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Anti-angiogenic treatment strategies for the therapy of endometriosis

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BACKGROUND: Angiogenesis, i.e. the development of new blood vessels from pre-existing ones, represents an integral part in the pathogenesis of endometriosis. During the last decade, an increasing number of studies have therefore focused on the anti-angiogenic treatment of the disease. The present review provides a systematic overview of these studies and critically discusses the future role of anti-angiogenic therapy in the multimodal management of endometriosis.

METHODS: Literature searches were performed in PubMed, MEDLINE and ISI Web of Knowledge for original articles published before the end of March 2012, written in the English language and focusing on anti-angiogenic approaches for the therapy of endometriosis. The searches included both animal and human studies.

RESULTS: Numerous compounds of different substance groups have been shown to exert anti-angiogenic effects on endometriotic lesions under experimental *in vitro* and *in vivo* conditions. These include growth factor inhibitors, endogenous angiogenesis inhibitors, fumagillin analogues, statins, cyclo-oxygenase-2 inhibitors, phytochemical compounds, immunomodulators, dopamine agonists, peroxisome proliferator-activated receptor agonists, progestins, danazol and gonadotropin-releasing hormone (GnRH) agonists. However, clinical evidence for their efficacy in anti-angiogenic endometriosis therapy is still lacking.

CONCLUSIONS: Anti-angiogenic compounds hold great promise for the future treatment of endometriosis because they may inhibit the establishment of new endometriotic lesions in early stages of the disease or after surgical treatment. Further experimental studies, controlled clinical trials in particular, are required now to clarify which compounds fulfil these expectations without inducing severe side effects in patients with endometriosis.

Key words: endometriosis / angiogenesis / vascularization / anti-angiogenic therapy / vascular endothelial growth factor

Introduction

Endometriosis is a benign gynaecological disease, which is characterized by the presence of endometriotic lesions consisting of functional endometrial glands and stroma outside the uterine cavity (Galle, 1989). The prevalence rate of the condition is high among women of reproductive age, causing significant annual costs in the healthcare system (Simoens *et al.*, 2007). Although some affected women may remain asymptomatic, endometriosis is typically associated with a wide spectrum of pain symptoms (Stratton and Berkley, 2011) and infertility (Garrido *et al.*, 2002; Bulletti *et al.*, 2010). This often leads to a severely limited quality of the patients' private and professional life (Gilmour *et al.*, 2008).

Current approaches for the treatment of endometriosis involve pharmacological therapy and surgical removal of endometriotic lesions. Because the proliferation and long-term survival of ectopic endometrial tissue is estrogen-dependent (Giudice and Kao, 2004), classical pharmacological therapies are primarily aimed at the suppression of endogenous estrogen production by the application of oral contraceptives, GnRH agonists, androgenic agents or aromatase inhibitors (Nothnick, 2010). However, this type of medication is associated with substantial side effects, which limits prolonged exposure, and endometriosis is likely to recur following treatment cessation (Fedele *et al.*, 1994; van Langendonckt *et al.*, 2008; Pullen *et al.*, 2011). Surgical removal of endometriotic lesions is not only temporarily effective, but also associated with a high recurrence rate (Fedele *et al.*, 1994; Guo, 2009). In addition, dependent on the localization of the lesion and the severity of the disease, surgical removal can be technically challenging and bears the risk of urological or colorectal complications. Thus, there is an urgent need for the development of novel treatment strategies for endometriosis, which guarantee the long-term cure of affected patients. For this purpose, key processes in the pathogenesis of endometriosis have been identified, which may serve as potential therapeutic targets.

One of these key processes is angiogenesis, i.e. the development of new blood vessels from the pre-existing ones (Carmeliet and Jain, 2011). In fact, similar to tumours and their metastases, survival of endometriotic lesions is crucially dependent on the establishment of an adequate blood supply (Groothuis *et al.*, 2005; Becker and D'Amato, 2007; May and Becker, 2008; Taylor *et al.*, 2009). Accordingly, early developing lesions, which are the most active ones, have a typically pink-red appearance because of their high vascular density (McLaren, 2000; Laschke *et al.*, 2011a; Fig. 1) and exhibit an increased number of immature pericyte-free microvessels when compared with the black lesions of later stages (Nisolle *et al.*, 1993; Matsuzaki *et al.*, 2001). Moreover, the peritoneal fluid from patients with endometriosis contains high amounts of various angiogenic growth factors and reduced concentrations of anti-angiogenic compounds (Laschke and Menger, 2007). Finally, the eutopic endometrium from patients with endometriosis has been shown to exhibit an increased angiogenic potential when compared with healthy women (Chung *et al.*, 2002; Hur *et al.*, 2006). This may contribute to the initiation of the disease by retrograde menstruation of highly angiogenic endometrial fragments into the peritoneal cavity. Based on these findings, endometriosis has been classified as a typical angiogenic disease, such as cancer, psoriasis or diabetic retinopathy (Healy *et al.*, 1998).

Since Judah Folkman's revolutionary idea of fighting cancer by attacking its blood supply (Folkman, 1996, 1971), anti-angiogenic therapy has been proposed as a promising strategy for several angiogenic diseases, including endometriosis. During the last decade, an increasing number of studies have focused on the treatment of endometriotic lesions by application of different anti-angiogenic compounds. In the present review, we provide a systematic overview of these studies and highlight the most interesting anti-angiogenic

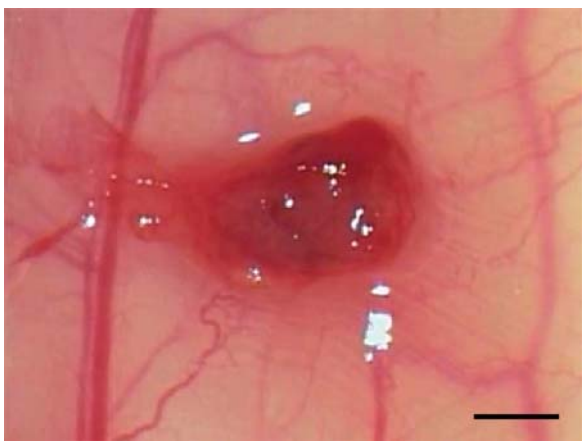

Figure 1 Typical macroscopic appearance of a developing endometriotic lesion, which was surgically induced under experimental conditions by suturing a mouse uterine tissue sample to the peritoneal wall of a recipient animal, according to Laschke *et al.* (2011a). Note the red colour of the lesion, which is caused by its high microvascular density and haemorrhages occurring during the early vascularization process. Scale bar: 1.6 mm.

Table I Inclusion and exclusion criteria for studies of anti-angiogenic treatment strategies in endometriosis in the present review, as listed in Table II.

Inclusion criteria	Exclusion criteria
Original articles	Editorials, letters to the editor, abstracts, duplicate papers, reviews, case reports
English language	Language other than English
All electronically listed publications in PubMed, MEDLINE and ISI Web of Knowledge until end of March 2012	Publications listed after March 2012
Studies focusing on anti-angiogenic effects of compounds on endometriosis	Studies focusing on basic mechanisms of angiogenesis in the eutopic endometrium
Animal and human studies, *in vitro* and *in vivo*	Studies analysing angiogenesis in endometriosis independent from application of anti-angiogenic compounds

approaches. Moreover, we critically discuss the potential future role of anti-angiogenic therapy in the multimodal management of endometriosis.

Methods

Literature searches were performed in PubMed, MEDLINE and ISI Web of Knowledge for original articles written in the English language and electronically listed until end of March 2012, which focused on anti-angiogenic treatment strategies for the therapy of endometriosis. The searches included the key words 'endometriosis', 'endometriotic', 'endometrium', 'endometrial' and 'ectopic endometrium', which were paired with the key words 'angiogenesis', 'vascularization' and 'anti-angiogenic'. The searches included both animal and human studies. Inclusion and exclusion criteria for the studies selected are shown in Table I.

Results

We detected 49 original articles fulfilling the inclusion criteria of our literature search (Fig. 2, Table II). Almost all of these articles reported experimental studies, which were performed in different *in vitro* and *in vivo* endometriosis models. The application and suitability of these models for the analysis of angiogenesis in endometriosis has previously been reviewed in detail (Laschke and Menger, 2007). In general, we found that the studies comprised many anti-angiogenic compounds, which were not restricted to one specific substance group. The anti-angiogenic properties of most of these compounds had already been demonstrated in tumour studies before they were analysed in the context of endometriosis. Table III provides an overview of their specific targets or mechanisms of action and a selection of relevant side effects reported in experimental and clinical studies.

Growth factor inhibitors

During the last years, several angiogenic growth factors have been identified, which are expressed in endometriotic lesions and released into the peritoneal fluid of patients with endometriosis (Taylor *et al.*, 2002). The most prominent and the most studied one is vascular endothelial growth factor (VEGF), which acts as a potent selective endothelial mitogen and survival factor (Leung *et al.*, 1989; Lazarus and Keshet, 2011). Of interest, highly active red endometriotic lesions contain the highest VEGF concentrations when compared with other lesion types (Donnez *et al.*, 1998). In addition, peritoneal fluid concentrations of VEGF correlate significantly with the stage of endometriosis (Shifren *et al.*, 1996).

VEGF is a dimeric glycoprotein, whose biological effects are primarily mediated by two high-affinity receptor tyrosine kinases on the surface of microvascular endothelial cells, i.e. VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR) (de Vries *et al.*, 1992; Millauer *et al.*, 1993). Hull *et al.* (2003) were the first to report that treatment with both a soluble truncated Flt-1-receptor and an affinity-purified VEGF-antibody significantly inhibits the growth of developing endometriotic lesions in nude mice by disrupting their immature microvasculature. Similar results were found by Nap *et al.* (2004; 2005) who treated endometriotic lesions with an anti-VEGF antibody in the nude mouse model and the chicken chorioallantoic membrane (CAM) assay . These findings indicate that blockade of VEGF signalling prevents the establishment of endometriotic lesions. In the future, this may be achieved by VEGF-targeted gene therapy (Rein *et al.*, 2010). However, VEGF targeting is currently much easier to realize in clinical practice by the application of an anti-VEGF antibody, such as bevacizumab (Avastin). Bevacizumab is a recombinant anti-VEGF monoclonal antibody, which is already approved by the US Food and Drug Administration (FDA) as a first-line treatment for patients suffering from metastatic colorectal cancer in combination with chemotherapy (Ferrara *et al.*, 2005). Recently, Ricci *et al.* (2011) demonstrated that treatment with this antibody significantly diminishes vascular density and cell proliferation and increases apoptotic cell death in surgically induced endometriotic lesions of BALB/c mice. Moreover, bevacizumab reduces VEGF levels in the peritoneal fluid of the animals. Nonetheless, despite these promising experimental findings it is unlikely that bevacizumab will ever be approved for endometriosis therapy, because this may be accompanied by severe side effects, such as hypertension, proteinuria, impaired wound healing, gastrointestinal perforation, thrombosis and bleeding (Kamba and McDonald, 2007).

The most potent stimulus for the up-regulation of VEGF is hypoxia (Shweiki *et al.*, 1992), which prevents the intracellular degradation of ubiquitously expressed hypoxia-inducible factor-1α (HIF-1α; Harris, 2002). Under hypoxic conditions, this factor translocates into the nucleus, heterodimerizes with HIF-1β/aryl hydrocarbon nuclear receptor translocator and binds to the hypoxia-responsive elements (HRE) on the gene encoding VEGF (Harris, 2002). Accordingly, Sharkey *et al.* (2000) showed that VEGF secretion from hypoxia-exposed endometrial stromal and glandular cell cultures markedly increases when compared with normoxic cell cultures. Becker *et al.* (2008) reported that targeting the hypoxia mechanism represents another option to block VEGF signalling in endometriosis. In fact, they found that HIF-1α is up-regulated in surgically induced peritoneal and mesenteric endometriotic lesions in mice, promoting the increased expression of VEGF. Treatment with 2-methoxyestradiol, an anti-angiogenic agent currently being tested in phase II trials for cancer (Kulke *et al.*, 2011), dose-dependently inhibits this process and suppresses lesion growth. Of interest, 2-methoxyestradiol has minimal toxicities even upon administration of high doses (Dahut *et al.*, 2006). However, owing to its extensive first pass metabolism and low solubility, subtherapeutic plasma concentrations of 2-methoxyestradiol have been observed despite large orally administered doses (Verenich and Gerk, 2010). First, these major pharmacokinetic problems have to be solved before 2-methoxyestradiol can successfully be launched into the market.

In light of the fact that endometriotic lesions not only express VEGF but also various other growth factors, it is obvious that the development of new blood vessels in endometriotic lesions is crucially dependent on the interaction of multiple signalling pathways (Fig. 3). To address this point, the effect of combined growth factor inhibition on the vascularization of endometriotic lesions was analysed in the dorsal skinfold chamber of Syrian golden hamsters (Laschke *et al.*, 2006a). This model allows for the detailed analysis of angiogenesis and microvascular network morphology in endometriotic lesions by means of intravital fluorescence microscopy (Laschke *et al.*, 2005). Endometriotic lesions were treated with the small molecule tyrosine kinase inhibitor SU5416, which solely suppresses the activity of VEGF receptor tyrosine kinase (Mendel *et al.*, 2000), or SU6668, which is a multipotent inhibitor of the tyrosine kinase activity of VEGF, basic fibroblast growth factor (bFGF) and platelet-derived

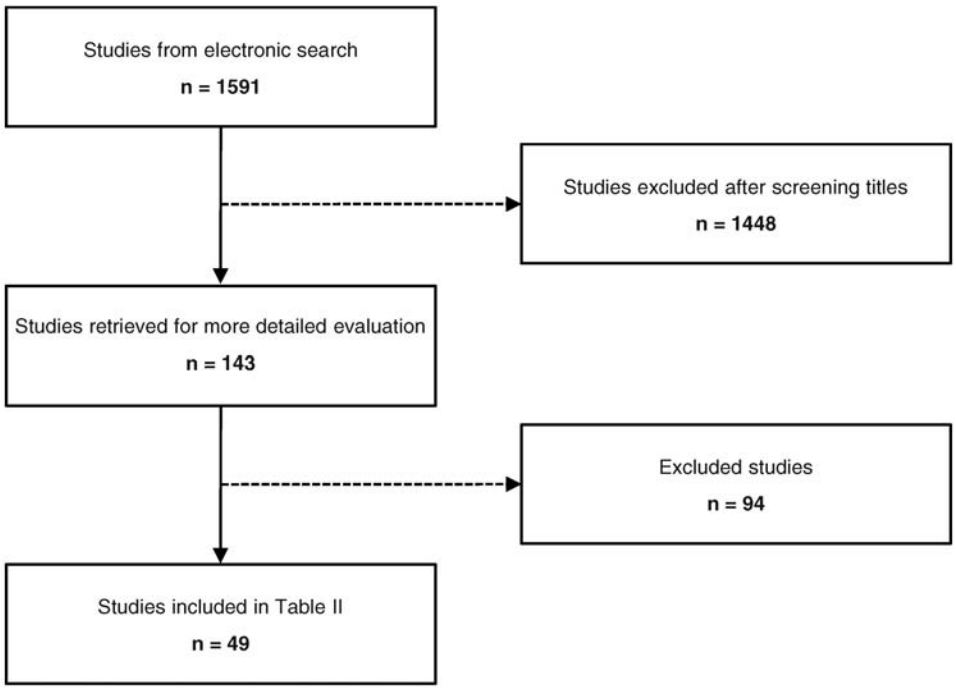

Figure 2 Flow diagram depicting selection of articles for review of studies focusing on the anti-angiogenic effect of different compounds on endometriosis, as listed in Table II.

growth factor receptors (Hoekman, 2001). Of interest, the combined inhibition of all three growth factors was much more effective in suppressing lesion vascularization and growth than blockade of VEGF alone (Laschke *et al.*, 2006a). These findings indicate that anti-angiogenic compounds, which target simultaneously different growth factor signalling pathways, may be highly effective in the future anti-angiogenic therapy of endometriosis.

Endogenous angiogenesis inhibitors

Endogenous inhibitors of angiogenesis are proteins or fragments of proteins, which are formed in the body and have been shown to inhibit the development of new blood vessels (Nyberg *et al.*, 2005). Many of these inhibitors are derived from extracellular matrix molecules, such as endostatin (Ribatti, 2009). This 20–22 kDa C-terminal fragment of type XVIII collagen, which was originally isolated and purified from conditioned media of murine hemangioendothelioma cells (O'Reilly *et al.*, 1997), binds to $\alpha_V\beta_1$ integrin and E-selectin on endothelial cells and is a broad spectrum angiogenesis inhibitor, affecting hundreds of pathways regulating the process of blood vessel development (Folkman, 2006). Accordingly, endostatin inhibits the proliferation and migration of endothelial cells and induces their apoptotic cell death (Dhanabal *et al.*, 1999a, b). Moreover, endostatin suppresses matrix metalloproteinase (MMP)-2, -9 and -13 activity and blocks the binding of VEGF to its receptor (Kim *et al.*, 2000, 2002). During the last years, several independent groups demonstrated that treatment with endostatin or short synthetic endostatin peptides inhibits angiogenesis of newly developing endometriotic lesions (Becker *et al.*, 2005, 2006a, b; Nap *et al.*, 2005; Jiang *et al.*, 2007) and already established ones (Nap *et al.*, 2004). Importantly, this type of treatment does not interfere with fertility and pregnancy in mice (Becker *et al.*, 2005, 2006a). Additional clinical data indicate a favourable toxicity profile of endostatin (Eder *et al.*, 2002). In fact, endostatin has virtually no toxicity and has revealed no problems with resistance even during administration to patients every day for up to >3.5 years without interruption (Folkman, 2006). However, a major prerequisite for the broad clinical applicability of this endogenous angiogenesis inhibitor in future endometriosis therapy is the synthesis of large quantities of pharmaceutical grade protein, which is still an unsolved problem (Ribatti, 2009).

Another endogenous inhibitor of angiogenesis is angiostatin, which is a 38 kDa fragment of plasminogen (O'Reilly *et al.*, 1994; Ribatti, 2009). Similar to endostatin, angiostatin affects multiple mechanisms of blood vessel development. For instance, angiostatin has been shown to suppress proliferation and to induce apoptosis of the endothelium (Sim *et al.*, 2000). Moreover, it inhibits VEGF and bFGF signalling (Sim *et al.*, 2000). The anti-angiogenic effects of angiostatin are mediated by its binding to various cell surface proteins, including ATP synthase, angiomotin, $\alpha_V\beta_3$ integrin, annexin II, angiostatin binding sequence protein, c-met and NG2 proteoglycan, as well as extracellular targets, such as tissue plasminogen activator (Wahl *et al.*, 2005). Dabrosin *et al.* (2002) treated endometriotic lesions in estrogen-supplemented ovariectomized mice by transient overexpression of the angiostatin gene, which was delivered to the peritoneum by a replica-deficient adenovirus vector. Gene therapy may overcome the major problem that angiostatin has a short half-life in the circulation and, thus, a short interval dosing is necessary to maintain its effects under clinical conditions (Beerepoot *et al.*, 2003; Wahl *et al.*, 2005). However, although effective, this type of treatment impaired normal

Table II Studies focusing on the anti-angiogenic effect of different compounds on endometriosis.

Substance group	Study	Compound	Species or cell culture/tissue type/transplantation site	Anti-angiogenic effects on endometriosis
Growth factor inhibitors	Becker *et al.* (2008)	2-Methoxyestradiol	C57BL/6 mice/mouse endometrium/peritoneal cavity	Suppression of HIF-1α and VEGF expression, reduced vascular permeability
	Hull *et al.* (2003)	Soluble truncated Flt-1 receptor, anti-VEGF antibody	Nude mice/human endometrium/subcutis	Disruption of immature microvessels
	Laschke *et al.* (2006a)	SU5416, SU6668	Syrian golden hamsters/hamster endometrium/dorsal skinfold chamber	Reduction of microvessel density, inhibition of vessel maturation
	Nap *et al.* (2004)	Anti-VEGF antibody	Nude mice/human endometrium/peritoneal cavity	Reduction of microvessel density, disruption of immature microvessels
	Nap *et al.* (2005)	Anti-VEGF antibody	Chicken/human endometrium/CAM assay	Reduction of microvessel density
	Rein *et al.* (2010)	VEGF-targeted gene therapy	Cell culture/human endometriotic cells	Induction of apoptotic cell death
	Ricci *et al.* (2011)	Bevacizumab	BALB/c mice/mouse endometrium/peritoneal cavity	Reduction of microvessel density, decrease of VEGF levels in peritoneal fluid
Endogenous angiogenesis inhibitors	Becker *et al.* (2005)	Murine endostatin	C57BL/6 mice/mouse endometrium/peritoneal cavity	No specific anti-angiogenic effects reported
	Becker *et al.* (2006a)	Murine short synthetic endostatin peptides mP-1 and mP-6	C57BL/6 mice/mouse endometrium/peritoneal cavity	Suppression of VEGF-induced endothelial cell migration
	Becker *et al.* (2006b)	Murine short synthetic endostatin peptide mP-1	NOD-SCID or C57BL/6-Tyr^{c} mice/mouse endometrium/peritoneal cavity	Inhibition of blood vessel sprouting
	Dabrosin *et al.* (2002)	Angiostatin gene therapy	C57BL/6 mice/mouse endometrium/peritoneal cavity	Reduction of microvessel density
	Jiang *et al.* (2007)	Recombinant human endostatin	SCID mice/human endometrium/subcutis	Suppression of VEGF expression, reduction of microvessel density
	Nap *et al.* (2004)	Endostatin	Nude mice/human endometrium/peritoneal cavity	Reduction of microvessel density, disruption of immature microvessels
	Nap *et al.* (2005)	Endostatin	Chicken/human endometrium/CAM assay	Reduction of microvessel density
Fumagillin analogues	Becker *et al.* (2006b)	Caplostatin	NOD-SCID or C57BL/6-Tyr^{c} mice/mouse endometrium/peritoneal cavity	Reduction of microvessel density
	Becker *et al.* (2011)	Lodamin	129S6/SvEvTac mice/mouse endometrium/peritoneal cavity	Reduction of circulating endothelial progenitor cells
	Nap *et al.* (2004)	TNP-470	Nude mice/human endometrium/peritoneal cavity	Reduction of microvessel density, disruption of immature microvessels
	Nap *et al.* (2005)	TNP-470	Chicken/human endometrium/CAM assay	Reduction of microvessel density
Statins	Bruner-Tran *et al.* (2009)	Simvastatin	Nude mice/human endometrium/subcutis	Reduction of microvessel density
	Cakmak *et al.* (2012)	Simvastatin	Nude mice/human endometrium/peritoneal cavity	Suppression of MCP-1 expression
	Esfandiari *et al.* (2007)	Lovastatin	Fibrin culture system/human endometrium	Inhibition of vascular sprouting
	Oktem *et al.* (2007)	Atorvastatin	Wistar rats/rat endometrium/peritoneal cavity	Reduction of VEGF levels in peritoneal fluid
	Sharma *et al.* (2010)	Atorvastatin	Cell culture/human ectopic and eutopic endometrial stromal cells	Reduction of VEGF, RAGE, EN-RAGE and COX-2 expression

COX-2 inhibitors	Dogan *et al.* (2004)	Rofecoxib	Wistar rats/rat endometrium/peritoneal cavity	Reduction of VEGF levels in peritoneal fluid
	Hull *et al.* (2005)	Nimesulide	Nude mice/human endometrium/subcutis	No anti-angiogenic effect
	Laschke *et al.* (2007)	NS398	Syrian golden hamsters/hamster endometrium/dorsal skinfold chamber	Reduction of microvessel density and VEGF expression
	Machado *et al.* (2010)	Parecoxib	Sprague-Dawley rats/rat endometrium/peritoneal cavity	Reduction of microvessel density, decreased expression of VEGF and Flk-1
	Olivares *et al.* (2011)	Celecoxib	BALB/c mice/mouse endometrium/peritoneal cavity	Reduction of vascularized lesion area
	Ozawa *et al.* (2006)	NS398	SCID mice/human endometriotic tissue/peritoneal cavity	Reduction of microvessel density and VEGF expression
Phytochemical compounds	Laschke *et al.* (2008)	EGCG	Syrian golden hamsters/hamster endometrium/dorsal skinfold chamber	Reduction of microvessel density and blood perfusion, inhibition of estrogen-stimulated VEGF expression
	Laschke *et al.* (2010)	Genistein	Syrian golden hamsters/hamster endometrium/dorsal skinfold chamber	Delayed lesion vascularization
	Laschke *et al.* (2011c)	4-Hydroxybenzyl alcohol	C57BL/6 mice/mouse endometrium/dorsal skinfold chamber	Reduction of microvessel density
	Rudzitis-Auth *et al.* (2012)	Xanthohumol	BALB/c mice/mouse endometrium/peritoneal cavity	Reduction of microvessel density, inhibition of endothelial cell proliferation
	Wang *et al.* (2011)	Puerarin	Chicken/human endometriotic tissue/CAM assay	Reduction of microvessel density, suppression of MMP-9, ICAM-1 and VEGF expression
	Xu *et al.* (2009)	EGCG	SCID mice/human endometrium/subcutis	Reduction of microvessel size and density, decrease of VEGF-A mRNA
	Xu *et al.* (2011)	EGCG	SCID mice/human endometrium/subcutis	Suppression of VEGF-C/VEGFR2 signalling
	Zhang *et al.* (2011)	Curcumin	Wistar rats/rat endometrium/subcutis	Reduction of microvessel density and VEGF expression
Immunomodulators	Laschke *et al.* (2006b)	Rapamycin	Syrian golden hamsters/hamster endometrium/dorsal skinfold chamber	Reduction of microvessel density, VEGF expression and endothelial cell proliferation
	Vlahos *et al.* (2010)	Pentoxifylline	Wistar rats/rat endometrium/peritoneal cavity	Decreased expression of VEGF-C and Flk-1
	Xu *et al.* (2012)	Lipoxin A4	BALB/c mice/mouse endometrium/peritoneal cavity	Reduced activity of MMP-9, decreased mRNA levels of VEGF
Dopamine agonists	Delgado-Rosas *et al.* (2011)	Quinagolide, cabergoline	Nude mice/human endometrium/peritoneal cavity	Reduction of microvessel density and angiogenic gene expression
	Gómez *et al.* (2011)	Quinagolide	Humans/human endometriotic lesions	Down-regulation of VEGF/VEGFR2, CCL2, RUNX1, AGGF1 and PAI-1
	Novella-Maestre *et al.* (2009)	Cabergoline	Nude mice/human endometrium/peritoneal cavity	Reduction of microvessel density, suppression of VEGF and Notch-4 expression, up-regulation of Ang-1 and Wnt
	Novella-Maestre *et al.* (2010)	Cabergoline	Nude mice/human endometrium/peritoneal cavity	Inhibition of VEGF and VEGFR-2 expression
PPAR agonists	Herington *et al.* (2011)	Pioglitazone	Nude mice/human endometrium/peritoneal cavity	Reduction of microvessel density
	Peeters *et al.* (2005)	Rosiglitazone	Cell culture/human transformed and primary endometrial cells	Suppression of VEGF expression
	Onalan *et al.* (2009)	Fenofibrate	Wistar rats/rat endometrium/peritoneal cavity	Reduction of VEGF levels in peritoneal fluid
Progestins, danazol and GnRH agonists	Katayama *et al.* (2010)	Dienogest	Wistar rats/rat endometrium/dorsal skinfold chamber	Reduction of microvessel density and blood perfusion, suppression of blood vessel maturation
	Khan *et al.* (2010)	Leuprolide acetate	Humans/human endometriotic lesions	Reduction of macrophage infiltration and microvessel density, increase of apoptotic cell death
	Matalliotakis *et al.* (2003)	Danazol	Humans/serum samples	Reduction of VEGF serum levels
	Mönckedieck *et al.* (2009)	Progesterone, dydrogesterone, dihydrodydrogesterone	Nude mice/human endometrium/peritoneal cavity	Suppression of bFGF, VEGF-A, Cyr-61 and MMP expression

Continued

Table II *Continued*

Substance group	Study	Compound	Species or cell culture/tissue type/transplantation site	Anti-angiogenic effects on endometriosis
Other agents	Feng *et al.* (2012)	Quinalizarin	C57BL/6 mice/mouse endometrium/dorsal skinfold chamber	Reduction of vascularized area and microvessel density
	Imesch *et al.* (2011)	Romidepsin	Cell culture/human immortalized epithelial endometriotic cells	Inhibition of VEGF gene transcription, protein expression and secretion, reduction of HIF-1α expression
	Krikun *et al.* (2010)	Immunoconjugate molecule Icon	Nude mice/human endometrium/peritoneal cavity	Disruption of tissue factor-expressing microvessels
	Nap *et al.* (2004)	Anginex	Nude mice/human endometrium/peritoneal cavity	Reduction of microvessel density, disruption of immature microvessels
	Nap *et al.* (2005)	Anginex	Chicken/human endometrium/CAM assay	Reduction of microvessel density

AGGF1, angiogenic factor with G patch and FHA domains 1; Ang-1, angiopoietin-1; bFGF, basic fibroblast growth factor; CAM, chorioallantois membrane; CCL2, chemokine ligand 2; COX, cyclo-oxygenase; Cyr-61, cysteine rich protein 61; EGCG, epigallocatechin-3-gallate; Flk-1, fetal liver kinase-1; Flt-1, fms-related tyrosine kinase 1; HIF-1α, hypoxia-inducible factor-1α; ICAM, intercellular adhesion molecule 1; MCP-1, monocyte chemotactic protein-1; MMP, matrix metalloproteinase; NOD-SCID, non-obese diabetic-severe combined immunodeficiency; PAI-1, plasminogen activator inhibitor-1; RAGE, receptor for advanced glycation endproducts; RUNX1, Runt-related transcription factor 1; VEGF, vascular endothelial growth factor.
The table also lists the species in which the analyses have been performed. Where appropriate, additional information is provided about the type of tissue used and the transplantation site for the experimental induction of endometriotic lesions.

ovarian function, as indicated by suppressed corpus luteum development, decreased sex steroid production and reduced ovarian and uterine weight (Dabrosin *et al.*, 2002). Thus, this therapeutic approach has to be further optimized by controlled local or targeted delivery of the angiostatic gene to minimize deleterious side effects on normal reproductive function.

Fumagillin analogues

Fumagillin is a naturally occurring antibiotic of *Aspergillus fumigatus* with anti-angiogenic activity (Ingber *et al.*, 1990). TNP-470 (formerly AGM-1470) is a highly potent semisynthetic derivate of fumagillin, which targets methionine aminopeptidase-2, affects cell-cycle regulation through induction of p53 and p21WAF1/CIP1 and prevents VEGF-induced endothelial permeability, intercellular gap formation and ruffle formation by suppression of Rac1 activation (Sin *et al.*, 1997; Nahari *et al.*, 2007; Benny *et al.*, 2008). Since its discovery, TNP-470 has been proved in various experimental and clinical studies to act as an effective angiogenesis inhibitor in different tumour types (Kruger and Figg, 2000). In line with these studies, Nap *et al.* (2004, 2005) showed that TNP-470 impairs the formation of endometriotic lesions in the CAM assay and the nude mouse model, which is associated with a decreased microvessel density of the ectopic endometrial tissue when compared with controls. However, despite these promising results, TNP-470 is rather unsuitable for the anti-angiogenic treatment of endometriosis in clinical practice because it exerts strong side effects on the female reproductive organs, including inhibition of endometrial maturation and corpora lutea formation as well as failure of embryonic growth during pregnancy (Klauber *et al.*, 1997). Another major drawback of TNP-470 is its neurotoxicity (Bhargava *et al.*, 1999). To overcome this, Satchi-Fainaro *et al.* (2004) synthesized a derivate of TNP-470, i.e. caplostatin, which is conjugated to a water-soluble synthetic *N*-(2-hydroxypropyl)methacrylamide copolymer. Thus, it does not cross the blood–brain barrier and exhibits a decreased accumulation in normal organs. Becker *et al.* (2006b) treated mouse endometriotic lesions with caplostatin and analysed their growth and vascularization over time using the non-invasive imaging technique of bioluminescence. Notably, they found that caplostatin suppresses angiogenesis within the lesions without exerting any general or specific toxic effects on reproductive function. Thus, this non-toxic fumagillin analogue may be a candidate for future anti-angiogenic therapy. However, caplostatin shares the major clinical limitation with TNP-470 that it exhibits a poor oral availability and extremely a short plasma half-life (Benny *et al.*, 2008). Therefore, Benny *et al.* (2008) created lodamin by conjugating TNP-470 to an amphiphilic polymer, which results in the assembly of micelles in which the drug is enclosed and protected from the acidic environment of the stomach. Of interest, Becker *et al.* (2011) recently found that lodamin treatment of endometriosis-bearing mice significantly decreases levels of circulating endothelial progenitor cells, which have been shown to act as major contributors to the vascularization of endometriotic lesions (Laschke *et al.*, 2011a, b).

Statins

Statins are a class of lipid-lowering drugs, which inhibit cholesterol synthesis by blocking 3-hydroxy-3-methylglutaryl-co-enzyme A reductase

Table III Specific targets or mechanisms of action and reported side effects of compounds, which have been shown to exert anti-angiogenic effects on endometriosis.

Substance group	Compound	Specific targets, mechanisms of action	Side effects reported in experimental (E) and clinical (C) studies
Growth factor inhibitors	Anti-VEGF antibody (= bevacizumab)	Neutralization of active VEGF-A (Ferrara *et al.*, 2005)	Hypertension, proteinuria, impaired wound healing, gastrointestinal perforation, thrombosis, bleeding (C) (Kamba and McDonald, 2007)
	2-Methoxyestradiol	Inhibition of the expression, nuclear accumulation and transcriptional activity of HIF-1α Induction of apoptosis through activation of caspase cascade Inhibition of tubulin polymerization by binding to the colchicine site of tubulin Induction of endothelial nitric oxide synthase (Verenich and Gerk, 2010)	Hot flashes, fatigue, diarrhoea, nausea, hyperglycaemia, anaemia, oedema, thrombosis, elevation of liver transaminases (C) (Dahut *et al.*, 2006)
	SU5416	Selective inhibition of the tyrosine kinase activity of VEGFR-2 (Mendel *et al.*, 2000)	Headache, fatigue, nausea, vomiting, diarrhoea, pain, hyperglycaemia, elevated prothrombin time (C) (Fury *et al.*, 2007)
	SU6668	Inhibition of the tyrosine kinase activity of VEGFR-2, PDGFR-β, FGFR-1 (Hoekman, 2001)	Fatigue, nausea, vomiting, diarrhoea, pain, flu-like complaints, anorexia, change of taste (C) (Kuenen *et al.*, 2005)
Endogenous angiogenesis inhibitors	Endostatin	Binding to $\alpha_v\beta_1$ integrin and E-selectin Pleiotropic action on hundreds of genetic pathways regulating angiogenesis Inhibition of endothelial cell proliferation and migration Induction of endothelial cell apoptosis Suppression of MMP-2, -9 and -13 activity Blockade of VEGF signalling (Kim *et al.*, 2000, 2002; Folkman, 2006)	No toxic effects on fertility and pregnancy (E) (Becker *et al.*, 2005, 2006a) No treatment-related side effects (C) (Eder *et al.*, 2002; Folkman, 2006)
	Angiostatin	Binding to ATP synthase, angiomotin, $\alpha_v\beta_3$ integrin, annexin II, angiostatin binding sequence protein, c-met and NG2 proteoglycan on the cell surface Binding to tissue plasminogen activator Inhibition of endothelial cell proliferation Induction of endothelial cell apoptosis Inhibition of VEGF and bFGF signalling (Sim *et al.*, 2000; Wahl *et al.*, 2005)	Suppression of ovarian function (E) (Dabrosin *et al.*, 2002) Erythema at injection site, fatigue, nausea, deep venous thrombosis (C) (Beerepoot *et al.*, 2003)
Fumagillin analogues	TNP-470 (= AGM-1470)	Inhibition of MetAP-2 Induction of p53 and p21WAF1/CIP1 Suppression of Rac1 activation (Sin *et al.*, 1997; Nahari *et al.*, 2007; Benny *et al.*, 2008)	Inhibition of endometrial maturation and corpora lutea formation, embryotoxicity (E) (Klauber *et al.*, 1997) Neurotoxicity, nausea, fatigue (C) (Bhargava *et al.*, 1999)
	Caplostatin	See TNP-470	No reported treatment-related side effects (E) (Satchi-Fainaro *et al.*, 2004; Becker *et al.*, 2006b)
	Lodamin	See TNP-470	No reported treatment-related side effects (E) (Benny *et al.*, 2008; Becker *et al.*, 2011)
Statins	Atorvastatin, Lovastatin, Simvastatin	Blockade of HMG-CoA reductase Inhibition of endothelial cell proliferation Induction of apoptosis by activation of the caspase cascade Down-regulation of VEGF synthesis Suppression of MMP secretion (Dulak and Józkowicz, 2005)	No reported treatment-related side effects on reproductive function (E) (Oktem *et al.*, 2007) Myopathy, diabetes mellitus, asymptomatic elevation of liver transaminases (C) (Mancini *et al.*, 2011)
COX-2 inhibitors	Celecoxib, Nimesulide, NS398, Parecoxib, Rofecoxib	Inhibition of COX-2 Inhibition of carbonic anhydrases Inhibition of PDK1 Induction of apotosis by inhibition of SERCA (Schönthal, 2007)	Cardiovascular events (myocardial infarction, stroke, thrombosis), hypertension, wound healing complications, renal failure or dysfunction, gastroduodenal ulcers (C) (Becker, 2005; Nussmeier *et al.*, 2005; Solomon *et al.*, 2005)
Phytochemical compounds	EGCG	Pleiotropic action on multiple molecular mechanisms including protection of DNA, inhibition of proteasome activity and gene expression, induction of apoptosis, cell-cycle regulation and cell proliferation (Chen *et al.*, 2011)	Anxiolytic activity, hypoglycaemic activity, hepatotoxicity (E) (Mereles and Hunstein, 2011) Nausea (C) (Chow *et al.*, 2003)

Continued

Table III *Continued*

Substance group	Compound	Specific targets, mechanisms of action	Side effects reported in experimental (E) and clinical (C) studies
	Curcumin	Pleiotropic interaction with numerous molecular targets including transcription factors, growth factors, protein kinases, inflammatory cytokines, enzymes, adhesion molecules and apoptosis-related proteins (Wilken *et al.*, 2011; Zhou *et al.*, 2011)	No reported treatment-related side effects (E) (Zhang *et al.*, 2011) No reported treatment-related side effects (C) (Wilken *et al.*, 2011)
	Puerarin	Pleiotropic interaction with numerous molecular targets including growth factors, anti-oxidative enzymes, MMPs, cell proliferation-related and apoptosis-related proteins (Liu *et al.*, 2012)	No reported treatment-related side effects (C) (Tan *et al.*, 2008)
	Genistein	Pleiotropic interaction with numerous molecular targets including transcription factors, growth factors, protein kinases, inflammatory cytokines, enzymes, adhesion molecules and apoptosis-related proteins (Shanmugam *et al.*, 2011)	Genotoxicity, infertility, disruption of oestrous cyclicity and ovarian function (E) (Stopper *et al.*, 2005; Jefferson *et al.*, 2007)
	4-Hydroxybenzyl alcohol	Pleiotropic interaction with numerous molecular targets including cytoprotective genes, neurotrophic factors, growth factors, anti-oxidative enzymes, MMPs and cell proliferation-related proteins (Descamps *et al.*, 2009; Laschke *et al.*, 2011c)	No reported treatment-related side effects (E) (Descamps *et al.*, 2009; Laschke *et al.*, 2011c)
	Xanthohumol	Pleiotropic action on numerous cellular mechanisms including proliferation, differentiation, apoptosis, inflammation and angiogenesis (Gerhauser *et al.*, 2002)	No reported treatment-related side effects (E) (Dorn *et al.*, 2010; Rudzitis-Auth *et al.*, 2012)
Immunomodulators	Rapamycin	Inhibition of mTOR Inhibition of VEGF signalling (Guba *et al.*, 2002)	Anaemia, leukopenia, thrombozytopenia, hypercholesterolemia, arthralgias, oedema, impaired wound healing, pulmonary toxicity, angioedema, nephrotoxicity (C) (Buhaescu *et al.*, 2006)
	Lipoxin A4	Multiple anti-inflammatory effects via activation of the FPR2/ALX receptor Inhibition of VEGF-stimulated angiogenesis (Baker *et al.*, 2009; Romano, 2010; Hao *et al.*, 2011)	No adverse effects on estradiol and progesterone levels or oestrus cycling (E) (Xu *et al.*, 2012)
	Pentoxifylline	Pleiotropic action on the production of inflammatory mediators and the responsiveness of immunocompetent cells to inflammatory stimuli Suppression of VEGF signalling (Olive *et al.*, 2004; Vlahos *et al.*, 2010)	Gastric discomfort, dizziness (C) (Olive *et al.*, 2004)
Dopamine agonists	Cabergoline	Binding to dopamine D2 receptor Inhibition of VEGFR-2 phosphorylation Suppression of Notch-4, VEGF and VEGFR-2 expression Up-regulation of Ang-1 and Wnt (Gomez *et al.*, 2006; Novella-Maestre *et al.*, 2009)	Cardiac valve regurgitation, nausea, headache, dizziness, fatigue, constipation (C) (Webster *et al.*, 1992; Schade *et al.*, 2007)
	Quinagolide	Binding to dopamine D2 receptor Down-regulation of VEGF/VEGFR-2, pro-angiogenic cytokines and PAI-1 (Gómez *et al.*, 2011)	Nausea, headache (C) No teratogenic effects (C) (Barlier and Jaquet, 2006)
PPAR agonists	Fenofibrate	Binding to PPAR-α Pleiotropic action on multiple processes including energy homeostasis, metabolism, inflammation and angiogenesis (Tyagi *et al.*, 2011)	Increase of plasma creatinine and homocysteine levels, myopathy, thrombosis, pulmonary embolism, pancreatitis (C) (Keech *et al.*, 2005; Bouhlel *et al.*, 2008)
	Rosiglitazone	Binding to PPAR-γ Pleiotropic action on multiple processes including energy homeostasis, metabolism, inflammation and angiogenesis (Tyagi *et al.*, 2011)	Myocardial infarction, fluid retention, weight gain, bone fractures (C) (Nissen and Wolski, 2007; Tolman, 2011)
	Pioglitazone	See rosiglitazone	Urinary bladder cancer, fluid retention, weight gain, bone fractures (C) (Tolman, 2011; Balakumar and Kathuria, 2012)

Progestins, danazol and GnRH agonists	Progesterone, dydrogesterone, dihydrodydrogesterone, dienogest	Binding to steroid hormone receptors (Sitruk-Ware, 2006; Mönckedieck *et al.*, 2009)	Breast pain, headache, acne, alopecia, migraine, weight gain, abnormal menstrual bleeding patterns, depression, decreased libido (C) (Guida *et al.*, 2010)
	Danazol	Induction of anovulation Increasing free testosterone (Canavan and Radosh, 2000)	Hirsutism, deepend voice, acne, fluid retention, weight gain, sweating, reduction in breast size, decreased HDL and increased LDL cholesterol (C) (Canavan and Radosh, 2000)
	Leuprolide acetate	Binding to the GnRH receptor (Wilson *et al.*, 2007)	Nausea, decrease in bone mineral density, decreased libido, depression, hot flashes, insomnia, headache, weight gain (C) (Wilson *et al.*, 2007)
Other agents	Anginex	Mimicking of β-sheet domains of anti-angiogenic agents (Griffioen *et al.*, 2001)	No reported treatment-related side effects (E) (Dings *et al.*, 2003)
	Romidepsin	Inhibition of HDAC Pleiotropic action on tumour suppressor gene transcription, cell-cycle regulation, apoptosis, angiogenesis (Coiffier *et al.*, 2012)	Infections, nausea, fatigue, thrombocytopenia, vomiting, diarrhoea (C) (Coiffier *et al.*, 2012)
	Quinalizarin	Inhibition of protein kinase CK2 (Feng *et al.*, 2012)	Unknown
	Immunoconjugate molecule Icon	Binding to aberrant tissue factor (Krikun *et al.*, 2010)	No adverse effects on fertility, no teratogenity (E) (Krikun *et al.*, 2010)

ATP, adenosintriphosphate; FGFR, fibroblast growth factor receptor; HMG-CoA, 3-hydroxy-3-methylglutaryl-co-enzyme A; MetAP-2, methionine aminopeptidase-2; mTOR, mammalian target of rapamycin; NG2, neuron-glial antigen 2; PDGFR, platelet-derived growth factor receptor; PDK1, 3-phosphoinositide-dependent protein kinase-1; PPAR, peroxisome proliferator-activated receptor; Rac1, Ras-related C3 botulinum toxin substrate 1; SERCA, sarcoplasmic/endoplasmatic reticulum calcium ATPase; VEGFR, vascular endothelial growth factor receptor.

(Brautbar and Ballantyne, 2011). They are widely used for the treatment of hypercholesterolemia and associated cardiovascular diseases. In addition, statins in high doses have been shown to exhibit anti-angiogenic activity, mediated by multiple mechanisms including the suppression of endothelial cell proliferation, induction of apoptotic cell death, down-regulation of VEGF synthesis and inhibition of MMP secretion (Dulak and Józkowicz, 2005).

Esfandiari *et al.* (2007) investigated the effect of statins on cell proliferation and angiogenesis in a novel *in vitro* model of endometriosis. For this purpose, human endometrial fragments were placed in a three-dimensional fibrin culture system and exposed to different concentrations of lovastatin. Of interest, they could demonstrate that lovastatin already suppresses vessel sprouting at the low concentration of 1 μM, whereas cell proliferation is only inhibited at the higher concentrations of 5–10 μM. Sharma *et al.* (2010) observed in atorvastatin-treated endometriotic stromal cells a significant inhibition of lipopolysaccharide-induced expression of genes encoding angiogenic factors, including VEGF. Oktem *et al.* (2007) tested the *in vivo* effect of atorvastatin in a rat model of surgically induced peritoneal endometriosis. They found that a low atorvastatin dose of 0.5 mg/kg per day increases the size of endometriotic lesions, whereas high doses of 2.5 mg/kg per day cause their regression and reduce VEGF levels in the peritoneal fluid of the animals. These are promising findings, taking into account that much higher atorvastatin doses of up to 175 mg/kg do not show any adverse effects on reproductive function (Oktem *et al.*, 2007). In the nude mouse model, 5 and 25 mg/kg simvastatin effectively inhibits growth and vascularization of developing endometriotic lesions (Bruner-Tran *et al.*, 2009) and suppresses the expression of monocyte chemotactic protein-1 (Cakmak *et al.*, 2012), which is known to stimulate the secretion of VEGF in endometrial stromal cells (Lin and Gu, 2005). Thereby, it should be mentioned that the discrepancy in the chosen statin doses in the described *in vivo* studies is related to the fact that atorvastatin is approximately two to four times more potent than simvastatin (Bruner-Tran *et al.*, 2009). This indicates that further studies are needed to identify the most suitable statins and their effective doses for the anti-angiogenic treatment of endometriosis. In this context, it has to be considered that the relatively high doses, which are normally required to induce anti-angiogenic effects, may increase the risk for typical side effects associated with statin therapy, such as myopathies (Dulak and Józkowicz, 2005; Mancini *et al.*, 2011).

Cyclo-oxygenase-2 inhibitors

Cyclo-oxygenases (COXs) are enzymes of the myeloperoxidase family, which catalyse the initial step of prostaglandin synthesis from arachidonic acid (Smith *et al.*, 1996). COX-1 is constitutively expressed, whereas COX-2 is the inducible isoform that is up-regulated during inflammatory and angiogenic processes, such as tumour growth or inflammatory bowel disease (Wang and Dubois, 2010; Yao *et al.*, 2011).

Several studies report that COX-2 is also crucially involved in the pathogenesis of endometriosis. COX-2 over-expression is found in both endometriotic lesions and eutopic endometrium of patients with endometriosis when compared with controls (Ota *et al.*, 2001; Matsuzaki *et al.*, 2004a; Ceyhan *et al.*, 2008; Horn *et al.*, 2009; Cho *et al.*, 2010). Additional experimental studies demonstrate that

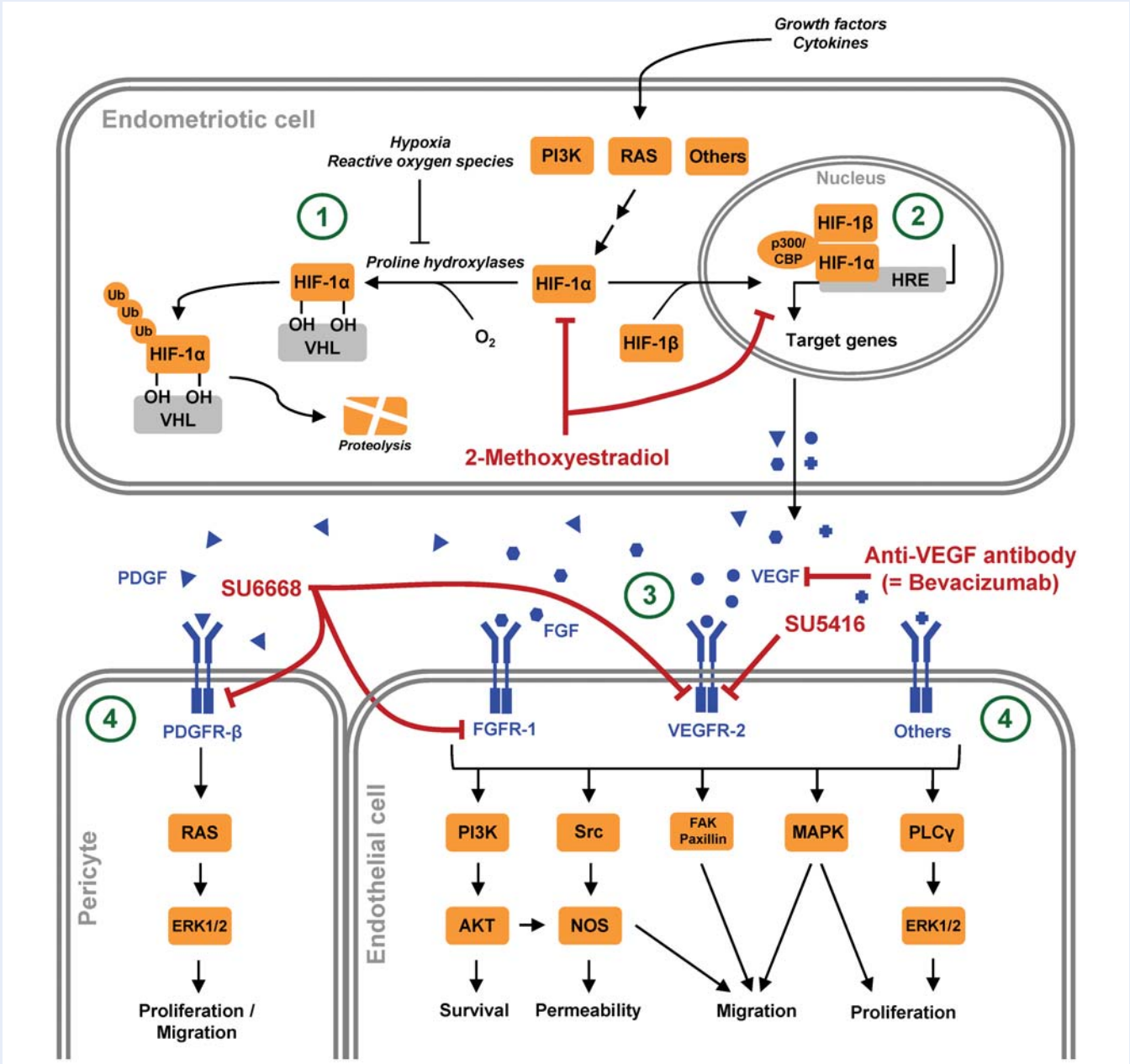

Figure 3 Angiogenic signalling pathways in endometriosis and specific targets of growth factor inhibitors, which have been shown to exert anti-angiogenic effects on endometriotic lesions, i.e. anti-VEGF antibody (= bevacizumab), 2-methoxyestradiol, SU5416 and SU6668. Under normoxia, HIF-1α is hydroxylated by proline hydroxylases following rapid VHL-dependent proteolysis (1). Under hypoxia, the proline hydroxylases are no longer active. HIF-1 translocates to the nucleus, where it targets genes (via HRE) encoding multiple proteins, including angiogenic growth factors (2). These growth factors are then secreted into the extracellular space where they bind to specific receptors located on the surface membrane of endothelial cells and pericytes (3). This leads to the activation of various intracellular signalling pathways, which regulate cell survival, proliferation, migration as well as vascular permeability (4). AKT, active human protein kinase; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; HIF, hypoxia-inducible factor; HRE, hypoxia-responsive elements; MAPK, mitogen-activated protein kinase; NOS, nitric oxide synthase; p300/CBP, p300/CREB-binding protein; PDGF, platelet-derived growth factor; PDGFR, platelet-derived growth factor receptor; PI3K, phosphatidylinositol-3-kinase; PLCγ, phospholipase Cγ; RAS, rat sarcoma GTPase; Src, tyrosine kinase; Ub, ubiquitin; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; VHL, von Hippel–Lindau protein.

treatment with COX-2 inhibitors prevents the implantation of endometrium to ectopic sites and induces the regression of established endometriotic lesions (Dogan *et al*., 2004; Matsuzaki *et al*., 2004b; Ozawa *et al*., 2006; Machado *et al*., 2010; Olivares *et al*., 2011). These results can partly be explained by the inhibition of angiogenesis. In fact, treatment with the COX-2 inhibitor NS398 significantly decreases VEGF expression and microvessel density in ectopic endometrial tissue in the dorsal skinfold chamber model (Laschke *et al*., 2007; Fig. 4). Besides this anti-angiogenic effect, application of NS398 further decreases the proliferation rate of endometrial cells and induces their apoptotic cell death (Laschke *et al*., 2007). Thus, inhibition of COX-2 seems to have beneficial effects on multiple cellular mechanisms, promoting the final regression of endometriotic lesions. However, experimental studies indicate that this is not necessarily achieved by each COX-2 inhibitor. Hull *et al*. (2005) reported that treatment with nimesulide neither affects blood vessel development nor the number or size of endometriotic lesions in the nude mouse model. Whether these results are specific for nimesulide or also transferable to other COX-2 inhibitors needs further clarification in appropriate endometriosis models.

Presently, non-specific COX inhibitors, such as Ibuprofen or Aspirin, are already widely used for pain treatment in endometriosis (Ebert *et al*., 2005). In comparison, specific COX-2 inhibitors bear the advantage that they exhibit many fewer gastrointestinal side effects (FitzGerald and Patrono, 2001). A first clinical trial indicated that they are also effective, safe and inexpensive in the management of endometriosis-associated pelvic pain (Cobellis *et al*., 2004). Considering their additional anti-angiogenic action, these specific COX-2 inhibitors seem to be ideal for the treatment of endometriotic lesions. However, at the time of writing, COX-2 inhibitors have not been approved for endometriosis. This may be related to the fact that there are not enough clinical data available about their possible side effects on fertility and pregnancy. In addition, COX-2 inhibitors, such as rofecoxib and valdecoxib, have been withdrawn from the market because of an excess risk of cardiovascular events in long-term users, including myocardial infarction, stroke and thrombosis (Becker, 2005; Nussmeier *et al*., 2005; Solomon *et al*., 2005). Thus, although COX-2 inhibitors may be a suitable component of the multimodal endometriosis therapy of the future, these compounds can only be recommended at present for short-term treatment of patients with severe endometriosis, who are at low risk for cardiovascular events, under clearly defined study conditions.

Phytochemical compounds

The demand for traditional medicine practices is rapidly rising in industrial countries (Wieser *et al*., 2007). Accordingly, an increasing number of phytochemical compounds are presently analysed in terms of novel therapeutic indications. This trend is driven by the hope that these compounds, of which many have already been used for thousands of years in traditional Chinese medicine, promote health and well-being, while minimizing toxicities and side effects.

Among women with endometriosis, Chinese herbal medicine has gained popularity as alternative pain therapy despite the lack of conclusive clinical evidence (Cox *et al*., 2003; Wieser *et al*., 2007). Moreover, recent studies could identify several phytochemical compounds which induce the regression of endometriotic lesions under experimental conditions. These include epigallocatechin-3-gallate (EGCG; Laschke *et al*., 2008; Xu *et al*., 2009, 2011), curcumin (Zhang *et al*., 2011), puerarin (Wang *et al*., 2011), genistein (Yavuz *et al*., 2007), 4-hydroxybenzyl alcohol (HBA; Laschke *et al*., 2011c) and xanthohumol (Rudzitis-Auth *et al*., 2012). These compounds typically act as pleiotropic agents, which influence multiple cellular mechanisms, such as proliferation, migration and apoptosis. Moreover, they inhibit the development of new blood vessels and, thus, can also be classified as anti-angiogenic agents.

The polyphenol EGCG is the major chemical component of green tea (Yang *et al*., 2006). Using dosages of EGCG that have been shown to be growth inhibitory in tumour studies, EGCG suppresses the estrogen-stimulated activation, proliferation and VEGF expression of isolated endometrial cells (Laschke *et al*., 2008). In line with these *in vitro* findings, EGCG further inhibits angiogenesis and blood perfusion

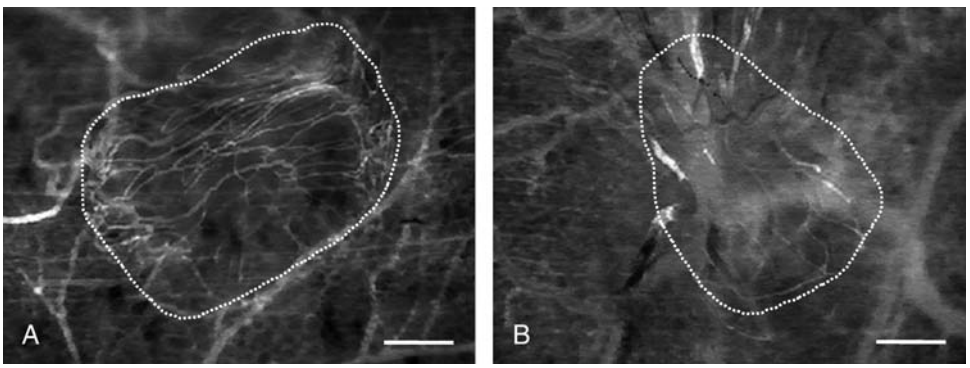

Figure 4 *In vivo* analysis of the anti-angiogenic effect of the COX-2 inhibitor NS398 on developing endometriotic lesions, according to Laschke *et al*. (2007). Endometriotic lesions (**A** and **B**, borders marked by dotted line) are induced by endometrial tissue transplantation into dorsal skinfold chambers of Syrian golden hamsters and analysed by intravital fluorescence microscopy in blue-light epi-illumination with contrast enhancement of the microvasculature by iv application of 5% fluorescein isothiocyanate-labelled dextran 150 000. Note that the lesion, which has been treated for 10 days with the COX-2 inhibitor NS398, exhibits a markedly reduced microvessel density (B) when compared with the vehicle-treated control (A). This is associated with a decreased lesion size. Scale bars: 130 μm.

of endometriotic lesions without affecting the development of new blood vessels in ovarian follicles (Laschke *et al*., 2008). Xu *et al*. (2009) induced endometriotic lesions by transplanting eutopic endometrium from patients with endometriosis into subcutaneous pockets of severely compromised immunodeficient mice. Treatment of these lesions with EGCG over 2 weeks resulted in a reduced microvessel size and density of the lesions and the adjacent tissues. In an additional study by the same group, detailed angiogenesis microarray and pathway analyses revealed that this effect may be primarily mediated by the selective suppression of the VEGF-C/VEGFR2 signalling pathway (Xu *et al*., 2011).

Curcumin is derived from the rhizome of the East Indian plant *Curcuma longa* and is the major component of the spice turmeric (Wilken *et al*., 2011). In a recent study, Zhang *et al*. (2011) demonstrated that increasing curcumin doses of 50–150 mg/kg gradually reduce the size of endometriotic lesions in rats, which is associated with a decreased microvessel density and VEGF expression of the ectopic endometrial tissue. Consistent with the fact that curcumin has been consumed as a dietary supplement for centuries and is considered pharmacologically safe (Wilken *et al*., 2011), the treated animals did not show any signs of side effects during the 4-week treatment period.

Puerarin is derived from the Chinese medical herb *Radix puerariae* and belongs to the group of phytoestrogens, which exhibit a structure similar to 17β-estradiol (Hwang and Jeong, 2008). Besides estrogenic activity, phytoestrogens can also have anti-estrogenic effects (Zhao and Mu, 2011), which makes them attractive for the treatment of endometriosis. Accordingly, puerarin inhibits estrogen-stimulated vascularization of human endometriotic tissue in the CAM assay by down-regulation of MMP-9, intercellular adhesion molecule-1 and VEGF expression (Wang *et al*., 2011). In contrast, genistein, another phytoestrogen isolated from soy products, only delays the angiogenic process during the initial establishment of endometriotic lesions in dorsal skinfold chambers, but does not affect the final vascularization of the lesions (Laschke *et al*., 2010).

HBA is the pharmacological active component of *Gastrodia elata Blume*, which is used as a traditional herbal medicine for the treatment of headache, tetanus and epilepsy owing to its analgesic, sedative and anti-convulsant effects (Hsieh *et al*., 2000; Yu *et al*., 2005). Recently, HBA has been shown to inhibit *in vivo* vascularization of endometriotic lesions, which were induced by endometrial tissue transplantation into mouse dorsal skinfold chambers (Laschke *et al*., 2011c). Additional *in vitro* experiments revealed that this may be related to the inhibition of multiple steps of the angiogenic process, including expression of angiogenic growth factors and MMPs, endothelial cell proliferation and migration as well as vascular sprouting (Laschke *et al*., 2011c).

Xanthohumol is a prenylated flavonoid isolated from hops, which acts as a pleiotropic cancer chemopreventive agent (Gerhauser *et al*., 2002). Rudzitis-Auth *et al*. (2012) found that treatment with this compound effectively inhibits the vascularization and growth of endometriotic lesions, which are surgically induced in the peritoneal cavity of BALB/c mice. Detailed immunohistochemical analyses showed that this is associated with a reduced proliferating activity of the microvascular endothelium in xanthohumol-treated lesions, whereas xanthohumol does not induce apoptotic death of endothelial cells. Moreover, this type of treatment does not affect proliferation and vascularization within the female reproductive organs (Rudzitis-Auth *et al*., 2012).

Taken together, these studies indicate that several phytochemical compounds may be suitable for the anti-angiogenic treatment of endometriosis. However, for this purpose most of these compounds would have to be administered in doses which cannot be achieved by simple dietary consumption because of their low concentrations in medicinal herbs and their poor bioavailability. This problem may be overcome by high-dose supplementation therapy because of recent progress in the stereo-selective total synthesis of specific compounds, as already described for EGCG (Nagle *et al*., 2006). Another problem is the lack of clinical evidence for the efficacy of natural medicinal herbs or synthetic phytochemical drugs in the treatment of endometriosis. Thus, there is a strong need for controlled clinical studies, which have to analyse the interaction of these compounds with other drugs and potential side effects in patients with endometriosis.

Immunomodulators

During the last decades, numerous studies have shown that abnormalities in the immune system play an important role in the aetiology and pathogenesis of endometriosis, as previously reviewed in detail (Paul Dmowski and Braun, 2004). Accordingly, immunomodulatory agents have been suggested for the treatment of the disease. In line with the fact that there is a close link between inflammation and angiogenesis (Fiedler and Augustin, 2006), some of these agents have been described to exert specific anti-angiogenic effects on endometriotic lesions. These include lipoxin A4 (LXA4; Xu *et al*., 2012), rapamycin (Laschke *et al*., 2006b) and pentoxifylline (Vlahos *et al*., 2010).

LXA4 is an endogenous eicosanoid, which is involved in the regulation of various inflammatory processes (Romano, 2010). Moreover, it has been shown *in vitro* and *in vivo* to inhibit VEGF-stimulated endothelial proliferation and angiogenesis (Baker *et al*., 2009; Hao *et al*., 2011). Of interest, both the endometrium in experimental endometriosis in rats and the tissues from patients with endometriosis show a higher expression of LXA4 receptor when compared with normal tissues (Motohashi *et al*., 2005). For these reasons, Xu *et al*. (2012) recently analysed for the first time the effect of LXA4 on angiogenesis in mouse endometriotic lesions. They found that treatment with LXA4 inhibits the activity of MMP-9 and decreases mRNA levels of VEGF in endometriotic lesions, resulting in a significant growth suppression and atrophy of their glands. However, the treatment does not alter serum estradiol and progesterone levels or disrupt estrus cycling.

Rapamycin (Sirolimus) is a mammalian target of rapamycin inhibitor, which is widely used as an immunosuppressive drug to prevent rejection in organ transplantation (Buhaescu *et al*., 2006). Of interest, rapamycin in immunosuppressive doses has also been demonstrated to inhibit tumour angiogenesis by decreasing VEGF production (Guba *et al*., 2002). Based on these results, the effect of rapamycin on endometriotic lesions was analysed in the dorsal skinfold chamber model (Laschke *et al*., 2006b). Daily treatment of the lesions with 1.5 mg/kg rapamycin induced their regression, which was associated with an inhibition of VEGF-mediated angiogenesis. In addition, rapamycin suppressed the proliferation of endometrial and endothelial cells. Thus, rapamycin also represents an effective inhibitor of angiogenesis in ectopic endometrial tissue. Nonetheless, owing to its immunosuppressive effect and risk profile it is questionable whether this compound will make its way into clinical endometriosis therapy (Buhaescu *et al*., 2006).

In contrast, pentoxifylline has already been tested in clinical trials as a potential drug for patients with endometriosis (Kamencic and Thiel, 2008; Lu *et al*., 2012). Pentoxifylline is a pleiotropic immunomodulating agent, which influences both the production of inflammatory mediators, such as tumour necrosis factor-α, and the responsiveness of immunocompetent cells to inflammatory stimuli (Olive *et al*., 2004). Recently, Vlahos *et al*. (2010) reported that pentoxifylline exerts an anti-angiogenic effect on developing endometriotic lesions in rats by suppressing VEGF-C and Flk-1 expression. Several other experimental studies demonstrated the regression of endometriotic lesions under pentoxifylline treatment (Nothnick *et al*., 1994; Mohammadzadeh *et al*., 2008). A major advantage of this drug is the fact that it does not inhibit ovulation and, thus, can be administered throughout the time period of attempting conception (Olive *et al*., 2004). Moreover, pentoxifylline is well tolerated with only minor side effects, such as gastric discomfort and dizziness (Olive *et al*., 2004). However, at the time of writing there is still not enough clinical evidence to support the use of pentoxifylline in the management of premenopausal women with endometriosis in terms of subfertility and relief of pain outcomes (Lu *et al*., 2012).

Dopamine agonists

A decade ago, Basu *et al*. (2001) made the interesting discovery that the neurotransmitter dopamine selectively inhibits the vascular permeabilizing and angiogenic activity of VEGF at non-toxic levels, revealing a new link between the nervous system and angiogenesis. This led to the idea to use dopamine agonists for anti-angiogenic therapy. In gynaecology, dopamine agonists, such as cabergoline, are currently used for the suppression of breast-feeding and treatment of hyperprolactinaemia (Gillam *et al*., 2006; Colao *et al*., 2007; Buhendwa *et al*., 2008). Importantly, cabergoline treatment during pregnancy does not increase the risk of spontaneous miscarriage, premature delivery or congenital abnormalities (Robert *et al*., 1996; Ricci *et al*., 2002).

Based on these reports, the Pellicer research group analysed the effect of cabergoline on growth and vascularization of endometriotic lesions in the nude mouse model (Novella-Maestre *et al*., 2009). They found that daily oral treatment with cabergoline over 14 days causes the regression of endometriotic lesions by suppression of cell proliferation and VEGF-mediated angiogenesis. They could further demonstrate that cabergoline treatment results in a significantly lower expression of VEGF and VEGFR-2 in endometriotic lesions (Novella-Maestre *et al*., 2010). Thus, they concluded that dopamine agonists may be successful in the treatment of peritoneal endometriosis. However, chronic cabergoline treatment is known to be associated with an increased incidence of cardiac valve regurgitation (Schade *et al*., 2007). Therefore, in an additional study they compared the efficacy of the non-ergot-derived dopamine agonist quinagolide with that of cabergoline in inhibiting angiogenesis and vascularization of endometriotic lesions (Delgado-Rosas *et al*., 2011). Because both compounds were equally effective, they decided to perform a clinical pilot study with quinagolide in hyperprolactinemic patients with endometriosis, who required a first surgical intervention and underwent a second-look laparoscopy (Gómez *et al*., 2011). Of interest, treatment with the dopamine agonist quinagolide induced a 70% reduction of endometriotic lesions, with 35% of lesions vanishing completely. Further histological analyses revealed that this was associated with a down-regulation of VEGF/VEGFR-2, pro-angiogenic cytokines and plasminogen activator inhibitor-1 within the lesions. These highly promising results and the beneficial side effect profile of quinagolide suggest that this compound should now be tested in larger clinical multicenter trials for its applicability in patients with endometriosis.

Peroxisome proliferator-activated receptor agonists

Peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors, which compromise three subtypes, i.e. PPAR-α, PPAR-γ and PPAR-β/δ (Tyagi *et al*., 2011). These nuclear receptors have a major regulatory function in energy homeostasis, metabolic processes and inflammation (Tyagi *et al*., 2011). Activation of PPAR-α reduces triglyceride levels and activation of PPAR-β/δ enhances fatty acid metabolism and modulates the development of atherosclerosis. In contrast, PPAR-γ activation mediates insulin sensitization and enhances glucose metabolism. Accordingly, effective PPAR agonists have been developed for the treatment of hypertrigliceridemia and type 2 diabetes mellitus in the form of fibrates and thiazolidinediones (Lalloyer and Staels, 2010). Some of these drugs have been shown to inhibit the development of new blood vessels, and, thus, may be useful for the treatment of angiogenic diseases (Biscetti *et al*., 2009).

Onalan *et al*. (2009) demonstrated for the first time in a rat model that treatment with the PPAR-α agonist fenofibrate causes regression of endometriotic lesions, which is associated with reduced VEGF levels in the peritoneal fluid. These results are rather surprising considering the fact that the peritoneal fluid of patients with endometriosis contains activators of PPAR-α that stimulate macrophage chemotaxis (Hornung *et al*., 2001). Peritoneal macrophages, in turn, are a major source of VEGF in endometriosis (McLaren *et al*., 1996). Thus, these contradictory findings indicate that further experimental studies are needed to clarify the exact role of PPAR-α in the pathogenesis of endometriosis and to identify potential applications of PPAR-α agonists in the treatment of the disease.

In contrast, the effects of PPAR-γ agonists on endometriosis have already been extensively analysed under experimental conditions during the last few years. Several rodent studies reported the regression of endometriotic lesions treated with a PPAR-γ agonist (Lebovic *et al*., 2004; Demirturk *et al*., 2006; Aytan *et al*., 2007; Olivares *et al*., 2011). In addition, Lebovic *et al*. (2007) demonstrated in the baboon endometriosis model that the size and overall number of endometriotic lesions is significantly reduced in animals treated with rosiglitazone and pioglitazone (Lebovic *et al*., 2010) when compared with placebo-treated controls. These results may be caused by the pleiotropic action of PPAR-γ agonists on multiple cellular mechanisms. In fact, Kavoussi *et al*. (2009) found that activation of PPAR-γ inhibits the attachment of endometrial cells to peritoneal cells. Moreover, PPAR-γ agonists have been shown to suppress VEGF expression in endometrial cells (Peeters *et al*., 2005) and to reduce the microvessel density in developing endometriotic lesions (Herington *et al*., 2011).

Taken together, these findings indicate that PPAR-γ agonists are promising drugs for the treatment of endometriosis. Accordingly, Moravek *et al*. (2009) published a first case series of three women with endometriosis, who were recruited as part of a prospective clinical trial and treated with rosiglitazone for 6 months. They found that

rosiglitazone was well tolerated by the patients and reduced endometriosis-induced pain in two patients, while one patient experienced no change. However, this clinical trial was not continued because rosiglitazone was shown to cause an increased risk of cardiovascular side effects (Nissen and Wolski, 2007). Meanwhile, pioglitazone has also been restricted in several countries, because the FDA warned that it may cause cancer in the urinary bladder (Balakumar and Kathuria, 2012). These examples clearly show that a major challenge for the establishment of PPAR-γ agonists in future endometriosis therapy is the identification of drugs with an acceptable side-effect profile.

Progestins, danazol and GnRH agonists

Progestins, danazol and GnRH agonists are drugs which are already widely used for endometriosis therapy because they reduce pain symptoms and effectively induce the regression of endometriotic lesions (Rodgers and Falcone, 2008). Noteworthy, several studies reported that these drugs also exert anti-angiogenic effects besides their well-known anti-hormonal activity.

Dienogest, an orally active progestin with a favourable safety and tolerability profile, has been shown to inhibit both embryonic and tumour cell-induced angiogenesis (Nakamura *et al.*, 1999). In line with these findings, Katayama *et al.* (2010) demonstrated in the rat dorsal skinfold chamber model that dienogest treatment suppresses vascularization of developing endometriotic lesions, as indicated by a decreased microvessel density and blood perfusion when compared with controls. Moreover, dienogest-treated lesions exhibit a reduced number of microvessels which stain positive for α-smooth muscle actin. Thus, dienogest seems to inhibit both the development and maturation of new blood vessels in endometriotic lesions, which may contribute to its proven clinical efficacy in endometriosis treatment.

Mönckedieck *et al.* (2009) investigated the effect of progesterone, dydrogesterone and its metabolite dihydrodydrogesterone on parameters of extracellular matrix degradation and angiogenesis involved in the development of endometriotic lesions in mice. Of interest, they found that these progestins suppress the transcription of angiogenic growth factors, including bFGF, VEGF-A and Cyr61, and of MMPs to a different degree. Such differences may be used in the future to identify those progestins, or progestin combinations, which are most effective in the treatment of endometriosis.

Matalliotakis *et al.* (2003) analysed the soluble levels of different growth factors and cytokines in the serum of patients with endometriosis and healthy women. They could demonstrate that patients with endometriosis exhibited significantly higher serum levels of VEGF when compared with controls. A 6-month treatment with the synthetic testosterone derivative danazol reduced these levels to a normal threshold.

Finally, Khan *et al.* (2010) analysed biopsy specimens from patients with endometriosis, adenomyosis and uterine myoma, who were treated for a variable period of 3–6 months with the GnRH agonist leuprolide acetate. They could show that GnRH agonist treatment decreases macrophage infiltration and microvessel density of endometriotic lesions, which is associated with an increased apoptotic cell death. Further studies now have to clarify whether these observations are related to the direct effect of leuprolide acetate on inflammation and angiogenesis at the tissue level or the indirect effect of hypoestrogenism. In fact, estrogen has been shown to increase VEGF mRNA expression in endometrial cells (Shifren *et al.*, 1996), which seems to be directly mediated by estrogen response sequences in the VEGF gene (Hyder *et al.*, 2000).

Other agents

In addition to the above listed groups of different compounds, some agents have been shown in individual reports to exert anti-angiogenic effects in endometriosis. These include anginex (Nap *et al.*, 2004, 2005), romidepsin (Imesch *et al.*, 2011), quinalizarin (Feng *et al.*, 2012) and the immunoconjugate molecule Icon (Krikun *et al.*, 2010).

Anginex is a synthetic β-sheet-forming peptide, which has been designed to mimic β-sheet domains of several anti-angiogenic agents, such as platelet factor-4, interleukin-8 and bactericidal-permeability increasing protein-1 (Griffioen *et al.*, 2001). Accordingly, anginex inhibits endothelial cell proliferation, adhesion and migration and induces apoptosis in these cells (Griffioen *et al.*, 2001). In the context of endometriosis, anginex has been demonstrated to suppress the formation of endometriotic lesions in the CAM assay and to reduce the number of established lesions in the peritoneal cavity of nude mice (Nap *et al.*, 2004, 2005). However, anginex has not yet been tested in clinical studies and, thus, is not well characterized in terms of potential side effects in humans.

Romidepsin belongs to the group of histone deacetylase (HDAC) inhibitors, which influence gene expression by enhancing acetylation of histones in specific chromatin domains (Emanuele *et al.*, 2008). HDAC inhibitors are suggested to be promising drugs for tumour therapy because they exert potent anti-cancer activities, including the inhibition of angiogenesis (Emanuele *et al.*, 2008). In a recent study, romidepsin has been shown to suppress the transcription, expression and secretion of VEGF in human epithelial endometriotic cells (Imesch *et al.*, 2011). This first report indicates that HDAC inhibitors may also play a role in the future anti-angiogenic treatment of endometriosis.

Quinalizarin is a selective inhibitor of protein kinase CK2, which is a serine/threonine kinase regulating a wide variety of biological processes, including angiogenesis (Kramerov *et al.*, 2008). Of interest, all three subunits of CK2 (α, α′ and β) are expressed in the stroma and glands of endometrial tissue and their activity is significantly reduced by quinalizarin (Feng *et al.*, 2012). In line with these findings, Feng *et al.* (2012) could demonstrate in the mouse dorsal skinfold chamber model of endometriosis that quinalizarin inhibits the vascularization of endometriotic lesions, which is associated with their regression. However, although the animals tolerated the daily treatment with quinalizarin well in this study, it is currently unknown which side effects on which different organ systems may be induced by targeting CK2.

Using an athymic mouse model of endometriosis, Krikun *et al.* (2010) demonstrated the anomalous expression of a tissue factor by endothelial cells in endometriotic lesions. Of interest, treatment with the immunoconjugate molecule Icon, which binds with high affinity and specificity to this aberrant tissue factor, largely destroyed endometriotic lesions by vascular disruption. Importantly, the treatment with Icon did not interfere with subsequent fertility nor did it have any teratogenic effects. Therefore, the authors concluded that Icon may be an ideal drug for women of reproductive age who are suffering from endometriosis and who desire subsequent fertility.

Potential impact of anti-angiogenic treatment in future endometriosis therapy

Numerous compounds have been analysed during the last years in terms of their anti-angiogenic activity in endometriosis. Typically, these compounds originally have been described as potential candidates for anti-angiogenic cancer therapy but many of their mechanisms of action are transferable to the treatment of endometriotic lesions. However, although cancer and endometriosis are similar in that they are crucially dependent on angiogenesis, the safety requirements for an anti-angiogenic therapy differ completely between the two entities. In fact, endometriosis is not a potentially life-threatening disease, unlike cancer. Moreover, most of the affected patients are young women in reproductive age, who desire to have children. Considering the fact that physiological angiogenesis is a major prerequisite for reproductive function (Reynolds *et al.*, 1992), anti-angiogenic compounds have to target specifically angiogenesis in endometriotic lesions or, at least, should not exert long-term side effects on blood vessel development within the ovary and uterus after stopping treatment. Accordingly, one of the major challenges in the future establishment of anti-angiogenic therapies is the detailed experimental and clinical evaluation of their potential side effects in young women and their risk of teratogenity in case of pregnancy. Moreover, because an anti-angiogenic therapy carries a high risk of impairing fertility, it may primarily be used to treat patients suffering from severe pain associated with endometriosis. For this purpose, promising candidates for therapy are, in particular, those anti-angiogenic compounds which have a favourable risk profile and have already been clinically approved for the safe treatment of other benign diseases.

Furthermore, it should be considered that the development of new blood vessels in endometriotic lesions is not solely driven by one angiogenic growth factor but is most probably mediated by various angiogenic signalling pathways (Laschke *et al.*, 2006a). This means that specific blockade of an individual factor may be compensated by redundant activity or up-regulation of other factors. To overcome this problem, the use of pleiotropic compounds, which target simultaneously different mechanisms of blood vessel development, may be appropriate. Nonetheless, because of the heterogeneity of endometriosis it is not likely that the application of any single anti-angiogenic agent will be sufficient to cure the disease. In fact, anti-angiogenic approaches typically induce the regression of a newly formed immature microvasculature but are not able to destroy mature pericyte-covered blood vessels (Benjamin *et al.*, 1999; Nap *et al.*, 2004). Therefore, rectovaginal endometriotic lesions, which are mainly composed of fibromuscular tissue with mature microvessels (Itoga *et al.*, 2003), may be resistant to anti-angiogenic therapy. On the other hand, anti-angiogenic compounds may effectively inhibit the establishment of new endometriotic lesions with strong angiogenic activity in early stages of the disease or after surgical treatment. Thus, they could gain major importance in the prevention or progression of endometriosis, contributing to a significant reduction in the high recurrence rates associated with the presently applied pharmacological and surgical treatment strategies. Moreover, the application of anti-angiogenic compounds in combination with other well-established drugs may be important in the development of novel therapeutic regimens for endometriosis, with fewer side effects and increased efficacy.

Conclusions

Angiogenesis represents an integral part in the pathogenesis of endometriosis and various anti-angiogenic agents have been proved in experimental studies to induce the regression of endometriotic lesions by targeting their blood supply. However, clinical evidence for the efficacy of anti-angiogenic treatment strategies in endometriosis is still lacking. Thus, there is an urgent need for controlled clinical trials to transfer the herein reported experimental findings from bench to bedside. For this purpose, anti-angiogenic compounds have to be identified, which exhibit an acceptable spectrum of side effects without affecting fertility or pregnancy in young women. If this succeeds, anti-angiogenic treatment strategies hold great promise as an important component of future endometriosis therapy.

Authors' roles

M.W.L. designed the study, identified the articles, drafted and revised the manuscript. M.D.M. designed the study and revised the manuscript. Both authors approved the final version of the manuscript.

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Conflict of interest

None.

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