

Review

Insights into iron and nuclear factor-kappa B (NF- κ B) involvement in chronic inflammatory processes in peritoneal endometriosis

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Summary. Endometriosis is a chronic pelvic inflammatory process. Local inflammation is known to play a role in pain and infertility associated with the disease, and may be extensively involved in molecular and cellular processes leading to endometriosis development. In this review, we focus on two inflammatory mediators clearly implicated in the pathogenesis of endometriosis, iron and NF- κ B, and their potential association. Iron is essential for all living organisms, but excess iron results in toxicity and is linked to pathological disorders. In endometriosis patients, iron overload has been demonstrated in the different compartments of the peritoneal cavity (peritoneal fluid, endometriotic lesions, peritoneum and macrophages). This iron overload affects numerous mechanisms involved in endometriosis development. Moreover, iron can generate free radical species able to react with a wide range of cellular constituents, inducing cellular damage. Overproduction of reactive oxygen species also impairs cellular function by altering gene expression via regulation of redox-sensitive transcription factors such as NF- κ B, which is clearly implicated in endometriosis. Indeed, NF- κ B is activated in endometriotic lesions and peritoneal macrophages of endometriosis patients, which stimulates synthesis of proinflammatory cytokines, generating a positive feedback loop in the NF- κ B pathway. NF- κ B-mediated gene transcription promotes a variety of processes, including endometriotic lesion establishment, maintenance and development. In conclusion, iron and

NF- κ B appear to be linked and both are clearly involved in endometriosis development, making these pathways an attractive target for future treatment and prevention of this disease.

Key words: Endometriosis, Inflammation, Iron, NF-kappaB, Macrophage

Endometriosis, an inflammatory disease

Endometriosis is defined as the presence of endometrial tissue outside the uterine cavity. It is one of the most common benign gynecological disorders, affecting approximately 10-15% of all women of reproductive age. This pathology is associated with various distressing symptoms, such as dysmenorrhea, dyspareunia, pelvic pain and subfertility. Despite an increasing number of studies on endometriosis, its etiology remains elusive due, in part, to its multifactorial characteristics. Indeed, a growing body of evidence suggests that a combination of genetic, hormonal, environmental, immunological and anatomical factors play a role in the pathogenesis of this disorder (Sidell et al., 2002; Giudice and Kao, 2004; Heilier et al., 2008; Montgomery et al., 2008; Rizner, 2009; Barrier, 2010).

There is general agreement that endometriosis is a chronic pelvic inflammatory process, and that this local inflammation plays a major role in the pain and infertility associated with the disease. Moreover, peritoneal inflammation may well be extensively involved in the molecular and cellular processes that lead to endometriotic lesion development (Harada et al., 2001). Numerous studies support this concept, reporting elevated numbers of activated immune cells, particularly

peritoneal macrophages (Halme et al., 1987; Dunselman et al., 1988; Weinberg et al., 1991), and increased levels of many cytokines and adhesion, growth and angiogenic factors (Bedaiwy and Falcone, 2003) in the peritoneal fluid of women with endometriosis. It has also been reported that endometriosis may be associated with systemic subclinical inflammation (Agic et al., 2006) and that serum cytokines could potentially serve as valuable biomarkers to predict its development (Gupta et al., 2006). A wide range of inflammatory mediators have therefore been studied in the context of endometriosis over the last few years.

In this review, we will focus on two inflammatory mediators that have been clearly implicated in the pathogenesis of endometriosis, iron and nuclear factor-kappa B (NF- κ B), and discuss their potential association.

Iron is an essential metal for almost all living organisms because of its involvement in a large number of iron-containing enzymes and proteins (Crichton et al., 2002). However, excess iron accumulation within tissues and cells can result in toxicity and is associated with the pathogenesis of a variety of diseases, such as thalassemia, hemochromatosis, HIV and neurodegenerative disorders (Crichton et al., 2002). Moreover, in case of hemorrhage, lysis of erythrocytes leads to iron overload, provoking iron-mediated damage, oxidative injury and inflammation (Xi et al., 2006). Iron was recently suggested to be involved in endometriosis development (Defrère et al., 2008; Kobayashi et al., 2009). Indeed, peritoneal iron overload has been conclusively demonstrated in endometriosis patients (Van Langendonck et al., 2002b,c; Lousse et al., 2009) and may induce oxidative stress in the peritoneal cavity (Van Langendonck et al., 2002a). Oxidative stress and proinflammatory cytokines are known to be potent activators of the NF- κ B pathway, which has been implicated in peritoneal endometriosis (Gonzalez-Ramos et al., 2007, 2010; Lousse et al., 2008). Induced NF- κ B activation then leads to expression of numerous proinflammatory genes like cytokines, which may provide positive feedback to the pathway.

In this manuscript, the current literature on iron and endometriosis is reviewed and potential causes of iron overload in the pelvic cavity are considered. A model of iron metabolism and storage in the pelvic cavity of endometriosis patients is proposed, emphasizing the key role of macrophages in these processes. Possible consequences of iron overload on NF- κ B activation via induction of oxidative stress are discussed. Finally, the literature on NF- κ B and endometriosis is also reviewed.

Iron overload in endometriosis: evidence of a relationship?

Twenty-two studies to date have demonstrated the presence of iron overload in the different compartments of the peritoneal cavity of endometriosis patients: peritoneal fluid, ectopic endometrial tissue, peritoneum

adjacent to lesions and macrophages (Defrère et al., 2008).

In peritoneal fluid from women with endometriosis, higher levels of iron (Arumugam, 1994; Arumugam and Yip, 1995; Van Langendonck et al., 2002c; Lousse et al., 2009; Polak et al., 2010), ferritin (Van Langendonck et al., 2002c; Polak et al., 2006; Lousse et al., 2009), transferrin (Tf) (Mathur et al., 1999; Lousse et al., 2009) and hemoglobin (Hb) (Van Langendonck et al., 2002b) were detected than in peritoneal fluid from control patients. In endometriotic lesions and peritoneum, histochemical data revealed the presence of iron conglomerates (Moen and Alvorsen, 1992; Petrozza et al., 1993; Van Langendonck et al., 2004; Van Langendonck et al., 2002c) and macrophages heavily laden with ferric pigment (Gaulier et al., 1983). In endometriotic cysts too, the presence of iron in cystic fluid was considered to be indicative of endometriosis (Sugimura et al., 1992; Takahashi et al., 1996; Iizuka et al., 1998; Yamaguchi et al., 2008). Mounting evidence also suggests that iron metabolism by macrophages is enhanced in the case of endometriosis. This is supported by the observation that endometriosis is characterized by the presence of macrophages heavily laden with hemosiderin inside the pelvic cavity (Gaulier et al., 1983; Stowell et al., 1997). Lousse et al. recently demonstrated increased iron storage (ferritin) in peritoneal macrophages of endometriosis patients compared to healthy subjects (Lousse et al., 2009).

Most cells protect themselves from iron toxicity by expressing inducible heme oxygenase-1 (HO-1) and scavenger proteins such as haptoglobin (Hp) and hemopexin (Hx), binding Hb and heme respectively. However, the increased iron load, observed in all compartments of the peritoneal cavity in endometriosis patients compared to controls, strongly suggests that iron homeostasis in the peritoneal cavity may be disrupted in these patients.

Origin of iron in the pelvic cavity in case of endometriosis

In the case of endometriosis, iron overload may originate from lysis of pelvic erythrocytes (Van Langendonck et al., 2004; Defrère et al., 2006). Retrograde menstruation is considered an essential step in the pathogenesis of peritoneal endometriosis, according to Sampson's theory (Sampson, 1927). This menstrual reflux, transporting endometrial tissue and red blood cells through the fallopian tubes into the peritoneal cavity, is a common physiological event in 90% of menstruating women with patent tubes (Halme et al., 1984). Why then does iron accumulate inside the pelvic cavity of some women but not others? One hypothesis is that in some patients peritoneal protective mechanisms might be overwhelmed by menstrual reflux, either because of its abundance, or because of defective scavenging systems (Van Langendonck et al., 2002a,b; Defrère, 2008).

bioavailable form. Conglomerates consisting of hemosiderin, another iron storage form, are found in conditions of iron overload, and are usually associated with toxic pathological states in humans. Iron conglomerates have also been observed in endometriotic lesions in women (Moen and Halvorsen, 1992; Petrozza et al., 1993; Van Langendonck et al., 2002c) and in a murine endometriosis model (Defrère et al., 2006; Van Langendonck et al., 2004).

Moreover, erythrocyte lysis induces Hb release in the peritoneal cavity. Hb forms a complex with Hp which is, in part, secreted by endometriotic lesions (Sharpe-Timms et al., 1998, 2000; Piva and Sharpe-Timms, 1999) and then endocytosed by macrophages (Kristiansen et al., 2001; Knutson and Wessling-Resnick, 2003). This is a physiological event involved in iron recycling from senescent red blood cells. However, in the case of endometriosis, macrophages are Hp-saturated (Sharpe-Timms et al., 2002), suggesting that scavenger mechanisms might be overwhelmed. Furthermore, macrophages are able to release ferritin (Knutson and Wessling-Resnick, 2003). Iron released by macrophages in the form of ferritin or Tf, or by erythrocyte lysis (Hb), results in increased peritoneal fluid iron concentrations in endometriosis patients (Van Langendonck et al., 2002c).

Dassen et al. recently showed that endometrial tissue expresses Hb, a heme-binding protein (Dassen et al., 2008). Metabolization of heme has also been found to occur within endometrial implants. Indeed, active red endometrial lesions strongly express HO, the enzyme catalyzing degradation of the heme moiety of Hb into iron, carbon monoxide (CO) and biliverdin (Van Langendonck et al., 2002b; Casanas-Roux et al., 2002). Iron is then incorporated into ferritin or hemosiderin in conditions of iron overload.

The presence of hemosiderin in ectopic endometrial tissue and macrophages, usually associated with toxic pathological states in humans, strongly suggests that existing peritoneal protective mechanisms might be overwhelmed in case of endometriosis.

Effect of iron overload on endometriosis development

Endometriosis is a multifactorial disorder involving numerous mechanisms and a wide range of cell types, including endometrial cells (stromal and epithelial), mesothelial cells, endothelial cells and immune cells (macrophages, lymphocytes, etc). Iron overload could impair the functionality of these different cell types, thereby contributing to the development of the disease. In a previous review, the effect of iron overload on endometrial tissue adhesion, endometriotic lesion proliferation, angiogenesis and endometriosis-associated subfertility was investigated (Defrère et al., 2008).

Briefly, the mesothelial lining, like other types of epithelium, might serve as a barrier to prevent adhesion of menstrual endometrial fragments to the peritoneal

lining (Dunselman et al., 2001). However, the mesothelium is a fragile membrane that can be easily damaged, creating adhesion sites on its surface, facilitating the development of endometriosis (Kokorine et al., 1997; Demir et al., 2004). The iron-binding protein Hb has been identified as one of the menstrual effluent factors harmful to mesothelium (Demir et al., 2004).

The effect of pelvic iron overload on endometriotic lesion proliferation was evaluated in a murine endometriosis model (Defrère et al., 2006). In this model, erythrocyte injection was shown to increase the proliferative activity of epithelial cells in lesions, whereas desferrioxamine (DFO) administration significantly decreased it, suggesting that iron overload may contribute to the further growth of endometriosis by promoting epithelial cell proliferation (Defrère et al., 2006). Iron is an absolute requirement for proliferation, as iron-containing proteins catalyze key reactions involved in DNA synthesis. In fact, deprived of iron, cells are unable to proceed from the G1 to the S phase of the cell cycle (Le and Richardson, 2002).

Since vascularization is essential for lesion development, the impact of iron on endothelial cells in endometriotic lesions should be analyzed. Indeed, iron has been found to promote monocyte adhesion to these cells (Kartikasari et al., 2004), by inducing adhesion molecules like intracellular adhesion molecule and vascular adhesion molecule (Wagener et al., 1997). Binding and transmigration of leukocytes through endothelium to gain access to inflamed sites is a key inflammatory process implicated in the development of many diseases, such as atherosclerosis and neurodegenerative disorders.

Endometriosis and infertility are commonly associated, and a decrease in acrosome reaction rates linked to increased iron concentrations was previously demonstrated in the peritoneal fluid of endometriosis patients (Arumugam, 1994). Furthermore, iron ingested by peritoneal macrophages in these patients may be responsible for their increased spermiphagy, and contribute to the subfertility often observed in such cases (Skowron, 2000).

In this review, we will examine the role of iron in the formation of reactive oxygen and nitrogen species, particularly in the activation of redox-sensitive transcription factor NF- κ B, which appears to be markedly involved in endometriosis development.

Iron, macrophages, oxidative stress and NF- κ B in endometriosis

Peritoneal macrophages are known to play an important role in the initiation, maintenance and progression of endometriotic lesions (Dunselman, 1995; Lebovic et al., 2001). They may exhibit differences in phenotype, as illustrated by higher expression of estrogen receptors α and β , differentiation markers (CD68, NCL-MACRO and HAM56) and inflammatory

cytokines (IL-1 β , TNF- α and IL-6) (Montagna et al., 2008). They have been found to be increased in number and more activated in case of endometriosis, releasing various products such as cytokines, and growth and angiogenic factors (Oral et al., 1996; Gazvani and Templeton, 2002; Lousse et al., 2010). In fact, activation of macrophages is an essential defense mechanism (acute inflammation), but in pathological conditions like endometriosis, their activation may become exacerbated and inflammation chronic (Santanam et al., 2002).

Physiological macrophage functions include phagocytosis, iron metabolism, antimicrobial properties and TNF-mediated cytotoxicity. Peritoneal macrophages are able to remove erythrocytes, damaged tissue fragments and, in all likelihood, endometrial cells from the abdominal cavity. At nontoxic concentrations, iron promotes the physiological functions of macrophages, but iron overload is also known to impair macrophage function. Lousse et al. (2009) recently showed iron storage levels to be higher in peritoneal macrophages of endometriosis patients than controls. Cellular iron storage within ferritin limits the capacity of iron to generate free radicals (Balla et al., 1992). However, continued delivery of iron to macrophages can overwhelm the capacity of ferritin to store and sequester the metal, causing oxidative injury to cells. Indeed, iron can act as a catalyst in the Fenton reaction ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \text{OH}^- + \text{OH}^\cdot$) to potentiate oxygen and nitrogen toxicity by generation of a wide range of free radical species, including hydroxyl radicals, OH^\cdot , or the peroxynitrite anion (ONOO^-) produced by a reaction between nitric oxide (NO) and the superoxide anion (O_2^-).

Hydroxyl radicals are among the most reactive free radical species known and have the ability to react with a wide range of cellular constituents, including amino acid residues and purine and pyrimidine bases of DNA, as well as attack membrane lipids, to initiate a free radical chain reaction known as lipid peroxidation. It is clear that reactive oxygen species (ROS) are generated within the cell in the course of normal cellular mechanisms, and that cells are usually adequately equipped with cytoprotective enzymes and antioxidants to combat their toxicity. However, when the balance between ROS production and antioxidant defense is disrupted, marginally higher levels of ROS are generated and oxidative stress may occur, leading to harmful effects. Oxidative stress has been proposed as a potential factor associated with endometriosis pathophysiology (Van Langendonck et al., 2002a; Szczepańska et al., 2003; Jackson et al., 2005; Gupta et al., 2006). Overproduction of ROS not only induces cellular damage, but may also impair cellular function by altering protein activity and gene expression (Dalton et al., 1999). Indeed, ROS play a key role in the regulation of redox-sensitive transcription factors like NF- κ B (Dalton et al., 1999), which has been implicated in endometriosis development (Guo, 2007; Gonzalez-Ramos et al., 2007, 2008, 2010), as described below.

Furthermore, NF- κ B-activated macrophages express and secrete proinflammatory, growth and angiogenic factors, such as iNOS, COX-2, IL-1, IL-6, IL-8, TNF- α and VEGF, contributing to endometriosis pathogenesis (Rana et al., 1996; Wu et al., 1999; Harada et al., 2001; She et al., 2002; Lousse et al., 2008, 2010), but also activating NF- κ B in endometriotic cells. This consequently promotes cell survival and pro-inflammatory cytokine production, self-perpetuating the inflammatory reaction in endometriotic lesions.

NF- κ B

NF- κ B is a transcription factor that plays a crucial role in inflammation, immunity, cell adhesion and invasion, cellular proliferation, apoptosis and angiogenesis (Viator et al., 2005). These cell processes are involved in the development of endometriosis and other diseases (Giudice and Kao, 2004; Viator et al., 2005). NF- κ B is activated by diverse proinflammatory stimuli like IL-1 β , TNF- α , LPS and oxidative stress. NF- κ B activation leads to expression of multiple genes implicated in inflammation (IL-1, IL-6, IL-8, iNOS, COX-2), immunity (IFN- γ , TNF α , RANTES, ICAM-1), apoptosis (c-IAP, A1/Bfl1, c-FLIP, p53, Bax), cell proliferation (cyclin D1, c-Myc, EGF), tissue invasion (MMP-1, uPA) and angiogenesis (VEGF). A complete list of NF- κ B-regulated genes is available at <http://www.nf-kb.org> (Viator et al., 2005; Perkins, 2007; Aggarwal, 2004; Karin, 2006).

Modulation of NF- κ B is cell type-specific and interacts with other pathways, providing a complex variety of cellular responses (Viator et al., 2005; Perkins, 2007). NF- κ B peptides construct dimers from five subunits: p50/p105 (NF- κ B1), p52/p100 (NF- κ B2), p65 (RelA), c-Rel, and RelB. These dimers bind to specific inhibitors of NF- κ B (I κ B), forming an NF- κ B-I κ B complex, which is inactive because it is unable to bind to DNA. In the cytoplasm, various stimuli trigger the pathway by activating the I κ B kinase (IKK) complex, phosphorylating NF- κ B -coupled I κ B peptides and inducing their polyubiquitination and fast proteolysis by the 26S proteasome. As a result, liberated and active NF- κ B dimers translocate to the nucleus, binding to DNA and activating gene transcription (Barnes, 1997; Lawrence et al., 2001; Hoffman et al., 2006).

NF- κ B in endometriosis

Constitutive activation of NF- κ B occurs in B cells, some monocyte cell lines, and malignant cells, but it is basally inactive in most other normal cells (Aggarwal, 2004). NF- κ B activity is present in eutopic human endometrium, confirming its key role in endometrial cell physiology and pathophysiology (Laird et al., 2000; King et al., 2001; Ponce et al., 2009). In vitro studies have revealed constitutive and inducible activation of NF- κ B in endometrial cells (Han et al., 2003; Cao et al.,

2005, 2006; Wieser et al., 2005; Chen et al., 2008), showing NF- κ B to be a proinflammatory, cell growth, angiogenic and tissue-remodeling factor in endometrial cells. In the case of ectopic endometrium, *in vitro* and *in vivo* studies have both found the NF- κ B pathway to be activated, implicating this inflammatory pathway in endometriosis. *In vitro*, basal and stimulated NF- κ B activation were demonstrated in endometriotic cells (Wieser et al., 2005; Lebovic et al., 2001; Sakamoto et al., 2003; Yamauchi et al., 2004; Yagyu et al., 2005; Horie et al., 2005; Grund et al., 2008). *In vivo*, constitutive activation of NF- κ B was evidenced in endometriotic lesions and pelvic macrophages in women, as well as endometriotic lesions induced in nude mice (Gonzalez-Ramos et al., 2007, 2008; Lousse et al., 2008).

Transcription modulated by NF- κ B and consequent cell responses are important in endometriosis pathophysiology. They are described in detail in the review by Gonzalez-Ramos (Gonzalez-Ramos et al., 2010) and only briefly mentioned below.

The link between NF- κ B activation and inflammation in endometriosis has been demonstrated both *in vivo* and *in vitro*. NF- κ B-dependent activation of proinflammatory genes, such as RANTES, ICAM-1, IL-1 or TNF- α , may provide positive feedback to the pathway, thus self-perpetuating macrophage recruitment and the inflammatory response in the peritoneal cavity of endometriosis patients (Guo, 2007; Gonzalez-Ramos et al., 2010).

The role of NF- κ B as a proliferative and antiapoptotic factor, conferring a prosurvival phenotype to endometriotic cells, has been proved in many studies (Gonzalez-Ramos et al., 2008; Yamamoto and Gaynor, 2001; Grumont et al., 1998; Karin and Lin, 2002). This proliferation and resistance of endometriotic cells to apoptosis contribute to endometriosis development (Beliard et al., 2004; Harada et al., 2004).

Adhesion and invasion are considered to be initial steps in endometriotic lesion formation. Adhesion of endometriotic cells involves expression of mediators of cell-cell and cell-matrix adhesion, such as integrins and cadherins (van der Linden et al., 1994; Bridges et al., 1994; Beliard et al., 1997; Regidor et al., 1998). Once endometrial tissue adheres to the peritoneal surface, endometrial proteolytic enzymes begin active remodeling of the extracellular matrix (ECM), leading to endometrial invasion of the submesothelial space of the peritoneum (Nisolle et al., 2000; Witz et al., 2003). Two main families of proteolytic enzymes are involved in this process: matrix metalloproteinases (MMPs) and the plasminogen/plasmin activation system (Bruner et al., 1997; Kokorine et al., 1997; Sillem et al., 1998; Yoshida et al., 2004). Numerous studies strongly suggest positive modulation of invasion-promoting enzymes by NF- κ B in endometriotic cells (Farina et al., 1999; Baldwin, 2001; Grund et al., 2008; Veillat et al., 2009).

Considerable evidence indicates that NF- κ B-mediated transcription of proangiogenic proteins

stimulates angiogenesis in endometriotic lesions (Celik et al., 2008; Yang et al., 2000; Sakamoto et al., 2003; Veillat et al., 2009), and angiogenesis is known to be an essential process in endometriotic lesion formation (McLaren, 2000; Donnez et al., 1998).

Therapeutic perspectives

Treatment with iron chelators like DFO has proved beneficial for certain disorders and is currently used for pathologies characterized by iron overload, such as β -thalassemia and hereditary hemochromatosis (Tam et al., 2003). In the same way, NF- κ B inhibitors like sulindac are used for the treatment of chronic inflammatory diseases, such as arthritis. In the context of endometriosis, DFO was found to decrease the number of lesions with iron deposits, iron concentrations in peritoneal fluid, and the percentage of iron-loaded pelvic macrophages in a murine model (Defrère et al., 2006). Moreover, DFO treatment effectively reduced cellular proliferation of lesions. In the same model, treating endometriosis with NF- κ B inhibitors was shown to decrease initial endometriotic lesion growth, reducing inflammation and cell proliferation and inducing apoptosis (Gonzalez-Ramos et al., 2008). Bupleurum, dahurian angelica root, curcumin, frankincense, licorice root, rhubarb, salvia root and tortoiseshell have all been cited as medicinal herbs with NF- κ B inhibitory properties useful in the treatment of endometriosis in women (Wieser et al., 2007).

In conclusion, iron and NF- κ B are closely linked and both are involved in endometriosis development. These two pathways therefore constitute an attractive and central therapeutic target for future treatment and prevention of this disease.

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Iron, inflammation and endometriosis

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Iron, inflammation and endometriosis

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Accepted April 18, 2011