

## Angiogenesis, lymphangiogenesis and neurogenesis in endometriosis

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### TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Eutopic endometrium
  - 3.1. Endometrial anomalies in endometriosis
  - 3.2. Angiogenesis
  - 3.3. Lymphangiogenesis
  - 3.4. Neurogenesis
4. Endometriotic lesions
  - 4.1. Angiogenesis
  - 4.2. Lymphangiogenesis
  - 4.3. Neurogenesis
  - 4.4. Cross-talk between lesions and eutopic endometrium
5. Summary and perspective
7. References

## 1. ABSTRACT

Endometriosis is a common, benign gynecological disease affecting 10 – 15% of reproductively aged women. It is characterized by the presence of endometrial-like tissue at sites outside the uterus. The most widely accepted theory of endometriosis pathogenesis proposes that shed menstrual endometrium can reach the peritoneum, implant and grow as endometriotic lesions. Angiogenesis, lymphangiogenesis and neurogenesis are implicated in successful ectopic establishment and the generation of endometriosis-associated symptoms. This review considers these processes as they occur in the eutopic endometrium and ectopic endometriotic lesions of women with endometriosis. Their regulation is interconnected and complex. Dysregulation in endometriosis occurs on a background of accumulating evidence that endometriosis is an endometrial disease with underlying genetic influences and cross talk with endometriotic lesions. Understanding the roles of angiogenesis, lymphangiogenesis and neurogenesis in endometriosis pathophysiology is essential for the development of novel therapeutic approaches.

## 2. INTRODUCTION

Endometriosis is a gynecological disorder defined by growth of tissue resembling endometrial glands and stroma outside the uterus (1). Around 10-15 % of women of reproductive age have endometriosis (2, 3). The most common symptoms of endometriosis are various types of pain and reduced fertility. In women with pelvic pain and/or infertility the prevalence of endometriosis is up to 50 % (4, 5). Endometriosis is the most common cause of chronic pelvic pain in women (6, 7); pain which can be debilitating and often has a negative impact on the ability to work, personal relationships and self-esteem (6, 8). In addition, endometriosis has a significant economic impact on society. Current estimates put the cost of endometriosis in terms of healthcare and loss of productivity in Europe in 2008 as €9579 per woman per annum (9). Two-thirds of that cost was attributable to productivity loss (€6298) with one-third (€3113) being for health care costs. Estimating 10% prevalence of endometriosis in women of reproductive age (15-49 years) results in an almost €50 billion cost to the North American economy per annum, almost €10 billion to the UK economy and €5.5 billion to the Australian economy.

## Angio-, lymphangio- and neuro-genesis in endometriosis

Endometriosis was recognized as peritoneal ‘ulcers’ on the surface of the bladder, intestine and uterus and described as a disease process over 300 hundred years ago in the late 17<sup>th</sup> century, as quoted in Knapp (10). Despite extensive investigation, the cause of the disease remains undefined, however the most widely accepted theory of pathogenesis proposes that endometrial fragments shed at menstruation can subsequently implant and grow on and into the peritoneum, forming endometriotic lesions (11). It is thought that shed endometrial cells and fragments can reach ectopic locations via retrograde menstruation (reflux through the fallopian tubes) (11, 12) and dissemination into the lymphatic and vascular circulations (13, 14).

Blood vessel, lymphatic vessel and nerve fiber formation and growth occur by processes known as angiogenesis, lymphangiogenesis and neurogenesis, respectively. There is considerable overlap and interaction between the molecular mechanisms by which these processes are controlled, and these three structures are often closely related during embryological development and where the major vascular and nerve supplies enter an organ (15-17).

Angiogenesis, lymphangiogenesis and neurogenesis are important processes in the endometrium, and particularly in endometriosis, due to their roles in wound healing, tumor growth and spread, and in pain generation. Uterine angiogenesis and lymphangiogenesis are critical for endometrial repair, regeneration, growth and differentiation, and are likely similarly regulated under the control of estrogen and progesterone (18-21). Angiogenesis and lymphangiogenesis are implicated in endometriosis pathogenesis (22, 23). Very little is known about endometrial or uterine neurogenesis, however it is thought to be important in generation of endometriosis associated pain symptoms and there are likely to be hormonal effects, as evidenced by highly significantly increased expression of nerve growth factor (NGF) in the proliferative compared to secretory phase (24), and denervation of the myometrium during pregnancy (25-30) with subsequent recovery of innervation (29, 31).

### 3. EUTOPIC ENDOMETRIUM

#### 3.1. Endometrial anomalies in endometriosis

There is mounting evidence that eutopic endometrium in women with endometriosis is fundamentally different to the endometrium of women without endometriosis although the appearance of the tissue on routine histology is almost identical to normal endometrium. The combination of decreased apoptosis (32-38); defective immune-surveillance (39, 40); and increased adhesiveness (41-53), proteolytic activity (46, 54-69), angiogenic potential (see section 3.2 of this review), proliferation (37, 70-74), and estrogen production (49, 75-84); with abnormal innervation (see section 3.4 of this review), indicates this tissue is predisposed to implantation and growth on peritoneal surfaces and ultimately development into endometriosis and the induction of associated symptoms.

These endometrial anomalies in endometriosis occur on a background of genetic predisposition. There is increasing evidence that endometriosis is inherited as a complex genetic trait in which several different genes conferring disease susceptibility interact with each other and the environment to produce the condition (85, 86). Endometriosis shows familial clustering (87, 88), concordance in monozygotic twins (89, 90) and a 6-9 times greater prevalence of the disease has been reported in first degree relatives of women with endometriosis compared with the rest of the population (91-93). A range of studies have attempted to identify specific susceptibility loci and gene variants associated with endometriosis, however as yet there are no conclusive findings (94-99).

While the precise pathophysiology of endometriosis remains unclear, that the eutopic endometrium of women with the disease shows a wide variety of anomalies compared to the endometrium of disease-free women indicates that the primary defect in endometriosis may be the eutopic endometrium (2, 100, 101).

#### 3.2. Angiogenesis

Angiogenesis in the female reproductive tract is highly regulated and critical for a number of processes, including endometrial growth and remodeling (20). Endometrial blood vessels are known to grow and regress through the menstrual cycle under the ultimate control of estrogen and progesterone, which act directly and indirectly via a variety of growth factors. Regulation of endometrial angiogenesis is complex. A large number of angiogenic factors and inhibitors have been identified in the endometrium and there is evidence that estrogen can both promote (102-104) and inhibit (105, 106) endometrial angiogenesis under different conditions.

The chief angiogenic growth factor in the endometrium is considered to be vascular endothelial growth factor-A (VEGF-A), with its receptors VEGFR-1, VEGFR-2, and neuropilin-1 (NRP-1). Other angiogenic promoters expressed in the endometrium include fibroblast growth factor (FGF), hepatocyte growth factor (HGF), tumor necrosis factor-alpha (TNF-alpha), platelet-derived endothelial cell growth factor (PDGF) and prokineticins (PK). Angiogenesis inhibitors such as thrombospondin-1 (TSP-1), plasminogen, and soluble VEGFR-1 are also present in the endometrium. Endometrial vascular remodeling is regulated by angiopoietins and their receptor tyrosine kinase (Tie), integrins, and matrix metalloproteinases (MMP) (107-109).

Studies comparing the eutopic endometrium from women with and without endometriosis have described a range of differences relating to angiogenesis, as summarized in Table 1.

Eutopic endometrium from women with endometriosis shows increased expression of the potent angiogenic factors VEGF-A, angiopoietin-1 (Ang-1), and Ang-2, and their receptors VEGFR-2 and Tie2, compared to normal uterine endometrium (64, 71, 110-118). In

**Table 1.** Endometrial expression of key angiogenic, lymphangiogenic and neurogenic factors and their receptors in women with compared to women without endometriosis

Primary function	Factor or receptor	References
Angiogenesis	<b>Increased expression</b>	
	Angiopoietin-1	115
	Angiopoietin-2	115-117
	Fibroblast growth factor	120
	Heparanase	116, 117
	Hepatocyte growth factor	71, 121, 122
	Receptor tyrosine kinase 2	115
	Vascular endothelial growth factor-A	64, 71, 110-114, 118
	Vascular endothelial growth factor/receptor-2	114
	<b>Decreased expression</b>	
	Prokineticin 1	125
	Thrombospondin-1	111
Lymphangiogenesis	<b>Increased expression</b>	
	Large range of growth factors conventionally considered angiogenic that are also potent promoters of lymphangiogenesis (e.g., angiopoietins, fibroblast growth factor and hepatocyte growth factor)	As detailed above
	<b>Decreased expression</b>	
	Insulin-like growth factor-1	141
	Insulin-like growth factor-2	141
	Vascular endothelial growth factor-C	112
Neurogenesis	<b>Increased expression</b>	
	Brain-derived neurotrophic factor	167
	Nerve growth factor	166
	Neurotrophin-4	167
	p75 receptor	166
Tyrosine kinase-A	166	

addition, expression of heparanase, an enzyme which releases extracellular matrix-resident angiogenic factors and induces an angiogenic response (119), angiogenic factors FGF-2 (120) and HGF (71, 121, 122) are increased in the endometrium of women with endometriosis. TSP-1, which inhibits vascular endothelial cell proliferation and angiogenesis (123), is down-regulated and lacks the normal menstrual cyclic variation in eutopic endometrium of women with the disease (64). Prokineticin is an angiogenic factor particularly involved in the vascular function of peri-implantation endometrium and early pregnancy (124) and thus it may be considered that its decreased expression in the endometrium of women with endometriosis is related to endometriosis associated infertility (125).

Overall, these studies indicate that the eutopic endometrium from endometriosis patients has greater angiogenic potential than endometrium from women without the disease. It has been hypothesized that the enhanced angiogenic tendencies of uterine endometrium from women with endometriosis allow shed endometrial fragments to attract a blood supply once they reach the peritoneum, ensuring their survival.

While endometrial angiogenic activity, studied by a number of techniques, is clearly increased in women with endometriosis (64, 71, 110, 111, 114, 115), we have

recently confirmed that total uterine blood vessel density is not different between women with and without endometriosis (23). Controversy existed in past literature as to whether endometrial blood vessel density was increased or not in endometriosis. Two small studies had indicated that blood vessel density was increased in the eutopic endometrium of women with endometriosis (71, 114), while others found no significant differences (126, 127). Importantly, however, density of newly forming blood vessels is increased in eutopic endometrium of women with endometriosis. A valuable clue to the importance of increased angiogenic activity in endometriosis is provided by the finding of significantly increased density of neoangiogenic blood micro-vessels in the superficial subepithelial layer during the secretory phase, the very tissue which is being shed at menstruation (23, 128). It is hypothesized that enhanced angiogenic tendencies of shed endometrium from women with endometriosis allow fragments to attract a blood supply once they reach the peritoneum and implant, ensuring their survival (1, 22).

### 3.3. Lymphangiogenesis

Relatively little is known specifically about endometrial lymphangiogenesis. Like angiogenesis, lymphangiogenesis almost certainly plays important roles in endometrial regeneration following menstruation, among other processes in the uterus. Endometrial lymphatic vessels are thought to grow and regress through the menstrual cycle under hormonal control similar to blood vessels. Uterine lymphangiogenesis is likely to occur primarily under the influence of VEGF-C and VEGF-D and their receptors VEGFR-2, VEGFR-3 and NRP-2. Of course, as in other tissues, there is considerable overlap between the mechanisms by which lymphangiogenesis and angiogenesis are controlled, with contributions from promoter and inhibitor molecules which also function in angiogenesis, such as angiopoietins, integrins, FGF, HGF and other VEGFs (129-131). Other growth factors identified as promoting lymphangiogenesis include insulin-like growth factors 1 and 2 (IGF-1 and -2) (132) and platelet-derived growth factor-BB (PDGF-BB) (133). Relatively few natural inhibitors of lymphangiogenesis have been identified. Among endogenous substances shown to have inhibitory effects on lymphangiogenesis are vasohibin-1 (134), interferon-alpha (135), soluble VEGFR-2 (136), transforming growth factor-beta (137), Semaphorin 3F (138), and neostatin, formed from proteolytic processing of collagen XVIII by MMP-7 (139, 140).

In addition to the increased endometrial angiogenesis in endometriosis, there is preliminary evidence to suggest changes in local lymphangiogenesis in women with the disease (summarized in Table 1). For example, VEGF-C gene expression is decreased in the endometrium of women with endometriosis compared to controls (112). Expression of other lymphangiogenic promoters is disturbed in the eutopic endometrium of endometriosis patients, with IGF-1 and IGF-2 reduced in epithelial cells (141). While there is no definitive evidence of altered expression of lymphangiogenic inhibitors in the eutopic endometrium of women with endometriosis, a

## Angio-, lymphangio- and neuro-genesis in endometriosis

number of these or related molecules have been implicated in endometriosis pathogenesis. For example, in endometriosis, VEGFR-2 (114), Semaphorin E (142) and MMP-7 (57, 66, 69) are increased in the eutopic endometrium, and transforming growth factor-beta is increased in the peritoneal fluid (143). Furthermore, the expression of a range of other primarily angiogenic factors and receptors that also function in lymphangiogenesis are increased in eutopic endometrium from women with endometriosis compared to control endometrium (detailed in section 3.2). While it is becoming increasingly apparent that endometrial lymphangiogenesis is disturbed in endometriosis, the precise details and implications are currently unclear.

This preliminary evidence of altered endometrial lymphangiogenesis in endometriosis is complemented by the finding of locally increased lymphatic micro-vessel density in these women. We have recently demonstrated significantly increased lymphatic vessel density within the basal-layer endometrium in women with endometriosis during the proliferative phase of the cycle, in comparison to women without the disease (23). In the basal endometrium, lymphatic vessels are larger and sometimes intimately associated with spiral arterioles and density is highly significantly increased compared to the functional layer in both women with and without endometriosis (21, 23). Lymphatic vessels of the functionalis are smaller and sparsely distributed (21, 23) but form an extensively anastomosing network of fine vessels extending almost to the surface epithelium (144, 145). Lymphatic vessel density in the functional layer does not appear to differ between women with and without endometriosis.

Lymphangiogenesis in endometriosis is particularly relevant due to the theory of lymphatic spread of endometriosis. This theory states that fragments of endometrial tissue can be disseminated into the lymphatic circulation at menstruation and cause endometriotic lesions (13, 14, 146). The hypothesis of dissemination of endometrial cells or fragments via the lymphatic system was developed based on observations of endometrial tissue in the form of an endometrial polyp in the lumen of a lymphatic vessel (147), endometriosis in pelvic lymph nodes (146, 148, 149), and endometriotic lesions at uncommon locations (150-154).

### 3.4. Neurogenesis

It is becoming increasingly clear that neurogenesis occurs in the uterus in relation to reproductive processes, such as pregnancy, and, probably to a certain extent, during the menstrual cycle, particularly in women with endometriosis. Neurogenesis occurs primarily through the dynamic regulation of axonal growth cones by attractant neurotrophic factors (155) and various repulsive molecules (156). These molecules interact with their specific substrates; thereby regulating distinct signaling cascades and activation pathways. It is these pathways that govern the proliferation, plasticity and sensitivity of the nerve fibers (157, 158). For instance, when NGF binds to tyrosine kinase A (TrkA) receptor it promotes the survival of sensory nerve fibers through the activation of the

Ras/phosphatidylinositol 3'-phosphate-kinase (Ras-PI3K), Ras/mitogen-activated protein kinase (Ras-MAPK) and phospholipase C-gamma 1 pathways (159). The end-products of these pathways are involved in the branching and morphology of the growing axons effecting remodeling of the growth cones (160, 161).

Molecules with important roles in neurogenesis include the novel neurotrophin-1/B cell-stimulating factor-3 (NNT-1/BSF-3) and the NGF, brain-derived neurotrophic factor (BDNF) (162), neurotrophin-3 (NT-3) (163), neurotrophin-4/5 (NT-4/5) (164) and glial-cell derived neurotrophic factor (GDNF) family members (165).

In women with endometriosis, uterine expression of neurotrophins, their receptors and other neuronally active molecules is increased compared to women without the disease (summarized in Table 1). Specifically, expression of NGF and its receptors TrkA and p75 is increased in women with endometriosis, particularly in the functional layer of the endometrium (166). Endometrial expression of BDNF, NT-3 and NT-4 has also been demonstrated with expression of BDNF and NT-4 significantly increased in endometriosis (167).

Furthermore, as detailed in sections 3.2 and 3.3, the expression of a range of primarily angiogenic and/or lymphangiogenic factors and receptors which are also neuronally active are known to be altered (mostly increased) in the eutopic endometrium from women with endometriosis compared to control endometrium. For example, VEGF-A, which is increased in eutopic endometrium from women with endometriosis (section 3.2), has neurotrophic qualities and can induce axonal growth and regeneration of peripheral sensory neurons via VEGFR-2 (168-170). Other eutopic endometrial disturbances in endometriosis related to neurogenesis include increased densities of neuroendocrine and immune cells that produce neurotrophins.

Neuroendocrine cells, which can produce neuromodulatory substances in response to neurogenic or chemical stimulation (171), are significantly increased in density in the endometrium of women with endometriosis (172). NGF and other neurotrophins, are produced by a range of immune cells including T cells, B cells, macrophages, natural killer cells (NK), mast and dendritic cells (173-178). Interestingly, a number of these immune cell populations are known to be increased in density in the eutopic endometrium of women with endometriosis (39, 40, 179-186) and this may play a role in facilitating locally disordered expression of neuronally active molecules in eutopic endometrium in endometriosis.

Further to findings of increased expression of neurogenesis promoters, the eutopic endometrium from women with endometriosis contains small, unmyelinated nerve fibers in the functional layer (187-191). These nerve fibers are not observed in women without endometriosis (187, 192). Nerve fibers in the functional layer of the endometrium are most likely sensory C and autonomic (190, 193). In women with endometriosis nerve fiber

## Angio-, lymphangio- and neuro-genesis in endometriosis

densities in basal endometrium and myometrium are also significantly increased compared to women without the disease (187). The presence of these nerve fibers in women with pain symptoms strongly suggests that in women with endometriosis the eutopic endometrium may be involved in the generation of pain symptoms (194). Increased local expression of neurotrophins may also directly contribute to the generation of pain symptoms. Specifically, NGF can act as a potent sensitizer of nociceptors (195, 196), while BDNF, NT-3 and NT-4 can also sensitize nociceptors and induce intense pain (196-198).

### 4. ENDOMETRIOTIC LESIONS

Endometriotic lesions are biochemically and functionally quite different to eutopic endometrium, however, it must be considered that these differences may be the result of the peritoneal environment which greatly differs from the intrauterine situation. In particular, estrogen production and metabolism are aberrant such that there is high estradiol ( $E_2$ ) synthesis with low inactivation and ultimately an excess of local  $E_2$  (compared with normal endometrium from women without endometriosis) (75, 79-82, 84, 199-201). Lesions are less clearly hormonally regulated and do not show the same cyclic changes as endometrium, that is, they are progesterone resistant (202-204). Furthermore, immune cells are recruited into endometriotic lesions in higher numbers than the eutopic endometrium, surrounding and normal peritoneum (39, 40, 205-210). These changes are related to the disturbed angiogenesis, lymphangiogenesis and neurogenesis in endometriotic lesions. Table 2 summarizes the expression of key molecules relevant to the processes of angiogenesis, lymphangiogenesis and neurogenesis in endometriotic lesions.

#### 4.1. Angiogenesis

Angiogenesis plays a crucial role in the establishment and growth of endometriotic lesions (211-213). A range of angiogenic proteins are synthesized in endometriotic lesions. The potent angiogenic factor VEGF-A is strongly expressed in endometriotic lesions (68, 110-112, 114, 214, 215). VEGF-A expression in endometriotic lesions has been described by some as higher than in eutopic endometrium (both from women with and without endometriosis) (68, 114, 215) and by others as similar to that of the eutopic endometrium (110) but higher than normal peritoneum (112). This may be because different types of endometriotic lesions show different expression profiles of VEGF-A and other angiogenic parameters. VEGF-A and expression levels of other angiogenic cytokines are increased in red, vascular peritoneal endometriotic lesions compared to older black or white scarred lesions (110, 111, 216). Furthermore, red lesions have higher vascularization, proliferative activity and expression of VEGFR-2 (114, 215, 217, 218), and express lower levels of angiogenesis inhibitors such as TSP-1 (111).

The angiogenic characteristics of endometriotic lesions also appear to differ between peritoneal, ovarian and deep lesions. Deep infiltrating endometriotic lesions of

the rectum have higher expressions of VEGF-A and VEGFR-2, and increased blood vessel density compared to peritoneal lesions (215). On the other hand, VEGF-A expression in glandular and stromal cells of ovarian endometriomas (112) and their contents (219) is lower than in peritoneal endometriotic lesions (111).

Further evidence of high angiogenic activity in endometriotic lesions is provided by increased expression of Ang-1 and Ang-2 compared to eutopic endometrium (both from women with and without endometriosis) (68, 220), and accumulation of high concentrations of soluble VEGF-A in peritoneal fluid from women with endometriosis (114, 214, 221, 222). Expression of the angiogenic factor PK-1 is also significantly increased in endometriotic lesions compared to eutopic endometrium (223).

Disrupted neuroendocrine and immune cell populations in peritoneal fluid contribute to angiogenesis. In the presence of  $E_2$ , the potent angiogenic factor, VEGF-A, and cytokines, interleukins (IL-1, IL-6, IL-8) and TNF-alpha, responsible for adherence and chemotaxis are secreted (224). Tissue remodeling and angiogenesis is augmented by MMPs. Endometriotic cells in the peritoneal fluid secrete MMP-1 stimulating an increase in MMP-2 causing proliferation. Adhesion occurs through increased action of soluble intercellular adhesion molecule 1 (sICAM-1) and the oxidative stress brought on by iron overload in peritoneal macrophages.  $E_2$  impacts regulated on activation, normal T-cell expressed and secreted (RANTES) releasing immunoregulatory cytokines (interferon-gamma [IFN-gamma] and IL-2) leading to maintenance of the inflammatory state (225). Interestingly, progesterone can exert immunosuppressive effects. It ameliorates the action of NK cells increasing their activity early in the disease but inhibiting cytotoxicity in more advanced disease (226). Diminished activity of progesterone in endometriosis contributes to increased release of angiogenic, proliferative and adhesion factors (VEGF, IL-1beta, MMP-2, sICAM-1).

#### 4.2. Lymphangiogenesis

In contrast to the established importance of lesion angiogenesis, relatively little is currently known about the roles of lymphatic vessels or lymphangiogenesis in the establishment and progression of endometriotic lesions. However, it is now apparent that lymphangiogenesis occurs in endometriotic lesions, and indications are that expressions of a range of lymphangiogenic growth factors are increased in endometriotic lesions compared to endometrium from women with and without endometriosis. Expression of potent lymphangiogenic promoter VEGF-C in peritoneal endometriotic lesions is higher than matched functional layer endometrium from women with endometriosis (112). VEGF-C and VEGF-D are expressed in the epithelium of DIE lesions (227). In addition, other growth factors known to promote lymphangiogenesis, such as IGF-1 and IGF-2, are increased in endometriotic lesions (71, 228-232) and peritoneal fluid from women with endometriosis (233, 234). Women with endometriosis have higher serum levels of another lymphangiogenic factor,

## Angio-, lymphangio- and neuro-genesis in endometriosis

**Table 2.** Summary of expression of key angiogenic, lymphangiogenic and neurogenic factors and their receptors in peritoneal, ovarian and deep infiltrating endometriotic lesions.

Primary function	Factor or receptor	Expressed in lesion types	Relative expression levels	References
Angiogenesis	Angiopoietin-1	Peritoneal Ovarian	• Increased in ovarian lesions compared to eutopic endometrium	68, 220
	Angiopoietin-2	Ovarian	• Increased in ovarian lesions compared to eutopic endometrium	68
	Prokineticin 1	Peritoneal	• Increased in peritoneal lesions compared to eutopic endometrium	223
	Thrombospondin-1	Peritoneal Ovarian	• Lower in red peritoneal than ovarian lesions or uterosacral ligament nodules • Increased in ovarian lesions compared to eutopic endometrium	111
	Vascular endothelial growth factor-A	Peritoneal Ovarian DIE	• Increased in all lesion types compared to eutopic endometrium and normal peritoneum • Highest in DIE, then peritoneal then ovarian lesions • Increased in red compared to black or white peritoneal lesions	68, 110-112, 114, 214, 215
	Vascular endothelial growth factor/receptor-2	Peritoneal DIE	• Increased in peritoneal and DIE lesions compared to eutopic endometrium • Increased in DIE compared to peritoneal lesions • Increased in red compared to black or white peritoneal lesions	114, 215
Lymphangiogenesis	Hepatocyte growth factor	Peritoneal	• Increased in red compared to black or white peritoneal lesions	71
	Insulin-like growth factor-1	Peritoneal Ovarian	• Decreased in ovarian compared to peritoneal lesions or eutopic endometrium	228-232
	Insulin-like growth factor-2	Peritoneal	• Unknown	232
	Vascular endothelial growth factor-C	Peritoneal Ovarian DIE	• Increased in peritoneal and ovarian lesions compared to matched eutopic endometrium but decreased compared to endometrium from women without endometriosis • Not significantly different to normal peritoneum	112, 227
	Vascular endothelial growth factor-D	DIE	• Unknown	227
Neurogenesis	Brain-derived neurotrophic factor	Ovarian	• Unknown	251
	Nerve growth factor	Peritoneal Ovarian DIE	• Increased in DIE lesions compared to peritoneal or ovarian	24, 246-251
	Neurotrophin-3	Peritoneal Ovarian	• Unknown	247, 251
	Neurotrophin-4	Ovarian	• Unknown	251
	p75 receptor	Peritoneal Ovarian DIE	• Unknown	246, 249-251
	Roundabout receptor-1	Ovarian	• Unknown	253
	Slit ligands	Ovarian	• Increased in ovarian lesions compared to eutopic endometrium	253
	Tyrosine kinase-A	Peritoneal Ovarian DIE	• Unknown	24, 249-251

FGF-2, than healthy controls, with positive correlation between its levels in peritoneal fluid and proliferative activity of endometriotic lesions (235).

As described in section 4.2, the expression of a range of other primarily angiogenic factors and receptors that also function in lymphangiogenesis are known to be increased in endometriotic lesions. For example, the expression of Ang-1 and Ang-2 is increased in endometriotic lesions compared to functional layer endometrial biopsies (68, 220).

Recently lymphatic micro-vessels have been demonstrated in peritoneal and DIE lesions for the first time (227, 236). Lymphatic vessel density is increased in the stroma of peritoneal endometriotic lesions compared to the surrounding sub-peritoneal tissue but not statistically significantly different to normal peritoneum (236). On the other hand, density of lymphatic vessels in DIE is significantly higher than corresponding healthy tissues (227). Lymphatic micro-vessels play an important role in

immune surveillance and increased stromal lymphatic vessel density parallels immune cell distribution in endometriotic lesions. The increases in immune cell and lymphatic vessel densities in the stroma of peritoneal endometriotic lesions may suggest targeting of the immune response at the core of lesions in an attempt to inhibit further development. However, immune cells may stimulate the development of endometriotic lesions in certain circumstances. Components of the immune environment almost certainly facilitate lesion establishment and progression. For example, certain immune cell populations, particularly macrophages, are capable of local secretion of a range of angiogenic factors, which may facilitate neovascularisation of the lesion (237, 238).

Efferent lymphatic drainage channels leaving uterine-draining lymph nodes traverse the pelvic side wall (239-241) and normal sub-peritoneal tissue contains numerous small lymphatic vessels (236, 242). As hypothesized by the lymphatic spread theory of endometriosis, some endometriotic lesions may form from

## Angio-, lymphangio- and neuro-genesis in endometriosis

endometrial tissue transported via the lymphatic system to the peritoneal cavity (13, 14). Endometrium from women with endometriosis is known to have the capacity to evade immune surveillance (40, 243), attach to and invade the sub-peritoneum (244, 245), then proliferate (70, 72), attract a blood supply (22) and persist as an endometriotic lesion.

### 4.3. Neurogenesis

Accumulating evidence indicates that neurogenic processes are involved in peritoneal endometriotic lesion development and maintenance. Disruptions to the local inflammatory response, local hormonal profiles and local angiogenesis all contribute to supporting neuronal growth. The presence of functional nerve fibers in peritoneal lesions suggests a critical role in pain processing and perception, although exact pathways remain unclear.

Neurotrophins, their receptors and other neuronally active molecules are expressed in endometriotic lesions. Neurotrophins: NGF and NT-3, and receptors: TrkA and p75, are present in endometriotic glands and stroma of peritoneal lesions, as well as ovarian and DIE lesions (24, 246-251). Interestingly, the strongest intensity of expression of NGF and its associated receptors has been noted in subperitoneal DIE lesions (24, 246-251), which correlates with high patient-reported pain (252). Ovarian endometriomas also express BDNF, NT-3, NT4/5 and increased slit ligands and their roundabout (Robo) receptors have been noted (251, 253). Other families of neuronal generation and guidance molecules are implicated in peritoneal endometriosis, although few have been fully investigated in this setting.

Increased density of immune cells and angiogenic potential in the peritoneal fluid of women with endometriosis is well documented. Additionally, recruited immune cell sub-populations in peritoneal lesions contribute to increased local neurotrophic factors (173-178). For example, increased activated macrophages and degranulating mast cells are noted in peritoneal endometriotic lesions (252). Activated macrophages secrete neuroattractant cytokines, providing a suitable environment for nerve ingrowth (186, 225, 226). Furthermore, degranulating mast cells are both influenced by, and affect, neurotrophins and their receptors (252, 254). Sprouting nerve fibers are afforded protection by the local immune environment. Increased VEGF expression in peritoneal fluid and lesions, combined with increased expression of other primarily angiogenic or lymphangiogenic factors that also influence neurogenesis, enhance nerve fiber growth (255).

Various neuronal processes occur, directly and indirectly, under the influence of the ovarian sex steroids. Previous studies have identified neuroprotective effects of estrogen and progesterone. In particular, E<sub>2</sub> has been implicated in expression of NGF and its receptors in *in vitro* and *in vivo* models. Up-regulation of NGF, p75 and TrkA in the presence of estrogen has been reported in the sensory neurons of dorsal root ganglia, uterine neurons and in the granulosa cells on the human preovulatory ovary (256-260). Neurite outgrowth has also been shown to be

promoted by E<sub>2</sub> (12, 261-263). The increased NGF expression in endometriotic lesions maintains the inflammatory state; further improving conditions for successful nerve sprouting (224, 225, 264).

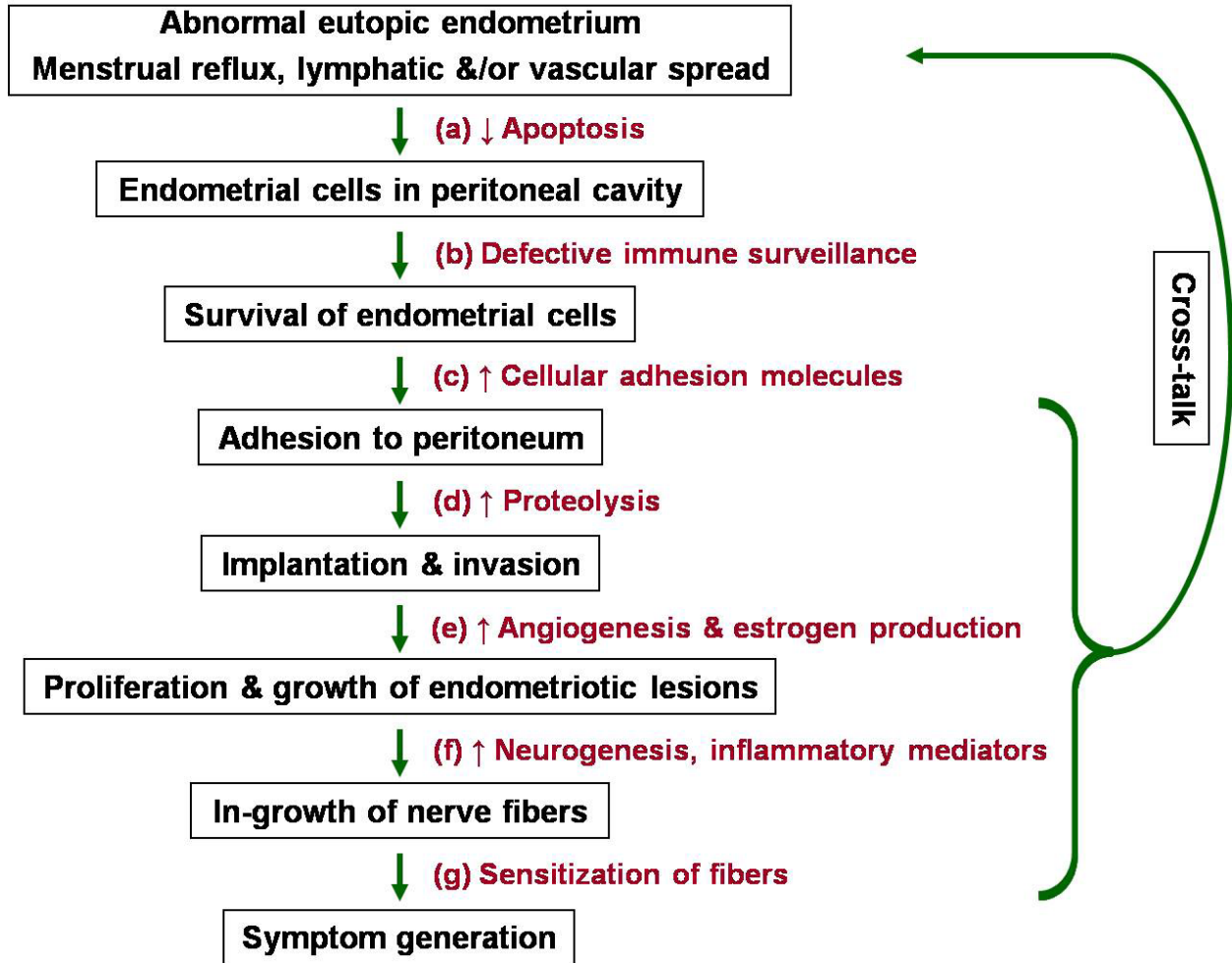
Nerve fibers are present in peritoneal endometriotic lesions (246, 247, 265-268), ovarian endometriomas (251, 269) and DIE lesions (249, 250). Significantly more nerve fibers are present in peritoneal endometriotic lesions compared to normal peritoneum (246, 247). Interestingly, nerve fiber density is also increased in uninvolved, microscopically normal peritoneum from women with endometriosis, even at a long distance from lesions (246). Nerve fibers are present in ovarian endometriomas in higher density than normal ovarian cortex from women with ovarian endometriosis and women without endometriosis (251, 269). DIE lesions are also richly innervated, with substantially greater density of nerve fibers than peritoneal lesions (249) and unaffected vaginal tissue (270). DIE lesions involving the bowel contain the highest densities of nerve fibers observed in endometriotic lesions (250).

Nerves in endometriotic lesions contain sensory, adrenergic and cholinergic fibers. These nerve fibers are pain conducting and may be related to the pain symptoms experienced by women with endometriosis. Increased density of nerve fibers suggests hyperinnervation; meaning that innervation in the urogenital peritoneum is somewhat disturbed in women with endometriosis. Given the plasticity of neuronal growth (see section 3.4), resultant nerve fibers have potentially abnormally heightened functionality. It is not just the increased presence nerve fibers that contribute to pain generation but their excitation thresholds may be compromised by abnormal neurogenesis (271). These pathways are yet to be explored in the peritoneal lesions of endometriosis.

### 4.4. Cross-talk between lesions and eutopic endometrium

In accordance with Sampson's theory of pathogenesis, it is widely thought that the primary defect in endometriosis lies in the eutopic endometrium. However, it is becoming apparent that interplay between eutopic endometrium and endometriotic lesions is more complex than abnormal eutopic endometrium resulting in establishment of endometriotic lesions. In addition to cross-talk between shed endometrial fragments and peritoneum during lesion establishment (272, 273), it is likely that the presence of endometriotic lesions influences the function of the eutopic endometrium. In fact, it has recently been demonstrated in a mouse model of endometriosis that cells from endometriotic lesions can migrate to the eutopic endometrium (274).

Interestingly, evidence from the baboon model of induced endometriosis indicates that the introduction of (large quantities of) endometrium and establishment of lesions in the peritoneal cavity is associated with subsequent changes in the eutopic endometrium. In the baboon model, a complex series of changes in endometrial gene and protein expression occur at different time points



**Figure 1.** Hypothesized pathway for the interconnecting roles of the vascular, lymphatic and nervous systems in the establishment of endometriosis and its associated symptoms.

during disease progression. Similar to anomalies of eutopic endometrium in women with endometriosis, in this model, proliferation and angiogenesis are locally increased and progesterone resistance is evident (275-279). It has been proposed that the progressive changes in gene expression in the eutopic endometrium of baboons with induced endometriosis result from epigenetic modifications due to the presence of ectopic lesions.

In women with endometriosis, the effects of ectopic lesions on the eutopic endometrium remain uncertain, and due to a range of reasons, this relationship is incredibly difficult to study. However, cross-talk between lesions and eutopic endometrium is likely to be a contributing factor in both endometriosis establishment and progression. In both the uterine and peritoneal environments, the interconnecting roles of the vascular, lymphatic and nervous systems are likely to contribute to the generation of endometriosis and its associated symptoms. While the details are currently unclear, a hypothesized pathway is presented in Figure 1, with

concurrent participation of eutopic endometrium, ovarian steroids and inflammatory mediators.

## 5. THERAPEUTIC IMPLICATIONS

Understanding angiogenesis, lymphangiogenesis and neurogenesis in endometriosis is relevant not only to elucidate the complex pathogenesis of the disease, but also to the development of novel therapeutic approaches. Due to the involvement of these processes in endometriosis establishment and progression, and in the generation of associated symptoms, in theory at least, their local disruption may have therapeutic benefits. Individual patient responses to conventional therapeutic approaches for endometriosis can widely vary, with some women experiencing continued or repeat troubling symptoms despite multiple surgeries and trialing a range of traditional medical treatment options (280). Endometriosis also has a high recurrence rate following treatment (281, 282). To delay or prevent recurrence is crucial for effective disease management and there is a need for new treatment approaches.



## Angio-, lymphangio- and neuro-genesis in endometriosis

Anti-angiogenic therapeutic approaches continue to be a focus of endometriosis research, with promising results in experimental models. A range of studies report significant suppression of angiogenesis and lesion regression with anti-angiogenic therapies targeted against a range of mechanisms in cell culture and animal models of endometriosis (283-292). Interestingly, anti-angiogenic treatment also decreases nerve fiber density in peritoneal endometriotic lesions in an animal model (293). However, in development of anti-angiogenic treatments for endometriosis, careful attention is required to assess the likely benefits and potential hazards of use in humans. A generalized anti-angiogenic effect could seriously impact processes like wound healing. Specifically, the requirement for interference with early lesion establishment processes, localization of effects and maintenance of normal reproductive function are crucial for minimizing the adverse effects of progressive endometriosis.

Novel anti-lymphangiogenic therapies may also play roles in endometriosis treatment in future. Anti-lymphangiogenic therapy is currently being explored as a novel treatment approach for cancer (294). In cancer, expression of lymphangiogenic factors can enhance metastatic tumor spread through lymphatic vessels (295, 296). Several studies have demonstrated positive correlations between VEGF-C or VEGF-D expression levels and the extent of lymphatic vessel invasion, lymph node involvement and distant metastasis (297-301). Inhibiting the actions of VEGF-C, VEGF-D or VEGFR-3 via blocking antibodies (300, 302-304), small molecule tyrosine kinase inhibitors (305-307) or soluble VEGFR-3 (297, 308, 309) has been shown to reduce metastases. There is, at least theoretically, potential for such anti-lymphangiogenic therapies to be useful in endometriosis, a condition associated with locally disturbed lymphangiogenesis and lymphatic transit of endometrial tissue.

In addition, it has recently been proposed that lymph node removal should be incorporated into surgical treatment for endometriosis (310) on the assumption that the resection of regional lymph nodes may decrease the recurrence rate of the disease. Given the risks of lymphedema following loss or impairment of lymphatic-transport capacity, this is a controversial suggestion. However, it is also thought provoking, and highlights the importance of lymphatic dissemination of endometrial tissue in this condition.

Given the importance of neurogenesis in the generation of pain symptoms in endometriosis, it is an attractive target for development of new therapeutics. In particular, blocking the NGF system is a novel approach to pain therapy showing promise in early clinical trials. NGF is known to be involved in pain transduction mechanisms in many chronic and inflammatory pain states. A specific blocking antibody for NGF (Tanezumab) effectively targets the NGF pathway in pre-clinical models and has demonstrated good results in phase I and II clinical trials for osteoarthritic and chronic low back pain treatment (311). The use of such an approach remains untested in

endometriosis but given the good safety and tolerability profiles to date, shows future potential.

In addition to targeted anti-neurogenic treatment approaches, one of the mechanisms of action for hormonal treatment of endometriosis appears to be suppression of neurogenesis. Hormonal treatment such as oral contraceptives and progestogens are currently widely used for endometriosis and effectively reduce pain symptoms in most women (280). The precise ways in which hormonal treatment alleviates endometriosis symptoms are somewhat unclear. However, treatment with oral progestogens or combined oral contraceptives has been shown to significantly decrease nerve fiber density and NGF expression in the endometrium and endometriotic lesions of women with endometriosis (166). Hormonal treatment also dramatically affects endometrial angiogenesis and lymphangiogenesis, with abnormal spiral arteriole development, vessel branching and tissue neovascularisation, increased superficial vascularity with fragile vessels that bleed easily and dilated thin-walled lymphatic vessels (312-317). Precisely how these changes in endometrial vasculature may impact endometriosis development and pain is unclear, however, reduction of endometrial and lesion innervation by hormonal treatment is almost certainly an important mechanism of action for controlling pain symptoms in endometriosis.

Interestingly, it is considered probable that progestogens and combined oral contraceptives have different effects on neurogenesis in endometriosis (although this has not been specifically studied as yet). Combined oral contraceptives contain estrogen, while progestogens on the other hand reduce estrogen levels (280, 318). Estrogen is known to elevate the levels of neurotrophins such NGF and its receptor TrkA and promote neuronal cell survival (319). As endometriosis is an estrogen-dependent condition, progestogen-only hormonal treatment is considered by some expert gynecologists to be a more appropriate treatment approach than combined oral contraceptive therapies containing estrogen (320).

## 6. SUMMARY AND PERSPECTIVE

Angiogenesis, lymphangiogenesis and neurogenesis play important roles in endometriosis. Increased angiogenesis, neurogenesis and possibly lymphangiogenesis in the eutopic endometrium are thought to facilitate the establishment and progression of endometriotic lesions. In addition, these processes, in both the ectopic lesions and the eutopic endometrium, are involved in the generation of endometriosis-associated symptoms, especially pain.

Endometrial tissue shed at menstruation reaches the peritoneal cavity via retrograde tubal flow, and possibly, at least in some cases, via the lymphatic circulation. In women with endometriosis, the increased angiogenic potential in the eutopic endometrium means that after attachment to and invasion of the peritoneum, this tissue can attract a new blood supply and persist as an endometriotic lesion. Accordingly, early, red flare

## Angio-, lymphangio- and neuro-genesis in endometriosis

peritoneal endometriotic lesions have increased vascularization, proliferative activity and expression of VEGF-A, other angiogenic cytokines and VEGFR-2 compared to older black or white scarred lesions.

Emerging evidence indicates that in the eutopic endometrium of women with endometriosis, lymphangiogenesis is disturbed, however, the precise details and implications are currently unclear. In women with endometriosis, transit of shed endometrium through the lymphatic circulation, may be related to the development of (certain types of) endometriotic lesions. The presence of lymphatic vessels in endometriotic lesions has recently been demonstrated. These lymphatic vessels almost certainly contribute to lesion development and function, including the infiltration of immune cells observed in lesions.

Neurogenesis is increased in the eutopic endometrium and endometriotic lesions from women with endometriosis, which have increased expression of neurotrophins, their receptors and nerve fiber densities compared to control tissues. While the precise mechanisms of pain in endometriosis are not yet clear, the presence of these nerve fibers and expression of nociceptive sensitizing substances is widely thought to make vital contributions to the generation of pain symptoms in this condition. Inflammation is also likely to be an important pain mechanism in endometriosis. Increased angiogenesis and immune cell infiltration related to lymphangiogenesis creates an inflammatory environment in endometriosis thought to activate silent nociceptors and to increase the sensitivity to and severity of visceral pain. Neuropathic pain associated with nerve injury also almost certainly occurs in endometriosis, and further to these pain mechanisms, central processing of pain signals appears to be abnormal in women with the disease who may experience hyperalgesia, allodynia and related sensory perception changes.

The local disruption of angiogenesis, lymphangiogenesis and neurogenesis are novel targets for endometriosis treatment due to their important roles in establishment and progression of the disease, and the generation of associated symptoms. A range of anti-angiogenic, anti-lymphangiogenic and anti-neurogenic therapeutic approaches are currently being investigated in other conditions and show exciting potential for benefits in endometriosis. There is a continuing need for development of new treatments for endometriosis, as patient responses to traditional approaches vary greatly and some women experience serious ongoing or recurrent symptoms.

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**Abbreviations:** NGF: nerve growth factor; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor; NRP: neuropilin; TNF: tumor necrosis factor; PDGF: platelet derived growth factor; MMP: matrix metalloproteinases; Tie: receptor tyrosine kinase; PK: prokineticin; TSP: thrombospondin; FGF: fibroblast growth factor; Ang: angiopoietin; HGF: hepatocyte growth factor; IGF-1: insulin-like growth factor; PI3K: phosphatidylinositol 3'-phosphate-kinase; MAPK: mitogen-activated protein kinase; NNT: novel neurotrophin; BSF: B cell stimulating factor; BDNF: brain-derived neurotrophic factor; NT: neurotrophin; GDNF: glial-cell derived neurotrophic factor; TrkA: tyrosine kinase receptor type 1; p75: low affinity neurotrophin receptor; E<sub>2</sub>: estradiol; IL: interleukin; sICAM: soluble intercellular adhesion molecule; RANTES: regulated on activation, normal T-cell expressed and secreted; Robo: roundabout receptor; IFN: interferon; DIE: deep infiltrating endometriosis.

**Key words:** Angiogenesis, Lymphangiogenesis, Neurogenesis, Endometriosis, Pathogenesis, Endometrium, Endometriotic lesion, Review

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