing to the neoplastic progression of endometriosis (Figure 1).

Genetic imprint
Ectopic endometriotic lesions are typically monoclonal, as has been demonstrated that glands of the endometriotic tissues are genetically derived from single precursor cells, in over 60% of cases, while may reach up to 100% in others (35, 36). In addition, monoclonality represents a known and principal characteristic of malignant cells as clonal outgrowth is thought to be an essential feature of human cancers (37). Moreover, as genomic instability is another fundamental characteristic of malignancies, it has been proposed that monoclonal endometriotic cells may harbor a neoplastic potential (38). In fact, almost half of ectopic endometriotic tissues carry somatic genetic alterations in chromosomal regions compared with normal endometrium tissues. Several variations are also noticed in malignancies arising from endometriotic lesions and are considered as potential causes inclining to malignant transformation (39). However, there is highly differentiation among diverse histological subtypes, while several studies failed to replicate findings, demonstrating that it doesn't represent a universal phenomenon. Nevertheless, endometriosis might be the product of several predisposing factors, such as genetic abnormalities and genomic imbalances in specific chromosomes, for the development of ovarian cancer.

In addition, genetic substrate is strongly associated with histological features, as subtypes of endometriosis associated ovarian cancers differ not only epidemiologically, but also molecularly. In fact the prevalence of endometriosis is estimated at 4.5% in serous, 1.4% in mucinous, 35.9% in clear cell, and 19% in endometrioid carcinomas. As a consequence genetic alterations are significant varying among separated histological entities.

Loss of heterozygosity (LOH)
Many different genetic variations have been involved in the pathogenesis of endometriosis associated ovarian malignancies (Figure 2). In fact, emerging evidences advocates a crucial role for genetic activation and inactivation mutations, as well as loss of heterozygosity (LOH) at different sites throughout the genome (36, 40). LOH represent a central mechanisms responsible for alterations that might end up to neoplasia. Occurs when one of the two chromosome segments is lost and commonly indicates regions of tumor suppressor gene inactivation. Supportive to the above, is the fact that LOH represents an almost universally phenomenon among endometriosis associated neoplasia, as is recognized in up to 95% of ovarian tumors. In contrast LOH is rare in ectopic endometrial lesions without hyperplasia or any signs of transformation. However, more interestingly, LOH has high presence in endometriotic tissues adjacent or contiguous to endometriosis associated cancer cells. This indicates a potential malignant genetic transition spectrum between two entities (41). Most common LOH is recognized in chromosome arms of 4q, 5q, 6q, 9p, 11q and 22q when both endometriosis and neoplasia exist (42). However, the most frequently detected LOH is on locus 10q23.3, where one of the most well-known and studied tumor suppression genes, Phosphatase and tensin homolog (PTEN), is encoded (43). LOH as well as mutations of this gene are frequent in numerous of neoplastic lesions and in ovarian cancers. Accumulating data demonstrate that PTEN inactivation is common among ectopic endometrial tissues and especially in endometriotic cysts. Those evidences are in favor of the plausible hypothesis that this may represents the first step of cell's malignant transformation. In fact, this may be the underlying
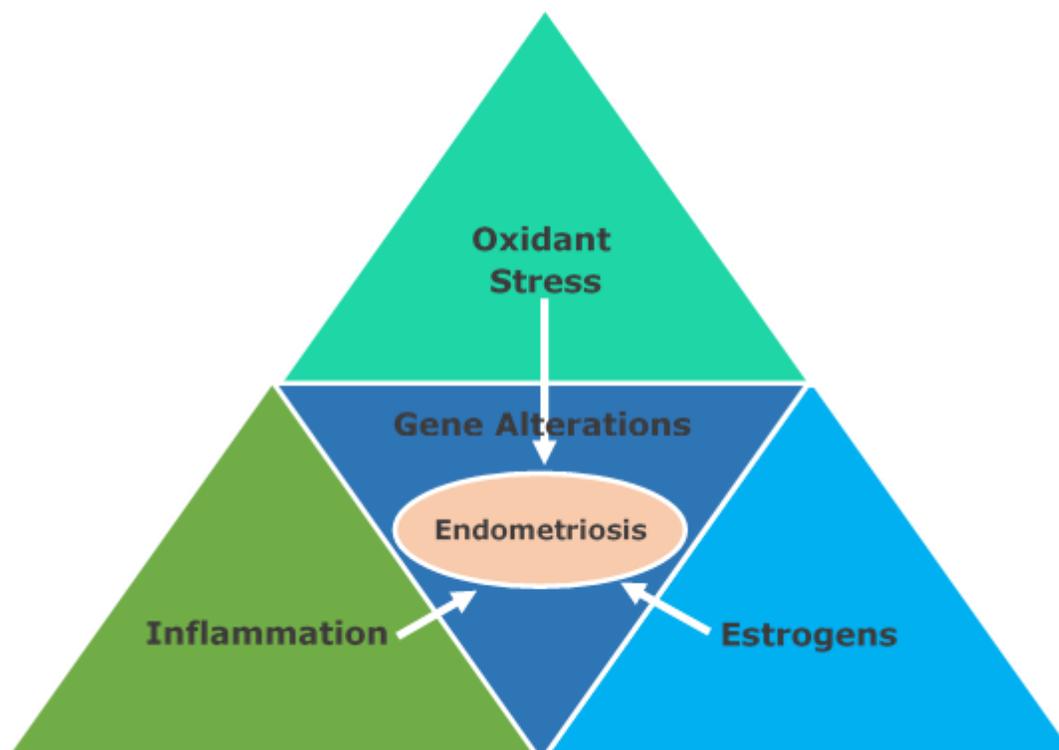
Figure 1. Schematic presentation of potential different mechanisms involved in the malignant transformation of endometriotic lesions. Please note that all those events are also associated with development of non-malignant endometriosis.

mechanism in up to 40% of endometriosis associated clear cell carcinomas (44). Future studies on LOH may multiply our knowledge on which alterations really act as redepositing factors for malignant transformation.

Tumor Suppression genes
Newer evidences focus on significant role of ARID1A inactivation mutations. ARID1A represents another tumor suppressor gene, encoding a protein involved in chromatin remodeling via the multi-protein Switch/Sucrose non-fermentable (SWI–SNF) complex (45). The SWI–SNF family is an epigenetic regulator that plays vital role in transcription and in the repair of DNA double-strand breaks by interacting with phosphorylation of γH2AX via a direct action on chromatin, while prevents DNA damage induced apoptosis (46, 47). In fact, ARID1A gene's mutations are present in up to 60% of clear cell cancers and 50% of endomitrioid cancers, while the incidence in endometriotic lesions is as high as 40%. However, interestingly these changes are not observed in high-grade serous ovarian carcinoma (48, 49).

Of at least equivalent significance seems to be the role of mutations in another gene regulating cell cycle, differentiation and apoptosis as well as DNA repair. Crucial part plays p53 gene (located at chromosome 17p13.1) as conserves stability by preventing genome mutation. However, inactivation of p53 may leads to disruption of its multilevel anticancer functions and allow uncontrolled cell development. Actually, gene mutations or LOH associated with chromosome 17 have been demonstrated in up to 50% of the
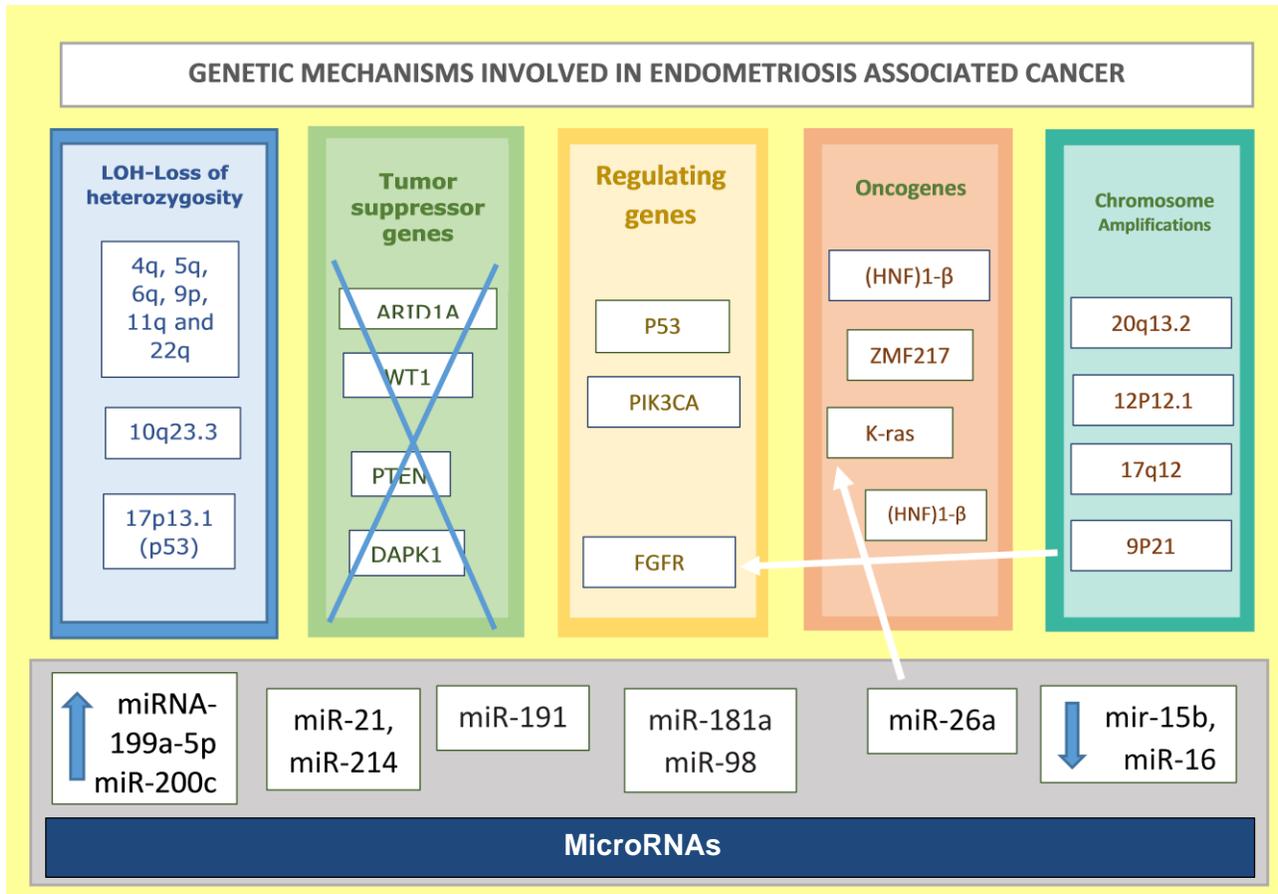
Figure 2. Summary of main genetic mechanisms involved in pathogenesis of endometriosis associated malignancies. Arrows indicate the correlations between different genetic mechanisms.

endometriotic cells those are located in close proximity to ovarian cancer cell (50, 51). P53's role seems to be of critical importance in development of serous ovarian cancer tumors, as almost all high-grade cancers of that subtype harbor mutations. In contrast, in development of clear cell carcinomas p53 mutations are relatively uncommon and possibly of not high significance. Another important panel of different mutations has been reported regarding Wilms tumor suppressor gene (WT1). In both endometriotic lesions and endometriotic associated tumors have been demonstrated WT1 gene inactivation (52).

Chromosome amplifications

Apart from chromosome loss, as predisposition factors for malignant transformation of endometriotic lesions have also been described chromosome amplifications. In fact, in clear cell carcinomas arising from endometriotic lesions DNA copy number gains are frequently observed, while somatic copy number alterations are rare in serous carcinomas. An area of emerging importance is located at chromosome 20 q13.2 region, which harbors a potential oncogene (ZNF217). This oncogene, that has long been demonstrated to be activated in breast cancer, may promote neoplastic transformation by increasing cell survival during telomeric crisis, and may promote later stages of malignancy by increasing cell survival (53). Another target of potential interesting is located in chromosome

9p21. Amplification of that region has been demonstrated in endometriotic lesions as well as in clear cell carcinomas developing in endometriotic substrate. It is associated with activation of EGFR, via over-expression of the receptors and multiplying its critical role in cell proliferation, apoptosis, angiogenesis and metastasis. Several other amplifications have been reported, however their potential role remains still unclear. Those alterations in genomic architectural profiles encompass a number of genes, including K-ras in 12p12.1, Hepatocyte nuclear factor (HNF)1-β in 17q12 and Polo-like kinases (PLK) that phosphorylate Emi1 (Early mitotic inhibitor-1) (54). The most appraisable mechanism of action underlying in chromosome amplification remains through oncogenes activation and overexpression, however further studies are needed to reveal potential mechanisms of action (55).

Oncogenes
Apart from suppression of tumor suppressing genes, overexpression of regulating genes or oncogenes may result in neoplasia. However, evidences of activation of oncogenes in endometriosis are limited and only for K-ras oncogene exist sufficient data supporting its role, especially in mucinous carcinomas development, while it has been shown to be activated in almost one third of 33% of low grade serous carcinomas (44). Additionally, overexpressed is also Hepatocyte nuclear factor (HNF)1-β. As this gene's dependent pathway inhibits apoptosis and stimulates glycogen synthesis and plays an important role in chemoresistance, its overexpression may contributes in cancer cell's energy provision, expansion and progression (56, 57).

Regulation genes
More clarified and of significant importance is the role of the phosphatidylinositol-3-kinase PI3K/AKT pathway enforced by PIK3CA activating mutations. PI3K/AKT pathway has important role in regulation of cell cycle, proliferation, cell adhesion formation and apoptosis. Activation of PIK3CA gene is a frequent phenomenon in endometriosis and regulates FOXO1 protein, a member of the forkhead-box O family and the decidua-specific gene IGF binding protein-1 (IGFBP-1), which are both involved in the decidualization of endometrial cells. Moreover, has been helpful for survival, adhesion and proliferation of endometrial cells in abdominal cavity, but its overexpression has also been demonstrated in up to 40% of clear cell carcinomas (58).

MicroRNAs (miRNA)
Despite of confidence evidences demonstrating that gene alterations represent a crucial factor promoting oncogenesis, emerging indications suggest that there could be a collaboration between different mutations in endometriosis associated ovarian tumorigenesis. In addition, novel evidences focus on MicroRNAs (miRNA), a group of single-stranded, noncoding, small RNA that regulate gene expression through inhibiting translation or promoting degradation of the target mRNAs. Their role remains partially unclear, but miRNAs dysregulation and abnormal expression has been demonstrated in the development of endometriosis associated ovarian cancer (59). Several miRNAs contribute to gene regulation during endometriosis development, as miRNA-199a-5p that enhance angiogenesis (60). Furthermore, miRNAs may interact with mechanisms of suppression of tumor suppressor genes or overexpression of oncogenes. In fact, prominent expression of miR-21, and miR-214 has been demonstrated to play a crucial role in oncogenesis procedures, as directly target PTEN and promote its deletion (61). On the other hand, there are indications that miR-26a is involved in stimulation of K-ras oncogene. Most evidences are available regarding potential role of MiR-191. MiR-191 is one of the most differentially

expressed miRNAs in pairwise comparisons among healthy controls and patients with endometriosis associated cancer, while its role has been demonstrated in several other cancer types. However, its targets in different types of cancer might be different. Raised miR-191 expression acts through NDST1 in gastric cancer, TIMP3 in colorectal cancer, CDK6 in thyroid follicular tumors and MDM4-C in ovarian cancer. As a consequence, despite the fact that miR-191 overexpression is persistent in endometriosis associated tumors, its downstream network is still not clarified. Accumulative evidences suggest that miR-191 may interact through a regulative role on Death-associated protein kinase 1 (DAPK1). DAPK1 is a tumor suppressor and a positive mediator of programmed cell death through interaction with several death-inducers such as oncogenes, INF-γ and TNF-α. As a consequence, its downregulation contributes to enhanced cell survival and reduced sensitivity to apoptotic signals. Another possible mechanism of action of miR-191, may be through regulation of the metalloprotease family members (MMPs) and especially Metalloproteinase inhibitor 3 (TIMP3) (62). Noteworthy, decreased levels of TIMP3 have been noticed in several malignancies, including endometrioid carcinomas. MMPs are important modulators of cells interactions with nearby tissues and may be related to migration and invasion of endometriotic epithelial and stromal cells. MiR-191 overexpression directly enhance elevations of TIMP3 levels, which increase malignant features and transformation of endometiotic cells. This mechanism of action is also the target for several others miRNAs, which have been found to be elevated in endometriosis associated tumors, such as miR-181a and miR-98 (63). In addition, several other miRNAs have been shown to be dysregulated in endometriosis associated cancer, but their mechanism of action remains enigmatic. Those include, but are not limited to upregulation of miR-200c and downregulation of mir-15b and miR-16 (61, 64) MiRNAs represent at

the moment one of the most promising fields for research that could enlighten our understanding on malignant transformation of endometriosic lesions in the ovaries.

In summary, there are not clear and conclusive incidences of association between endometriosis and endometriosis associated cancers, however current data demonstrate that underlying genomic characteristics may play a role in specific histological subtype's malignant transformation processes and further research is required.

Linked effecting factors

As endometriosis represents a disease of multifactor etiology, it's suggested that apart of hesitant and unconvincing genomic alterations, several other procedures, including oxidative stress, inflammation, and hyperestrogenism accumulate to malignant transformation of endometriosis in the ovaries, but underlying mechanisms remain enigmatic.

Oxidative stress has been recognized as a vital factor for progression of endometriosis. In conditions of hemorrhage and hemolysis, heme and free iron are produced and as pro-oxidant factors can induce oxidative stress and DNA damage. The endometriotic cells are particularly prone to DNA damage due to direct exposure to oxidant factors (65). Effects are mediated by cellular antioxidant defense. However, the ability to survive the oxidative action, promoted by antioxidant enzymes such as cytochrome P450 and GST, may be a predisposing factor for further alterations. As each endometriotic cell displays noteworthy differences with regard to the level of responsiveness to free radicals or antioxidant defense, some cells undergo genomic changes associated with defective genomic repair, incomplete DNA replication, and finally genomic instability. Their ability to avoid apoptosis, survive and proliferate effectively despite of oxidative stress may contributes to malignant transformation. The altered balance between prooxidant and antioxidant activities in

association with genomic instability and mutations may have an impact on malignant transformation of endometriosis (66-68).

Moreover, inflammation induced procedures are essential in both establishment and progression of endometriosis and carcinogenesis. Inflammatory cells secrete growth factors and proinflammatory cytokines, including MMPs, interleukins, intercellular adhesion molecules and tumor necrosis factors, inducing cell survival and proliferation, angiogenesis, inhibition of apoptosis, expansion, invasion of nearby tissues and production of oxidant factors that cause DNA damages. Several studies have shown local inflammation in ectopic endometriotic lesions and higher sensitivity of endometriotic cells to cytokines may contributes to presentation of carcinomatous features through increased synthesis of prostaglandin E2 (PGE2) (69-72).

In addition to oxidative stress and inflammatory processes, important role demonstrates hormonological microenvironment in both entities. Endometriosis is an estrogen dependent disease and establishment of a rich in estrogen microenvironment is of crucial importance for development and proliferation of ectopic lesions. In addition, estrogen represent a risk factor for the development of neoplasia in estrogen dependent tissues. Both higher expression of aromatase enzyme and polymorphisms of enzymes 17betahydroxysteroid dehydrogenase have been proposed and supported by studies (73).

Aromatase catalyzes the conversion of androstenedione to estrone and testosterone to estradiol and higher levels have been demonstrated in ectopic endometrial tissues compared to eutopic endometrium. Such activity results in high local levels of estrogen promoting endometriosis development. Other data focus attention on 17β-hydroxysteroid dehydrogenase enzyme types 1(HSD17B1) and 2 (HSD17B2) (74-76). HSD17B1 poses the ability to catalyze the conversion of estrone to the more biologically active estradiol in the final step of estrogen synthesis. Studies suggest that HSD17B1 polymorphisms, which can potentially cause alterations in their biological function, play an important role in endometriosis, while other studies underestimate their importance. On the other hand HSD17B2 has reverse action and catalyzes the inactivation of estradiol to estrone and in endometriosis, mutations are present. Independently of the predominant disorder, elevated estrogen levels trigger cyclooxygenase-2 (COX-2) production, giving rise to increased PGE2 formation. PGE2 is involved in tumor progression but poses a significant role in hormonal regulation by stimulating aromatase activity and establishing a positive feedback loop in favor of continuous estrogen production (77). Excessive estrogen formation, through estrogen receptor type alpha (ERa) may be involved in potential carcinomatous transformation, as the existence of such a mechanism has been previously described. Accumulating to this action may also be the fact that ERa levels are higher in active endometriosis compare to eutopic endometrium (77). Furthermore, as endometriotic lesions seem to have higher relative progesterone resistance, progesterone's role, which repress estrogen receptors and competes estrogens action, is limited.

Concluding remarks
Endometriosis is a relatively common benign disease in females of reproductive age, but the risk of malignant transformation of endometriotic lesions has been strongly underestimated in the past, although the risk of developing ovarian carcinoma from endometriosis is remains low. The exact molecular mechanisms that may be involved remain unclear, but novel procedures have strongly increased our knowledge. Genetic alterations, in several different genetic locations that may modify cell's cycle, proliferation and ability to attach, or even direct activation of oncogenes or suppression of tumor suppressor,

individually or in interaction, may contribute to development of malignant features. That genomic instable substrate, in association with oxidative stress, inflammatory processes and estrogen abundance may partially contribute in advance of ovarian cancerous lesions in ground of endometriosis.

Abbreviations

COX-2	cyclooxygenase-2;
DAPK1	Death-associated protein kinase 1;
Era	estrogen receptor type alpha;
HSD17B1	17β-hydroxysteroid dehydrogenase enzume type 1;
HSD17B2	17β-hydroxysteroid dehydrogenase enzume type 2;
IGFBP-1	IGF binding protein-1;
LOH	loss of heterozygosity;
miRNA	MicroRNAs;
MMPs	metalloprotease family members;
PGE2	prostaglandin E2;
PTEN	Phosphatase and tensin homolog gene;
SWI–SNF	Switch/Sucrose non-fermentable complex;
TIMP3	Metalloproteinase inhibitor 3;
WT1	Wilms tumor suppressor gene;

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