Biomedicine & Pharmacotherapy 106 (2018) 163–174

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Endometriosis: Perspective, lights, and shadows of etiology

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ARTICLE INFO

Keywords:
Endometriosis
Oxidative stress
Inflammatory chemokine
Hormone and genetic

ABSTRACT

Endometriosis refers to the growth of ectopic endometrial tissue outside the uterine cavity. About 10–15% of female in reproductive age suffer from endometriosis. Several etiologies – such as oxidative stress, inflammatory factors and cytokines, genetic etiology, and hormone role – have been reported for endometriosis. Indeed, oxidative stress leads to abnormalities by the production of ROS and RNS. The mechanism of endometriosis genesis is a complicated process that concerns the alterations in cellular immunity. Also, endometriosis is a hormonal response that illustrates stimulation in steroid hormone production. Genetic polymolymorphisms and epigenetic factors are also important in endometriosis initiation and progression. This review paper presents the role of oxidative stress, reactive oxygen species (ROS), and antioxidants and inflammatory, genetic, and epigenetic factors involved in the initiation and progression of the endometriosis.

1. Introduction

The endometrium is originated from intermediate mesoderm via mesenchymal to epithelial transition during the evolvement of the urogenital system [1]. Endometriosis (EMS) is described as the implantation of ectopic endometrial tissue outside the uterine cavity. Through this process, the endometrial cells escape the lining of the endometrium [2]. EMS is one of the most common gynecological disorders affecting about 10–15% of all women of reproductive age. Also, it is seen in 30% of all infertile women [3], leading to the impaired quality of life for women of reproductive age. EMS is associated with anomalies including dysmenorrhea, dyspareunia, gastrointestinal problems, fatigue, headaches, deep pelvic pain, lower abdominal pain both with and without back pain, or psychiatric disturbances such as family relationship problems or mood symptoms [4]. The average time of the onset of symptoms until diagnosis of EMS is about 5 to 10 years [5]. Pelvic inflammation as a classic feature of EMS, not only is caused by the endometriotic lesions but also is a factor promoting ectopic proliferation and growth of endometrial tissue [6]. There are several mechanisms to explain the pathophysiology of endometriosis. In addition to the classic hypothesis (including retrograde menstruation), some other mechanisms have been recently introduced that may involve the pathogenesis and development of EMS. These mechanisms include coelomic metaplasia, iatrogenic direct implantation, lymphatic and vascular metastasis, mesenchymal cell differentiation or induction, and embryonic rest [7]. The presence of early-onset endometriosis in newly menarcheal or pre-menarcheal girls shows a different kind of endometriosis in these patients with a pathogenesis different from retrograde menstruation. Brosens et al. [7] hypothesized that during neonatal uterine bleeding, which occurs in 3–5% of 3–5 day neonates, endometrial stem cells may disseminate in the pelvic cavity and lead to early onset endometriosis. Sampson's retrograde menstruation theory cannot explain the early onset endometriosis in pre-menarcheal girls but neonatal uterine bleeding may be considered as the initial retrograde flux [8]. There are three aspects eminent in the pathogenesis of EMS. Firstly, with the viewpoint of endometrial tissue, numerous genes are differentially expressed in the ectopic endometrium compared with those in the eutopic and normal endometrium, which may play pivotal roles in the development of EMS [9]. Secondly, higher expression of mitochondrial cytochrome P450 side chain cleavage enzyme (P450scc) and hydroxysteroid 17-dehydrogenase in ectopic endometrial tissue elevates local estrogen levels, which affects biological activities of endothelial stromal cells and leads to the development of EMS [10]. Finally, the immunological aspect plays an important role in the maintenance of immune homeostasis to prevent potentially severe autoimmunity [9]. Three forms of EMS include endometriotic implants

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https://doi.org/10.1016/j.biopha.2018.06.109
Received 23 February 2018; Received in revised form 31 May 2018; Accepted 18 June 2018

on the surface of the pelvic peritoneum and ovaries “peritoneal EMS”, ovarian cysts lined by endometrioid mucosa “endometriomas”, and a complex solid mass comprised of endometriotic tissue mixed with adipose and fibromuscular tissue, indwelling between the rectum and the vagina “rectovaginal endometriotic nodule” [11]. This issue, which is associated with enhanced local of 17-β estradiol (E2), leads to immunological abnormalities, activation of peritoneal macrophages, and cytokine productions, with overexpression of nuclear factor-kappa B (NFκ-B), cyclooxygenase-2 (COX-2), aromatase, and other inflammatory factors involved in EMS [12]. The American Society for Reproductive Medicine classifies EMS into four stages, with stage I and II representing initial stages and III and IV representing advanced stages [13]. Of the abovementioned theories, three are the main classic theories to explain the etiology of EMS; i.e., the implantation theory given by Sampson, the coelomic metaplasia theory given by Mayer, and the theory of implantation and growth of endometrium upon retrograde menstrual reflux [14,15]. Implantation theory comments that retrograde menstruation and the flow back of endometrial tissue through the fallopian tubes into the peritoneal cavity may potentially lead to implantation of endometrial cells [15]. According to Mayer’s theory, EMS is characterized by the transformation of peritoneal cells into muellerian-type cells under the effect of hormonal alteration [16]. Finally, the induction theory combines two other theories and suggests that endogenous biochemical or immunological factors induce differentiation of undifferentiated cells to endometrial cells [17]. None of these hypotheses and theories, however, could elucidate this multifaceted disease. So far, investigators agree that multiple factors; particularly genetic, immunologic and environmental conditions are involved in its pathophysiology [18]. Thus, recent studies have proposed the role of other factors in the expansion of EMS [19]. According to recent studies on incomprehensible infertility, oxidative stress (OS) may be part of the reason in the pathophysiology of endometriotic lesions [19–21].

In this review, we study the role of oxidative stress, reactive oxygen species (ROS), and antioxidants and inflammatory, genetic, and epigenetic factors involved in the initiation and progression of the endometriosis.

2. Oxidative stress in endometriosis

Oxidative stress (OS) is caused by a balance disruption between reactive oxygen species (ROS) production and the antioxidant protection capacity [19]. ROS can affect some factors including lipids, proteins, nucleic acids, and carbohydrates at the cellular surface [22]. Both enzymatic and non-enzymatic antioxidants participate in cell defense against oxidative damage. Enzymatic antioxidants consist of superoxide dismutase (SOD), catalase, glutathione reductase, and glutathione peroxidase. Non-enzymatic antioxidants include vitamin E, heme, vitamin C, taurine, glutathione, vitamin A, carotenoids, selenium, astaxanthin, etc. [23,24]. Extra production or decreased removal of ROS causes excess OS, which is responsible for the development of numerous diseases such as EMS [24]. Inflammatory system triggers oxidative stress in the peritoneal fluid [25–27]. In EMS cases, iron overload has been recognized in numerous components of the peritoneal cavity (PC), peritoneal fluid (PF), endometriotic lesions, peritoneum, and even macrophages [28]. Iron overload works by affecting the mechanisms of OS involved in endometriotic lesions progress [29]. Iron and nuclear factor-κB (NF-Kb) show a linkage and both can promote EMS, which can be a smart target for future treatment approaches [28].

Moreover, an inflammatory-like endometrial response induced by endometrial toxins such as dioxin may exacerbate the expansion of EMS [30]. Additionally, in EMS patients, defense mechanisms against oxidative stress are defected [30]. Also, in patients in the advanced stages of the disease, serum levels of paraoxonase-1, an enzyme that inhibits an oxidative change of low-density lipoprotein cholesterol, is decreased [31] while the level of oxidized LDL (ox-LDL) in peritoneal fluid is increased [32]. Many studies showed that vitamins C and E supplementation are capable of reducing the markers of oxidative stress [33]. Patients treated with antioxidant supplementation showed decreased OS markers in peripheral blood while the concentration of antioxidants was increased [34].

In addition to local oxidative stress generated by endometriotic lesions, systemic oxidative stress can affect red blood cells (RBC) and serum levels of oxidative stress markers such as HSP-70b’ and oxidatively modified stress markers. Besides, endometriosis may lead to biochemical changes including membrane oxidation and glutathione (GSH) reduction in circulating RBCs generating systemic oxidative stress in these patients [35]. Thioredoxin (TRX) as a cell product generated in response to oxidative stress plays a protective role in inflammation and cell injury caused by oxidative stress. Both truncated TRX 80 and cytosolic TRX 1 are considered as systemic oxidative stress markers [26]. Serum levels of TRX in women with endometriosis are similar to control group but TRX binding protein-2 (TBP-2) levels are significantly lower in the patients with endometriosis, resulting in the higher rate of TRX/TBP-2 in these patients. TBP-2 negatively regulates the expression and biological function of TRX. Therefore, a higher TRX/TBP-2 ratio represents a higher oxidative stress in these patients [36].

2.1. Nitric oxide and endometriosis

In an oxidative stress scenario, reactive nitrogen species (RNS) play a role as important as ROS. RNS includes nitroxyl ion, peroxynitrite anion, nitric oxide and nitrosyl-containing compounds [37]. Women with EMS have evaluated levels of eNOS and iNOS in their peritoneal fluid. In addition, eNOS has an expression pattern through the menstrual cycle similar to alpha (5) and beta (3) integrin (IαVβ-3), an important factor in uterine receptivity. Both of these proteins are detected in the endometrial glandular epithelium. During the EMS, an increase in the eNOS expression level leads to a decrease in the expression of IαVβ-3, which leads to declined embryo implantation rate in EMS patients [24].

NO has a dual effect on a female reproductive system, which can be physiologic or pathologic. Physiologic functions 1) regulate endometrial microvasculature, 2) control the endometrial stromal edema production, which is necessary for embryo implantation, and 3) promote uterus myometrium contractions to help the normal menstrual cycle [24].

Increased NO levels are involved in EMS-related angiogenesis through the stimulation of VEGF expression [38]. Nitrite levels of peritoneal fluid in healthy women are lower than those of serum levels and EMS can increase the nitrite concentrations in PF. Recent studies have demonstrated that the NO concentration is higher in the PF of EMS patients [39,40] and this level of NO is produced by eNOS [41,42] patients with EMS show higher levels of NO [43,44] and NOS [41,44] in their endometrium.

2.2. Oxidant and antioxidant enzymes

Women with EMS show altered expression of enzymes involved in protection against oxidative stress in their endometrium. Manganese and copper/zinc superoxide dismutase [45] and glutathione peroxidase [46] are overexpressed in the eutopic endometrium of women with EMS or adenomyosis. In contrast to normal women who have a cyclic alteration in the level of the expression of the enzymes [45,47], both superoxide dismutases are overexpressed throughout the cycle in patients with EMS [45]. Additionally, PON-1 activity is lower in the serum of women with EMS and this difference is strongly associated with the stage of the disease. The activity of other enzymes such as metalloprotease is considerably lower in follicular fluid of patients with EMS compared with normal women [48]. However, the serum level of this enzyme in women with endometriosis is higher. Catalase is also in higher concentrations in the serum of these patients in mild to severe EMS, which can be interpreted as a result of the overproduction of these