Endometriosis and oxidative stress

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Recent literature on the subject supports the notion that oxidative stress plays a key role in the pathogenesis of endometriosis and its evolution and symptom presentation. The main symptoms of endometriosis, namely chronic pain and infertility, are contingent on the establishment of chronic inflammation, with dysregulation of the immune system and multiple cell functions, including the control of ROS generation. Targeting oxidative stress could prove a winning strategy to manage both endometriotic lesion progression by curbing the hyperproliferative phenotype acquired by endometrial cells and inhibiting iron overload, and also endometriosis-associated symptoms.

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1. Introduction

Endometriosis is a chronic disease characterized by implantation and growth of endometrial-like tissue, including glands and stroma, outside the uterine cavity [1][2]. It affects about 10% of women of childbearing age and is associated with debilitating chronic pelvic pain and infertility [3][4], causing significant impairment to quality of life and inevitably impacting social, occupational, and psychological aspects, too [5].

Although the pathophysiology of endometriosis remains poorly understood, various biological processes are known to be key players in its development and progression. These implants acquire other crucial characteristics such as unrestrained growth through steroid receptivity dysregulation [1][2][6][7], as well as proangiogenic features [8][9]. Moreover, the inflammatory response and immune system modulation promoting ectopic endometrium implantation initially, and implant maintenance and progression subsequently, also appears to be pivotal [2][10]. Oxidative stress, namely disequilibrium between production and neutralization of reactive oxygen species (ROS), has been shown to be present in these processes and looks to play a key role in disease pathogenesis and evolution [11][12][13].

As described by Nisolle and Donnez [14], there are three forms of the disease, as endometriotic lesions can develop (i) on the peritoneum as superficial disease, (ii) inside the ovaries as cysts, and (iii) as deep-infiltrating disease most commonly observed in the rectovaginal septum. Current treatment options include surgical ablation or excision of lesions in the pelvic cavity or hormone therapy to suppress lesion proliferation [1]. Furthermore, assisted reproductive technology (ART) should be offered to infertile endometriosis patients who are unsuitable candidates for natural conception [15]. Previous surgery, advanced disease stage, and association with

adenomyosis and ovarian and/or deep nodular endometriosis appear to be linked to poorer ART outcomes [16][17], but in vitro fertilization (IVF) is still the most effective strategy to manage infertility in these patients [15][16][17][18].

There is a clear clinical need for new therapeutic approaches, not only to treat endometriosis-related symptoms such as chronic pain and infertility but also to curtail its recurrence and progression. Oxidative stress may be a potential therapeutic target for both objectives, as it plays a crucial role in disease development and evolution.

2. ROS and Antioxidant Defense

The clinical importance of oxygen toxicity was not fully appreciated until an epidemic of retrolental fibroplasia (severe retinopathy) occurred in the early 1950s [19]. Indeed, oxygen at high partial pressures is toxic to the respiratory, cardiovascular, nervous, and gastrointestinal systems. Toxicity results from the formation of ROS, which are chemically reactive molecules produced naturally within biological systems.

ROS are actually intermediaries produced by normal oxygen metabolism but are known to have deleterious effects. To protect themselves, cells have developed a wide range of antioxidant systems to limit the production of ROS, inactivate them, and repair cell damage [12][13][20][21][22][23]. In healthy individuals, ROS and antioxidants are balanced, but when the balance is tipped toward an overabundance of ROS, oxidative stress is triggered and can impact the entire reproductive lifespan of a woman, as reported by Ruder et al. [20].

It is clear that ROS are generated within cells in the course of normal cellular mechanisms and that cells are adequately equipped with a range of cytoprotective enzymes and antioxidants to combat their toxicity [12][13][20][21][23]. One of the master regulators of cytoprotective defense against oxidative stress is the nuclear factor erythroid 2-related factor 2/Kelch ECH associated protein 1 Activation and translocation to the nucleus of Nrf2 initiates the transcription of a number of genes, known as antioxidant response elements, involved in redox homeostasis and protection from oxidative stress-related injury [24]. This response includes an increase in antioxidant systems such as superoxide dismutase (SOD) and catalase (CAT), elevated autophagic cell activity for repair of various cell compartments, and also mitochondrial biogenesis [25][24].

However, excessive release of ROS induces cellular damage and likely alters cellular function by regulating protein activity and gene expression. Indeed, ROS play an essential role in regulating the transcription factor nuclear factor kappa B (NFkB), which has been implicated in endometriosis [2][26]. This transcription factor triggers the expression of multiple genes encoding proinflammatory cytokines, growth and angiogenic factors, adhesion molecules, and inducible enzymes nitric oxide synthase (NOS) and cyclooxygenase (COX) [27][28]. All these constituents are expressed by activated peritoneal macrophages and are involved in the pathogenesis of endometriosis by inducing endometrial fragment adhesion, proliferation, and neovascularization [27][29].

3. Origin of Oxidative Stress in the Peritoneal Cavity

Understanding the role of hemoglobin (Hb), heme, and the iron-induced redox balance in endometriosis has given rise to several hypotheses to explain why oxidative stress is triggered in the case of pelvic endometriosis [13] and is potentially involved in its pathophysiology. Erythrocytes, apoptotic endometrial tissue, and cell debris swept into the peritoneal cavity by menstrual reflux and macrophages have all been suggested as possible inducers of oxidative stress [12][30][31][32][33][34][35].

Erythrocytes are likely to release pro-oxidant and proinflammatory factors such as Hb and its highly toxic by-products heme and iron into the peritoneal environment. While iron and heme are fundamental to living cells, unless they are properly chelated, free iron and (to a lesser degree) heme play key roles in the formation of deleterious ROS [35][36][37][38].

However, erythrocytes are observed in the peritoneal cavity of 90% of menstruating women [14], so it is puzzling why some patients develop macroscopically visible peritoneal endometriotic lesions while others do not [39]. One theory is that peritoneal protective mechanisms may be swamped by menstrual reflux in some patients, either because of its abundance or due to defective scavenging systems [35][36][37][38].

In case of hemorrhage, lysis of erythrocytes results in iron overload, which in turn causes iron-mediated damage, oxidative injury, and inflammation [40][41][42], so iron may well be implicated in endometriosis development [23][38][40][42]. A crucial defense mechanism counteracting the effects of hemorrhage is mediated by haptoglobin (Hp), which binds to extracellular Hb, thereby weakening its oxidative and inflammatory potential. Moreover, Hp promotes the clearance of Hb via the CD163 scavenger receptor present on macrophages [41].

As in most tissue, activated macrophages recruited inside the pelvic cavity of women play a vital role in the degradation of erythrocytes, as indicated by the presence of numerous iron-laden macrophages in the peritoneal fluid of endometriosis subjects [28][29] and mice injected intraperitoneally with erythrocytes [35]. Macrophages generally phagocytose senescent erythrocytes or endocytose the Hb–Hp complex [41]. Thus, Hb and heme metabolism by heme oxygenase (HO) releases iron, which is then integrated into ferritin in macrophages or returned to the iron transporter transferrin via peritoneal fluid [43].

Iron conglomerates have also been encountered in endometriotic lesions [32][38], composed of hemosiderin, another iron storage form found in conditions of iron overload and usually associated with toxic pathological states in humans. Iron storage is significantly greater in peritoneal macrophages of endometriosis patients than in controls [38]. Cellular iron storage within ferritin limits the ability of iron to generate ROS, conferring an antioxidant effect [38]. However, continued delivery of iron to macrophages may overwhelm the capacity of ferritin to store and sequester the metal, causing oxidative damage to cells.

In many other tissues, iron is known to induce oxidative stress, resulting in macromolecular oxidative damage, tissue injury, and chronic inflammation [34][42][44]. It was therefore suggested that oxidative stress could be responsible for local destruction of the peritoneal mesothelium, creating adhesion sites for ectopic endometrial cells [12][28][45] and promoting invasion [11][46][47].

Heme oxygenase-1 (HO-1) is a heme-degrading enzyme strongly upregulated by heme that shields cells from heme-induced oxidative stress by generating beneficial molecules such as carbon monoxide (CO), bilirubin, and ferritin. Indeed, induction of HO-1 is accompanied by increased ferritin synthesis, scavenging of free iron, and, ultimately, protection against its adverse effects [48]. Bilirubin is an important antioxidant defending against oxidative damage and inflammation [49], while CO is a soluble gas acting as a signal molecule.

HO-1, which has a number of triggers such as ROS, free heme, heavy metals, and cytokines [23][50], is able to break down Hb and release iron from heme. Together with iron, HO-1 boosts levels of CO and biliverdin, both of which play a unique protective and antioxidant role, as well as possessing anti-inflammatory and antiapoptotic properties. HO-1-induced cytoprotective effects require co-expression of ferritin, but CO has been shown to exert significant cytoprotective, anti-inflammatory, and antiapoptotic properties all by itself [23][31].

In endometriosis patients, Hb concentrations were found to be higher in peritoneal fluid, and stronger HO expression was observed in ectopic endometrium, particularly red lesions, compared to eutopic endometrium and mesothelial cells [12][31]. However, since inducible HO-1 was weakly expressed by macrophages and mesothelial cells that make up the majority of cells in the peritoneal cavity, and because there was no concomitant upturn in peritoneal fluid levels of its final by-product bilirubin, it strongly infers that detoxifying systems, while present, may be inadequate to metabolize Hb in the case of endometriosis [32][38].

In conclusion, oxidative stress arises when the balance between ROS production and antioxidant defense is disrupted [12][21][30][47] due to either insufficient antioxidant protection or excess ROS production.

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