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Pigment Epithelium-Derived Factor: Chemistry, Structure, Biology, and Applications

Review Article

Role of Pigment Epithelium-Derived Factor in Stem/Progenitor Cell-Associated Neovascularization

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Running title: PEDF in Stem/Progenitor Cells

Abstract

Pigment epithelium-derived factor (PEDF) was first identified in retinal pigment epithelium cells. It is an endogenously produced protein that is widely expressed throughout the human body such as in the eyes, liver, heart, adipose tissue; it exhibits multiple and varied biological activities. PEDF is a multifunctional protein with antiangiogenic, antitumorigenic, antioxidant, anti-inflammatory, antithrombotic, neurotrophic, and neuroprotective properties. More recently, PEDF has been shown to be the most potent inhibitor of stem/progenitor cell-associated neovascularization. Neovascularization is a complex process regulated by a large, interacting network of molecules from stem/progenitor cells. PEDF is also involved in the pathogenesis of angiogenic eye disease, tumor growth, and cardiovascular disease. Novel antiangiogenic agents with tolerable side effects are desired for the treatment of patients with various diseases. Here, we review the value of PEDF as an important endogenous antiangiogenic molecule; we focus on the recently identified role of PEDF as a possible new target molecule to influence stem/progenitor cell-related neovascularization.

Keywords: Neovascularization; Pigment epithelium-derived factor; Stem/progenitor cells

1. Introduction

In the 1980s, pigment epithelium-derived factor (PEDF) was identified and isolated from primary human fetal retinal pigment epithelial cells [1]. It is a 50-kDa secreted glycoprotein that is a noninhibitory member of the serpin (serine protease inhibitor) superfamily of proteins; its gene (*SERPINF1*) is located on chromosome 17p13 [2]. PEDF is an endogenously produced protein widely expressed throughout the human body such as in the eye, liver, heart, and adipose tissue, which exhibits multiple and varied biological activities [3, 4]. PEDF was initially identified as a neurotrophic factor that differentiates retinoblastoma cells into non-proliferating neurons [5]. PEDF has also been shown to be neuroprotective for motor neurons [6], hippocampal neurons [7], dopaminergic midbrain neurons [8] and striatal neurons [9] in different toxin-induced models of neurodegeneration. These effects are parallel to the effects of PEDF on neurogenesis in the context of the neurovaculature. Thereafter, it was further discovered that PEDF also had potent antiangiogenic activity, greater than any other known endogenous factor [10, 11]. The implications of this discovery have proven to be extensive, and many studies have investigated the role of PEDF in various pathological conditions, including chronic inflammatory disease [12], cardiovascular disease [13, 14], angiogenic eye disease [15], diabetic complications [16], and cancer [17-20].

Although most research has been done in ocular neovascular and neurodegenerative diseases, over the past few years, PEDF has been described as a multifaceted protein with antiangiogenic, anti-atherosclerosis, antitumorigenic, antioxidant, anti-inflammatory, antithrombotic, neurotrophic, and neuroprotective properties (**Figure 1**) [4]. Neovascularization is a complex process regulated by a large interacting network of molecules from stem/progenitor cells [21-24]. More

recently, PEDF has been shown to be the most potent inhibitor of stem/progenitor cell-mediated neovascularization [25]. Novel antiangiogenic agents with tolerable side effects are desired for the treatment of patients with various diseases [20, 26]. Here, we review the value of PEDF as an important endogenous antiangiogenic molecule; we focus on the recently identified role of PEDF as a possible new target molecule to influence stem/progenitor cell-related neovascularization therapeutically.

2. Stem/Progenitor Cells and Neovascularization

Angiogenesis and vasculogenesis are the major types of postnatal neovascularization. Angiogenesis is the process where new vessels grow from preexisting blood vessels; whereas vasculogenesis is the process of blood vessel formation occurring by *de novo* production of bone marrow (BM) stem/progenitor cell-derived endothelial cells (ECs), which in turn, form blood capillaries (**Figure 2**) [27]. Neovascularization is an important process in the functional recovery of pathological conditions, such as wound healing and ischemic diseases. Hypoxia is an important driving force for neovascularization in various ischemic conditions through stimulation of the expression of many cytokines and growth factors such as vascular endothelial growth factor (VEGF), platelet-derived growth factor, insulin-like growth factor, and fibroblast growth factor (FGF), which play critical roles in induction of neovascularization [28]. Other cellular components including monocytes, T cells, neutrophils, and platelets play significant roles in the induction and modulation of neovascularization. Various stem/progenitor cells are also recruited to the ischemic sites and play crucial roles in neovascularization [29]. Preclinical studies have shown that stem/progenitor cells with or without a combination of growth factors induce neovascularization in ischemic tissues in various animal models [30, 31].

Following ischemia, various angiogenic factors and cytokines are upregulated and promote homing of stem/progenitor cells to the site of injury [32]. It has been shown that circulating stem/progenitor cells could be incorporated into the neovasculature within the ischemic tissue and could differentiate into ECs [33, 34]. Stem/progenitor cells can also differentiate into other supporting cells, which deliver growth factors and cytokines to ischemic tissue and promote angiogenesis through paracrine effects [35]. These cells primarily include various leukocytes as well as fibroblasts and pericytes [36-38]. Stem/progenitor cells in peripheral blood have been shown to differentiate into both early endothelial progenitor cells (EPCs), which function through paracrine effects, and late EPCs, which function directly through vasculogenesis [39, 40].

In the context of EPC biology, vasculogenesis includes the *de novo* formation of vessels via *in situ* migration, proliferation, differentiation, and/or incorporation of BM-derived EPCs into the regenerating vasculature [41]. BM-derived EPCs can localize to vascular structures during skeletal and cardiac ischemia [41, 42],wound healing [43], tumor growth [44], and corneal neovascularization [45]. EPCs also produce a variety of proangiogenic cytokines and growth factors, promoting proliferation and migration of preexisting ECs, activation of angiogenesis, and contributing to vascular regeneration and the re-establishment of tissue homeostasis [46]. Therefore, EPCs function via activation and support of vasculogenesis and may also be major players involved in the activation and mediation of angiogenesis [47], the process of new vessel formation, via *in situ* proliferation and migration of preexisting ECs [48]. This paracrine aspect of EPC activity, reflecting its indirect contribution to neovascularization, was confirmed by several reports demonstrating the presence of various cytokines and other secreting proangiogenic factors in EPCs

[49, 50] .

3. Ocular Biology

Most diseases cause blindness due to neovascularization. Neovascularization is a complex process regulated in adult tissues by a large interacting network of molecules. Hemorrhaging vessels cause edema and damage to surrounding tissues, particularly the retina. Microvascular lesions often cause severe retinal detachment and loss of vision [51]. PEDF was shown to prevent retinal cell death and counter the abnormal vessel growth induced by VEGF in the eye. Therefore, PEDF has been shown to be the most potent inhibitor of angiogenesis in the mammalian eye and is involved in the pathogenesis of angiogenic eye disease such as proliferative diabetic retinopathy.

The retina is subject to degenerative conditions leading to blindness. Although retinal regeneration is possible in lower vertebrates, it does not occur in the adult mammalian retina. Arnhold *et al*. determined the potential of adenovirally transduced bone marrow stromal cells (BMSCs) to differentiate into retinal pigment epithelial (RPE)-like cells and evaluated possible rescue effects after transplantation into the retinas of rats [52, 53]. Through an adenoviral vector expressing PEDF, BMSCs were transduced before subretinal transplantation into rats. They showed, for the first time, that BMSCs have the ability to adopt an RPE-like morphology after subretinal grafting into rats. Furthermore, BMSCs were able to induce significant rescue effects for the preservation of photoreceptor cell nuclei. These rescue effects could be increased in dystrophic rats with an adenoviral vector carrying the PEDF gene. Their findings indicate a possible therapeutic option of PEDF for the treatment of photoreceptor cells and visual loss originally caused by degeneration of the RPE layer [54].

Choroidal neovascularization is a common cause of severe and irreversible visual loss; however, the treatment of choroidal neovascularization has been hindered by its complex and poorly understood pathogenesis [55]. BM-derived cells are postulated to contribute to choroidal neovascularization [56], but little is known about their therapeutic potential for the treatment. Hou *et al*. reported that BM-derived mesenchymal stem cells (MSCs) transplanted by intravenous injection into a laser-induced mouse model of choroidal neovascularization were specifically recruited into the lesions, where they differentiated into multiple cell types and participated in the process of neovascularization. Engineered MSCs with PEDF at the choroidal neovascularization site inhibited the growth of choroidal neovascularization and stimulated regressive features. Their results suggest that MSCs contribute to choroidal neovascularization and could serve as delivery vehicles of antiangiogenic PEDF for the treatment of a range of choroidal neovascularization-associated eye diseases [57].

Retinal stem cell (RSC) research also offers unique opportunities for developing applications for retinal regeneration therapy. The ciliary body of adult mammals represents a source of quiescent RSCs. These neural progenitors have limited self-renewal potential *in vitro*, but this potential can be improved by mitogens. Marzo *et al*. tested combinations of PEDF with FGF during RSC growth to evaluate self-renewal and subsequent differentiation into retinal-like neuronal cell types. It was shown that PEDF might be a modulator during cell division promoting the generation of stem/progenitor cells. Thus, PEDF may contribute to the amelioration of RSC expansion, offering a source of alternative therapy in regenerative medicine (**Figure 3**) [58, 59].

Human embryonic stem cell-derived RPE transplantation is a promising therapy

for atrophic age-related macular degeneration (AMD). However, future therapeutic approaches might entail co-transplantation of embryonic stem cell-derived RPE with retinal progenitor cells (RPCs) as a replacement source for lost photoreceptors. Zhu *et al*. determined the effect of polarization of embryonic stem cell-derived RPE monolayers on their ability to promote survival of RPCs. They found polarized embryonic stem cell-derived RPE cells secrete high levels of PEDF that can support RPC survival suggesting that polarization of embryonic stem cell-derived RPE would be an important feature for the promotion of RPC survival in future cell therapy for atrophic AMD [60]. In addition, Vaajasaari *et al*. reported the differentiation of functional RPE-like cells from several stem cell lines in culture conditions. The differentiated cells were able to secrete PEDF characteristic of native RPE cells. Their results showed that RPE-like cells can be differentiated in xeno-free, defined culture conditions, which is mandatory for good manufacturing practice-production of these cells for clinical use [61].

Proliferative diabetic retinopathy is characterized by pathological retinal neovascularization. PEDF contains an N-terminal 34-amino acid peptide (PEDF-34). Longeras *et al*. presented data that PEDF-34 also possesses antivasculogenic activity; PEDF-34 attenuates EPC mobilization from the BM into circulating blood during retinal neovascularization [62]. Since PEDF controls the neuroprotective and antineovascular regulatory axis that determines cell growth, it could be used in combination therapeutic strategies for ocular neovascular diseases [63].

4. Cancer Biology

Cancer remains a major medical problem associated with considerable morbidity and mortality [64]. It is important for researchers to improve the current therapeutic

agents for cancer treatment, particularly targeting inhibition of tumor growth, survival, and metastasis. Cancer stem cells (CSCs), a special subpopulation of tumor cells, are considered to be tumor-initiating cells. More recently, these cells have also been identified as initiators of tumor neovascularization [65]. Vasculogenic mimicry—a newly defined pattern of tumor blood supply—provides a special passage without ECs and is conspicuously different from neovascularization. The biological features of the tumor cells that form vasculogenic mimicry remain unclear. CSCs are believed to be tumor-initiating cells, capable of self-renewal and multipotent differentiation, which resemble normal stem cells in phenotype and function. CSCs have recently been shown to contribute to vasculogenic mimicry formation as well as angiogenesis. The importance of vasculogenic mimicry in tumor progression suggests that it could constitute a novel therapeutic target for cancer [66].

Many researchers are investigating the crucial role of the proangiogenic factor VEGF in tumor angiogenesis, where the formation of new blood vessels carrying essential nutrients to the tumor cell becomes a critical factor for tumor growth [67]. Since VEGF plays an integral role in mediating tumor angiogenesis and tumor cell survival, current efforts are dedicated to developing therapeutic agents against VEGF; one emerging candidate is PEDF [68]. PEDF has recently shown promise as a potential antitumor agent, causing both direct and indirect tumor suppression. Here, we briefly introduce the unique antitumor properties of PEDF and discuss its role as an effective antiangiogenic, antiproliferative, and pro-differentiation factor (**Figure 4**).

The poor outcome of cancer gene therapy in clinical trials relates, in part, to insufficient gene delivery to tumor sites. MSCs represent a new tool for the delivery of therapeutic agents to tumor cells [69, 70]. Fitzgerald *et al.* used tumor cells

over-expressing PEDF to establish PEDF as both a metastatic suppressor and a neuroprotectant in the brain *in vivo* [71]. Gao *et al*. used a nude mice model of hepatocellular carcinoma (HCC) to evaluate the potential of genetically modified human MSCs to function as an effective delivery vehicle for therapeutic genes. MSCs derived from the BM were efficiently engineered to express human PEDF by lentiviral transduction, then tested *in vitro* for high-level expression and bioactivity of the transgenic protein. The preferential homing of MSCs toward HCCs was confirmed by *in vitro* and *in vivo* migration assays. *In vivo* efficacy experiments showed that intravenous injection of PEDF-expressing MSCs significantly suppressed both the growth of primary liver tumors and the development of pulmonary metastases. Moreover, MSC-based PEDF gene delivery moderately increased systemic levels of human PEDF. Immunohistochemistry of primary liver tumors demonstrated lower microvessel density in mice treated with MSC-PEDF than in control mice. This study shows, for the first time, the tropism of MSCs derived from the BM for HCC. MSCs can be genetically modified *ex vivo* to express the PEDF gene that has therapeutic efficacy against HCC. Their results suggest a potential role of MSCs as a targeted, therapeutic delivery vehicle for the treatment of HCC. Although this study indicates that PEDF is a good therapeutic agent worthy of assessment in HCC, the same approach might also be exploited in the treatment of patients with other tumor types [72]. A better understanding of the contribution of PEDF and CSCs to neovascularization should elucidate the mechanisms of cancer initiation and progression as well as establish new concepts for cancer diagnosis and treatment [73, 74].

5. Cardiovascular and Neurovascular Biology

Cardiovascular and neurovascular diseases are worldwide causes of morbidity and mortality [75-79]. Stem cells and EPCs have been studied as novel and promising strategies for the treatment of these vascular-associated diseases [35]. Adult peripheral blood contains BM-derived EPCs with properties and markers that are similar to embryonic-derived angioblasts [80]. Recent studies have shown that BM-derived stem/progenitor cells can repair the endothelium, in contrast to the traditional concept that postnatal tissue revascularization was achieved by neighboring endothelial replication [81]. The progressive impairment of endothelial function and integrity starts a cascade of events leading to microcirculation damage [82], atherosclerosis, and common cardiovascular and neurovascular diseases such as coronary heart disease (CHD), myocardial infarction (MI), heart failure (HF), peripheral arterial disease (PAD), dementia, and stroke [83]. The proliferation rate of ECs is very low in adults, which limits the contribution of ECs to neovascularization. EPCs promote vascular repair and provide the rationale for autologous stem cell therapy [84]. Recently, EPCs have been vigorously investigated in various fields of medicine. Changes in EPC number have also been investigated in diseases other than cardiovascular and neurovascular diseases, such as metabolic disorders, neoplastic pathologies, rheumatic disease, chronic kidney disease, and chronic obstructive pulmonary disease [35]. In this section, we discuss the role of PEDF as a possible new target molecule to therapeutically influence cardiovascular and neurovascular diseases.

PEDF has been characterized in cardiovascular systems. It has a protective role in atherosclerosis, the main cause of CHD, MI, and HF, due to its anti-inflammatory, antioxidant, and antithrombotic effects in the vessel wall and platelets. Expression of PEDF by ECs is essential for the inhibition of proliferation and migration of smooth

muscle cells after balloon injury [85]. The antioxidative properties of PEDF have been shown to block TNF-α-induced EC activation [86]. These observations suggest that PEDF might have beneficial effects on atherosclerosis by suppressing inflammatory proliferative responses to injury. Additionally, PEDF has strong antiangiogenic effects by inducing apoptosis [87] in ECs and by regulating the expression of other angiogenic factors. Local blocking of PEDF (e.g., in ischemic tissue in the heart) might favor angiogenesis, induce neovascularization, and lead to increased perfusion of the injured tissue. In contrast, local overexpression of PEDF restricted to atherosclerotic lesions might block angiogenesis, inflammation, and thrombosis at these sites and thus counteract destabilization and rupturing of the lesion otherwise caused by inflammatory activation [88] and excessive angiogenesis, thereby inhibiting subsequent thrombus formation [89].

In our previous study, we described a streamlined method for the rapid isolation, growth, and *ex vivo* expansion of late outgrowth ECs from Wharton jelly of a human umbilical cord; we evaluated the ability of these cells to re-endothelialize and inhibit neointimal hyperplasia in injured femoral arteries of mice. We also examined the direct effects of EPC-conditioned medium on the migration and proliferation of human aortic smooth muscle cells and the role of PEDF in these effects. Our results showed that EPC transplantation led to rapid re-endothelialization of denuded arteries, which resulted in significant inhibition of neointimal thickening. This was the first report demonstrating that EPCs derived from an umbilical cord aid in accelerating re-endothelialization and attenuating vascular remodeling at sites of arterial injury; these effects were closely associated with PEDF [90]. These findings have implications for a novel PEDF-related and cell-based therapy for cardiovascular and neurovascular diseases.

MSCs can ameliorate MI injury; however, MSCs from older donors are less efficacious than those from younger donors. More recently, Liang *et al*. determined how age-related expression of PEDF affects MSC therapeutic efficacy for MI. Their data showed that PEDF expression was increased in MSCs from old mice compared to young mice resulting in significantly impaired therapeutic efficacy in old MSCs, compared with that in young MSCs, for treatment of mice subjected to MI. PEDF overexpression in young MSCs impaired the beneficial effects against MI injury and induced cellular profile changes in the infarct region that was similar to administration of old MSCs. Knocking down PEDF expression in old MSCs improved MSC therapeutic efficacy and induced a cellular profile similar to administration of young MSCs. PEDF secreted by MSCs regulated the proliferation and migration of cardiac fibroblasts. These data provide the first evidence that the paracrine factor PEDF plays a critical role in the regulatory effects of MSCs against MI injury. Furthermore, the impaired therapeutic ability of aged MSCs is predominantly caused by increased PEDF secretion [91]. These findings indicate PEDF as a promising novel genetic modification target for improving aged MSC therapeutic efficacy.

Vascular and neural tissues are delicately intertwined in functional neurovascular units. This co-dependence emerges early in development with the coordinated growth and tissue modeling of both cellular elements [92]. Stem/progenitor cells in the developing central nervous system and in neurogenic regions of the adult brain are stimulated to self-renew and generate more neurons by factors released from various vascular cells [93]. In the mammalian brain, neurogenesis persists in 2 germinal areas, the subventricular zone (SVZ) and the hippocampus, where continuous postnatal neuronal production seems to be supported by neural stem cells (NSCs) [94]. Ramírez-Castillejo *et al*. identified PEDF as critical for the communication between

vascular and neural cells in an adult NSC niche, the SVZ [95]. A single factor that can stimulate brain tumor cells to differentiate and, at the same time, cut off their blood supply has unlimited therapeutic value. PEDF levels decline with aging, possibly contributing to cell senescence and to age-related susceptibility to cancer [96]. These data demonstrate that PEDF is a niche-derived regulator of adult NSCs and provide evidence for a role for PEDF in NSC maintenance.

The potential of NSCs for brain repair dependents on their capacity for self-renewal. Recent evidence for the close apposition of adult periventricular NSCs and blood vessels have confirmed the findings [93, 95] that factors derived from the vasculature contribute to regulation of the adult NSC pool [97, 98]. A new study by Andreu-Agulló *et al*. revealed that the vasculature-derived PEDF promotes the Notch signaling-dependent renewal of adult periventricular NSCs through an unconventional mechanism [99]. They found that Notch was active in astroglia-like NSCs but not in transit-amplifying progenitors of the murine subependymal zone and that the level of Notch transcriptional activity correlated with self-renewal and multipotency. Moreover, dividing NSCs appeared to balance renewal with commitment via controlled segregation of Notch activity. PEDF enhanced Notch-dependent transcription in cells with low Notch signaling, thereby subverting the output of an asymmetrical division to the production of 2 highly self-renewing cells. Mechanistically, PEDF induced a non-canonical activation of the nuclear factor (NF)-κB pathway. These data provide a basis for stemness regulation in vascular niches and indicate that Notch and PEDF cooperate to regulate self-renewal [99].

6. Conclusions

PEDF has been described as a natural angiogenesis inhibitor with neurotrophic

and immune-modulation properties [100]. It balances stem/progenitor cell-associated angiogenesis in the eye, as well as cardiovascular and neurovascular systems, and blocks tumor progression. The mechanisms underlying most of these events are not completely clear; however, it appears that PEDF acts via multiple high affinity ligands and cell receptors. In this review article, we summarized the current knowledge on the important endogenous antiangiogenic molecule PEDF; we focused on the recently identified role of PEDF as a possible new target molecule to influence stem/progenitor cell-related neovascularization. We discussed the multimodal activities of PEDF and addressed the therapeutic potential of PEDF in treating angiogenesis-, neurodegeneration-, and inflammation-related diseases. However, many questions remain to be resolved; these specific points must be addressed prior to initiation of any human clinical trials using PEDF peptides.

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Conflict of Interests

The authors declare that there is no conflict of interests.

Figure Legends

Figure 1. The medicinal properties (antiangiogenic, anti-atherosclerosis, antitumorigenic, antioxidant, anti-inflammatory, antithrombotic, neurotrophic, and neuroprotective properties) of PEDF.

Figure 2. Schematic representation of postnatal neovascularization (angiogenesis and vasculogenesis).

Figure 3. Schematic representation of choroidal neovascularization. PEDF was shown to prevent retinal cell death and counter the abnormal vessel growth induced by VEGF in the eye.

Figure 4. Schematic representation of CSC participation in vasculogenic mimicry and neovascularization initiated by the presence of EPCs. Like in tumor angiogenic sprouting, neovascularization starts with the secretion of proangiogenic factors (such as VEGF) by the tumor under hypoxia. The proangiogenic factors circulate into the bloodstream towards the bone marrow, targeting the release of EPCs. The activated EPCs form a column from the existing blood vessel. PEDF has antitumor properties as an effective antiangiogenic, antiproliferative, and pro-differentiation factor.

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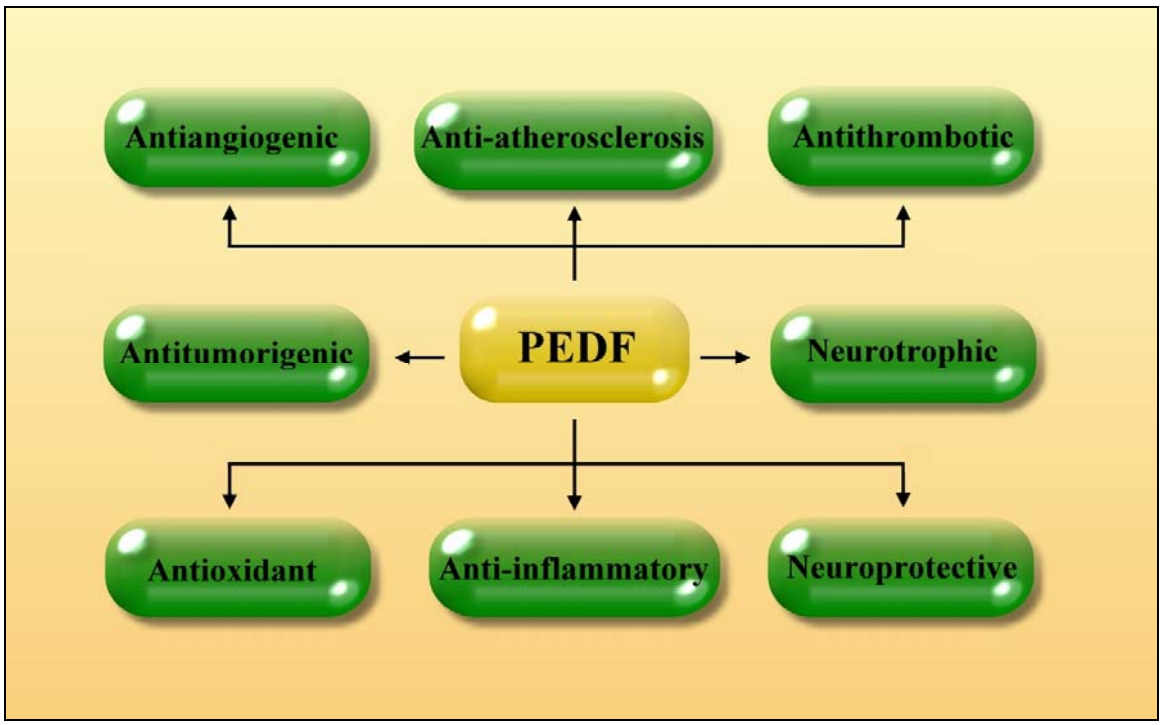
Antiangiogenic
Anti-atherosclerosis
Antithrombotic
Antitumorigenic
PEDF
Neurotrophic
Antioxidant
Anti-inflammatory
Neuroprotective

Figure 1

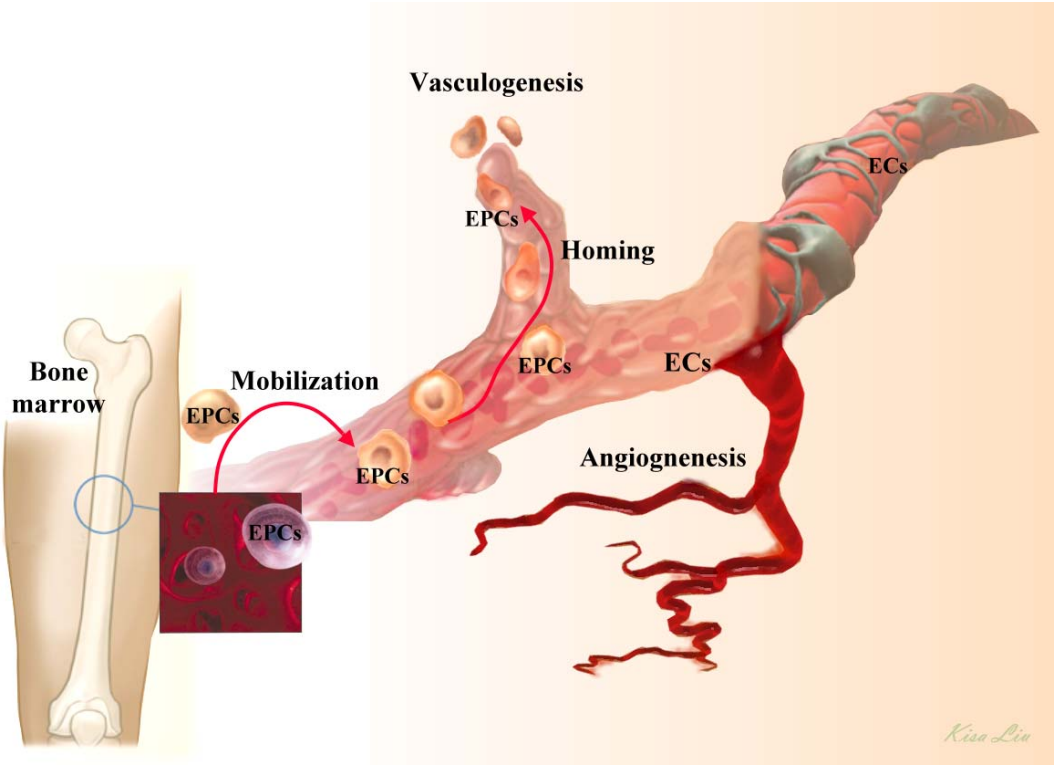
Vasculogenesis
ECs
EPCs
Homing
EPCs
ECs
Bone
marrow
Mobilization
EPCs
EPCs
Angiognenesis
EPCs
Kisa Liu

Figure 2

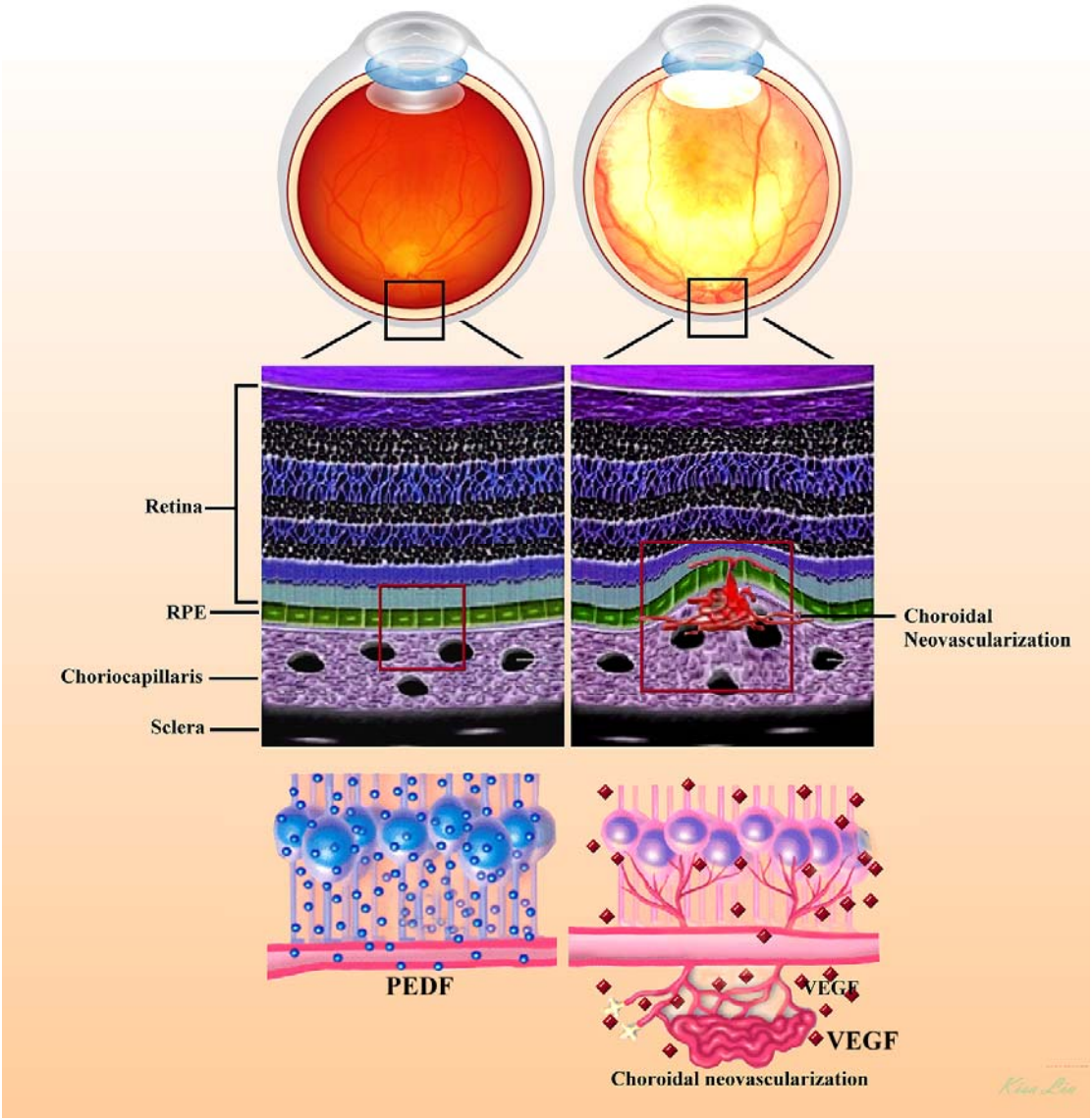
Retina
RPE
Choriocapillaris
Sclera
Choroidal
Neovascularization
PEDF
VEGF
VEGF
Choroidal neovascularization

Figure 3

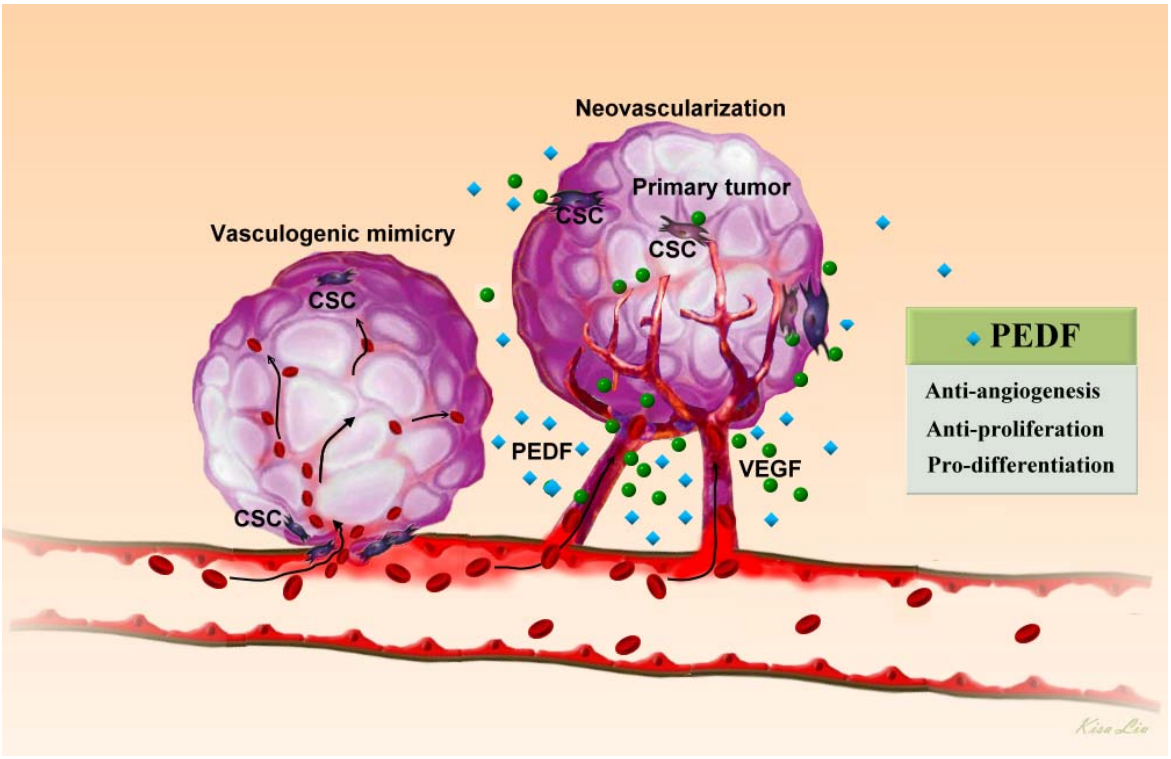
Neovascularization
Primary tumor
CSC
CSC
Vasculogenic mimicry
CSC
PEDF
VEGF
CSC
PEDF
Anti-angiogenesis
Anti-proliferation
Pro-differentiation

Figure 4