Role of pigment epithelium-derived factor in the reproductive system

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Abstract

The physiological function of the female reproductive organs is hormonally controlled. In each cycle, the reproductive organs undergo tissue modifications that are accompanied by formation and destruction of blood vessels. Proper angiogenesis requires an accurate balance between stimulatory and inhibitory signals, provided by pro- and anti-angiogenic factors. As with many other tissues, vascular endothelial growth factor (VEGF) appears to be one of the major pro-angiogenic factors in the female reproductive organs. Pigment epithelium-derived factor (PEDF) is a non-inhibitory member of the serine protease inhibitors (serpin) superfamily, possessing potent physiologic anti-angiogenic activity that negates VEGF activity. The role of PEDF in decreasing abnormal neovascularization by exerting its anti-angiogenic effect that inhibits pro-angiogenic factors, including VEGF, has been investigated mainly in the eye and in cancer. This review summarizes the function of PEDF in the reproductive system, showing its hormonal regulation and its anti-angiogenic activity. Furthermore, some pathologies of the female reproductive organs, including endometriosis, ovarian hyperstimulation syndrome, polycystic ovary syndrome, and others, are associated with a faulty angiogenic process. This review illuminates the role of PEDF in their pathogenesis and treatment. Collectively, we can conclude that although PEDF seems to play an essential role in the physiology and pathophysiology of the reproductive system, its full role and mechanism of action still need to be elucidated.

Reproduction (2014) **148** R53–R61

Introduction

Pigment epithelium-derived factor (PEDF), encoded by *SERPINF1* gene, is a secreted glycoprotein that belongs to the non-inhibitory members of the serine protease inhibitors (serpin) superfamily (Becerra *et al.* 1995). PEDF was first purified by Tombran-Tink *et al.* (1991) from conditioned media of human retinal pigment epithelium and identified as a neurotrophic agent capable of converting Y79 retinoblastoma tumor cells into differentiated non-proliferative neurons (Steele *et al.* 1993).

Later, Dawson *et al.* (1999) showed that besides its neurotrophic properties, PEDF can also act as a potent inhibitor of angiogenesis. PEDF was first characterized as an anti-angiogenic factor that regulates the vascularity of ocular compartments in the eye (Bouck 2002). It was shown to be involved in the pathogenesis of angiogenic eye diseases, such as proliferative diabetic retinopathy and others (Volpert *et al.* 2002). The anti-angiogenic activity of PEDF was found to be selective and reversible; i.e., it targets only newly forming vessels, spares the existing ones, and does not interfere in the transient vigorous creation of new vessels needed, for example, in times of injury (Bouck 2002). It is clear today that PEDF is

expressed throughout the body and regulates angiogenesis; its level was found to be altered under pathological conditions in which unrestrained angiogenesis is involved, such as cancer, diabetes, endometriosis, ovarian hyper-stimulation, and more (Becerra & Notario 2013, Chuderland *et al.* 2013a). Finally, PEDF is accepted as one of the most potent anti-angiogenic factors in the body, hence it can be considered as a highly effective treatment of angiogenesis-related pathologies. In this review, we focus on the role of PEDF in the reproductive system, as an anti angiogenic physiological-regulator and as a potential therapeutic agent.

PEDF post-translational modifications

Most cells express PEDF transcripts, and the mature gene product is mainly secreted as a soluble monomeric glycoprotein (Becerra & Notario 2013). PEDF undergoes N-glycosylation that occurs at the Asn285 site. In addition, Maik-Rachline *et al.* (2005) demonstrated that PEDF is a phosphoprotein, which has several phosphorylation sites that determine its function as either neurotrophic or anti-angiogenic (Maik-Rachline & Seger 2006). The neurotrophic activity is mediated by PKA

that phosphorylates PEDF on Ser 227, whereas the anti-angiogenic activity is mediated by CK2 that phosphorylates PEDF on Ser 24 and Ser 114. In addition, induction of PKA followed by CK2 phosphorylation exhibits its most potent anti-angiogenic and neurotrophic activities (Maik-Rachline & Seger 2006). On top of its neurotrophic and anti-angiogenic activities (Simonovic *et al.* 2001), PEDF was shown to function as an anti-inflammatory (Wang *et al.* 2008) and anti-oxidative factor (Yamagishi *et al.* 2005, Bar-Joseph *et al.* 2014).

PEDF receptors

The multiplicity of PEDF functions lead the researchers to assume that there is more than one receptor for PEDF, which cater to its different functions (Maik-Rachline & Seger 2006). Up to date, several putative receptors have been suggested to take part in PEDF mechanism of action that includes: patatin-like phospholipase domain-containing 2 (PNPLA2; PEDF-R^N), that is involved in neurotrophic activity of PEDF; laminin receptor (LR PEDF-R^A; (Alberdi *et al.* 1999, Bernard *et al.* 2009, Filleur *et al.* 2009)); lipoprotein receptor-related protein 5 (LPR5; Wnt co-receptor (Anne *et al.* 2013)); and cell surface F1F0-ATP synthase (Notari *et al.* 2010) that mediates PEDF anti-angiogenic activity.

PEDF and vascular endothelial growth factor

Growing amount of evidence indicates that under physiological conditions, a delicate balance exists between PEDF and vascular endothelial growth factor (VEGF), and that PEDF may counteract the pro-angiogenic activity of VEGF. For example, in adult retinal pigment epithelial cells, oxidative stress conditions reduce the level of PEDF without affecting VEGF level, thereby disrupting the angiogenic balance between PEDF and VEGF, giving a selective advantage to the angiogenic-promoting activity (Ohno-Matsui *et al.* 2001) that can lead to the development of choroidal neovascularization in age-related macular degeneration (AMD). Treatment with recombinant PEDF (rPEDF) restored the angiogenic balance and by that alleviated AMD symptoms (Popp *et al.* 2013). In addition, the balance between PEDF and VEGF affects the fate of fibroblasts, where high PEDF level and low VEGF level are correlated with fibroblast quiescence; once the cells start to divide, the ratio is reversed. However, this controlled reversible angiogenic balance is interrupted in tumor-associated angiogenesis in a manner that resetting the 'angiogenic switch' is no longer possible (Pollina *et al.* 2008).

Our knowledge regarding the mechanism by which PEDF regulates VEGF is still evolving; in bovine retinal microvascular endothelial cells, PEDF regulates the translocation of the intracellular domain of VEGF receptor 1 (VEGFR1) and its phosphorylation,

destructing the ability of VEGFR2 to induce angiogenesis (Cai *et al.* 2006). In porcine retinal endothelial cells, it was suggested that PEDF inhibits VEGF-induced vascular permeability and angiogenesis through the SRC kinase pathway (Sheikpranbabu *et al.* 2010). In cancer cells, PEDF affects VEGF activity indirectly by downregulating the expression of HIF1 α (Yang *et al.* 2009). Other studies conducted in endothelial cells showed that survival and apoptotic cascades occur simultaneously within a single cell; the switch between the processes depends on changes in the balance between PEDF and VEGF (Pollina *et al.* 2008). However, detailed studies are still required to fully understand the mechanism behind these networks (Manalo *et al.* 2011).

Angiogenesis in the reproductive system

Angiogenesis in adults is usually in a quiescent state, with the exception of the female reproductive system and wound healing (Fraser & Lunn 2000). To achieve a proper angiogenesis, an accurate balance between pro- and anti-angiogenic factors must be maintained (Manalo *et al.* 2011); any failure in angiogenesis can lead to diverse pathologies.

The female reproductive system (i.e., ovaries and uterus), unlike any other organ, undergoes cyclic modifications orchestrated by alternating periods of hormonal stimulation and angiogenesis. On the one hand, the development of new blood vessels in the ovary and uterus is essential to guarantee the necessary supply of nutrients and hormones (Shimizu *et al.* 2012) that allows oocyte maturation and supports embryo implantation and early pregnancy. On the other hand, destruction of blood vessels is a crucial step that terminates one reproductive cycle and embarks on the next one. This dynamic angiogenesis is regulated by a balance between pro- and anti-angiogenic factors. Like in many other tissues, VEGF appears to be one of the major pro-angiogenic factors in the female reproductive organs (Fraser 2006); however, less is known regarding the anti-angiogenic factors.

The expression of PEDF in various fetal and adult human tissues was examined more than a decade ago by multi-tissue northern blotting assays. This analysis demonstrated a dominant expression of PEDF in the reproductive system organs; though, the function of PEDF in these organs remained obscure till recently. The potent anti-angiogenic nature of PEDF and its ability to regulate VEGF activity make this protein a potential regulating factor in the reproductive system. Understanding the balance between PEDF and VEGF in the reproductive system may help to decipher the pathophysiology of reproductive angiogenesis-related reproductive pathologies and hint at a new therapeutic approach.

The role of PEDF in ovarian physiology and pathology

Stromal blood vessels are the follicular source of nutrients and oxygen, which passively diffuse into primordial and primary follicles. The follicular growth is associated with the development of an autonomous blood capillary network that is restricted to the outer theca layer. The granulosa cells layer becomes vascular only after ovulation toward creation of the corpus luteum (CL). The entire process of CL formation is accompanied by sprouting of blood vessels toward the intrafollicular granulosa cells (Phan *et al.* 2006). Thus, a tight regulatory mechanism to supervise the process is mandatory. It was shown that endothelial cells undergo proliferation while incubating in a conditioned culture medium of the theca cells derived from follicles of all developmental stages. However, the response of endothelial cells to granulosa cells conditioned culture medium was dependent on follicle developmental stage: inhibited by follicular-phase granulosa cells and stimulated by pre-ovulatory granulosa cells, just before the follicle turns into a highly vascular CL (Gruemmer *et al.* 2005, Fraser 2006). These observations indicate the existence of a modular switch between pro- and anti-angiogenic factors in granulosa cells. Till recently most of the research has been directed toward characterization of ovarian pro-angiogenic factors, predominantly the VEGF family (Ferrara 2004). The most significant member of the family is VEGF-A (hereafter VEGF), which is produced in a number of isoforms, VEGF 165 being the most prominent in the ovary (Tesone *et al.* 2005). Studies have shown that inhibition of VEGF and VEGFR2 can impair follicular development or prevent ovulation (Fraser 2006). However, even after 70 years of research, the literature dealt more with the nature of the physiological pro-angiogenic factor of the ovary than with that of the anti-angiogenic one. Two anti-angiogenic candidates were suggested, thrombospondin (TPS; Osz *et al.* 2014) and hyaluronic acid (Tempel *et al.* 2000). TPS was found to be expressed in and secreted from granulosa cells regulated by gonadotropins. Knockout of TPS receptor has been correlated with increased ovarian vascularization and VEGF expression (Osz *et al.* 2014). Hyaluronic acid, which is produced by cumulus cells, inhibits the activity of endothelial cells *in vitro*, an activity that is not hormonally regulated (Tempel *et al.* 2000).

The expression of PEDF in the ovary was first reported by Cheung *et al.* (2006), showing that silencing PEDF expression can cause carcinogenesis of ovarian surface epithelium. Recently, we have characterized the physiological role of PEDF in the ovary, showing that PEDF is expressed in human and rodent ovaries, produced and secreted by granulosa cells in a hormonally dependent manner (Chuderland *et al.* 2013b). The secreted PEDF possesses an anti-angiogenic effect, as demonstrated by *in vitro* inhibition of human umbilical vein endothelial cells (HUVECs) proliferation, migration, and tube formation. We found that mimicking *in vitro* the

hormonal changes occurring around ovulation; namely, an increase in estradiol (E_2) level, upregulation of luteinizing hormone, and an increase in progesterone (P_4) level, led to the downregulation of PEDF expression and secretion. As in other tissues, we have further demonstrated that the expression of PEDF is inverse to that of VEGF; human chorionic gonadotropin (hCG) causes a decrease in the expression of PEDF and an increase in the expression of VEGF, both *in vivo* and *in vitro* (Chuderland *et al.* 2013a). We and others have shown that granulosa cells express PEDF-R^N (Kämpfer *et al.* 2014) and that *in vitro* stimulation with rPEDF downregulates VEGF mRNA synthesis in a dose-dependent manner (Chuderland *et al.* 2013a). The direct *in vitro* effect of rPEDF on VEGF biosynthesis in granulosa cells suggests that PEDF, produced by granulosa cells, exerts its effects in an autocrine or/and paracrine fashion.

Several reproductive disorders are associated with impaired ovarian angiogenesis; two distinct ones are ovarian hyperstimulation syndrome (OHSS) and polycystic ovary syndrome (PCOS). OHSS is associated with unrestrained formation of blood vessels and increased capillary permeability; PCOS is characterized with an excessive vascular formation (Amin *et al.* 2003). Thus, the development of therapies to these syndromes depends mainly on understanding the mechanism of ovarian angiogenesis (Soares 2011). OHSS is an iatrogenic complication, caused by ovarian stimulation with exogenous gonadotropins and ovulation induction by hCG to trigger oocyte maturation, particularly during IVF treatments (Humaidan *et al.* 2010). OHSS appears to be induced by ovarian release of vasoactive, angiogenic substances that cause extensive angiogenesis, vascular hyper-permeability, leakage, and extravagation of fluids from the blood vessels into the extravascular space with consequent clinical manifestations of ascites and edema (Albert *et al.* 2002). The pathophysiology of OHSS is not fully clear, though it is known that impaired angiogenic balance lies at the core of the syndrome and women with PCOS are at high risk to develop OHSS. Other conditions that are associated with OHSS are as follows: large number of recruitable follicles, high E_2 level, rapidly increasing E_2 level, size and number of stimulated follicles, number of oocytes retrieved, low body weight, and BMI. VEGF is considered to be the main factor that causes increased vascular permeability and a hallmark for OHSS in humans and rodents (Bates & Harper 2002). Increased VEGF levels in both serum and ovaries were associated with a higher probability of developing OHSS and its clinical manifestations (Soares 2011). We have recently shown that PEDF takes part in the pathogenesis of OHSS (Chuderland *et al.* 2013a); reduced level of PEDF was detected in the ovaries of mice stimulated to develop OHSS (Fig. 1). Given that OHSS may be a life threatening syndrome, many suggestions how to bypass the syndrome have been

Figure 1 OHSS pathophysiology and treatment. (A) Pathophysiology – IVF treatment, which includes stimulation with gonadotropins, may result in increased number of recruited follicles and thereby elevation of secreted E_2 . Stimulation by hCG increases the level of VEGF and decreases that of PEDF, thereby causing ovarian hyper-vascularization; OHSS. (B) Treatment – treatment with recombinant PEDF along with gonadotropins prevents excess production of VEGF, thereby preventing ovarian hyper-vascularization; OHSS prevention.

made during the years by both basic scientists and clinicians. Triggering ovulation by gonadotropin-releasing hormone analog instead of hCG and *in vitro* oocyte maturation were two of the clinical suggestions to avoid the risk of developing OHSS, though both dramatically decreased pregnancy rate (Humaidan *et al.* 2005, de Ziegler *et al.* 2012). Researchers suggested therapeutic approach for OHSS by targeting the VEGF pathway; for example, the use of SU5416, a synthetic compound developed to inhibit angiogenesis in cancer patients through the VEGF pathway. This compound was highly effective in the treatment of OHSS induced in mice (Gomez *et al.* 2002), but, the severe side-effects caused by SU5416, and the concern that it might interfere with early pregnancy, ruled it out from use in otherwise healthy women (Kuenen *et al.* 2003). The use of dopamine agonists that inhibit the phosphorylation of VEGFR2, and thereby can selectively inhibit VEGF-induced vascular permeability in OHSS, has been suggested recently. The tolerability of dopamine agonists among patients and the fact that they do not interfere with IVF outcome make them a promising treatment for OHSS (Soares 2011). Recent meta-analysis of nine studies concluded that dopamine agonist may prevent OHSS; however, it was found to be less effective for the treatment of OHSS (Baumgarten *et al.* 2013). We showed that replacement therapy with rPEDF alleviates OHSS

signs in a mouse model. Administration of rPEDF together with high doses of gonadotropins prevented weight gain, ovarian enlargement, and vascular hyper-permeability by inhibiting the excessive expression of VEGF. Furthermore, we found that administration of rPEDF had no negative effect on ovulation, implantation, and ongoing pregnancy. These findings may suggest a possible therapeutic advantage of rPEDF in OHSS because it restores the level of VEGF to the physiological range without impairing its normal functions, as is evident in both *in vitro* and *in vivo* experiments. We hypothesize that PEDF alleviates OHSS by suppressing VEGF, though this still needs to be proven (Fig. 1).

PCOS is currently the most common endocrine disorder in women of reproductive age (about 7–10% of women worldwide). The pathophysiology of this syndrome is not fully understood though several risk factors were found to be associated: genetic background, metabolic disorders (insulin resistance (IR) and hyper-insulinemia), and the *in utero* environment (Nandi *et al.* 2014). Increased production and secretion of ovarian VEGF is common in women suffering from this disease. VEGF overproduction is thought to be a trigger for the development of OHSS, frequently seen in this group of patients (Gomez *et al.* 2011). In 2011, PEDF was suggested to take part in the pathogenesis of PCOS (Yang *et al.* 2011), where it was shown that elevated level of

PEDF in the serum is associated with IR and PCOS; however, the conclusion of this study was challenged because of the small group of patients. In 2012, it was reported that PEDF level in the serum of PCOS patients is not elevated (Joham *et al.* 2012). The authors showed that the increased level of PEDF in the serum is associated with metabolic risk factors such as IR, but PEDF level was not altered compared with the matching controls (age and BMI; Lecke *et al.* 2013). Finally, in 2013, it was reported that changes in the level of PEDF in the serum of women with PCOS was closely associated with inflammation processes (Cheng *et al.* 2013). Under other, not related pathologies, it was demonstrated that changes in serum PEDF level are not necessarily reflected in its level in organs of interest (Katakami *et al.* 2008). We demonstrated an increased level of VEGF and a decreased level of PEDF in ovaries of PCOS-induced mice (Fig. 2); namely, a change in the physiological balance of PEDF and VEGF that can theoretically be shifted back by exogenous treatment with rPEDF. However, a broader scope research is needed to clarify the role of PEDF in PCOS pathogenesis and its therapeutic potential.

The role of PEDF in endometrial physiology and pathology

The human endometrium undergoes extensive cyclic morphological and biochemical modifications during each menstrual cycle of a woman's fertile life. These modifications include regeneration, breakdown, and shedding of the endometrial tissue; all regulated by the ovarian steroids E_2 and P_4 and their receptors (Smith 2001). However, up to date it is not clear how these

steroids specifically regulate endometrial angiogenesis, mainly due to species-related variations as well as timing deviations and different experimental designs (Girling *et al.* 2007, Das *et al.* 2009). The pro-angiogenic activity of E_2 was suggested in mice, null for estrogen receptor α that failed to develop uterine angiogenesis (Johns *et al.* 1996), and in ovariectomized mice that showed a rapid proliferation of endometrial endothelial cells under E_2 stimulation (Heryanto & Rogers 2002). The role of P_4 in endometrial angiogenesis is less established. *In vivo* studies show that administration of P_4 combined with low doses of E_2 inhibited endothelial cells proliferation; but upon its administration with high doses of E_2 , proliferation of endometrial endothelial cells was significantly increased (Heryanto & Rogers 2002). The effects of E_2 and P_4 are attributed to differential spatiotemporal expressions of pro-angiogenic factors in the uterus (VEGF, angiogenin, fibroblast growth factors, and others; Girling & Rogers 2009). As in the ovary, the best characterized pro-angiogenic factors are the members of the VEGF family. Various studies have demonstrated the presence of different VEGF isoforms in the endometrium (Ancelin *et al.* 2002), including VEGF 165, VEGF 121, VEGF 145, and VEGF 189, all regulated by hormones. VEGF 165 is believed to be the dominant isoform in human endometrium, as it is in the ovary, and its expression is altered dynamically during the menstrual cycle (Lash *et al.* 2012). Yet, the specific mechanisms leading to angiogenesis, migration, and/or proliferation of endometrial endothelial cells still need to be elucidated (Girling & Rogers 2009).

The first report for PEDF function in the endometrium was given by Palmieri *et al.* (1999); they followed age-related changes in the level of PEDF and their effect on tumorigenicity. This group reported that PEDF level decreased with age and suggested that this decrease can contribute to the age-related increase in cancer incidence. When characterizing the physiological role of PEDF in the uterus, we found that PEDF is dynamically expressed in the endometrium of humans and rodents during the menstrual and estrus cycles, respectively (Chuderland *et al.* 2013c, 2014), in a reciprocal manner to VEGF expression. Using a mouse model and human endometrial cell line, we found that E_2 and P_4 regulate the expression of PEDF. E_2 induces a decrease in PEDF level, whereas P_4 administered after E_2 priming induces an increase. We have further demonstrated the expression of PEDF-R^N in human endometrium, localized mainly at the endometrial glands, and showed that rPEDF downregulates VEGF expression *in vitro* (Chuderland *et al.* 2014).

During the last decade, it had become clear that endometrial angiogenesis is a multi-step, multi-factorial process (Girling & Rogers 2005). Abnormal endometrial angiogenesis may contribute to the development of several endometrium-related pathologies – including endometrial cancer (Weigelt & Banerjee 2012),

Figure 2 Counter regulation of PEDF/VEGF levels in PCOS. Pregnant ICR mice were administered once daily with di-hydro-testosterone (PCOS; $n=4$) or with oil (control; $n=4$) on days 16–19 of pregnancy. Female offsprings were allowed to grow to reproductive age (8 weeks). Ovaries were subjected to real-time PCR analysis with specific primers for PEDF or VEGF; calibrated with HPRT. *Significantly different from control value ($P<0.05$).

endometriosis (Soares *et al.* 2012), menorrhagia (Bouchard 2011), breakthrough bleeding (Lockwood 2011), and repeated implantation failure, secondary to impaired endometrial receptivity (Torry *et al.* 2007).

Endometriosis is a gynecological condition in which endometrial tissue (lesions) is present outside of the uterus usually on the peritoneum and ovaries, and is associated with infertility, dysmenorrhea, dyspareunia, and chronic pelvic pain. This pathology is rather common among reproductive-age women (10%) and even more among infertile women (50%; Mansour *et al.* 2010). Though the necessity of angiogenesis and the involvement of VEGF (Laschke *et al.* 2011) in the development and maintenance of endometrial lesions outside the uterus are clear, not much is known regarding the mechanisms behind the process (Soares *et al.* 2012). Yet, one can postulate that PEDF/VEGF balance is important for the maintenance of normal endometrium functions, and that impairment of the physiological equilibrium may be associated with angiogenesis-related endometrial pathologies as endometriosis. The expression level of PEDF was found to be significantly lower in the endometrium (Sun *et al.* 2012), endometrial lesions (Sun *et al.* 2012), peritoneal fluid (Chen *et al.* 2011) and serum (Chen *et al.* 2012) of women with endometriosis than that in the same organs of healthy women. On the other hand, whether VEGF is elevated in women suffering from endometriosis is still debatable (May *et al.* 2010).

To date, the two endometriosis therapeutic approaches are either induction of an amenorrheic – hypoestrogenic state, by suppressing ovarian estrogen secretion or surgery; both of them are not recommended to women planning pregnancy (de Ziegler *et al.* 2010). Though it is clear that a specific anti-angiogenic therapy may be the solution to this syndrome, the current available anti-VEGF drugs induce severe side effects.

Dopamine agonist was also suggested as a treatment for endometriosis. However, not only does dopamine have unpleasant side effects, it also lacks the ability, at least in mice, to reduce the size of endometrial lesions, by more than 30%. To date, there is only a single non-randomized pilot study carried out in ten human patients, showing a decrease in lesions area, 18–20 weeks after initiation of dopamine treatment (Soares *et al.* 2012). We (Chuderland *et al.* 2013c) and others (Chen *et al.* 2011, Zhao *et al.* 2012) have recently suggested the use of PEDF for treating endometriosis. Sun *et al.* (2012) showed that PEDF gene treatment inhibits the growth of human endometriotic cells *in vivo* when transplanted to a nude mouse model; they have further showed that this treatment reduces VEGF level and angiogenesis in the lesion (Sun *et al.* 2012, Zhao *et al.* 2012). We showed that treatment with rPEDF eradicates endometrial lesions as well as causes a significant decrease in the level of VEGF in the lesions. An egg factor is also a symptom of women suffering from endometriosis (Barcelos *et al.* 2009). We found that rPEDF treatment

improved significantly ovulation rate of rats with induced endometriosis (Chuderland *et al.* 2013c); yet, a more extensive research regarding the functions of PEDF in the reproductive system needs to be carried out in order to clarify whether it can improve oocyte quality.

Conclusion and prospective

Angiogenesis is an essential process in the women reproductive system. This is a tightly regulated mechanism orchestrated by pro- and anti-angiogenic factors. Angiogenesis lies also at the core of several reproductive-associated disorders. Though PEDF was characterized as one of the most potent anti-angiogenic factors in the body, its function in the reproductive system was neglected, and up until recently there were virtually no data regarding its putative role/s. We have recently started to characterize PEDF regulation and function in the reproductive system, showing its dynamic expression during the hormonal/menstrual cycle. We have also illustrated its therapeutic potential for treating these pathologies. On top of PEDF anti-angiogenic activity, this protein is known to possess anti-inflammatory (Wang *et al.* 2008) and anti-oxidative properties (Yamagishi *et al.* 2005), both are important processes involved in the physiological regulation of the female reproductive system. Oxidative stress and inflammation were found to be correlated with infertility in women, leading us to hypothesize that PEDF can serve also as a gonadal protectant. However, in order to understand and to benefit from PEDF function in the reproductive system its mechanism of actions needs to be illustrated. Revealing the complexity of PEDF regulation in the reproductive system can shed light on diverse reproductive-related pathologies as well as their potential therapies.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

Funding

This work was partially supported by German Israel foundation no. I-2318-1084.2/2012.

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Received 13 May 2014

First decision 24 June 2014

Revised manuscript received 10 July 2014

Accepted 21 July 2014