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REVIEW

Pro-endometriotic niche in endometriosis

BIOGRAPHY

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KEY MESSAGE

A pro-endometriotic niche established by an existing lesion is a supportive micro-environment for the progression of endometriosis. Impaired immune surveillance is a predisposing factor for the invasion of endometriosis. The hypoxic milieu, dysregulation of mesothelial-to-mesenchymal transition, remodelling of extracellular matrix, and abnormal neoangiogenesis within the lesion are important characteristics of a pro-endometriotic niche.

ABSTRACT

Endometriosis is a complex and heterogeneous disorder of unknown aetiology. This benign disease possesses special biological behaviours that mimic those of malignant tumours. A pro-endometriotic niche established by an existing lesion is a supportive micro-environment for the progression of endometriosis. After the accumulation of cells by an existing lesion, these components display distinct characteristics that impair immune surveillance. Subsequent retrograde menstruation of endometrial stromal cells into the pro-endometriotic niche facilitates endometriotic progression from early initiation to an advanced lesion. This study aimed to highlight the innovative role of the pro-endometriotic niche in endometriosis, and to provide valuable treatment targets for endometriosis.

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KEYWORDS

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Micro-environment
Pro-endometriotic niche

BACKGROUND

Endometriosis is a common but complex gynaecological disease, defined as the ectopic presence of endometrial tissue outside the uterus, usually attached to the pelvic peritoneum. The prevalence of endometriosis is 10–15% in women of reproductive age (*Khan et al., 2013*) and up to 20–48% in infertile women (*Liang and Yao, 2016*). Dysmenorrhoea, chronic pelvic pain and infertility are typical symptoms of endometriosis (*D'Hooghe and Hummelshoj, 2006*). Although many theories have been proposed to explain the pathogenesis of endometriosis, such as Mullerianosis, coelomic metaplasia and transplantation, Sampson's theory of retrograde menstruation is the most widely accepted. This theory suggests that, during menstruation, an endometrial fragment exits the uterus through the fallopian tubes and attaches itself to the peritoneal surface (the lining of the abdominal cavity) where it can proceed to form endometriosis (*Sampson, 1927*). However, a discrepancy arises in that only approximately 10% of women develop endometriosis, whereas retrograde menstruation is observed in most women, suggesting that other factors may be involved in this process (*Giudice and Kao, 2004*). An inflammatory environment within the pelvis may contribute to the pathophysiology of pain perception in symptomatic women with endometriosis (*Stratton and Berkley, 2011*). The innate or acquired survival of ectopic endometrial cells and dysregulation of the immune clearance mechanism are predisposing factors towards the implantation of endometrial cells (*Burney and Giudice, 2012*).

Although endometriosis is widely acknowledged to be a benign gynaecological disease, it possesses malignant features similar to tumours, such as invasion, metastasis, apoptosis resistance and angiogenesis (*Chan et al., 2017*). A recent study found that two phases contribute to the development and maintenance of endometriosis: an immune-predominant phase and a hormone-predominant phase. The initiation phase includes the stages of immune modulation, attachment and angiogenesis (<72 h after disease initiation), whereas the advanced phase includes the proliferation and paracrine signalling stages of disease (*Burns et al., 2018*). It has been reported that the dynamic process of endometriotic progression in the peritoneal cavity is related to changes in the micro-environment (*Lin et al., 2018; Yang et al., 2017*). Since the peritoneal cavity is important for the establishment of endometriosis, an existing lesion can also aggravate this susceptible milieu, which is favourable for the advanced progression of lesions (*Burns et al., 2018*). This supportive and receptive micro-environment undergoing a series of changes in endometrial stromal cell (ESC) colonization and endometriotic progression is termed the 'pro-endometriotic niche'. However, the mechanism involved in the formation of this fertile soil for the progression of an endometriotic lesion from early initiation remains unclear.

The aim of this study is to summarize the underlying mechanisms of pro-endometriotic niche formation, and to highlight its significant role in the progression of endometriosis. Theoretical elaboration of the potential micro-environment provides new insight into the pathogenesis of endometriosis. Targeted therapy against the formation of a pro-endometriotic niche can be an important treatment strategy to interfere with the progression of endometriosis.

ENDOMETRIOSIS-DERIVED COMPONENTS IN PRO-ENDOMETRIOTIC NICHE FORMATION

Based on Sampson's theory, lesions in the peritoneal cavity can secrete multiple factors and impair immune surveillance, which 'prepares' the local micro-environment for cell colonization even before their arrival. During the progression of endometriosis, existing lesions in the peritoneal cavity are facilitated to transform the environment into a susceptible state that can promote advancement of the initial lesion. Endometriosis-derived components are considered to be prerequisites for formation of the pro-endometriotic niche (FIGURE 1).

Endometriosis-derived secreted factors

Various factors secreted from endometriotic lesions are believed to promote pro-endometriotic niche formation. Indoleamine 2, 3-dioxygenase (IDO) is an intracellular haem enzyme that has been proven to be an important immunosuppressive factor (*Soliman et al., 2010*). High expression of IDO1 in endometriotic lesions could regulate the expression of p53, matrix metalloprotease 9 (MMP-9) and cyclo-oxygenase-2 (COX-2) via phosphorylation of the c-Jun N-terminal kinase signalling pathway, therefore enhancing ESC survival and inhibiting cell apoptosis in the peritoneal cavity (*Mei et al., 2013*). Researchers also demonstrated high expression of lysyl oxidase (LOX) in endometriotic lesions. Overexpression of LOX down-regulates the actin alpha 2 (*ACTA2*) and tissue inhibitor of metalloproteinase 3 (*TIMP3*) genes, leading to abnormal communication of the peritoneum and ectopic endometrium. LOX also reduces expression of the Fas ligand and interleukin-10 (IL-10), enhancing local inflammation and decreasing cell apoptosis (*Ruiz et al., 2015*). As intercellular communication modulators in endometriosis, exosomes also play important roles in endometriotic progression. Exosomes are vesicles carrying a variety of bioactive molecules such as RNAs, DNAs, proteins and lipids (*Colombo et al., 2014*). Overexpression of an exosomal-specific miRNA, miR21, could mediate angiogenesis in the progression of endometriosis (*Harp et al., 2016*).

Endometriosis-derived cytokines and chemokines

The secretion and modulation of chemokines and cytokines produced by endometriotic lesions are necessary stages for the regulation of a pro-endometriotic niche. Increased secretion of monocyte chemotactic protein-1 (MCP-1) from endometriotic lesions can enhance macrophage recruitment in the human body or in rat models (*Haber et al., 2009*). C-X-C motif chemokine ligand 12 (CXCL12), a chemokine protein, could also promote the migration of natural killer (NK) cells (*Bellelis et al., 2013*) and bone-marrow-derived stem cells (BMSC) into the peritoneal cavity (*Hopman and DiPersio, 2014*). After mobilization of these cells, endometriotic lesions secrete multiple cytokines for cellular transformation into pro-endometriotic status. IL-15 and transforming growth factor-beta (TGF-β) can weaken the killing activation of NK cells (*Guo et al., 2016; Yu et al., 2016*). Abnormal secretion of IL-8 enhances the apoptosis of activated T lymphocytes (*Sikora et al., 2017*). Endometriosis-derived chemokine

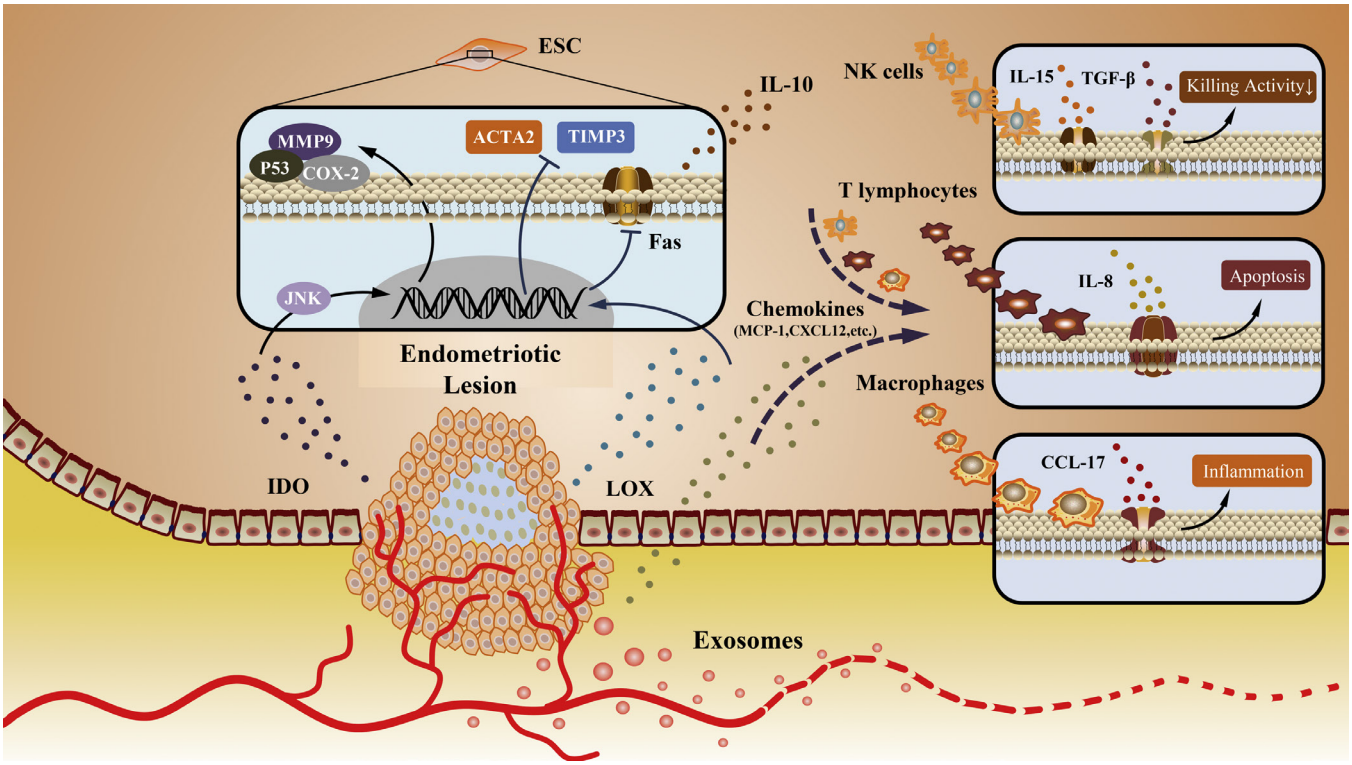

FIGURE 1 Endometriosis-derived components in the pro-endometriotic niche. High expression of indoleamine 2, 3-dioxygenase (IDO1) from the endometriotic lesion regulates the expression of p53, matrix metalloprotease 9 (MMP9) and cyclo-oxygenase-2 (COX-2) via c-Jun N-terminal kinase (JNK) signalling, which enhances the survival of endometriotic stromal cells (ESC) and inhibits their apoptosis. Expression of lysyl oxidase (LOX) from the endometriotic lesion not only disturbs communication between the peritoneal epithelium and ectopic endometrium by down-regulating the actin alpha 2 (*ACTA2*) and tissue inhibitor of metalloproteinase 3 (*TIMP3*) genes, but also enhances inflammation and decreases apoptosis of ESC by reducing expression of the Fas ligand and interleukin-10 (IL-10). Overexpression of specific exosomes mediates angiogenesis in the endometriotic milieu for disease progression. Chemokines [e.g. monocyte chemoattractant protein 1 (MCP-1), C-X-C motif chemokine 12 (CXCL12)] from the endometriotic lesion recruit multiple immune cells into the micro-environment. After accumulation of immune cells in the pro-endometriotic niche, IL-15 and transforming growth factor-beta (TGF-β) from the lesion can reduce the killing activation of natural killer (NK) cells. Abnormal secretion of IL-8 into the milieu enhances the apoptosis of T lymphocytes. Chemokine (C-C motif) ligand 17 (CCL17) from endometriosis can modulate the secretion profile of macrophages to promote inflammation.

(C-C motif) ligand 17 (CCL17) has been reported to modulate the secretion profile of macrophages during chronic inflammation (*Zhou et al., 2017*). These chemokines and cytokines from endometriotic lesions create an inflammatory and immunosuppressed environment, facilitating establishment of the pro-endometriotic niche.

IMMUNOSUPPRESSION IN PRO-ENDOMETRIOTIC NICHES

According to Sampson's theory, endometriosis develops as a consequence of the retrograde flow of endometrial fragments to the ectopic site through the fallopian tubes during menstrual shedding. The presence of endometrial tissue in the peritoneal cavity is considered to be an important 'seed' for advanced endometriosis. After this retrograde menstruation into the peritoneal cavity, ESC act as foreign materials exposed to the activated immune system. Their survival is restricted by the recruitment of immune cells, which act to eliminate them. This is one of the reasons why most women experiencing retrograde menstruation will not go on to develop endometriosis. However, these 'strangers' in the micro-environment modulated by an endometriotic lesion are able to avoid detection and eradication by re-education of infiltrating immune components (*Kitamura et al., 2015*). Therefore, establishment of an immunosuppressive micro-environment is a necessary precursor for advanced endometriosis (*Scheerer et al., 2016*) (FIGURE 2).

Macrophages

Many studies have demonstrated the abnormal distribution of macrophages within the peritoneal cavity of patients with endometriosis (*Hutter et al., 2013*). Peritoneal macrophages of patients with endometriosis can secrete high levels of proIL-1β, facilitating the escalation of peritoneal inflammation (*Chan et al., 2017; Sikora et al., 2016*). The interaction of macrophages and ESC through the CCL17–C-C chemokine receptor type 4 axis contributes to the high level of IL-6 in the ectopic milieu, aggravating the inflammatory condition (*Zhou et al., 2017*). Exacerbation of inflammation turns into a vicious cycle to further entrap macrophages. Furthermore, researchers have found that macrophages can down-regulate the expression of IL-24 and its receptor in ESC. The suppression of IL-24, on the one hand, restricts the expression of Ki-67, proliferating cell nuclear antigen, COX-2 and CD82, which are involved in modulating the proliferation and invasiveness of ESC. On the other hand, abnormally low levels of IL-24 can result in the recruitment of macrophages by CD82/CCL2 signalling and the impaired phagocytosis of macrophages

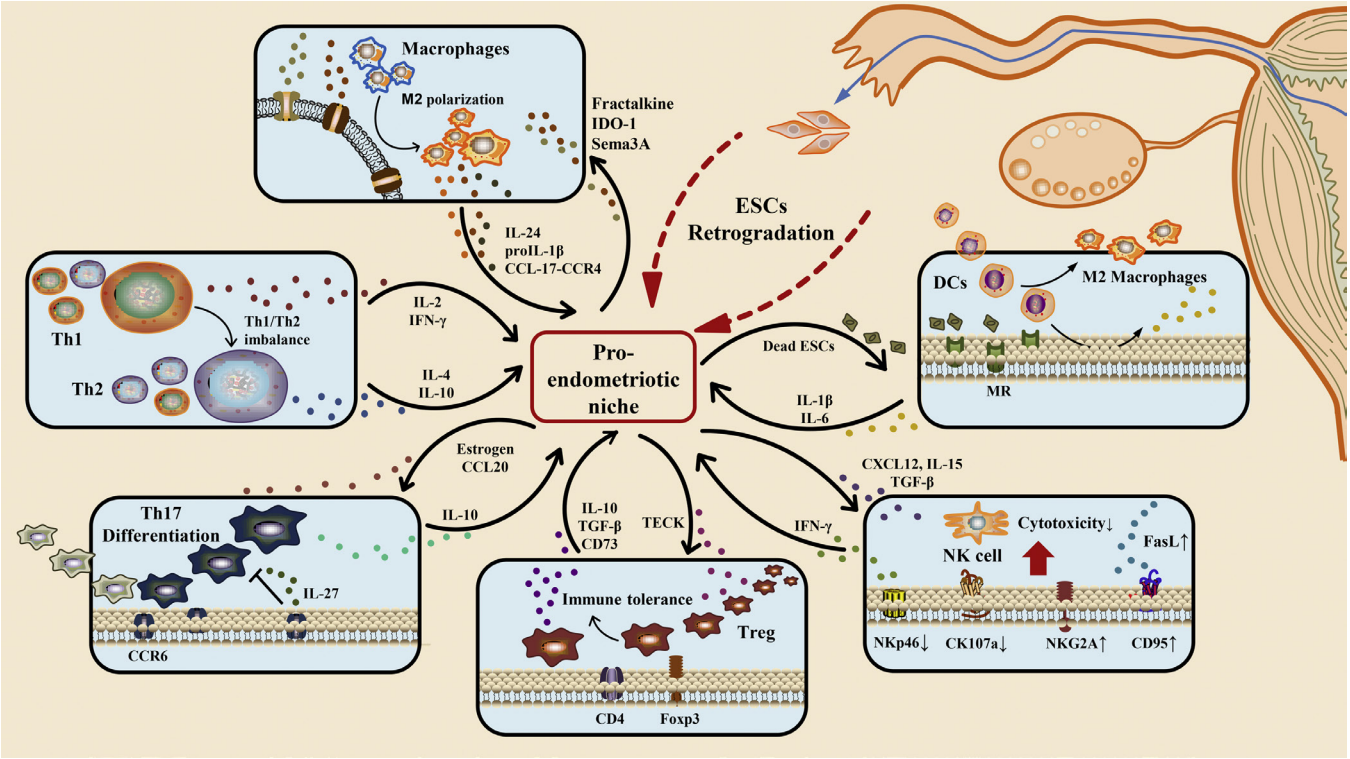

FIGURE 2 Dysfunction of immune components stimulated by the pro-endometriotic niche. Secreted factors [such as fractalkine, indoleamine 2, 3-dioxygenase 1 (IDO-1) and semaphorin3A (Sema3A)] could regulate the polarization of macrophages to an M2 phenotype, leading to release of cytokines [such as interleukin-24 (IL-24) and chemokine (C-C motif) ligand 17 (CCL17)] into the pro-endometriotic niche. The differentiation of precursor monocytes in the peritoneal cavity can skew away from dendritic cells (DC) to a macrophage fate. Stimulated by dead endometriotic stromal cells (ESC), DC secrete IL-1β and IL-6 via mannose receptors (MR). Molecular components [C-X-C motif chemokine ligand 12 (CXCL12), IL-15 and transforming growth factor-beta (TGF-β)] from the pro-endometriotic niche could decrease cytotoxicity receptors, NKp46 and CK107a, and increase inhibitory receptor NKG2A on natural killer (NK) cells, resulting in decreased cytotoxicity and increased apoptosis. Thymus-expressed chemokine (TECK) recruits regulatory T (Treg) cells into the peritoneal cavity, which induces immune tolerance by releasing IL-10 and TGF-β. CCL20 from the endometriotic lesion recruits chemokine receptor type 6 (CCR-6)-expressing helper T lymphocyte 17 (Th17) cells. Oestrogen stimulates the secretion of IL-27, which inhibits Th17 differentiation and promotes secretion of IL-10. Immature Th17 cells and increased IL-10 promote the formation of immune tolerance. The helper T lymphocyte 1/helper T lymphocyte 2 (Th1/Th2) ratio in the pro-endometriotic niche may skew towards Th2, mediating anti-inflammatory reactions via secretion of IL-4 and IL-10. Dysfunction of immune components in the pro-endometriotic niche may facilitate the survival of ESC. IFN-γ, interferon-gamma.

by the COX-2–prostaglandin E2 axis, contributing to the survival, growth and implantation of ectopic endometrium, and promoting the progression of endometriosis (*Shao et al., 2016*).

As an important member of the immune system, macrophages are characterized as having classically (M1) or alternatively (M2) activated phenotypes. M1 macrophages produce pro-inflammatory cytokines and chemokines (*Laskin et al., 2011*), whereas M2 macrophages secrete anti-inflammatory cytokines and growth factors (*Ferrante and Leibovich, 2012*). Specifically, an abnormal endometriotic milieu can induce M2 polarization of macrophages, leading to the development and invasiveness of endometriosis (*Bacci et al., 2009*). Complex macrophage plasticity has also been demonstrated to be dependent on the initiation of endometriosis. Fractalkine is a macromolecular protein derived from ESC, which is increased significantly in the peritoneal cavity of women with endometriosis (*Wang et al., 2014*). High levels of fractalkine can recruit macrophages into the ectopic milieu and induce M2 polarization of macrophages (*Wang et al., 2014*). Semaphorin3A (Sema3A), a member of the semaphorin family, is a chemorepulsive agent that can inhibit axonal outgrowth. Sema3A/NRP-1 signalling has been proven to have the same function as fractalkine (*Casazza et al., 2013; Liang et al., 2015*). IDO1 in the peritoneal cavity can reduce the phagocytic ability of macrophages, and promote M2 polarization by the induction of IL-33 secretion (*Mei et al., 2014*).

Overall, the macrophages in endometriosis display a tolerant cytokine profile, resulting in impaired phagocytic and antigen-presenting abilities. These compromised macrophages establish an immunosuppressive pro-endometriotic niche to assist in further progression of endometriosis.

Natural killer cells

NK cells are innate lymphoid cells with the ability to kill malignant or infected cells. Once they are recruited into the peritoneal cavity by C-X-C motif chemokine 12 (CXCL12), their characteristics are changed markedly by the endometriotic lesion. NK cells in the peritoneal fluid of women with endometriosis have reduced cytotoxicity (*Thiruchelvam et al., 2015*). Both the natural cytotoxicity receptor, NKp46 (*Funamizu et al., 2014*), and a cell surface marker for cytotoxicity, CK107a (*Jeung et al., 2015*), are reduced significantly in

peritoneal NK cells of endometriosis. In contrast, CD94/NKG2A, the inhibitory cytotoxic receptor, is significantly increased in peritoneal NK cells (*Galandrini et al., 2008*). High expression of FasL and its CD95 receptor in NK cells can promote the survival of endometrial fragments in the peritoneal cavity (*Sturlese et al., 2011*). In addition, interferon-gamma (IFN-γ), a key NK cell cytokine, loses its function of stimulating the apoptosis of ectopic endometrial cells (*Nishida et al., 2005*). IL-15 derived from ESC down-regulates the killing activation of NK cells, and therefore promotes the immune escape of ESC (*Yu et al., 2016*). Thrombin and thromboxane A2 released by ESC can induce platelet activation. Platelet-derived TGF-β1 in peritoneal fluid mediates the down-modulation of NKG2D expression (*Guo et al., 2016*), disturbing the co-stimulatory signals to T cells and activation of NK cells (*Groh et al., 2001*).

As a consequence, properties of NK cells altered by endometriotic lesions and ectopic ESC indicate impaired immune surveillance in the peritoneal cavity, which subsequently promotes the survival of ESC for advanced implantation.

T lymphocytes

In addition to macrophages and NK cells, accumulating evidence in recent years has extended knowledge regarding the types of immune cells in endometriosis. T lymphocytes are one of the important adaptive immune components thought to contribute to the pathogenesis of endometriosis. Helper T lymphocytes 1, 2 and 17 (Th1, Th2 and Th17) and regulatory T (Treg) cells are four distinctive subtypes of T lymphocytes that have been widely studied in the immune micro-environment of endometriosis (*Yuan et al., 2017*).

Studies in mice demonstrated that effector lymphocytes could be divided into two types, Th1 and Th2, based on their pattern of cytokine secretion following stimulation (*Mosmann et al., 2005*). The Th1 and Th2 imbalance hypothesis is based upon this concept. Th1 cells are secretors of predominantly pro-inflammatory cytokines, principally IL-2, IFN-γ and IL-1β, while Th2 cells produce anti-inflammatory cytokines, principally IL-4 and IL-10 (*Niu et al., 2017*). The Th1/Th2 imbalance hypothesis has been proposed to participate in the inflammatory response of endometriosis based on their different patterns of secretion (*OuYang et al., 2008*). The skew of Th1/Th2 elucidates a transformation from the Th1-mediated pro-inflammatory milieu to the Th2-mediated tolerant milieu, which is considered to be one of the potential mechanisms of immune escape (*Podgaec et al., 2007, 2010*).

Th17 cells are helper T lymphocytes that also play a vital role in the pathogenesis of endometriosis. Increased Th17 cells and their cytokine profiles have been observed in the peritoneal fluid of women with endometriosis (*Gogacz et al., 2016*). There are abundant Th17-derived pro-inflammatory cytokines, such as IL-17A, IFN-γ and IL-1β, in the peritoneal fluid of patients with endometriosis. However, anti-inflammatory cytokines such as IL-10 and IL-4 are also elevated in advanced endometriosis (*Chang et al., 2017*). This contradictory phenomenon is consistent with the skew of Th1/Th2, in that the initial pro-inflammatory milieu tends towards anti-inflammation during the advanced stage. Stimulated by IL-1β, tumour necrosis factor-alpha (TNF-α) and IL-17A, endometriotic tissue secretes CCL20 to recruit Th17 cells (*Hirata et al., 2010*). Given that TNF-α is secreted from macrophages, it is possible that Th17 cells secreting IL-17A may act synergistically with macrophages to enhance CCL20 secretion and lead to enforced recruitment of Th17 cells. As an oestrogen-dependent disease, a high level of oestrogen significantly promotes the secretion of IL-27 from macrophages, which inhibits Th17 differentiation and promotes IL-10 production from Th17 cells, leading to the formation of an immune tolerance pattern in the late stage of endometriosis (*Chang et al., 2017*). With the progression of this disease, the recruitment of macrophages and IL-27 will form a vicious cycle in a positive feedback loop for accumulation of immunosuppressive Th17 cells. Initial infiltration of Th17 cells and subsequent tolerant changes of Th17 cells promotes maturation of the pro-endometriotic niche, facilitating the progression of endometriosis.

Another emerging focus on the pathogenesis of endometriosis is the role of a specialized anti-inflammatory population of T lymphocytes termed 'Treg cells'. Treg cells are potent suppressors of inflammation and are essential in preventing destructive immunity. Many studies have shown a large number of Treg cells in the peritoneal fluid of women with endometriosis, suggesting decreased elimination of ectopic endometrial cells (*Berbic et al., 2010; Olkowska-Truchanowicz et al., 2013*). During the retrograde flow of ESC into the peritoneal cavity, thymus-expressed chemokines derived from ESC could initiate local immune tolerance by up-regulating the quantity and function of Treg cells (*Li et al., 2014*). In turn, these Treg cells could stimulate the development of advanced endometriosis through IL-10, TGF-β and CD73. Therefore, altered characteristics of Treg cells by earlier lesions protect the 'stranger', allowing advanced progression of endometriosis.

Although Treg cells exhibit an immunosuppressive feature in the endometriotic micro-environment, the exact proportion of Treg cells in endometriosis remains controversial (*de Barros et al., 2017*). In contrast to the increased proportion of Th17 cells in endometriosis, the proportion of Treg cells does not differ significantly between endometriotic lesions and endometrium (*Basta et al., 2010; Osuga et al., 2011*). More interestingly, TGF-β does not only stimulate the development of Treg cells, but can also mediate differentiation of Th lymphocytes (*Gogacz et al., 2016*). Since Th17 and Treg cells have distinct functions, Bettelli first proposed a reciprocal relationship between Th17 and Treg cells (*Bettelli et al., 2006*). Current studies suggest that the Th17/Treg ratio in the local environment in endometriosis is skewed towards Th17 cells (*Takamura et al., 2015*). Excessive IL-17 from Th17 cells can induce severe inflammation, which causes tissue damage in endometriosis (*Saito et al., 2011*). However, as discussed above, IL-17 and macrophages can synergistically inhibit Th17 differentiation, whereas macrophages significantly promote rapid growth and implantation of ectopic lesions (*Chang et al., 2017*). Although the balance between immune activation and immune silence in endometriosis remains unclear, multiple components in the peritoneal cavity can compete against the inflammatory Th17 cells, and regulate the immune tolerance of Th17 and Treg cells, although TGF-β mediates the differentiation.

Dendritic cells

Dendritic cells are specialized antigen-presenting cells that can sense the local micro-environment, direct the pro- or anti-inflammatory response of T lymphocytes, and encourage the activation of humoral or cytotoxic responses (*Manicassamy and Pulendran, 2011*). The development of endometriosis

is reported to be dependent on the presence of endogenous dendritic cells (*Pencovich et al., 2014*). Na et al. even suggested that peritoneal fluid of patients with endometriosis skewed the differentiation of precursor monocytes away from dendritic cells to a macrophage fate (*Na et al., 2008*). Additionally, these macrophages may be the M2 phenotype, which possesses pro-angiogenic features for the growth of endometriosis (*Bacci et al., 2009*). Moreover, a significant reduction in dendritic cells could result in larger endometriosis-like lesions and markedly reduce the activation of T lymphocytes (*Stanic et al., 2014*). To clarify the characteristics of dendritic cells, their classification seems necessary. Recently, a high proportion of dendritic cells with mannose receptors have been found in the peritoneal fluid of patients with endometriosis (*Izumi et al., 2017*). Mannose receptors are responsible for recognition and phagocytosis of antigens (*Kerrigan and Brown, 2009*). Mannose receptors on peritoneal dendritic cells can enhance the phagocytosis of dead ESC. Dendritic cells secrete IL-1β and IL-6, contributing to the escape of immune surveillance and Th17 differentiation (*Izumi et al., 2017*). In short, dendritic cells in endometriosis contribute distinctly to a state of immune silence in the pro-endometriotic niche.

IMPLANTATION AND PROLIFERATION OF ENDOMETRIOTIC STROMAL CELLS IN THE PRO-ENDOMETRIOTIC NICHE

Immunosuppression of the pro-endometriotic niche in the peritoneal cavity promotes survival and accumulation of ESC through re-education of the focal immune system. However, successful progression to advanced endometriosis is a complex multistage process. After the accumulation of ESC in the peritoneal cavity, a hypoxic micro-environment takes shape, accompanied by remodelling of the extracellular matrix (ECM) and angiogenesis. However, this pattern of implantation is not simply about the interaction between ESC and the peritoneum; the prior presence of a pro-endometriotic niche creates a fertile platform to influence their interaction.

Hypoxic milieu

Implantation into the peritoneum is merely a face-to-face attachment without transportation of oxygen and nutrition. The local altered hypoxic micro-environment may be an unavoidable stress that ESC have to face. An elevated level of hypoxia inducible factor-1α (HIF-1α) in ESC is a trigger for the secretion of multiple cytokines (*Lee and Tsai, 2017*). The secretion of leptin induced by HIF-1α can stimulate the proliferation of ESC (*Wu et al., 2007*). Overexpression of COX-2 stimulated by hypoxic conditions results in the abnormal production of prostaglandin E2, which stimulates steroidogenesis, angiogenesis and immune suppression in endometriosis (*Wu et al., 2011*). In addition, a hypoxic milieu promotes angiogenesis via IL-8 from macrophages, leading to increased migration of ESC (*Hsiao et al., 2014*). These studies describe a network of processes induced by hypoxia, leading to the activation of abnormal inflammation (FIGURE 3). The development

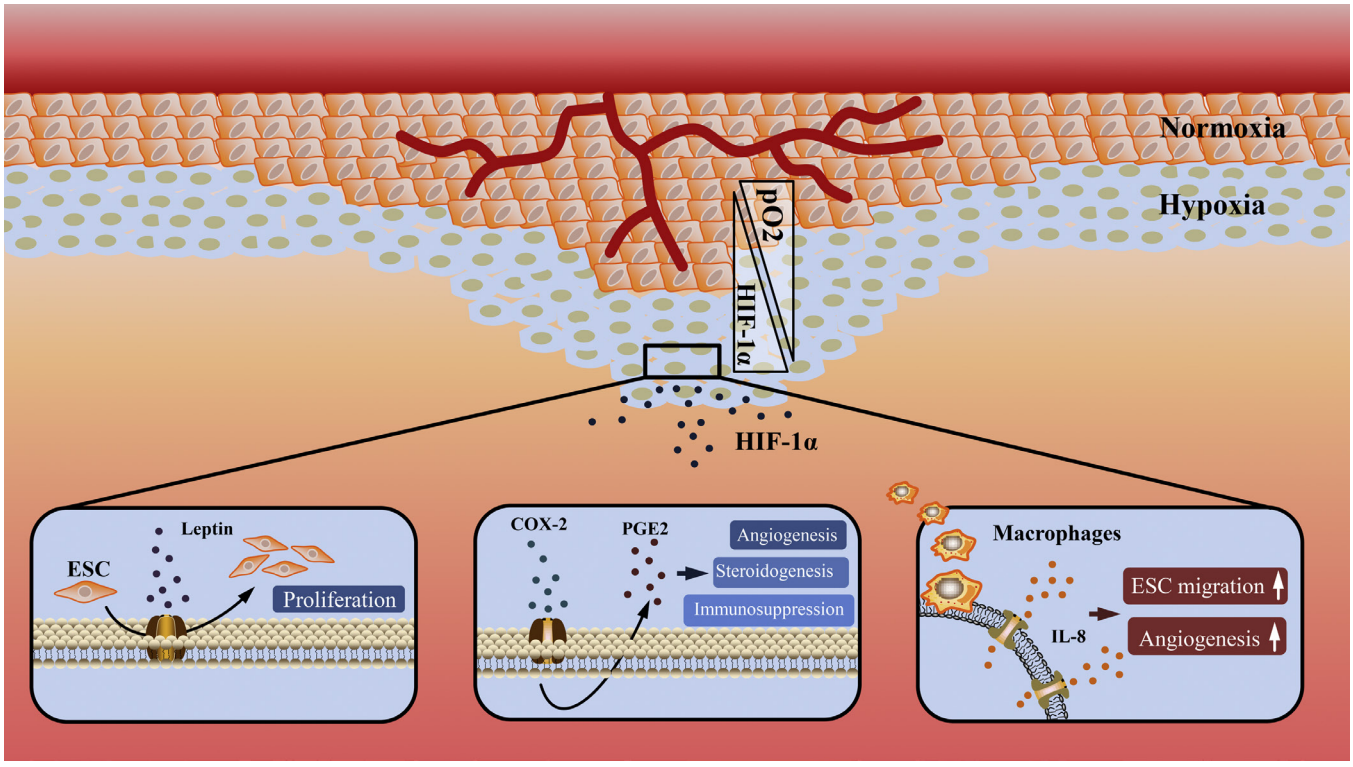

FIGURE 3 Role of hypoxia inducible factor-1α (HIF-1α) in the pro-endometriotic niche. During the initial communication of endometriotic stromal cells (ESC) with the peritoneal wall, the surviving ESC have to face hypoxic stress. The hypoxic milieu activates aberrant expression of HIF-1α in the pro-endometriotic niche. High levels of HIF-1α induce secretion of multiple components in the endometriotic milieu. Secretion of leptin induced by HIF-1α stimulates the proliferation of ESC. Overexpression of cyclo-oxygenase-2 (COX-2) induced by HIF-1α promotes abnormal production of prostaglandin E2 (PGE2). PGE2 in the micro-environment mediates steroidogenesis, angiogenesis and immunosuppression. Hypoxic conditions can also stimulate the secretion of interleukin-8 (IL-8) from macrophages, which promotes angiogenesis in endometriosis.

of endometriosis has been shown to be directly proportional to the severity of the hypoxic milieu, which enhances the importance of hypoxia in the pro-endometriotic niche for exacerbation of the disease.

Mesothelial-to-mesenchymal transition

The peritoneal cavity is lined by a continuous single layer of mesothelial cells (*Zhang et al., 1999*). Under pathological conditions, mesothelial cells can lose their polarity and gradually acquire a fibroblast-like phenotype, which is termed 'mesothelial-to-mesenchymal transition' (MMT) (*Aguilera et al., 2005*). Stimulated by inflammatory mediators and a low pH, MMT can serve as a trigger for peritoneal fibrosis and angiogenesis (*Aguilera et al., 2005*). MMT is a complex process that is involved in the alteration of cellular architecture and deep molecular reprogramming (*Rynne-Vidal et al., 2015*). During MMT, mesothelial cells possess increased capacity to migrate and invade the submesothelial compact zone (*Capobianco et al., 2017*). Recent studies have confirmed that peritoneal mesothelial cells undergo MMT, contributing to cellular adhesions (*Sandoval et al., 2016*). As endometriosis is an oestrogen-dependent disease, hepatocyte growth factor from macrophages is up-regulated by oestrogen in the peritoneal cavity, which can mediate MMT of the peritoneum (*Ono et al., 2015*). Therefore, the process of MMT may be triggered and maintained by the surrounding microenvironment. A pro-endometriotic milieu supports the formation of a suitable cradle to promote adoption of the 'seed' into the ectopic site by MMT.

Adhesion and extracellular matrix remodelling

Attachment of ESC and morphologic alterations of the peritoneum are inadequate to establish the lesion. Adhesions of ESC and remodelling of the ECM have been observed as a subsequent interaction between ESC and the peritoneum (*Umezawa et al., 2012*). Integrins are cell surface adhesion receptors supporting the adhesion of ectopic ESC to the peritoneum (*Gullberg et al., 1992*). Intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, two members of the integrin adhesion protein family, are also known to be increased in the peritoneum (*Kyama et al., 2008; Witowski et al., 2009*). Additionally, various subtypes of cadherin expressed on peritoneal cells may play an active role in mediating endometrial–peritoneal cell interactions (*Young et al., 2013*).

Matrix metalloproteases (MMP) are a group of collagenase proteins that are capable of remodelling ECM and creating space for cellular invasion and migration (*Sternlicht and Werb, 2001*). MMP are present in the peritoneal fluid and in endometriotic lesions (*Itoh et al., 2012*). After adhering to the peritoneal lining, endometrial fragments are able to produce MMP that can facilitate their invasion (*Koks et al., 2000*). Moreover, IL-1, TNF-α and TGF-β from pro-endometriotic niches have been demonstrated to stimulate MMP-1, -2 and -3 expression (*Pitsos and Kanakas, 2009*). Treatment of endometriotic lesions with IL-8 could also induce increased expression of MMP-2 and -9 *in vitro* (*Sikora et al., 2017*). Additionally, tissue inhibitors of matrix metalloproteinases (TIMP) are specific MMP inhibitors that could restrict the activity of MMP. The MMP-9/TIMP-1 protein ratio is significantly higher in women with endometriosis compared with women without this disease, enhancing the degradation of the ECM (*Collette et al., 2006*).

Abnormal accumulation of cell surface adhesion factors and aberrant MMP in the micro-environment endow fragments with invasive ability and alter the ECM architecture, hence promoting the adhesion and invasion of endometriosis.

Angiogenesis

Angiogenesis regulated by multiple factors is the most important mechanism involved in the progression of early endometriosis (*Sheveleva et al., 2016*). The expression of vascular endothelial growth factor A (VEGF-A) and its receptor are significantly higher in endometriotic lesions and peritoneal fluid, which indicates ongoing processes of vascularization and cell proliferative activity (*Bourlev et al., 2006*). The expression of proangiogenic factor prokineticin-1 is significantly increased in endometriotic lesions (*Lee et al., 2010*), while the expression of thrombospondin-1, an angiogenesis inhibitor, is decreased (*Tan et al., 2010*). These molecules reveal a high proangiogenic property in the endometriotic milieu which is conducive to disease invasion. In addition, immunosuppressive cells in the pro-endometriotic niche also promote angiogenesis of endometriosis, which is mediated by pro-angiogenic and pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and TNF-α (*Tariverdian et al., 2007*).

Multiple studies have concentrated on the functions of immune cells, and pro-inflammatory and pro-angiogenic molecules in angiogenesis, but systemic stem cells also have a role in disease progression. BMSC are bone-marrow-derived non-haematopoietic stromal cells that are capable of differentiating into multiple types of cells. BMSC have been found to contribute to the pathogenesis of endometriosis (*Hufnagel et al., 2015*). Many studies have clarified that chemoattraction of BMSC towards ESC is mediated by the oestradiol-regulated CXCL12–CXCR4 axis (*Wang et al., 2015*). After the engraftment of BMSC into the lesion (*Asahara et al., 1999*), circulating BMSC also get incorporated into the growing vasculature of the endometriotic lesion (*Becker et al., 2011*). They are able to enhance angiogenesis in endometriosis through the increased secretion of MCP-1 and VEGF along with pro-inflammatory cytokines (*Koippallil et al., 2015*). Thus, attraction of BMSC by the lesion in the peritoneal cavity implicates the pro-endometriotic traits of BMSC in the progression of endometriosis.

IMPLICATIONS OF THE PRO-ENDOMETRIOTIC NICHE FOR ENDOMETRIOSIS INTERVENTION

Targeting the components involved in pro-endometriotic niche formation and consequently preventing the progression of endometriosis may be a promising strategy for the treatment of endometriosis. Blocking the molecular components derived from the endometriotic lesion, suppressing the recruitment and activity of immunosuppressive cells, inhibiting the mobilization of BMSC and constricting the angiogenesis process may represent potential approaches to preventing the progression of endometriosis. Glucosaminylmuramyl dipeptide, an immunomodulatory drug, can prevent hyperactivation of macrophages (*Antsiferova et al., 2013*). Signal transducer and activator of transcription 3 regulates the interaction between M2 macrophages and ESC, and targeting it impairs the immunosuppressive state

in the pro-endometriotic niche (*Itoh et al., 2013*). Reduction of oestradiol can decrease chemokine CXCL12 and reduce BMSC accumulation, which may help in the treatment of endometriosis (*Wang et al., 2015*).

All therapeutic strategies discussed above focus on one or a few components within the pro-endometriotic niche. Integrative targeting of multiple molecular and cellular events in the pro-endometriotic niche may be more efficient in the treatment of endometriosis. A combination of U0126 (an MEK inhibitor) and MK2206 (an AKT inhibitor) is more effective than each drug alone in the inhibition of ESC survival and proliferation (*Matsuzaki et al., 2017*). Synthetic therapy with telmisartan and parecoxib could induce the regression of endometriotic lesions through a reduction in microvessel density, inhibition of cell proliferation and promotion of ESC apoptosis (*Nenicu et al., 2017*). However, these targeted therapies are highly toxic, and further experiments are needed before wide application in women of reproductive age.

Furthermore, the recurrence of endometriosis after operative intervention is also worth noting. The overall recurrence rates range between 6% and 67% (*Morgante et al., 1999; Vignali et al., 2005*). Many scholars think that the recurrent lesion might originate from either residual lesion or de-novo cells coming through retrograde bleeding (*Bozdag, 2015*). The risk of recurrence increases if the lesion are not removed completely during the initial surgery. Even after surgery or medical treatment, immunological factors are not prone to decrease, and might maintain an inflammatory environment suitable for recurrence. Thus, pro-endometriotic niches and residual lesions play an important role in the recurrence of endometriosis. Targeting the pro-endometriotic niche and postoperative treatment may be of significant value in the prevention of postoperative recurrence in the future.

CONCLUSION

Based on Sampson's theory, it is proposed that a pro-endometriotic niche, a permissive and supportive environment, is established in endometriosis before the formation of an advanced ectopic lesion (FIGURE 4). However, the exact mechanism of this dynamic process and the function of molecular and cellular components in the pro-endometriotic niche remain unclear. Better understanding of the

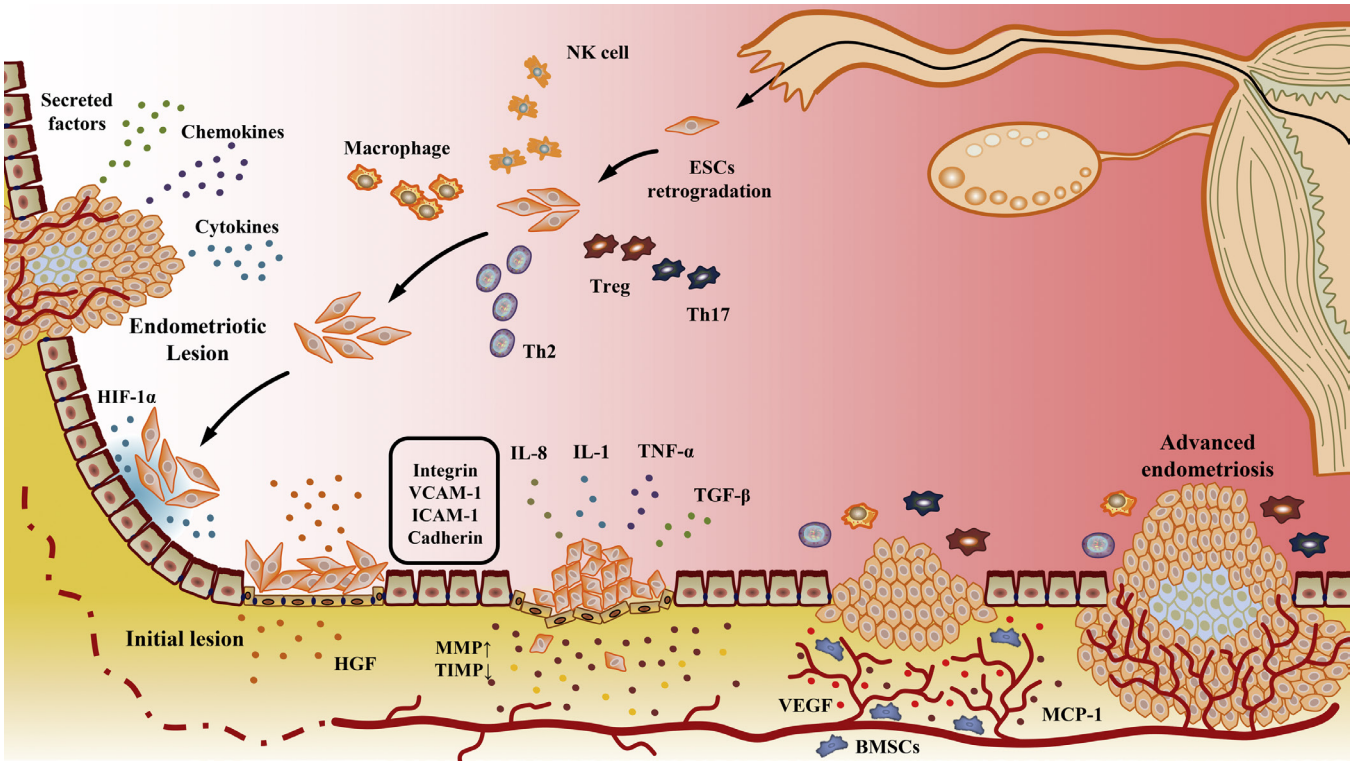

FIGURE 4 Establishment of an advanced lesion mediated by the pro-endometriotic niche. Dysregulation of secreted factors, chemokines and cytokines from an existing endometriotic lesion initiates the formation of a pro-endometriotic niche. Recruitment and activation of immune cells [e.g. macrophages, natural killer (NK) cells, regulatory T (Treg) cells, helper T lymphocyte 17 and 2 cells (TH17 and Th2 cells)] stimulate the maturation of this immunosuppressive environment, promoting the survival of endometriotic stromal cells (ESC). ESC communicate with the peritoneum under hypoxic stress. Hepatocyte growth factor (HGF) from the pro-endometriotic niche up-regulates matrix metalloproteases (MMP), facilitating the reprogramming and reconstruction of the extracellular matrix (ECM) (changes in integrins, vascular cell adhesion molecule 1 (VCAM-1), intercellular adhesion molecule 1 (ICAM-1), cadherin]. Subsequently, it creates a supportive soil for the implantation and invasion of ESC. In addition to vascular endothelial growth factor (VEGF) and monocyte chemoattractant protein 1 (MCP-1) promoting angiogenesis, bone-marrow-derived stem cells (BMSC) in the milieu activated by VEGF and MCP-1 accelerate angiogenesis in the pro-endometriotic niche. Therefore, the pro-endometriotic niche directs the establishment of advanced endometriosis from the initial lesion and leads to the progression of endometriosis. IL, interleukin; TGF-β, transforming growth factor-beta; TNF-α, tumour necrosis factor-alpha; HIF-1α, hypoxia inducible factor-1α; MMP, matrix metalloproteases; TIMP, tissue inhibitors of metalloproteinases.

mechanism that drives the establishment of the pro-endometriotic niche will inspire new strategies for early diagnosis and treatment of endometriosis.

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