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Integrating modern approaches to pathogenetic concepts of malignant transformation of endometriosis

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Abstract. In the present study, we summarize the role of the shared and independent (epi)genetic background between endometrioid carcinoma (EC) and clear cell carcinoma (CCC), two histological subtypes of endometriosis-associated ovarian cancer (EAOC). Using the PubMed database, we conducted a literature review of various studies related to the malignant transformation of endometriosis. Both endometriosis and EAOC face potential environmental hazards, including hemoglobin (Hb), heme and free iron, which induces DNA damage and mutations. Although EC is distinguished from CCC due to different morphologies, both represent common environmental profiles and maintain the similar (epi)genomic abnormalities with multiple overlaps and share similar molecular signatures. By contrast, EAOC also has disease-specific gene signatures corresponding with each histological subtype: Estrogen receptor promotes EC cell proliferation ('go') and hepatocyte nuclear factor-1β (*HNF-1β*) induces CCC cell cycle arrest ('stop') under oxidative stress conditions. This model underscores a subtype-dependent 'go or stop' dichotomy, possibly through better ability to adapt in a changing environment. It was found that cyst fluid Hb and iron concentrations were significantly lower in EAOC when compared to benign ovarian endometrioma (OE), supporting the hypothesis that the redox imbalance plays a key role in the pathogenesis of EAOC. There are at least two phases of iron carcinogenesis and tumor progression: The initial wave of iron-induced oxidative stress and DNA mutations would be followed by the second big wave of subsequent synthesis of the antioxidants, which diminishes cellular oxidative stress capacity, increases apoptosis resistance and promotes tumor initiation and progression. Special emphasis is given to novel pathophysiological concepts of malignant transformation of endometriosis.

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Introduction

Endometriosis is defined as the presence of the ectopic implantation of endometrial glands and stroma at extra-uterine sites. Endometriosis is a common, chronic inflammatory disease that affects ~10% of women of reproductive age (1,2). The common symptoms of this disease are dysmenorrhea, dyspareunia, chronic pelvic pain and infertility (1,2). Epidemiologically, endometriosis has been reported to increase the risk of certain types of malignancies, particularly for ovarian endometrioid carcinoma (EC), clear cell carcinoma (CCC), low-grade serous carcinoma and seromucinous neoplasms (3-6). CCC and EC of the ovary are the two most common types of ovarian cancer, which arise from endometriosis (4-6). Endometriosis is found in approximately 20% of EC and CCC cases, presents adjacent to the tumor, and has direct topological continuity with the carcinoma (3). Patients with endometriosis-associated ovarian cancer (EAOC) belong to the relatively younger-aged population, and have early-stage and low histological grade tumors compared with non-EAOC patients (7). EAOC tumors frequently occur in perimenopausal and early postmenopausal women. Ovarian cancer is known to develop in approximately 1% of women with endometriosis (4). Endometriosis may be related to an increased risk of EAOC; however, the underlying mechanism remains largely unknown. Over the past decade, a dramatic shift has occurred in our understanding of the pathophysiology of EAOC.

The aim of the present study was to provide an overview of the current pathophysiological concepts of the malignant transformation of endometriosis. We summarize recent knowledge about the role of the shared and independent (epi)genetic background between EC and CCC, and the current hypotheses regarding the pathophysiology of the malignant processes.

Data collection methods

A computerized literature search was conducted to identify relevant studies reported in the English language. We collected a comprehensive literature search from the PubMed and Embase databases up to April, 2018, combining the keywords 'endometriosis', 'endometriosis-associated ovarian cancer', 'endometrioid carcinoma', 'clear cell carcinoma', 'pathogenesis', 'carcinogenesis', 'oxidative stress', 'hemoglobin', 'iron', 'inflammation', 'endothelial cells', 'extracellular matrix' and 'microenvironment'. A variety of combinations of these

terms were used, depending on which database was searched. Furthermore, the references of each article were searched to identify potentially relevant studies. Publications of original studies and review articles were included, while those documenting opinions, points of view or anecdotes were discarded.

Results

The mechanisms underlying the malignant transformation of endometriosis. The gene expression profile-based clustering divided ovarian cancer into two groups, type I and type II, which is generally based on the potential clinical and translational value of the dualistic model of ovarian carcinogenesis (8,9). Type I ovarian cancer consists of patients with low-grade serous, mucinous, EC, CCC and slow-growing tumors, while type II is composed of patients with rapidly-growing high-grade serous carcinoma (HGSC) and highly aggressive malignancies (8,9). EAOC belongs to the type I category and consists of two major subtypes originating from EC and CCC, which exhibits different pathological and clinical features, characterized by unique morphologies and responses to treatment (6).

EC may occur during an estrogenic mode of action due to the observed induction of estrogen receptor (ESR) isoforms (10-14). Estrogen is considered to be involved in ovarian cancer progression (15). The Wnt/β-catenin signaling pathway regulated by estrogen is highly activated in EC and inhibits oxidative stress-induced cell apoptosis (16-18). By contrast, estrogens are known to produce reactive oxygen species (ROS) and are implicated in cellular carcinogenesis, as chronic oxidative stress promotes cell growth, survival and the tumorigenic potential of breast cancer cells (19). In the present study, we provide an update on the recent advances in the understanding of the reduction-oxidation (redox)-related molecular signaling and imbalance in the cellular redox state in malignant transformation of endometriosis (8,20-27). The pathogenesis of the malignant transformation of endometriosis remains obscure; however, the results of several studies support the hypothesis that the redox imbalance, inflammatory/immune response, cell cycle regulation and hormone activity are the deregulated functions and act in a dynamic epigenetic network (20,22,23,24).

Redox imbalance: Possible unexpected results. Repeated episodes of hemorrhage occur in endometriosis throughout menstruation (23). Red blood cells accumulate in ovarian endometrioma (OE) and in the pelvic cavity through retrograde menstruation. The destruction of red blood cells leads to the release of Hb, heme and free iron (22,28). While Hb provides life-sustaining oxygen delivery, extracellular free Hb produces toxic heme degradation products and is a source of ROS due to inherent peroxidase activity (22,28,29). These findings are consistent with and are supported by *in vitro* experimental data (30) and *in vivo* clinical data (31). Yamaguchi *et al* presented, for the first time, that the iron-induced persistent oxidative stress within the endometriotic cyst leads to dynamic changes in the oxidative environment, which may play a crucial role in the process of endometriosis carcinogenesis (30). The authors reported that patients with endometriotic cysts had significantly higher cyst fluid concentration of free iron (100.9 mmol/l = 5,635 mg/l), compared to those with non-endometriotic cysts (0.075 mmol/l = 4.19 mg/l) (30). Free iron concentrations in CCC (4.27 mmol/l = 238 mg/l) were 20-fold lower than those in endometriotic cysts (30). Since free iron has a propensity to induce oxidative stress, DNA damage, protein modification and lipid peroxidation, we hypothesized that patients with EAOC would have much higher levels of iron-related compounds compared with those with benign OE. Therefore, Yoshimoto *et al* extensively investigated cyst fluid levels of iron-related compounds in benign OE and EAOC (31). The median ± SD concentrations of total iron, heme iron and free iron for OE and EAOC cysts were 244.4±204.9 mg/l vs. 14.2±36.6 mg/l (total iron), 303.9±324.4 mg/l vs. 27.6±53.4 mg/l (heme iron), and 13.5±16.2 mg/l vs. 3.9±2.7 mg/l (free iron), respectively (31). The concentrations of total iron, heme and free iron in EAOC were 17-, 11- and 3-fold lower than those in OE, respectively (31). There are no significant differences in cyst fluid concentrations of iron-related compounds between patients with CCC and those with EC. Several assays for the measurement of iron-related compounds are available: In a previous study, there was a significant difference in the cyst fluid iron levels between the two methods (30,31), which may be due to the different chelate colorimetric assay methods and differences in their analytical performances. Notwithstanding these limitations, patients with EAOC had much lower levels of iron-related compounds compared with those with benign OE.

Hemoglobin, heme and free iron in endometriotic cysts can lead to distortion in the homeostatic redox balance, the so-called redox imbalance (22). Total iron is composed of heme iron and nonheme iron (free catalytic form of iron, Fe^{2+}). Free iron is labile and catalyzes the Fenton chemical reaction, resulting in the generation of hydroxyl radical ($^{\bullet}OH$) as follows: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {}^{\bullet}OH$. The iron-dependent Fenton reaction has been shown to lead to genomic alterations, including a *Cdkn2a/2b* deletion and a *Met* amplification, during carcinogenesis in an animal model (32). Yoshimoto *et al* found, for the first time, that the great majority of iron in the cyst fluid is considered to be heme iron, but not free iron (31). Hemoglobin and heme iron are oxidized from the oxyhemoglobin (oxyHb-Fe^{2+}) to the methemoglobin (metHb-Fe^{3+}) with generation of the superoxide anion (O_2^-) as an autoxidation as follows: Hb-Fe^{2+} (oxyHb) + $O_2 \rightarrow$ Hb-Fe^{3+} (metHb) + O_2^-. Since heme iron is abundant in the cyst fluid of benign OE, autoxidation, rather than the Fenton reaction, may be the main process accomplishing the oxidative reaction.

It would be of interest to determine the origin and biological function of metHb that is abundantly expressed in benign OE. Peritoneal concentrations of nitric oxide (NO) metabolites (nitrite and nitrate) in patients with endometriosis have been shown to be significantly higher than those in patients with non-endometriosis (33). Inducible NO synthase (iNOS) is an enzyme that catalyzes the production of NO from L-arginine. The mRNA level of *iNOS* has also been shown to be higher in the endometriosis group than in the non-endometriosis group (34). Thus, the serum NO level is elevated in the endometriosis group as compared to the control group due to the induction of iNOS. NO can oxidize oxyHb to metHb as follows (35): $HNO + 2[HbO_2]^{2+} \rightarrow 2[Hb]^{3+} + NO_3^- + HO_2^-$. Therefore, metHb is known as an oxidative stress marker and

causes production of free radicals to induce oxidative stress by reacting with peroxides (hydrogen peroxide, lipid hydroperoxides) (29). MetHb is downregulated in EAOC when compared to benign OE, which supports the hypothesis that paradoxically, a shift in the balance between oxidants and antioxidants in EAOC is in favor of antioxidants (24). Glutathione, one of the most abundant endogenous antioxidant, is responsible for the conversion of metHb to oxyHb (36). It plays a role in repairing damage induced by oxidative stress in cancer cells and stops the process of cancer cachexia (36). Glutathione constitutes the survival advantage for cancer cells and is required for cancer initiation and progression (37,38). To date, a number of studies have demonstrated that the oxidant-antioxidant imbalance plays a critical role in the initiation and progression of multistage carcinogenesis of endometriosis (23,30,39-41). These studies support the redox imbalance hypothesis that there are at least two stages of iron carcinogenesis and tumor progression: The initial wave of iron-induced oxidative stress would be followed by the second big wave of subsequent synthesis of the antioxidants, which diminishes cellular oxidative stress capacity, increases apoptosis resistance and promotes tumor initiation and progression.

Similar epigenetic modifications: Gene-environment interactions. The practical and theoretical implications was discussed with regard to the current knowledge of epigenetic modifications in benign OE and EAOC. An excess of heme iron and non-heme iron is toxic to cell and tissue components. Hackett *et al* reported the quantification of total iron from the hematoma folllowing an intracerebral hemorrhage in an animal model (42). Neuronal cell death was observed at a concentration of ~1.0 $\mu g/cm^2$ (42). The iron concentration of the brain tissue at the periphery of the hematoma has also been shown to be ~400 mg/l in two human subjects (43). The iron concentration in OE (244.4 mg/l) is almost similar to intracerebral hemorrhage (400 mg/l), suggesting that endometriotic cells may face the crisis of death. Under prolonged stressful conditions, endometriotic cells must cope with various internal and external ROS for survival. The choice between cell survival and death depends on the net result of ROS production and their elimination by antioxidative enzymes (44). High levels of ROS promote DNA damage and cell death, although perhaps surprisingly, low levels of ROS are known to be associated with the development of tumors and then the process of carcinogenesis (22-24,31). Thus, an imbalance in the cellular redox state may play an important role in the mechanism of its long-term carcinogenic effect; gene-environment interactions may modify an individual's susceptibility to this type of cancer.

High ROS levels damage the mitochondrial DNA and promote its mutation, which affects the epigenetic control mechanisms of nuclear DNA, by decreasing the activity of some methyltransferases, thus causing DNA hypomethylation (45). ROS-induced oxidative stress is associated not only with global/genome-wide DNA hypomethylation, but also with tumor suppressor gene promoter-specific aberrant hypermethylation via the upregulation of the expression of DNA methyltransferases (46). CpG clusters are susceptible to oxidative DNA damage to cytosine in the Fenton reaction, which is the main cause of cytosine-to-thymine transition mutations (47,48). Therefore, the dynamics of DNA methylation at CpG clusters can drive an increased likelihood of genetic mutations. Epigenetic mechanisms and then genetic mutations are considered to contribute to the necessary plasticity of endometriotic cells. Recent studies have attempted to link genetic modifications with epigenetic or environmental risk factors for EAOC (23,49). These results shed light onto the mechanisms underlying the associations of environmental stimuli and redox imbalance with risk of developing EAOC.

Defective CpG methylation affects several genes involved in endometriosis malignant transformation, such as Runt-related transcription factor 3 (*RUNX3*), human mutL homolog 1 (*hMLH1*), E-cadherin (*CDH1*), Ras-association domain family of gene 2 (R*ASSF2*), *p16*, AT-rich interactive domain-containing protein 1A (*ARID1A*) and phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*) by promoter hypermethylation (50). By contrast, steroidogenic factor-1 (*SF-1*), a transcriptional factor essential for estrogen biosynthesis, has been shown to be hypomethylated and aberrantly expressed (51). Furthermore, oxidative stress (exogenous H_2O_2) downregulates *ARID1A* mRNA and protein expression (39,52,53). Oxidative stress recruits DNA methyltransferase to chromatin (54), and also modifies the expression of CpG demethylases, such as ten-eleven translocation (*TET*) and jumonji (*JMJ*) genes (49). These genes may be involved in the development of endometriosis and its malignant transformation. The epigenetic switch occurs even in benign endometriosis (49).

Similar genetic abnormalities. Furthermore, endometriosis and EAOC harbor not only multiple somatic gene mutations, but also epigenetic modifications. Herein, we provide overview of the possible pathogenesis of malignant transformation of endometriosis that have exhibited distinct tumor morphological and phenotypical features, but have suggested similar (epi)genetic abnormalities. EC is distinguished from CCC due to different morphologies, but both represent common environmental profiles (53) and maintain the similar genomic abnormalities with multiple overlaps and share similar molecular signatures (54). Recent microarray, targeted sequencing and whole genome studies have identified that somatic mutations of AT-rich interaction domain 1A (*ARID1A*), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*), *PTEN*, KRAS proto-oncogene, GTPase (*KRAS*), catenin beta 1 (*CTNNB1*) and mutL homolog 1 (*MLH1*) were commonly found across EAOC (55-61). EAOC and adjacent endometriotic lesions exhibited common multiple cancer driver gene mutations, suggesting that they can share extensive genetic similarity, a common genomic origin and a common lineage (62-65).

We hypothesized that endometriotic cells would acquire (epi)genetic modifications required for survival among the harshest and poorest environments. The cells selected for oxidative resistance enable clonal expansion/differentiation and could survive (66). Indeed, endometriosis is considered to be monoclonal in origin and neoplastic in nature (67). Surprisingly, mutations of classical cancer driver genes have been observed in 4% of a histopathologically benign OE and 26% of deep infiltrating endometriosis in cancer driver genes, including *ARID1A*, *KRAS*, *PIK3CA* and *PPP2R1A* (64,65).

The existence of somatic driver mutations occurring in the epithelial glandular cells but not the stromal cells of the same endometriosis lesion (64) implies that endometriotic epithelial cells might incur an advantage through selective survival or proliferation and that the stromal cells are resistant to environmental hazards.

CCC-specific (epi)genetic profile. Despite a similar genetic profile, EAOC tumors present a different biological profile (68). Several studies have provided new insight into the signaling pathway of genes differentially expressed between EC and CCC. The interpretation of differentially expressed genes has verified the dysregulated biological functions related to glucose utilization, cell cycle regulation and hormone metabolism, that plays important role in the development of EAOC (60,68-70). Transcription factor hepatocyte nuclear factor-1β (*HNF1B*) was identified as a biomarker of ovarian CCC histology, but not EC, with the hypomethylation of the *HNF1B* promoter influencing the characteristic biology (60,68,70-75). Endometriosis is composed of two subgroups: HNF-1β-positive and -negative cells (71). The expression patterns have been shown to be similar in a contiguous transition from endometriotic cells to atypical cells to CCC (60). HNF-1β-positive endometriotic cells may represent a prototypical lineage of CCC cells. Much interest has been focused on HNF-1β, which is commonly upregulated in endometriosis and CCC. HNF-1β is associated with the normal development of the liver, pancreas, gut, lungs and kidneys, and its mutations represents the frequent occurrence of familial forms of type 2 diabetes (68). The exact biological function of the HNF-1β gene in CCC has been widely reported: This gene plays key roles in glycogen synthesis, anti-oxidative defense, anti-apoptosis, resistance to anticancer agents and cell cycle regulators at G2/M transition (73,76,77).

First, in the elegant review, Mandai *et al* provided new insight into the biological impact of CCC in a tumor microenvironment via the upregulation of HNF-1β expression (68). HNF-1β upregulates glucose uptake and glycolysis to give rise to an increased yield of lactate in CCC, which is known as the Warburg metabolic phenotype (68,78). The Warburg effect benefits cancer cells to avoid excess ROS generation and thus gains increased survival advantage in iron-rich stressful environments such as endometriosis. The genes involved in glucose homeostasis, including dipeptidyl peptidase 4 (*DPP4*) (79) aldolase B (*ALDOB*) (80), glucose transporter-1 (*GLUT-1*) gene and several key enzymes in the glycolytic process (78), are downstream targets of *HNF1B*. HNF-1β thus may be a key regulator of glycolysis, gluconeogenesis and glucose homeostasis.

Second, HNF-1β actually reduces and protects cancer cells from oxidative stress by markedly changing antioxidant activity (78,81,82). HNF-1β may repair damage caused by oxidative stress and can promote survival by upregulating antioxidant proteins via binding with antioxidant response element (37,68,81,83,84). This gene upregulates the synthesis of glutathione (GSH), a powerful antioxidant (85). HNF-1β also triggers ROS resistance in CCC cells via rBAT, a cystine transporter (68). Thus, HNF-1β reduces oxidative stress and confers ROS resistance and a survival advantage in CCC cells (37,68).

Finally, it would also be of interest to determine the mechanisms underlying the protective effects of HNF-1β on cells against any cytotoxicity and genotoxicity caused by ROS when CCC cells were exposed to a stressful environment. DNA damage occurs continually through various intrinsic and extrinsic stressors such as ROS, ultraviolet radiation, smoking and errors during replication (86). In endometriosis, environmental hazards, including hemoglobin, heme and iron, induce lesions in genomic DNA. The cellular DNA damage response (DDR) comprises the coordinated actions of DNA repair and checkpoint systems that regulate a spectrum of processes before replication, where cell cycle arrest enables DNA repair to occur (86). The DDR also promotes cell death when the damage is beyond repair. If excessive damage exists, the DDR activates cell death and eliminates the damaged cells by apoptosis. Two key regulators of the DDR cell cycle checkpoints include ataxia telangiectasia mutated (*ATM*) and ataxia telangiectasia mutated and rad3-related (*ATR*) (86). ATR responds to a broad spectrum of DNA damage, including replication-associated DNA damage, while ATM is activated by DNA double-strand breaks (86). A number of studies have vigorously investigated the association between redox imbalance and cell cycle signaling pathways in CCC (73,77,83,87-89), while no studies have focused on the influence of ROS on the pathogenesis of EC, at least to the best of our knowledge. Shigetomi *et al* investigated the role of HNF-1β in regulation of the cell cycle arrest in response to DNA damage in the CCC cell line, TOV21G (87). Flow cytometric analysis of cell cycle profiles indicated that HNF-1β inhibited cell cycle progression (87). Fig. 1 illustrates the typical flow cytometry histograms of the results. HNF-1β-expressing TOV21G cells exhibited a marked increase in the proportion of cells in the G2/M phase following exposure to a genotoxic agent, bleomycin, for 24 h (62.1 vs. 42.3%) (87). The knockdown of endogenous HNF-1β attenuated G2/M phase cell cycle arrest and stimulated cell death (28.0 vs. 18.2%) (87). It would also be of interest to determine which genes and their signaling pathways enhance and accelerate cell cycle arrest at G2/M phase. Shigetomi *et al (*87) and Ito *et al* (89) explored the activated and interconnected signaling network of HNF-1β to identify novel downstream targets (Fig. 2). HNF-1β promotes TOV21G cell survival through Chk1 phosphorylation (87,89). As previously demonstrated, the inactivation of *HNF1B* with siRNA suppressed Claspin protein expression, but failed to inhibit *Claspin* mRNA expression (89). Claspin transmits a replication stress signal from ATR to Chk1 and functions as an adaptor protein required for Chk1 activation. In CCC cells, HNF-1β, but not ATR, are essential for the upregulation of Claspin protein expression, suggesting that this gene functions as a Claspin protein post-translational modification. Ito *et al* vigorously identified potential modifiers of Claspin protein relevant to HNF-1β biology (89). To date, >450 unique protein modifications have been identified, including phosphorylation, acetylation, ubiquitination and SUMOylation through post-translational modification (90). Phosphorylation is one of the most common and reversible intracellular post-translational modifications of serine and threonine residues (91). Acetylation is a modification of the lysine residues (92). Ubiquitination is a widely studied method of post-translational protein modification (4). Claspin

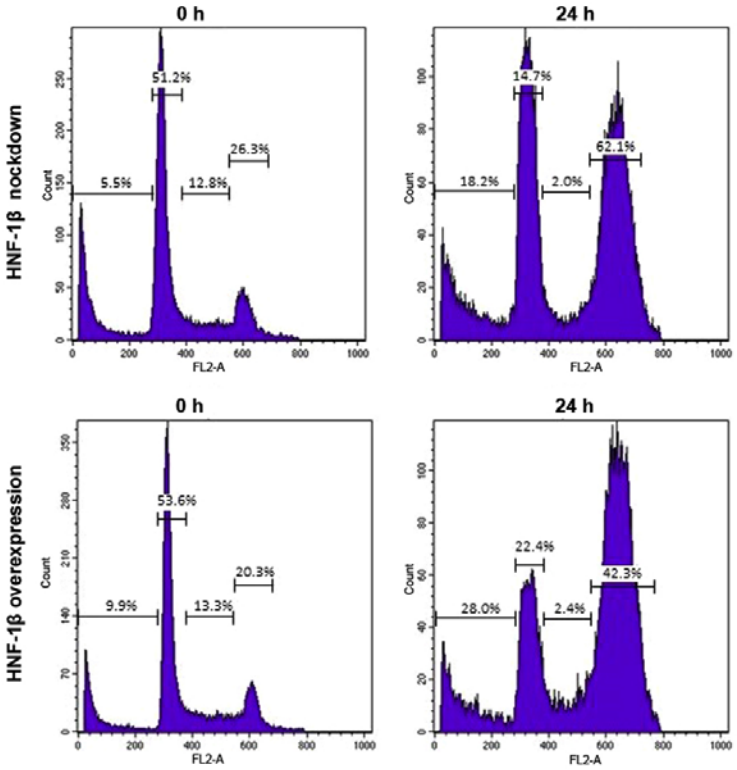

Figure 1. HNF-1β induces cell cycle arrest at the G2/M phase: Typical flow cytometry histograms (87). HNF-1β^{+}-TOV21G clear cell carcinoma cells were transfected with control siRNA or HNF-1β siRNA. Cells were fixed at 24 h following bleomycin treatment and stained with propidium iodide (PI). Each graph represents percentages of the cells in the various phases of the cell cycle. HNF-1β, hepatocyte nuclear factor-1β.

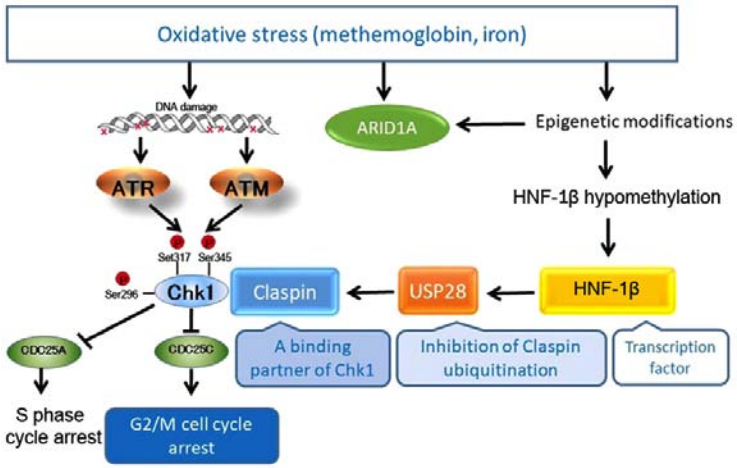

Figure 2. HNF-1β-dependent signaling pathway. The HNF-1β-dependent DNA damage checkpoint is essential for the maintenance of genome integrity after genotoxic stress, and also for cell survival. In response to genotoxic stress-induced DNA damage, Chk1, a downstream target of ATR, stops cell cycle progression at G2/M phase, and allows cells to repair damaged DNA for survival. USP28 mediates a novel pathway of HNF-1β-dependent cell cycle arrest, DNA replication and cell survival, via the HNF-1β/USP28/Claspin/Chk1/CDC25C signaling pathway (89). HNF-1β, hepatocyte nuclear factor-1β; USP28, ubiquitin specific protease-28.

is reportedly regulated by ubiquitin-dependent proteasomal degradation, whereas the ubiquitin-specific processing protease (USP) 28- and USP29-mediated deubiquitination inhibits its degradation (93). Martín *et al* reported that USP29 controls the stability of Claspin by deubiquitination (94). However, HNF-1β did not stimulate the upregulation of USP29 protein in CCC cells. Ito *et al* identified, for the first time, a novel regulator of Claspin, USP28, as a direct downstream target of HNF-1 (89). USP28 interacts with Claspin and is able to deubiquitinate it. With these results, USP28 is identified as a novel player in the HNF-1β-Chk1 pathway and the control of DNA replication, via the HNF-1β-USP28-Claspin-Chk1-CDC25C pathway (89). This pathway contributes to a loss of G2/M checkpoint control, which accumulates genomic and chromosomal instability and then paves the way for further major genetic changes.

Although the impact of HNF-1β on the cell cycle arrest at G2/M phase under oxidative stress conditions is recognized

in CCC, the role of HNF-1β in oxidative stress-induced endometriosis carcinogenesis remains poorly defined. When endometriotic cells are exposed to genotoxic oxidative stressors such as hemoglobin, heme or free iron, the HNF-1β gene may also be epigenetically hypomethylated and is demonstrated as a positive modulator of cell survival, through the HNF-1β signaling pathway. This hypothesis needs to be verified in future studies.

EC-specific (epi)genetic profile. Endometriosis is an estrogen-dependent disease. The enzyme aromatase P450 is expressed aberrantly in endometriosis and catalyzes the final step of estrogen production and upregulates the expression of prostaglandin E2 (PGE2) and macrophage migration inhibitory factor (MIF), which, in turn, induces the expression of aromatase within endometriotic lesions (55). The effects of estrogen on stromal cell PGE2 production may be mediated in a feed-forward manner. MIF is a cytokine marker of M2 polarization of macrophage which facilitates the onset and progression of endometriosis. Such an interplay with a positive feedback cycle is involved in cell proliferation and apoptotic resistance of endometriosis, and then its malignant transformation.

There are two types of estrogen receptors (ESRs), ESR1 (also known as ERα) and ESR2 (ERβ). The ESR expression level has been shown to be higher in EC and high-grade serous than in CCC and mucinous carcinoma (95). Among EAOC, ESR positivity has been shown to be significantly higher in EC (91%), but lower in CCC (8%) (60). ESR gene expression is modulated by a number of factors, such as DNA methylation of the promoter region, histone deacetylation, chromatin remodeling, or heme and iron binding (58). The interrelation between the ESR expression and these factors is complex, as genetic characteristics and environmental factors can mutually impact upon each other. The significant up- and downregulation of ESR has been shown to be associated with marked epigenomic alterations: ESR2 is the predominant ESR in endometriosis due to the hypomethylation of promoter CpG islands, whereas ESR1 levels are lower in endometriosis (69). EC shares estrogen-dependent oncogenic pathways and signaling network. A hyperestrogenic state or the upregulation of ESR expression may be shared in common with benign and malignant endometriosis, which may denote that endometriosis has carcinogenic potential. Furthermore, G-protein-coupled estrogen receptor-30 (GPR30) is the novel estrogen-responsive receptor G protein-coupled estrogen receptor 1, GPER (96). GPR30 expression is higher in EAOC than in benign OE (96). The upregulation of ESR expression is associated with a better clinical outcome in ovarian cancer (95) and CCC (14), suggesting the role of ESR in tumor initiation or the early development of primary EC, but not in EC progression.

Taken together, EAOC is a heterogeneous disease, with at least two intrinsic subtypes, EC and CCC. Although the role of DNA methylation in EAOC development is not yet fully understood, its profiling defines cancer subclasses differing in clinicopathologic characteristics, molecular profiles and survival. Genes with promoter hypermethylation and hypomethylation are consistent in cancer function and characteristics of concordant methylation. The promoter hypomethylated ESR gene is reversely correlated with the promoter hypermethylated *HNF1B* gene in EC (58,60,97). A low expression of ESR (95) and high expression of HNF-1β (71) are identified as potential biomarkers for CCC.

Other crucial aspects. We discuss the potential involvement of microenvironment in endometriosis and its malignant transformation. The dysfunctional regulation of immune and inflammatory microenvironment, extracellular matrix remodeling, or new blood vessel formation is a crucial aspect of pathogenesis of endometriosis and its malignant transformation. Ovarian cancer is initially associated with pelvic inflammatory disease, such as endometriosis, demonstrating a similarity between the processes of inflammation and carcinogenesis. Endometriotic cells adapt to survive in the unique microenvironment conditions with high levels of iron, inflammatory cytokines and chemokines (98). Microenvironment-cell interplay may modulate the major signaling pathways associated with cell cycle regulation, growth factor signaling, immune and inflammatory pathways, and the extracellular matrix remodeling, which results in phenotype transformation (99). Researchers have focused on the function of matrix metalloproteinase (MMPs) (100), lysyl oxidases (LOXs) and nuclear factor κ-light-chain-enhancer of activated B (NF-κB) in the pathophysiology of inflammation and EAOC (101). Several studies have identified the NF-κB-dependent multiple oncogenic pathways in endometriosis (102) and highlight its malignant transformation (103). MMP-2 promotes angiogenesis during endometriosis progression via the cyclooxygenase (COX)-2/PGE2/pAKT axis (104). The upregulation of lysyl oxidase (LOX) expression is involved in extracellular membrane degradation, invasive and metastatic potential of endometriosis (105). The disruption of epithelial-stromal communication networks elicits a feed-forward loop involving endometriosis to drive inflammation, which may be relevant in diseases such as EAOC.

In addition, chemokines are key players in the activation and are recruitment of immune cells at sites of inflammation. The CXCR4/CXCL12 axis is functional in endometriosis and plays a role in a number of diverse cellular functions, including immune surveillance, inflammation response, tissue homeostasis, and tumor growth and metastasis (106). CXCR4 expression is upregulated by vascular endothelial growth factor (VEGF), and plays an important role in the malignant transformation of endometriosis (107). Furthermore, the microvascular endothelium of ectopic endometrial tissue originates from circulating endothelial progenitor cells mobilized from the bone marrow, which is also controlled by the CXCL12/CXCR4 axis (108). The neovascularization of endometriotic lesions is not only driven by angiogenesis, but also vasculogenesis from circulating endothelial progenitor cells (108). Thus, angiogenesis and vasculogenesis play an integral part in the establishment and growth of endometriotic lesions and malignant transformation (108,109). Therefore, these changes in the microenvironment are necessary to accumulate enough epigenetic, genetic and pathological alterations for malignant transformation of endometriosis (110).

Discussion

In the present study, we provide a literature review of various lines of evidence supporting the concept of an altered redox

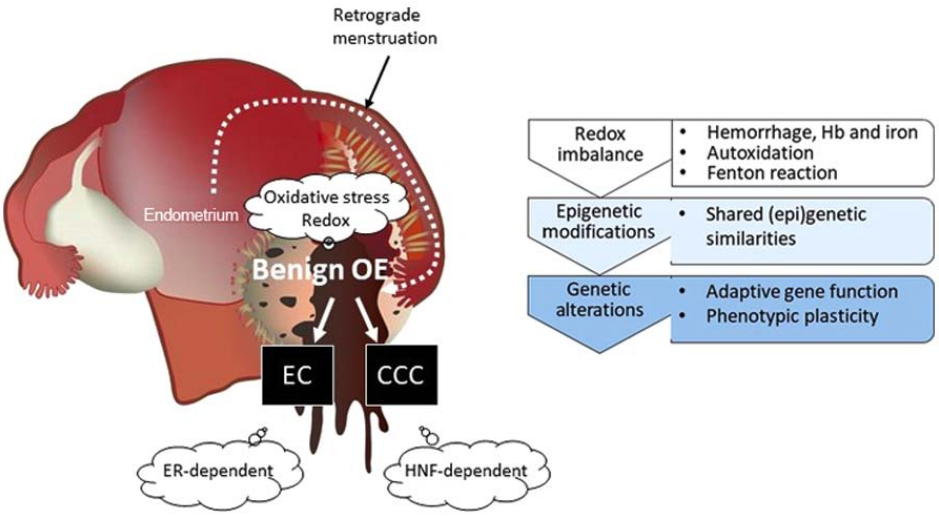

Figure 3. The concept of an altered redox environmental model for malignant transformation of endometriosis. EAOC consists of different histological subtypes mainly originating from EC and CCC. First, repeated episodes of hemorrhage occur in endometriosis throughout menstruation. Extracellular free hemoglobin produces toxic heme degradation products and is a source of ROS. Hemoglobin, heme and free iron in endometriotic cysts cause redox imbalance. Second, there is a link between environmental stimuli and (epi)genetic modifications. EC is distinguished from CCC due to different morphologies, but both represent common environmental profiles and maintain the similar genomic abnormalities with multiple overlaps and share similar molecular signatures, including ARID1A, PIK3CA, PTEN, or KRAS. Finally, ESR and HNF-1β proteins are mutually exclusive in EAOC. HNF-1β-positive and ESR-negative endometriotic cells may represent a prototypical lineage of CCC cells. The positive ESR expression and negative HNF-1β expression is a frequent finding in EC. EAOC tumors had enrichment of cancer-specific gene signatures corresponding with each histological subtype: ESR induces EC cell proliferation ('go') and HNF-1β induces CCC cell cycle arrest ('stop') for a survival mechanism in response to several stresses. EAOC, endometriosis-associated ovarian cancer; EC, endometrioid carcinoma; CCC, clear cell carcinoma; ARID1A, AT-rich interactive domain-containing protein 1A; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PTEN, phosphatase and tensin homolog deleted on chromosome 10; HNF-1β, hepatocyte nuclear factor-1β.

environmental model for malignant transformation of endometriosis. Fig. 3 summarizes the current knowledge about the role of the shared and independent (epi)genetic background between EAOC tumors, and their interaction with environmental stimuli. We initially updated the epigenetic, genetic and environmental backgrounds of EAOC and surveyed the examples of environmentally induced epigenetic changes. Despite the differences in morphology between EC and CCC, they share remarkable (epi)genetic similarities and enrichment for driver somatic mutations affecting *ARID1A*, *PTEN* and *KRAS* genes (55-61). The hemoglobin, heme and free iron accumulated during endometriosis development are a prerequisite to modification of genomic DNA for prompt cellular responses to oxidative stress (58). An excess of heme iron and nonheme iron participates in the Fenton reaction generating the toxic hydroxyl radical. Autoxidation of oxyHb to metHb always occurs due to abundant heme iron in the contents of benign OE. Autoxidation, rather than the Fenton reaction, might be the main process accomplishing the oxidative reaction in endometriosis (31). Redox biology is considered to alter (epi)genetic events. Environmentally-induced epigenetic alterations may result in a change of the adaptive gene function, leading to phenotypic plasticity. Endometriosis is predisposed to develop into EAOC through the progressive accumulation of epigenetic alterations (3,4,6,9) during obvious redox imbalance (20,23). However, there is only limited knowledge of the mechanisms through which environmental factors affect gene function.

In addition, a previous approach identified different genetic backgrounds between EAOC tumors (60). By comparing the gene expression profile, at least two differentially expressed genes were identified in EC and CCC. A positive ESR expression and negative HNF-1β expression is a frequent finding in EC, but not in CCC (58,60). EC may develop in the setting of estrogen-driven pathway (111). On the other hand, HNF-1β-dependent ovarian cancer arising from endometriosis is substantially more associated with CCC than with EC (11,60,77,83,87,89). Immunohistochemical data have indicated that atypical endometriosis is a precursor lesion molecularly similar to adjacent invasive cancer (60). Pre-malignant endometriotic cells exposed to mixture of genotoxic oxidative stressors inhibit cell proliferation and promote cell cycle arrest at G2/M phase for DNA damage repair through the HNF-1β/USP28/Clasipin/Chk1 pathway (89). Therefore, HNF-1β induces cell cycle arrest, DNA damage and genomic instability, thereby promoting erroneous DNA repair and can predispose to CCC. EAOC tumors had enrichment of cancer-specific gene signatures corresponding with each histological subtype: ESR induces EC cell proliferation ('go') and HNF-1β induces CCC cell cycle arrest ('stop'). This model underscores a subtype-dependent dichotomy between 'go' and 'stop' in EAOC, through potentially better ability to adapt in a changing environment (Fig. 3).

In conclusion, a special emphasis is given to current pathophysiological concepts of malignant transformation of endometriosis, including redox imbalance, environmental stimuli-induced (epi)genetic modifications and mutually exclusive expression of ESR and HNF-1β genes for a survival mechanism in response to several stresses.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors' contributions

YY, NK and KO collected the data regarding the epigenetic and genetic abnormalities and the underlying mechanism of endometriosis transformation using the PubMed database. NK, KO and CY performed the literature search and supervised the study. HK and CY made substantial contributions to the conception of the study. HK contributed to the study design and interpretation of the included research studies. The final version of the manuscript has been read and approved by all authors.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare no potential competing interests with respect to the research, authorship and publication of this article.

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