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ENDOMETRIOSIS

The role of iron in the pathogenesis of endometriosis

HIROSHI KOBAYASHI, YOSHIHIKO YAMADA, SEIJI KANAYAMA, NAOTO FURUKAWA, TAKETOSHI NOGUCHI, SHOJI HARUTA, SHOZO YOSHIDA, MARIKO SAKATA, TOSHIYUKI SADO, & HIDEKAZU OI

Department of Obstetrics and Gynecology, Nara Medical University, Nara, Japan

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Abstract

Background. Endometriosis may cause symptoms including chronic pelvic pain and infertility, and increases susceptibility to the development of ovarian cancer. Genomic studies have started to delineate the wide array of mediators involved in the development of endometriosis. Understanding the mechanisms of endometriosis development and elucidating its pathogenesis and pathophysiology are intrinsic to prevention and the search for effective therapies.

Method of study. The present article reviews the English language literature for biological, pathogenetic and pathophysiological studies on endometriosis. Several recent genomic studies are discussed in the context of endometriosis biology.

Results. Severe hemolysis occurring during the development of endometriosis results in high levels of free heme and iron. These compounds oxidatively modify lipids and proteins, leading to cell and DNA damage, and subsequently fibrosis development. Recent studies based on genome-wide expression analysis technology have noted specific expression of heme/iron-dependent mediators in endometriosis. The heme/iron-dependent signaling pathway of endometriosis, which is providing new insights into the regulation of inflammation, detoxification and survival, is discussed.

Conclusion. Several important endometriosis-specific genes overlap with those known to be regulated by iron. Other genes are involved in oxidative stress. Iron has a significant impact on endometriotic-cell gene expression. This review summarizes recent advances in the heme/iron-mediated signaling and its target genes, outlines the potential challenges to understanding of the pathogenesis and pathophysiology of endometriosis, and proposes a possible novel model.

Keywords: *Endometriosis, iron, heme, oxidative stress*

Introduction

Endometriosis is defined by the development of endometrial tissue outside the uterus. It is a benign disease and is clinically associated with pelvic pain and infertility. The incidence of endometriosis is about 10% worldwide [1]. The widely accepted Sampson's theory of the etiology of endometriosis is that it originates from the implantation and invasion of cells from retrograde menstruation to particularly the pelvic peritoneal cavity. Recent findings indicate that the influence of the local environment is crucial in the development of endometriosis [2]. Furthermore, endometriosis may develop from metaplasia of celomic epithelial cells lining the pelvic peritoneum. This could be an explanation for endometriosis occurring in the ovary. The latter is thought to arise from the ovarian surface epithelium, a single cell layer on the surface of ovaries, and its invagination (cortical inclusion cyst) [3]. Thus, the implantation and the metaplasia theories describe the mechanism of initiation of endometriotic lesions. Both estrogens production and progesterone dysregulation may contribute to the initiation and promotion of endometriosis [3]. The conditions for the initial development of endometriosis are induction of attachment, invasion angiogenesis, cell growth and survival. The additional factors contributing to the establishment and persistence of endometriotic lesions probably include hormonal imbalance, genetic predisposition and altered immune surveillance. The mediators that contribute to inflammatory response and fibrosis are likely involved in the development of the symptoms of this process. In the present review article we focus

Correspondence: H. Kobayashi, Department of Obstetrics and Gynecology, Nara Medical University, 840 Shijo-cho, Kashihara 634–8522, Japan. Tel: 81 744 29 8877. Fax: 81 744 23 6557. E-mail: hirokoba@naramed-u.ac.jp

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primarily on these advances and review recent data on the biology, pathogenesis and pathophysiology of this tumor.

We searched Medline databases for a 10-year period (1998–2008), combining the keywords 'endometriosis' and 'iron' with the term 'expression profile' of specific named genes.

Expression profiles of genes involved in endometriosis

Several studies based on genome-wide expression analysis technology have clarified the genes involved in endometriosis [4–6]. The expression profiles of genes generally involved in endometriosis have been determined predominantly using oligonucleotide microarrays. The discovery of critical somatic gene alterations in endometriosis and understanding how each of them contributes to the pathogenesis and pathophysiology of this disease may ultimately lead to more accurate diagnosis and the design of more efficient therapeutic strategies [7]. Close to a dozen gene expression profiling studies have been published so far. Many genes preferentially overexpressed in endometriosis have been identified [4–19]. The characteristic upregulated genes included those encoding cytokines and chemokines, (pro)inflammation molecules, growth factors, signal transduction molecules, hormones (reduced progesterone responsiveness), proteases, cell adhesion molecules, stress response and detoxification molecules. Included genes encode molecules involved in the cell cycle (cyclins, CDK); growth factors (IGF-II, IGFBP, HGF, c-met, EGFR, PPAR, histone deacetylase); signal transduction (GRAP, JNK, TOPK, PAFR); transcription factors (HNF-1β, NF-κB, AP-1, STAT); hormones (ER, PR, reduced progesterone responsiveness); cytokines and inflammation (S100A8, IL-1, IL-6, IL-8, TGF-β, RANTES, BLTR, lipocalin); proteases (MMP-2, MMP-3, MMP-9, MT-MMP, TIMP, uPA, uPAR, PAI-1, granzyme A); adhesion molecules (β-catenin, E-cadherin, (pro)collagen, VCAM); and stress response and detoxification (HO, GPX, MT, aldose reductase, cytochrome c oxidase, mitochondrial ATPase coupling factor, cytochrome P-450, NADH–ubiquinone oxidoreductase, ferritin, UDP-glucosyltransferase, SUI1, LTF, thioredoxin reductase, CD163, RAB6KIFL, apolipoprotein B, PENK) (Figure 1, left panel).

These interesting candidate susceptibility genes are discussed in more detail in the following sections.

Cell cycle molecules

Cyclins and CDK. Cyclins are a family of regulatory proteins that play a pivotal role in controlling the cell cycle. The expression of p53, MDM2, and p21Waf1

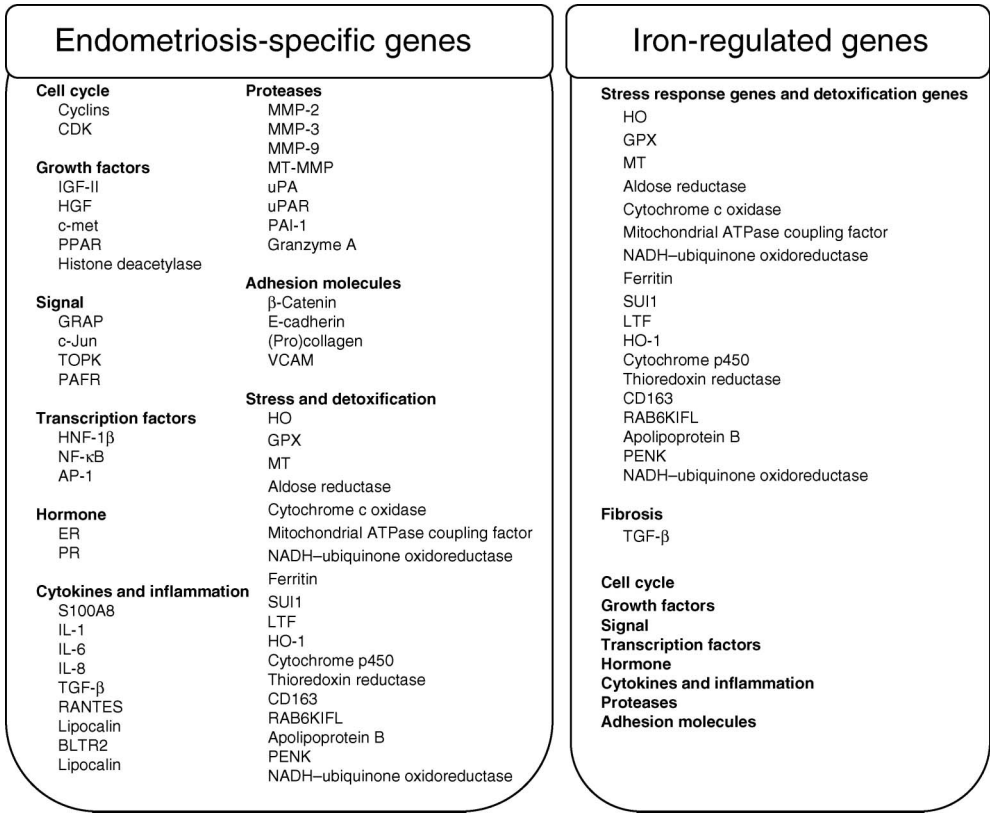

Figure 1. Comparison between the endometriosis-specific genes and the iron-regulated genes. Several endometriosis-specific genes overlap with those regulated by iron. (For explanation of acronyms, please see text.)

suggests a role for these oncoproteins in the regulation of endometriotic cell growth [20]. Increased p21 expression was found in ovarian endometriomas compared with peritoneal endometriosis or benign tumors [21]. Expression of the cyclin-dependent kinase (CDK) inhibitor p27Kip1 is involved in the progression of peritoneal endometriosis [22]. Although this disease has histological features of benign tumor, endometriosis shares with malignant ovarian tumors certain alterations in cell cycle-related proteins.

Growth factors

IGF. Insulin-like growth factor (IGF)-I prevents apoptosis and has mitogenic action on endometrial cells. The peritoneal fluid of women with endometriosis contains increased IGF-I bioavailability, which is produced by limited hydrolysis of urokinase-type plasminogen activator (uPA) on IGF-binding protein (IGFBP) [23]. Both IGFBP and uPA mRNA expression are also increased in endometriotic lesions vs. eutopic endometrium. Recent studies on IGF-I raised attention to its role in the growth of endometriotic lesions.

HGF and c-met. Hepatocyte growth factor (HGF) levels in serum and peritoneal fluid were significantly increased in women harboring blood-filled red peritoneal lesions and may be clinically useful to predict the activity of pelvic endometriosis [24]. There are many reports on the biological actions of HGF in endometriosis [25,26]. The peritoneum and endometriotic stromal cells appear to be major sources of HGF in peritoneal fluid [26]. Endometrial and endometriotic stromal cells expressed the Met receptor, which was activated by endogenous and exogenous HGF [26]. Interleukin (IL)-6 and tumor necrosis factor (TNF)-α are involved in the production of HGF by endometrial stromal cells and may be involved in the growth of endometriosis by an autocrine or paracrine mechanism [25]. HGF enhanced stromal cell proliferation and uPA-dependent invasion [26]. Thus, the HGF/Met system is strongly involved in the pathogenesis of endometriosis by promoting stromal cell proliferation and invasion.

PPAR. Peroxisome proliferator-activated receptor (PPAR)-γ ligands are ligand-activated nuclear transcriptional regulators [27]. A growing body of evidence points to PPAR-γ ligands as potent anti-inflammatory drugs *in vitro* and *in vivo* [28]. PPAR-γ can reduce monocyte migration *in vitro* that is induced by peritoneal fluid from women with endometriosis [29]. An activator of PPAR-γ, rosiglitazone, was found to cause regression of experimental endometriosis [30]. Furthermore, the use of PPAR-γ ligands to reduce chemokine production and inflammation may be a productive strategy for future therapy of endometriosis.

Histone deacetylase. Histone acetylation and remodeling of chromatin structure is an important regulatory mechanism in the control of gene transcription [31]. Histone deacetylase catalyzes the opposing deacetylation reaction. Trichostatin A, a histone deacetylase inhibitor, was previously found to suppress proliferation, the expression of cyclooxygenase (COX)-2 induced by IL-1β and the constitutive or TNF-α-stimulated activation of nuclear factor (NF)-κB in endometriotic cells, suggesting that histone deacetylase inhibitors are a promising class of compounds for novel and more effective medical treatment of endometriosis [32].

Signaling molecules

JNK and p38. Iinflammatory changes are involved in the progression of endometriosis. Activated macrophages in the peritoneal cavity generate oxidative stress. As a result of such stress, an inflammatory reaction with secretion of growth factors, cytokines and chemokines is generated [33]. Such a pro-oxidant environment promotes the growth of endometriotic lesions. Mitogen-activated protein kinase (MAPK) could play a role as a pivotal intracellular signal transducer in such inflammation of endometriotic cells. MAPK pathways consist of extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 cascades. The JNK and p38 pathways are involved in stress response, including oxidative stress. The p38 phosphorylation rates in endometriotic tissues were significantly higher than those in eutopic endometrial tissues of the same patients [34].

GRAP. Endometriosis has been considered an autoimmune disease, since increased number and activation of peritoneal macrophages and decreased T-cell and natural killer (NK)-cell cytotoxicities are the alterations in cellular immunity and result in inadequate removal of ectopic endometrial cells from the peritoneal cavity. T-cell activation is induced by ligation of the antigen-receptor (TcR/CD3) as well as co-receptors such as CD28. CD28 binds to several intracellular proteins including the growth factor receptor-bound protein-2 (GRB2) and cooperates with Vav1 in the regulation of T-cell stimulation [35]. The level of Vav1 transcript in endometriosis was markedly higher than the control level [36]. Vav1 could efficiently cooperate with T-cell receptor signaling to enhance nuclear factor of activated T cells (NFAT)-dependent transcription [36]. GRB2-related adaptor protein (GRAP) is expressed in B cells and is downregulated following B-cell antigen receptor ligation. GRAP is a novel SH3-SH2-SH3

adaptor protein that couples tyrosine kinases to the Ras pathway. The GRAP expression in B cells appears to regulate antigen receptor-mediated signaling events [37]. B lymphocyte stimulator (BLyS) protein was found elevated in the serum of endometriosis patients, suggesting a model for the pathology (initiation) of endometriosis where BLyS-responsive cells interact with retrograde menstrual tissues to give rise to endometriosis lesions [38].

TOPK. Accumulating data suggest that alterations in cell-mediated immunity contribute to the pathogenesis of endometriosis [39]. Aberrant immune responses during retrograde menstruation may be involved in the development of endometriosis. A decrease in the number of NK cells in the blood of women with endometriosis was noted. Decreased T-cell and NK-cell cytotoxicities are the alterations in cellular immunity and result in inadequate removal of ectopic endometrial cells from the peritoneal cavity. Lymphokine-activated killer T (T-LAK) cells possess cytotoxic functions against cancer and endometriotic cells [40]. T-LAK cell-originated protein kinase (TOPK), a novel T-LAK-specific protein kinase, is a member of the p38 kinases [39,41]. As described above, this pathway is associated with stress response. NK-cell activity was significantly downregulated in endometriosis patients. The current picture on the function of NK cells is complex and contains images of both disease-promoting and disease-preventing roles: the former includes activating type 1 T helper (Th) cells and macrophages and actual killing of target tissue cells; and the latter might have protective regulatory roles, which includes production of type 2 Th cytokines [4].

PAFR. Platelet-activating factor (PAF) is a potent phospholipid mediator [42]. It acts by binding to a unique G-protein-coupled, seven-transmembrane receptor – platelet-activating factor receptor (PAFR) – and activates multiple intracellular signaling pathways, including nitric oxide release in the inflammatory response [7,43]. The peritoneal fluid of women with endometriosis contains an increased number of activated macrophages. Endometriosis is associated with increased levels of PAF and decreased PAF acetylhydrolase activity in peritoneal fluid, showing pelvic inflammation. Factors influencing implantation of retrograde menstrual debris include the long-term pooling of peritoneal fluid which contains hemoglobin. It has been reported that hemoglobin induces high levels of PAF in macrophages [44].

Transcription factors

HNF-1β. Microarray analysis revealed recently that hepatocyte nuclear factor (HNF)-1β was significantly upregulated in endometriosis and clear cell carcinoma of the ovary [45]. This is probably responsible for the frequent occurrence of clear cell carcinoma in endometriosis. Upregulation of HNF-1β expression has been reported in endometriosis, including the atypical and inflammatory endometriosis lesions [46]. HNF-1β expression may be a genetic common lineage among the mid-to-late secretory endometrium, endometriosis and clear cell carcinoma of the ovary [46].

NF-κB and AP-1. Chemically induced oxidative stress is associated with the activation of some transcription factors such as NF-κB, activator protein-1 (AP-1), hypoxia inducible factor-1 (HIF-1), signal transducer and activator of transcription (STAT) and CCAAT/enhancer binding protein (C/EBP), but not HNF. The transcription factor NF-κB activates proinflammatory, proliferative and antiapoptotic genes in many cell types. Constitutive NF-κB activation was observed in women with peritoneal endometriosis [47]. AP-1 activation is critical for TNF-α-induced IL-6 expression in endometriotic cells [48]. The mRNA and protein levels of HIF-1α were greater in ectopic endometriotic tissue compared with its eutopic counterpart [49].

Hormones

ER (estrogen receptor) and PR (progesterone receptor). There are a number of abnormalities in the expression of aromatase, 17β-hydroxysteroid dehydrogenase type 2 and the PR-B/PR-A ratio in endometriosis tissue. Endometriosis is an estrogen-dependent disease. Estrogen is an extremely potent mitogen for endometriosis, while progesterone inhibits the mitogenic action of estrogen and enhances differentiation. It has been speculated that endometriosis is resistant to progesterone action [50].

Cytokines and inflammation molecules

IL-1, IL-6 and IL-8. Increased levels of several proinflammatory cytokines are secreted by either immune or endometrial cells. These cytokines promote implantation and growth of ectopic endometrium by inducing proliferation and angiogenesis by inducing gene transcription of vascular endothelial growth factor [51].

S100A8. S100 and its receptor have been implicated in the activation of oxidative stress and inflammatory pathways in many cell types. Among S100 proteins, S100 calcium-binding protein A8 (S100A8) is involved in vascular remodeling in endometriotic angiogenesis [52]. Src kinase plays an important role in S100A8-mediated inflammatory gene expression.

TGF-β1. Serine protease plasmin activates transforming growth factor (TGF)-β1 after being

converted from plasminogen by uPA [53]. TGF-β1 activity is increased at sites of endometriosis due to enhanced production of both TGF-β1 and uPA by glandular epithelium. The physical appearance of the severity of dysmenorrhea appears to be related to the expression of TGF-β1 in nerve fibers [54]. Furthermore, TGF-β1 is the cytokine most causatively associated with endometriosis characterized by fibrosis (see the section 'Potential heme/iron target genes' below).

RANTES. Peritoneal fluid macrophages are activated in women with endometriosis. Regulated on activation, normal T-cell expressed and presumably secreted (RANTES) is a member of the CC chemokine family of proteins that plays an essential role in inflammation by recruiting macrophages to inflammatory sites [55]. The presence of a number of markers of inflammation (IL-1, IL-8 and RANTES) has been demonstrated in the peritoneal fluid of endometriosis [56]. RANTES expression was stimulated by IL-1 produced from peritoneal-fluid macrophages [57].

Lipocalin. Lipocalin, also known as α_1-microglobulin, is a glycoprotein present in plasma and all tissues. It has a number of immunosuppressive properties, such as inhibition of antigen-induced lymphocyte-cell proliferation, cytokine secretion [58] and the oxidative burst of neutrophils [59]. Several recent findings suggest that lipocalin may be a radical reductant and scavenger *in vivo*. Thus, lipocalin is involved in reduction and scavenging of biological pro-oxidants, such as heme and heme proteins.

BLTR. Leukotriene B4 (LTB4), a potent leukocyte chemoattractant, is known to promote several inflammatory diseases, including endometriosis [60]. The G-protein-coupled receptors BLTR-1 and BLTR-2 and PPAR are the currently known LTB4 receptors (BLTR) [61]. The mechanism of endometriosis is similar to that of bronchial asthma [62]. LTB4 and BLTR are present in the smooth muscle cells of uterine tissue [62]. LTB4 receptor antagonist has significant therapeutic value for the treatment of endometriosis in an animal model [63]. It is likely that antileukotriene therapy would be efficacious in the treatment and prevention of human endometriosis [62]. These results suggest that LTB4 is an important mediator and its receptors, BLTR-1 and BLTR-2, play critical and sequential roles during the development of endometriosis.

Proteases

MMP-2, MMP-3 and MMP-9, and MT-MMP. Because endometriotic tissue is capable of implantation and invasion, it resembles neoplastic tissue. This biological behavior is likely regulated by cell adhesion molecules and enzymes that degrade the extracellular matrix. Matrix metalloproteinases (MMPs; MT, membrane-type) appear to be involved in the invasive establishment of endometriosis [64]. Proinflammatory cytokines are functionally linked to various classes of MMPs. Endometriotic tissue exhibits altered expression patterns of MMP and its tissue inhibitor (TIMP) which favor tissue invasion/remodeling [65].

uPA, uPAR and PAI-1. The plasminogen-activating system is also suggested to participate in degradation of the extracellular matrix and modulation of cell adhesion and migration. Epithelial and stromal cells from endometriotic tissue release uPA, plasminogen activator inhibitor (PAI)-1 and uPA receptor (uPAR) [66]. The higher release of PAI-1 from endometriotic stromal cells might have importance for the invasive growth.

Granzyme B. Granzyme B is involved in the rapid induction of target cell apoptosis during granule-mediated killing in the cytotoxic lymphocytes. This enzyme is also produced by granulosa cells of the human ovary and has the ability to cleave extracellular substrates, including cartilage proteoglycan and aggrecan [67]. It is considered to be associated with tissue remodeling of endometriosis.

Adhesion molecules

β-Catenin. The adhesion complex E-cadherin, together with β-catenin, was reduced in endometriotic lesions, which might contribute to detachment and implantation as the first step of development of endometriotic cells [68].

VCAM. Endometriosis is a pelvic inflammatory process that secretes various cytokines. TNF-α-mediated p38 MAPK was shown to upregulate vascular cell adhesion molecule (VCAM) [69]. The regulated expression of VCAM on the surface of leukocytes, epithelial cells and vascular endothelial cells is essential for controlling migration of cells [70]. Women with endometriosis had higher serum concentrations of soluble VCAM-1 [71]. Aberrant mRNA expression of VCAM-1 in endometrium and peritoneum [72] suggests that VCAM expression is involved in the pathogenesis of endometriosis.

(Pro)collagen. The early lesion is an active stage of endometriosis, invading the extracellular matrix. Changes of extracellular matrix proteins, including procollagen, are characteristic for endometriosis-dependent angiogenesis. The amino-terminal propeptides of type III procollagen, an indicator of collagen metabolism, are increased in sera of patients with early endometriosis and demonstrate that the

subtle lesion of endometriosis is an active stage of the disease [69].

Glucose metabolism

Cytochrome P-450. Cytochrome P-450 aromatase is the key enzyme for estrogen biosynthesis, which plays an important physiological and pathophysiological role in endometriosis [73]. Estrogen is known to influence glucose homeostasis with dominant effects. ERs regulate the glucose transporter GLUT4 that is contributing to the glucose metabolism and insulin resistance [74].

Stress response and detoxification

Oxidative stress and inflammatory reaction have been implicated in the pathogenesis of endometriosis. Endometriosis cells exhibit oxidative DNA damage, metaplasia and markedly reduced function compared with normal endometrium [75]. Included are heme oxygenase (HO), glutathione peroxidase (GPX) and metallothionein (MT), lipid peroxidation (aldose reductase), cytochrome c oxidase, mitochondrial ATPase coupling factor, cytochrome P-450, NADH–ubiquinone oxidoreductase and ferritin (see the section 'Potential heme/iron target genes' below). Many endometriosis-specific genes are involved in stress response and detoxification.

UDP-glucosyltransferase. Several toxins such as heme and iron might be involved in the pathogenesis and development of endometriosis (see below). Glucosylation represents a detoxification process for animals. Inactivation of toxins by glycosylation could be a prominent natural mechanism for resistance [76]. The mammalian enzymes play a central role in metabolism and detoxification of toxic chemicals [76]. For example, UDP-glucosyltransferase detoxifies the active metabolite of irinotecan, 7-ethyl-10-hydroxycamptothecin (SN-38) [77]. This protein is considered to promote general detoxification. The detoxification system including UDP-glucosylation might detoxify toxins in women with endometriosis.

Thioredoxin reductase. Increased generation of reactive oxygen species (ROS) leads to impaired cell injury. To counteract ROS-mediated injury, cells can induce a number of genes encoding detoxifying enzymes and antioxidant proteins such as thioredoxin reductase, HO-1, γ-glutamylcysteine synthethase, glutathione-*S*-transferase and NAD(P)H:quinone oxidoreductase, superoxide dismutase, catalase and glutathione [78]. Thiols are representative scavengers of ROS. Redox-sensitive signaling factors such as thioredoxin reductase and thioredoxin may represent central pro-survival factors [79].

LTF. Lactotransferrin (LTF), an oxidative stress-associated parameter, is a multifunctional iron- and zinc-binding protein [80]. LTF presents in the secondary granules of polymorphonuclear leukocytes, which are regulated by estrogen in the reproductive tract [81]. Furthermore, it inhibits the catalytic domain of MMP-2 by zinc chelation [82].

CD163. Cluster of differentiation 163 (CD163) is the macrophage receptor for endocytosis of haptoglobin–hemoglobin complexes [83]. Hemoglobin can become toxic by mediating oxidative stress-induced inflammation. Highly efficient systems remove the toxic and proinflammatory hemoglobin, haptoglobin, heme and iron from the circulation and local sites of tissue damage [84]. The hemoglobin–heme system may be involved in the pathogenesis and/or development of endometriosis (see below).

SUI1. DNA damage can be induced by exogenous agents or by endogenous processes involving the generation of ROS [85]. In the presence of oxidative stress, ROS might increase growth and adhesion of endometrial cells in the peritoneal cavity, leading to endometriosis and infertility [86]. Putative translation initiation factor (SUI1) mRNA is regulated by genotoxic and endoplasmic reticulum stress. The stress induction of SUI1 mRNA is conserved in both humans and rodents and occurs in a p53-independent manner [87].

RAB6KIFL. The first genetic models of endometriosis in mice are based on the activation of an oncogenic ras family [88,89]. The small GTPase RAB6 is the Rab family form of the p21 ras superfamily, is involved in retrograde Golgi–endoplasmic reticulum trafficking and may function as a post-endoplasmic reticulum quality control system [90]. RAB6 interacting, kinesin-like (RAB6KIFL) was localized to the Golgi apparatus [91]. The carboxyl-terminal domain of RAB6KIFL contains the RAB6-interacting domain, inhibits the effects of RAB6-GTP on intracellular transport [91]. Thus, activation of RAB6KIFL may be involved in the development of endometriosis.

GRP78. Endometriotic cells are subject to endoplasmic reticulum stress. Glucose-regulated protein (GRP78) is an immunoglobulin heavy-chain binding protein (BiP) and appears to serve as an endoplasmic reticulum stress signaling regulator [92]. This protein is a major endoplasmic reticulum chaperone with calcium-binding and antiapoptotic properties.

Apolipoprotein B. Apolipoprotein B is the critical protein component of very-low-density lipoprotein, low-density lipoprotein and lipoprotein(a), the major atherogenic lipoproteins [93]. There is a linkage

between the development of endometriosis and increased level of apolipoprotein B. Increased oxidative stress and inflammation are associated with the development of endometriosis. Hemoglobin-, heme- and iron-induced oxidative stress induces an increase in oxidized phospholipids on apolipoprotein B particles. Oxidative stress-mediated lipid peroxidation modifies intracellular fat absorption and may decrease efficiency in assembling and transporting apolipoprotein B [94]. Apolipoprotein B binds ferritin by hemin-mediated binding. These facts demonstrated that apolipoprotein B might regulate iron-mediated oxidative stress. These data allow us to speculate that iron-mediated oxidative stress in endometriosis may be regulated by apolipoprotein B.

PENK. There is strong evidence that proinflammatory cytokines may be involved in endometriosis pathophysiology. It is not clear, however, whether endometriosis-related pain is caused by inflammation [95]. There is evidence that the opioid and its receptor system are altered by the cytokines elaborated during inflammatory pain [96]. Several potential candidate genes that might be involved in endometriosis pain pathways have recently been identified [97], for example tyrosine kinase receptor B (TrKB), μ-opioid receptor (MOR), serotonin transporter (5HTT) and proenkephalin (PENK). Oxidative stress influenced the expression of the opioid peptide gene, PENK. PENK gene encodes the opioid peptides Met- and Leu-enkephalin, and is highly expressed in neurons and lymphocytes [98], implicating the well-known role of opioid peptides in pain transmission. The expression levels of TrKB and MOR genes in endometriosis are modulated by gonadotropin-releasing hormone agonist or progestin [97].

Expression profiles of genes that are regulated in eutopic endometrium of women with endometriosis

Dysregulation of various genes in the eutopic endometrium of women with moderate/severe-stage endometriosis has been reported by Burney and colleagues [5]. They conducted gene expression analysis to test menstrual cycle-dependent differences in the eutopic endometrial gene expression profiles of women with endometriosis, compared with healthy controls. Interesting candidate genes were identified: upregulated genes included those encoding S100A8, SUI1, LTF, GRAP, CD163, topoisomerase (DNA) II, 170 kDa (TOP2A), RAB6KIFL, apolipoprotein B, PENK, TOPK, BLTR-2, PAFR, VCAM, granzyme A, MAPK and TGF-β. On the other hand, downregulated genes encoded PR (hormone receptor), cytochrome P-450 (progesterone-responsive gene), osteopontin (OPN; progesterone-regulated gene), MT (minimize ROS activity), GPX (minimize ROS activity), forkhead box O1A (FOXO1A; induction of apoptosis), mitogen-inducible gene 6 (MIG6; negative regulator of epidermal growth factor receptor-mediated mitogenic signaling) and IGFBP-1 (minimize IGF activity). These changes in the endometrial transcriptome are secondary to reduced progesterone responsiveness [5].

The most likely direct target genes for reduced progesterone responsiveness might be the upregulated genes identified in the endometrium of subjects with endometriosis [5]. Several important genes that are upregulated in eutopic endometrium of women with endometriosis also overlap with those regulated by the oxidative stress and detoxification system. ROS can act as secondary messengers and control various signaling cascades [99]. Endometrial tissue outside the uterus establishes itself on the peritoneum due to oxidative stress-induced signaling such as enhanced survival, angiogenesis, attachment, invasion and growth. Collectively, the expression of progesterone resistance genes followed by oxidative stress response is essential to our understanding of the development of endometriosis.

Potential heme/iron target genes

Clinical observation suggests that the most important and specific causal factor for the development of endometriosis may be a prolonged exposure to blood. The persistence of blood at the site of endometriosis development is important to understanding both the induction and the promotion of this disorder. Hemolysis of red blood cells was observed in endometriosis. Heme is released from hemoglobin after hemorrhage and is present at high concentrations in endometriosis, suggesting effects of heme released from hemoglobin [100].

Heme is a ubiquitous molecule with an active iron center carrying a high affinity for oxygen. Free heme and iron stimulate local inflammatory reactions [100]. Inflammation is a defense system and prevents further damage. Heme and iron act as pro-inflammatory molecules. These molecules generate intracellular ROS and subsequently activate the transcription factors NF-κB, AP-1 and SP-1 [101–103]. Heme also activates neutrophil responses: neutrophil chemotaxis, cytoskeleton reorganization, oxidative burst, production of ROS and IL-8, and transcriptional activation [1]. Iron is one of the breakdown products of heme through the enzymatic reaction of heme oxygenases (HO-1, HO-2, HO-3) [100]. Free iron catalyzes the formation of ROS as the highly toxic hydroxyl radical through Fenton chemistry [104]. This metal synergizes with ROS to regulate the expression of oxidative stress response genes, including HO and other detoxification enzymes, possibly through activation of transcription

factors such as NF-κB [104,105], which in turn stimulates COX-2 expression and production of prostaglandin $F_{2\alpha}$, an inflammatory mediator [97]. Consequently, free iron and ROS synergistically damage lipids (lipid peroxidation), proteins and DNA through oxidative stress by generating ROS, which influences many aspects of cell function including oxidative stress, energy metabolism, cell cycle regulation and tissue fibrosis [104]. Detoxification is a protective mechanism for survival from the redox environment produced by heme or iron. Heme induces HO-dependent p21 expression, provoking cell cycle arrest [100,106]. When large amounts of heme or iron accumulate, the detoxification systems get overwhelmed. Recently, Yamaguchi and associates [107] confirmed in an *in vitro* study that abundant free iron in the contents of endometriotic cysts was strongly associated with greater oxidative stress and frequent DNA mutations. Considerable evidence suggests that iron-induced ROS are implicated in the pathogenesis of endometriosis [108].

Comparing the endometriosis-specific genes that have previously been described [5,6,19,36] with the iron-regulated genes [3,100,109,110], several important endometriosis-specific genes overlap with those known to be regulated by iron (Figure 1, right panel). Some of these results were confirmed by experiments with iron chelators [3], demonstrating that the expression of some endometriosis-specific genes was upregulated in the presence of free iron. Several classes of related genes are responsive to cellular iron levels. Included are those encoding HO-1, GPX, MT and ferritin (antioxidative stress); aldose reductase (lipid peroxidation); cytochrome c oxidase subunits II and III, mitochondrial ATPase coupling factor and NADH–ubiquinone oxidoreductase (energy metabolism); and TGF-β (fibrosis). Network analysis of the expression revealed that the expression of genes upregulated by free iron tightly links to cell cycle, growth factor, protease and adhesion molecules, and cytokine expression, signal transduction and transcription factor activation [111–115]. The sum total biological effect of these genes is to increase cell proliferation, matrix structure, antioxidation, lipid peroxidation, energy metabolism, fibrosis, and the metabolism of iron itself. Iron may affect additional genes by causing oxidative stress on one hand, and on the other hand enhance expression of genes associated with a protective response to stress. Therefore, iron-mediated genes might not only be excellent endometriosis-specific molecular markers but also molecular targets for therapy of endometriosis. This section considers effects mediated through heme/iron-dependent biochemical changes, in particular stress response and detoxification, energy metabolism and fibrosis [104]. The identification of genes targeted directly by free iron and indirectly by iron-derived ROS is essential to our understanding of the pathophysiology of endometriosis.

Stress response and detoxification

HO. Hemoglobin accumulates in the peritoneal fluid and chocolate cyst of women with endometriosis. Heme greatly potentiates cell killing mediated by ROS. As defense against such stress, cells upregulate HO-1 and ferritin. The redox-active ferrous ion is released from the storage protein ferritin by ROS. Redox-active iron further activates/generates ROS and thus perpetuates their damaging effects. The enzymatic degradation of heme is regulated by microsomal HO isoenzymes, a potent oxidative and cellular stress-responsive system [103]. The function of HO is to catalyze the conversion of heme to carbon monoxide, iron and biliverdin, which is subsequently converted to bilirubin by biliverdin reductase [101,104,116]. Biliverdin and its product bilirubin are powerful antioxidants. HO-1 is highly inducible under inflammatory conditions in response to reactive oxygen and nitrogen species (superoxide, hydrogen peroxide, hydroxyl radicals and peroxynitrite) [103]. The expression of HO-1 is regulated by transcription factors (NF-κB, AP-1 and nuclear factor E_2-related factor-2) and some of their upstream kinases (MAPK, phosphoinositide-3-kinase, protein kinases A and C) [103]. Thus, HO plays a significant role to detoxify heme. In human endometrium HO-1 was constitutively expressed, whereas HO-2 expression was greater in the secretory phase [104]. Furthermore, HO is strongly expressed in ectopic endometrium, especially in red lesions [117]. The HO system, although expressed, might be insufficient to detoxify heme in women with endometriosis. Lack of adaptation in an iron-rich environment led to extensive cell damage. In this regard, induction of these enzymes has shown beneficial effects in several pathologic conditions, including endometriosis. These data allow us to speculate that heme and iron are highly involved in the pathogenesis and/or development of endometriosis.

GPX. In addition to HO, protective enzymes exist such as GPX, MT, superoxide dismutase and catalase [118]). Oxidative stress plays its role in regulating GPX at the transcriptional level [3]. The GPXs include four different selenoenzymes. They are known for their ability to reduce organic and inorganic hydroperoxides [119,120]. Low GPX status and activity in the peritoneal fluid of women with endometriosis probably influence the development of endometriosis [121].

MT. MT is also a strongly inducible stress response gene. Hemopexin-mediated heme transport into cells stimulates the expression of HO [122] and MT

[123]. The proposed role of MT is as an intracellular antioxidant. The ability of endometrium to determine high protection against DNA damage (MT expression) observed in normal endometrium during the menstrual cycle phases seems to be fundamental for pathological features of endometriosis [124].

Lipid peroxidation (aldose reductase). Oxidation of unsaturated phospholipids results in the generation of aldehyde side-chains that remain esterified to the phospholipid backbone. Aldose reductase catalyzes the reduction of several aldehydes ranging from lipid peroxidation products to glucose [125]. This metabolism may be a critical regulator of the proinflammatory and immunogenic effects of oxidized phospholipids [125]. Novel functions regulated by IL-1β include genes involved in free radical protection. Changes in aldose reductase were upregulated by free iron and IL-1β [126]. Various factors, such as cytokines including IL-1β released by activated macrophages in the peritoneal fluid, may locally affect the oxidant status of ectopic endometrium. These results provide new insights into the role of iron and IL-1β in disorders of the endometrium, especially in implantation-related infertility and endometriosis [126].

Cytochrome c oxidase. The gene encoding cytochrome c oxidase is reported to be regulated by iron in rat intestine [127]. The enzyme contains redox-active metal sites: heme iron binuclear center. The heme iron catalyses electron transfer from the substrate to the oxygen reduction site [128].

Ferritin. Ferritin is a 24-subunit protein composed of two subunit types, termed heavy chain (H) and light chain (L) [42]. Ferritin-H is ubiquitous and contains a ferroxidase site, whereas ferritin-L is catalytically inactive and unique to animals [129]. Ferritin is an intracellular iron-storage protein, thereby serving as an additional antioxidant [130]. Iron is an important transcriptional regulator of ferritin expression [116]. An antioxidant-responsive element (ARE) sequence was reported in the ferritin-L and -H genes. The ARE mediates transcriptional response to oxidative stress by increasing expression of a diverse set of proteins involved in redox homeostasis such as thioredoxin reductase, thioredoxin, quinone reductase, heme oxygenase and glutathione [129,131]. The increase in ferritin synthesis is also mediated by HO and hemin [108,132]. Ferritin inhibits ROS-mediated signal pathways possibly through suppression of JNK cascade activation [129] and minimizes opportunities for uncontrolled iron chemistry and oxidative stress. The majority of cells exposed to high levels of free iron undergo cell death or apoptosis in endometriotic cells. In cells that escape the death, which have sustained overexpression of ferritin as one of the adopted protective mechanisms, the cells continuously receive toxic stimulation and generate low levels of ROS during the long latency period. Prolonged exposure to hemorrhage or free iron would be a 'driving force' to select cell populations that are able to become an origin of survival [62]. Therefore, ferritin expression confers apoptosis resistance on endometriotic cells. In addition to ferritin, iron plays a crucial role on the posttranscriptional regulation of transferrin receptor (TfR) and divalent metal transporter-1 (DMT1) mRNAs during differentiation of normal human erythropoietic cells [103].

Energy metabolism

Mitochondrial ATPase coupling factor-6. Mitochondrial ATPase coupling factor-6 (CF6) is a novel endogenous inhibitor of prostacyclin [133]. A significantly increased plasma CF6 level was found in diabetics compared with controls. CF6 might be an obvious marker of impaired endothelium and might contribute to vascular damage in diabetes [133]. Circulating CF6 is elevated in human hypertension and modulated by salt intake presumably via ROS [134].

NADH–ubiquinone oxidoreductase. Generation of ROS may contribute to inactivation of enzymes and enzyme complexes (ribonucleotide reductase, NADH–ubiquinone oxidoreductase, cytochrome c oxidase), which results in dysfunction of the mitochondrial electron transport chain. Complex I (NADH–ubiquinone oxidoreductase) is the multiprotein assembly of the mitochondrial oxidative phosphorylation system; the final biochemical cascade of events leading to the production of ATP [135]. In mammalian cells mitochondrial complex I provides about half of the proton motive force needed to make ATP. ROS-induced inactivation of NADH–ubiquinone oxidoreductase may facilitate apoptosis of endometriotic cells. Very little is known about whether CF6 and NADH–ubiquinone oxidoreductase are involved in the development of endometriosis.

Fibrosis

TGF-β. Iron and the iron-mediated generation of ROS may contribute to upregulation of genes encoding profibrotic and proinflammatory molecules, such as TGF-1β and monocyte chemoattractant protein-1 [100,136]. TGF-β is one of the key mediators that induce fibrotic and inflammatory changes in various organs [137]. Alteration of iron metabolism contributes to the development of chronic inflammation and fibrosis [108]. The possible link between iron, tissue fibrosis and upregulation of TGF-β is best known in the liver in humans and animal models [3,124,128,135]. Recent studies have

also suggested that iron may have a role in the TGF-β upregulation and tissue fibrosis in other organs, including the kidney [19,117] and the heart [118]. The crucial role of TGF-β in the development of endometriosis has been demonstrated by *in vitro* and *in vivo* experiments [138].

Conclusion

This review summarizes current knowledge regarding the pathogenesis of endometriosis. From the above, it is clear that iron has a significant impact on the gene expression of endometriotic cells. Many of the genes upregulated in endometriosis are already known to be regulated by iron. Others are genes already known to be involved in oxidative stress. Therefore, the important endometriosis-specific genes overlap with those regulated by iron. Furthermore, the interesting genes included in the profiles of heme/iron target genes are those encoding HO, ferritin and TGF-β (stress response genes and detoxification genes). Several classes of related genes described above are directly or indirectly responsive to cellular iron levels. The differentially expressed genes provide insights into endometriosis and its clinical behavior. The high correlation in our review of specific genes upregulated in endometriosis with the possible heme/iron target genes suggests that iron and iron-mediated oxidative stress are distinct molecular signatures for pathogenesis and pathophysiology of endometriosis. Examination of the gene lists upregulated in endometriosis reveals the presence of several genes whose expression patterns implicate them in cell survival, antiapoptosis, energy metabolism and detoxification.

Due to its unique structure providing the surface area of ectopic endometrium with blood, endometriosis is continuously vulnerable to oxidants that come in touch with blood (persistent contact with iron and heme), which makes it susceptible to varying degrees of chronic inflammation and oxidative tissue injury. Iron and heme show significant free radical activity by their ability to degrade DNA. The greater durability of chronic oxidative stress appears to be one of the principal reasons for their greater developmental potential. The random deletion of certain tumor suppressor genes, possibly from oxidative stress, would occur in endometriosis. ROS are a double-edged sword – they serve as key signal molecules in physiological processes but also have a role in pathological processes involving persistent endometriosis. We hypothesize from the expression patterns and target genes that iron may play an important role in the clinical behavior of endometriosis. Collectively, we speculate that the development of endometriosis is the result of chronic oxidative damage secondary to the hemolytic deposition of iron in the endometriotic lesions.

Prevention and treatment

Ectopic endometriotic cells require essential metal ions, including iron, for growth and proliferation. Pathological accumulation of the iron within endometriosis aggravates the generation of ROS and elicits oxidative stress-induced toxic effects. Therefore, therapeutic targets include the inhibition of iron-mediated specific proteins and the inhibition of free radical damage on DNA. Many experimental chelators have been shown to be effective as anticancer agents. Among them, dexrazoxane, deferoxamine, deferiprone and triapine have reached the stage of clinical testing or application. Deferiprone has been shown to be effective in cancer prevention and treatment [139]. Deferasirox is a new, once-daily oral iron chelator, recently approved as first-line therapy in the treatment of transfusional chronic iron overload [140,141]. Taken together, chelating iron may be used for the prevention and treatment of endometriosis.

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