PEDF in the Retina

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Abstract

Pigment epithelium-derived factor (PEDF) is a protective protein of the eye, with neurotrophic and anti-angiogenic activities. It was discovered as a secreted factor from retinal pigment epithelium. The interphotoreceptor matrix and

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vitreous humor contain soluble and diffusible PEDF protein, which interacts with glycosaminoglycans, collagen, and cell-surface receptors to act on retina cells. Sequence alignment reveals that PEDF is a member of the serpin superfamily. PEDF shares hallmark features of serpins including the conserved tertiary structure with an exposed peptide loop towards its C-end. However, it is classified as a noninhibitory serpin. This review will summarize studies on the role of PEDF in the retina, in particular its anti-angiogenic, antiapoptotic, and anti-inflammatory properties. Studies with established animal models for retina diseases have demonstrated the importance of PEDF in the eye. In addition, PEDF is considered an important marker for retinal pigment epithelium derived from stem cells. The therapeutic potential of PEDF will be emphasized.

12.1 Introduction and Morphology of the Retina and Retina Disorders

The human eye functions to detect and send information to the brain, where it is processed and converted to visual images. The transparent cornea and the lens of the eye allow light to enter the eye, while the changing diameter of the pupil regulates the amount of entering light. The lens focuses light onto the retina. The retina is the innermost layer of the eye responsible for transmitting images formed by the lens to the brain by way of the optic nerve. Light must pass through several layers of cells before reaching the cells responsible for the transmission of visual information.

The retina is composed of ten layers consisting of many types of neurons connected by synapses (Fig. 12.1). The photoreceptors process the light stimulus and are composed of two types of cells: rods, which are responsible for night vision, and cones, which are responsible for color vision. The human retina contains over 6 million cone cells and over 120 million rod cells. The outer pigmented layer of the retina is composed of a monolayer of hexagonal cells called the retinal pigment epithelium (RPE). The apical, or innermost, side of the RPE layer interacts with the photoreceptor layer, while the basolateral side faces the Bruch's membrane, an inner layer of the choroid. The RPE plays many roles in the eye. The RPE is responsible for absorbing the light that is focused on the retina by the lens. The RPE is also responsible for the daily phagocytosis of the outer segments of photoreceptors, a critical immune function. It obtains nutrients from the blood and supplies these nutrients to the photoreceptors. In the visual cycle, the RPE supplies retinal, a form of vitamin A, to photoreceptors. The RPE also secretes growth factors and cytokines to maintain the homeostasis of the neural retina. One of these factors is pigment epithelium-derived factor (PEDF).

The many layers of the retina constitute a complex network of components critical for maintaining eye health and development. Disruption of the retinal layers, including the RPE layer, can lead to a host of retinal diseases and disorders such as macular degeneration, retinitis pigmentosa, and diabetic retinopathy, leading to severe loss of vision. To combat this, the retina possesses several protective

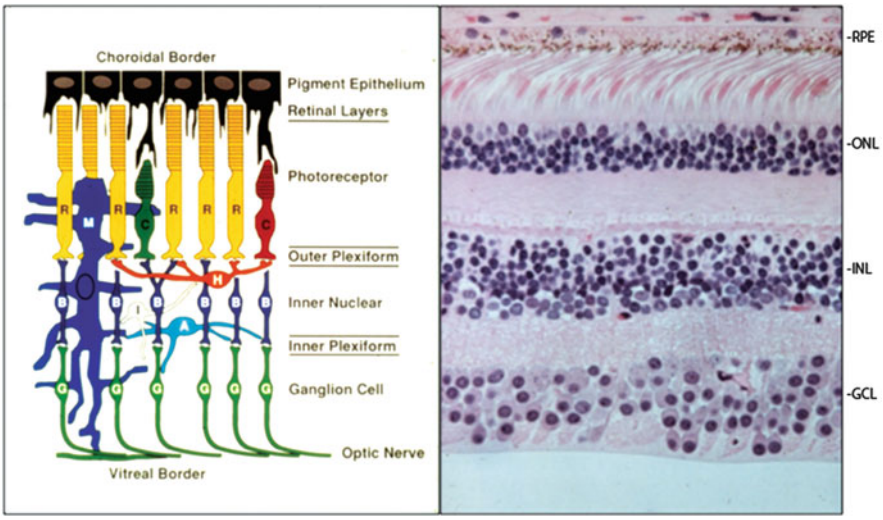

Fig. 12.1 Layers of the retina. (**a**) A scheme illustrating the layers of the retina composed of retinal ganglion cell layer (GCL), inner plexiform layer, inner nuclear layer (INL), outer plexiform layer, outer nuclear layer (ONL), external limiting layer, photoreceptor layer, retinal pigment epithelium (RPE). Labels of cell types correspond to ganglion cell (G), amacrine cell (A), bipolar cell (B), horizontal cell (H), Muller cell (M), rod photoreceptor cell (R), and cone photoreceptor cell (C). (**b**) Immunohistochemistry of a human retina

molecules and mechanisms involved in the regulation of retinal health. One such molecule is PEDF, which has been shown to be critical in eye health and possesses therapeutic value in treating diseases of the retina.

12.2 PEDF in the Retina

Although the *SERPINF1* gene that encodes PEDF is expressed by different ocular and non-ocular tissues and cells, the RPE expresses the highest levels of PEDF in the retina (Becerra et al. 2004). It was first reported that RPE-conditioned media induces neuronal differentiation in human Y79 retinoblastoma cells (Tombran-Tink and Johnson 1989). PEDF was purified from RPE-conditioned media and identified as the neurite-promoting factor in human retinoblastoma Y79 cells (Steele et al. 1993). Later on, PEDF was identified in the interphotoreceptor matrix of mammalian eyes as the bona fide factor with differentiating activity on Y79 cells (Wu et al. 1995).

The human *SERPINF1* gene maps to chromosome 17p13.1-pter (Tombran-Tink et al. 1994). The *SERPINF1* gene contains eight exons and seven introns (Tombran-Tink et al. 1996). Sequencing analysis reveals that its messenger RNA is 1.5 kb (Steele et al. 1993), with an open reading frame that encodes a human polypeptide of 418 amino acids with a secretion signal peptide of 20 amino acid residues at its N-end and a glycosylation site at Asn285–Thr287. The mature product is secreted

as a monomeric glycoprotein with a molecular weight of 50 kDa (Steele et al. 1993; Wu et al. 1995). The polarized RPE secretes PEDF in a preferred directional fashion towards its apical side into the interphotoreceptor matrix that bathes the outer segments of photoreceptors (Becerra et al. 2004).

The *SERPINF1* gene is expressed in fetal and adult human RPE cells (Tombran-Tink et al. 1995) as early as 17 weeks of gestation, suggesting a role in retinal development. PEDF is detected throughout the human retina (Karakousis et al. 2001). At 18 weeks of gestation, PEDF is present in horizontal cells in the outer part of the inner nuclear layer. At 21.5 weeks of gestation, PEDF is present in cytoplasmic granules in the RPE, ganglion cells of the inner nuclear layers, and differentiating cones. In the adult retina, PEDF is detected in the RPE and interphotoreceptor matrix as well as in photoreceptors and in inner retinal cell types (Karakousis et al. 2001). Aging retinal cells show a significant decrease in PEDF expression (Tombran-Tink et al. 1995). Interestingly, the PEDF distribution pattern in the developing eye is in agreement with the avascularity of the vitreous and aqueous humor and its neurotrophic role in the neural retina.

12.3 PEDF Is a Member of the Serpin Family

Amino acid sequence analysis and protein comparison data indicate that the PEDF sequence shows strong homology to members of the serine protease inhibitor (serpin) gene superfamily (Steele et al. 1993). The linear structure of PEDF possesses the accepted range of homology with other known serpins, which is between 23 and 26 % sequence identity (Steele et al. 1993) (Fig. 12.2). The overall folded structure contains the serpin-exposed peptide loop towards its carboxy end (Becerra et al. 1995). The crystal structure of PEDF further reveals that its tertiary structure is that of a serpin (Simonovic et al. 2001). Interestingly, folded PEDF has an asymmetric surface-exposed charge distribution, with a highly basic lysine-rich region on one side, and a highly acidic aspartic-acid-rich region on the opposite side, necessary for heparin and collagen binding, respectively (Fig. 12.3). When compared to other known serpins, it is clear that this charge distribution is unique to PEDF.

PEDF has been shown to behave as a substrate rather than an inhibitor of serine proteases (Becerra et al. 1993). Its P1 site is the residue leucine, specific for inhibition of leucyl-proteases, such as chymotrypsin. However, PEDF does not inhibit chymotrypsin, nor other leucyl-proteases such as cathepsin G, nor does it form an inhibitory complex with serine proteases (Becerra et al. 1993). It lacks the characteristic thermal stability of cleaved inhibitory serpins, and upon cleavage, PEDF does not undergo the conformational change from a stressed-to-relaxed heat-stable form (Becerra et al. 1995). Other noninhibitory serpins such as ovalbumin, angiotensinogen (Stein et al. 1989), and maspin (Pemberton et al. 1995) also lack this conformational change. A feature that some noninhibitory serpins share is the presence of unfavorable residues on the N-terminal side of its P1 leucine for insertion of the serpin loop into sheet A, which might be the cause of the lack of stressed-to-relax conformational change. Interestingly, cleaved PEDF at its serpin-

Fig. 12.2 Amino acid sequence alignment of human PEDF, alpha 1-antitrypsin (A1AT_HUMAN) and antichymotrypsin (AACT_HUMAN). Human PEDF shares 27 % sequence identity and 42 % homology with antitrypsin. Human PEDF shares 27 % sequence identity and 44 % homology with antichymotrypsin

exposed loop is still able to retain its neurotrophic activity, confirming that its homologous reactive loop is dispensable for its neurotrophic activity. Thus, PEDF is classified as a noninhibitory serpin, and its biological activity is independent of its serine inhibition potential. It is believed that during evolution, PEDF lost its inhibitory function and gained other functions specific for PEDF (Table 12.1).

12.4 Biological Effects of PEDF in the Retina

12.4.1 Neuronal Differentiating Activity

PEDF is capable of morphologically differentiating Y79 retinoblastoma cells to a neuronal phenotype (Steele et al. 1993). Differentiated Y79 cells express the neuronal markers neuron-specific enolase and neurofilament proteins (Steele et al. 1993). PEDF promotes the increase and maturation of pigment granules in

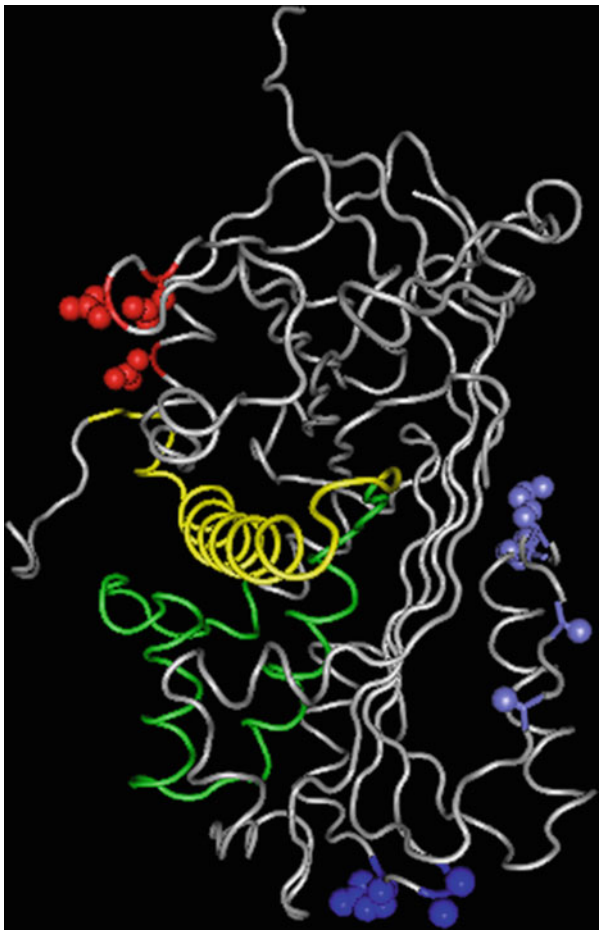

Fig. 12.3 Crystal structure of human PEDF with functional sites highlighted in color code from PDB 1IMV: neurotrophic region (*green*), anti-angiogenic region (*yellow*), collagen-binding region (*red*), heparin-binding region (*blue*), HA-binding region (*purple*)

Table 12.1 Summary of PEDF biological activity and targets in the retina

PEDF biological activity	Target
Neurotrophic	Retinoblastoma cells, Muller cells, retinal neurons
Prosurvival, antiapoptotic	Photoreceptors, retinal ganglion cells, retinal progenitor cells
Anti-angiogenic	Ocular endothelial cells
Anti-inflammatory	Muller cells and retinal ganglion cells
Stem cells, self-renewal	Retinal stem cells and human embryonic stem cells

neonatal rat pigment epithelial cells, suggesting that PEDF plays a role in RPE cell differentiation (Malchiodi-Albedi et al. 1998; Jablonski et al. 2000) reported that PEDF is morphogenetic for photoreceptors by supporting development of

photoreceptor neurons during the final stages of retinal morphogenesis. The loss of differentiation of photoreceptor outer segments (Jablonski et al. 2000) and Muller cells (Jablonski et al. 2001) in *Xenopus* tadpole eyes is rescued when exogenous PEDF is introduced. PEDF promotes neurite outgrowth of retinal cells (Tanimoto et al. 2006) and can also enhance survival and axon regeneration of retinal ganglion cells (Vigneswara et al. 2013).

12.4.2 Prosurvival and Antiapoptotic Effects

PEDF is a prosurvival factor for retinal cells in vitro and in vivo. PEDF protects retinal neurons in culture against serum starvation and hydrogen peroxide-induced apoptotic cell death (Cao et al. 1999; Murakami et al. 2008; Subramanian et al. 2013). It is also protects cone photoreceptor cells from death by light damage (Rapp et al. 2014). Furthermore, it enhances survival of retinal ganglion cells and protects them against cytotoxicity (Pang et al. 2007; Vigneswara et al. 2013; Unterlauft et al. 2014).

PEDF has a protective effect in vivo in models of retinal degenerations. A group of inherited retinal diseases, collectively termed retinitis pigmentosa (RP), is characterized by the progressive and specific loss of photoreceptors, the light-transducing neurons of the retina. One advantage of retina field is the availability of animal models for retina degeneration. The *rd1*/*rd1* mouse is an autosomal-recessive mutant, in which a nonsense mutation in the rod photoreceptor-specific β-*phosphodiesterase* (β-PDE) gene leads to a rapid and massive death of photo-receptors in homozygous animals. In another model, a null mutation in the *peripherin*/*rds* gene, which encodes a structural component of photoreceptor outer segments, causes a protracted, apoptotic loss of photoreceptors. Mutations in both β-PDE and *peripherin*/*rds* have also been found in patients affected by dominant forms of retinal degenerations. Injection of PEDF protein into these models *rd1*/*rd1* and *rds*/*rds* can protect photoreceptors against degeneration due to death by apoptosis (Cayouette et al. 1999). PEDF also protects photoreceptors against light-induced damage. Injection of PEDF into the vitreous of rats prior to constant light exposure resulted in protection of photoreceptor function and morphology (Cao et al. 2001). A combination of PEDF and basic fibroblast growth factors improved functional protection on photoreceptors. Intraocular gene transfer of adenoviral PEDF vectors increases retinal cell survival by preventing apoptosis in pressure-induced ischemia (Takita et al. 2003).

Elucidation of the mechanism of the antiapoptotic activity of PEDF in the retina is of current interest. A receptor for PEDF in the retina with high affinity for PEDF has been identified as PEDF-R (Notari et al. 2006), which is required for the prosurvival activity of PEDF (Subramanian et al. 2013). PEDF-R is a member of the PNPLA2 family (patatin-like phospholipase A2). It is present on the surface of the retina and RPE cells. In the rat retina, PEDF-R is distributed in the inner segments of the photoreceptors and in less intensity in other neural retina cells (Notari et al. 2006). Subcellularly, the PEDF-R protein is found in plasma

membranes as well as surrounding lipid droplets, where it is also known as adipose triglyceride lipase. PEDF-R is present in the plasma membrane of cone photoreceptor-derived 661W cells, which are known to respond to PEDF prosurvival effects (Rapp et al. 2014). The PEDF-R enzyme exhibits phospholipase as well as triglyceride lipase activities. It can catalyze the release of fatty acids from phospholipids, although the substrate specificity of PEDF-R is still unknown. Upon binding PEDF, the phospholipase activity of PEDF-R is enhanced (Notari et al. 2006). Therefore, fatty acids are considered putative bioactive mediators for the PEDF/PEDF-R system. In this regard, the retina contains phospholipids enriched in omega-3 fatty acids, which, in together with its derivatives like neuroprotection D1 and synaptimide, have demonstrable neuroprotective, neurite outgrowth, and anti-inflammatory properties (Bazan et al. 2013; Kim and Spector 2013). In neonatal rat R28 cells, an apoptosis-inducing factor-related pathway is an essential target of PEDF-mediated antiapoptotic activity (Murakami et al. 2008). PEDF protects R28 cells by upregulation of the antiapoptotic *B-cell lymphoma 2 (Bcl-2)* gene. Genetic silencing *Pnpla2* in R28 cells showed that PEDF-R is critical for PEDF-mediated cell survival and antiapoptosis effects (Subramanian et al. 2013). Pharmacological blocking PEDF from binding to PEDF-R with a synthetic receptor peptide leads to attenuation of the PEDF-mediated prosurvival activity. The current understanding of the mechanism of action in PEDF/PEDF-R-mediated survival activity involves the binding of PEDF to PEDF-R, which causes the release of fatty acids from plasma membranes. The release of fatty acids leads to the upregulation of *Bcl-2* ultimately leading to retinal cell survival, through a yet unknown mechanism. Further studies of the interaction between PEDF and PEDF-R will provide more insight into the mechanism of antiapoptotic activities.

12.4.3 Anti-angiogenic

A balance of proangiogenic and anti-angiogenic factors is required for ocular health. In contrast, uncontrolled angiogenesis is a common hallmark of many ocular diseases. Interestingly, the distribution of PEDF in the eye correlates with ocular avascularity. PEDF is a potent inhibitor of angiogenesis and acts as an antagonist of the proangiogenic factor vascular endothelial growth factor (VEGF) (Dawson et al. 1999). In contrast to the preferential basolateral secretion of VEGF (Blaauwgeers et al. 1999), the RPE secretes PEDF from its apicolateral side into the interphotoreceptor matrix (Becerra et al. 2004). PEDF is also present in the cornea of several mammalian species, where it prevents neovascularization (Dawson et al. 1999). In addition to VEGF, PEDF can inhibit the migration of endothelial cells in the presence of a variety of angiogenic factors, including platelet-derived growth factor, fibroblast growth factor interleukin-8, and lysophosphatidic acid. While VEGF levels increase, PEDF levels decrease in hypoxic conditions, indicating an inverse relationship of PEDF with VEGF (Notari et al. 2005).

Pathological retinal neovascularization is a feature of diabetic retinopathy and other ocular disorders characterized by retinal hypoxia. Oxygen-induced retinopathy in rodents is a model of retinal neovascularization in which vessels invade the inner retina. Choroidal neovascularization is one of the most important landmarks of neovascular age-related macular degeneration. Experimental choroidal neovascularization is performed by laser-induced breakage of the Bruch's membrane of rodents, which results in invasion of choroidal vessels into the RPE and neural retina (Campos et al. 2006). The inhibitory effects of PEDF on choroidal and retinal neovascularization in vivo have been proven by delivering purified protein by viral-mediated gene transfer into the vitreous, interphotoreceptor matrix, or subconjunctiva space (Mori et al. 2001, 2002a, b; Duh et al. 2002; Amaral and Becerra 2010). Huang et al. (2008) have shown that PEDF-deficient mice show increased retinal vasculature (Huang et al. 2008) implying that PEDF is an important regulator of the balance of retinal vascularization.

Several groups have reported on the mechanism of action of PEDF as an anti-angiogenic factor. Structure-function relationships have shown that a stretch of 34 amino acids from the amino-terminal end of the PEDF polypeptide, termed the 34-mer (positions 44-77), is responsible for the PEDF-mediated anti-angiogenic activity (Filleur et al. 2005; Amaral and Becerra 2010; Longeras et al. 2012). The pathways targeted by PEDF for inhibiting neovascularization have been summarized before (Becerra and Notario 2013). It appears that PEDF effects are cell context, and it can interact with a variety of partners and receptors including laminin receptor, cell-surface ATP synthase, gamma-secretase pathway, FAS/FASL pathway, etc.

12.4.4 Anti-inflammatory

PEDF can decrease the levels of proinflammatory cytokines. In addition to being an angiogenic factor, VEGF is also proinflammatory factor capable of upregulating expression of ICAM-1, another inflammatory factor (Lu et al. 1999). Therefore, as PEDF is a VEGF antagonist, it is considered anti-inflammatory. Zhang et al. (2006) have reported that a rat model of endotoxin-induced uveitis (EIU), characterized by retinal vascular hyperpermeability, shows decreased levels of PEDF and increased levels of proinflammatory cytokines (Zhang et al. 2006). Furthermore, PEDF injections into rat models of streptozotocin-induced diabetes and oxygen-induced retinopathy decrease vascular hyperpermeability and retinal inflammatory factors. In hypoxic conditions, PEDF reduces inflammatory factors TNF-α and ICAM-1 expression in cultured retinal capillary endothelial cells. Silencing of PEDF in retinal Muller cells results in the increase of VEGF and TNF-α secretion (Zhang et al. 2006).

Wang et al. (2013) have reported that injections of human recombinant PEDF protein into vitreous and subconjunctiva also lower the levels of anti-inflammatory molecules in the DKO rd8 mouse model of retina degeneration (Wang et al. 2013).

In addition they observed attenuation of focal lesion, less photoreceptor and RPE degeneration, and lower expression of apoptotic molecules.

12.4.5 Stem Cells and Self-Renewal

Retinal stem cell research is emerging as an attractive clinical therapy tool. There are several successful studies of differentiation of human embryonic stem cells and RPE human-induced pluripotent stem cells, which yields cells similar to those of native RPE. The ciliary body of adult mammals represents a source of quiescent retinal stem cells, which are neural progenitors with a limited self-renewal potential in vitro. De Marzo et al. (2010) have shown that a combination of PEDF and fibroblast growth factor supplemented in the media of retinal stem cells can influence positively their self-renewal (De Marzo et al. 2010). In experiments where human embryonic stem cell-derived RPE was being evaluated for its ability to promote survival of retinal progenitor cells, differentiated RPE cells were able to secrete high levels of PEDF capable of supporting retinal progenitor cell survival (De Marzo et al. 2010). The observations imply that PEDF can serve to overcome the limitation of the self-renewal potential of stem cells.

Several other research groups have used PEDF as a key marker of RPE derived from stem cells. Differentiated RPE cells derived from human embryonic and induced pluripotent stem cells have been generated and display hallmark functions of RPE (Vaajasaari et al. 2011). In addition to phagocytosis of photoreceptor outer segments, RPE derived from human embryonic and induced pluripotent stem cells secrete PEDF (Klimanskaya et al. 2004; Vaajasaari et al. 2011). Zhu et al. (2011) have reported that polarized human embryonic stem cell-derived RPE secrete large amounts of PEDF towards its apical side (Zhu et al. 2011) and that the conditioned media from the polarized human stem cell-derived RPE exhibits cells' survival effects on human fetal retinal progenitor cells, which were decreased when a blocking antibody to PEDF was added to the media. These results imply that PEDF plays an important role in retinal progenitor cell growth and protection.

12.5 Therapeutic Implications of PEDF in Retinal Diseases

The neuroprotective, anti-angiogenic, and anti-inflammatory properties of PEDF make it an attractive therapeutic agent. Decreased ocular levels of PEDF are reported for many ocular diseases including neovascularization (Duh et al. 2004), age-related macular degeneration (Holekamp et al. 2002), neuroretinal dystrophies (Ogata et al. 2004), and diabetic retinopathy (Spranger et al. 2001). So far, there are no known reports of toxicity by PEDF. For example, PEDF overexpressed in neonatal mice (Wong et al. 2004) yielding levels up to 3.5-fold than endogenous levels had no significant toxic effect. Strategies involving the delivery of PEDF and PEDF functional peptides could prove useful in treating many ocular diseases.

The photoreceptor protective properties of PEDF may serve to develop therapeutic drugs from this protein for preventing blindness originated by photoreceptor cell death. Some promising results of preclinical experiments with PEDF have been reported. As mentioned above, administration of PEDF protein into the vitreous results in lowering apoptosis of photoreceptors in retinal degeneration models *rd1* and *rds*. Intraocular gene transfer of PEDF for a mouse model of light-induced photoreceptor degeneration in Lewis rats results in photoreceptor cell rescue (Imai et al. 2005). Intravitreal injection of PEDF-impregnated nanoparticles delays photoreceptor degeneration by inhibiting apoptosis in Royal College of Surgeons (RSC) rats (Akiyama et al. 2012). Ocular therapies where patients are treated with PEDF could prove useful in delaying photoreceptor degeneration, thus preventing vision loss.

The anti-inflammatory effects of PEDF can be beneficial towards glaucoma, which is characterized by loss of retinal ganglion cells caused by increases in proinflammatory factors (Tezel et al. 2001). PEDF expression is reduced with age in the eyes of the DBA/2J glaucoma mouse model (Zhou et al. 2009). Transfection of PEDF in DBA/2J mice results in reduced retinal ganglion cells, reduced loss of the nerve fiber layer, and reduced expression of proinflammatory factors (Zhou et al. 2009).

The ability for PEDF to regulate neovascularization makes its therapeutic potential in many ocular diseases evident. It has been established that the imbalance of proangiogenic and anti-angiogenic factors plays a role in retinal neovascularization. In this regard, Gao et al. (2001) reported that there is a five-fold increase in VEGF and a two-fold decrease in PEDF in ischemia-induced rats with retinal neovascularization (Gao et al. 2001). To compensate the imbalance that is permissive to angiogenesis, several research groups have administered PEDF into animal models of ocular angiogenic diseases. For example, in transgenic mice with VEGF expression and a mouse model of choroid neovascularization, PEDF gene transfer results in regression of ocular neovascularization by promoting apoptosis of retinal cells with lesions (Mori et al. 2002b). Gene transfer of an adenoviral vector expressing PEDF results in higher intraocular levels of PEDF and suppressed choroid neovascularization (Gehlbach et al. 2003).

An imbalance of angiogenic regulators in the eye is also a hallmark of diabetic retinopathy (DR). Patients suffering from DR have an increase in retinal neovascularization caused by lack of blood flow, in which angiogenic factors are upregulated, while anti-angiogenic factors are downregulated. The anti-angiogenic properties of PEDF may constitute the base for potential therapies for DR patients. Spranger et al. (2001) have reported that the ocular fluids from patients with proliferative diabetic retinopathy show lower levels of PEDF than non-diabetic patients (Spranger et al. 2001). Patients who previously had photocoagulation, a surgery used to treat abnormal blood vessels in DR patients, showed higher levels of PEDF than those who did not. In a diabetes-like retinopathy mouse model, overexpression of PEDF via gene transfer leads to long-term prevention of neovascularization (Haurigot et al. 2012). The single injection also results in normalization of intraocular levels of VEGF and other proangiogenic molecules.

Additional complications of DR also benefit from PEDF treatment. Two PEDF derivatives of the anti-angiogenic region (positions 60–77) and neuroprotective region (positions 78–121) of PEDF were used to examine the effects of retinal complications caused by diabetes (Liu et al. 2012). In mouse retinas, the neuroprotective peptide reduces proinflammatory cytokines and prevents diabetes-induced microglia activation, retinal ganglion cell death, and inner plexiform layer thinning. Both peptides reduce vascular leakage. PEDF has therapeutic potential towards preventing patient loss for patients with DR.

The macula is a central part of the retina responsible for detailed vision. Macular degeneration results in central vision loss. Age-related macular degeneration (AMD) affects older adults. Choroidal neovascularization is a characteristic of the neovascular form of AMD called wet AMD, a severe form that can lead to retinal detachment. The levels of PEDF in patients with choroidal neovascularization due to AMD have been examined (Holekamp et al. 2002). Undiluted vitreous samples from patients with neovascular AMD have lower levels of PEDF. The vitreous of patients with AMD has lower levels of anti-angiogenic activity, probably due to lower levels of PEDF. In a study of Taiwan Chinese patients with AMD, a PEDF Met72Thr allele was found to be a possible risk factor for neovascular AMD (Lin et al. 2008). The other form, called dry AMD, is more prevalent than the wet one, in which photoreceptors undergo atrophy and RPE degeneration by yet unknown genetic and/or environmental causes. Elevation of proinflammatory cytokines is associated with these AMD forms. The mouse retina does not have a macula; therefore, mouse models for AMD mimic certain features of human AMD such as focal photoreceptor atrophy and RPE degeneration (Chu et al. 2012). The DKO rd8 mouse model retina shows some features of geographic atrophy with focal photoreceptor lesions, and its retina and RPE has decreased PEDF levels (Wang et al. 2013). Injection of PEDF into DKO rd8 mouse eyes shows attenuation of focal lesion, less photoreceptor and RPE degeneration, and lower expression of apoptotic and inflammatory molecules. The irreversible vision loss caused by AMD can be attenuated by PEDF treatment. Thus, the neurotrophic, anti-angiogenic, and anti-inflammatory properties of this interesting serpin point to promising PEDF-based therapies for AMD.

12.6 Conclusion

PEDF is a multifunctional protein and a member of the serpin family. It is ubiquitously expressed throughout the body and plays an important protective role in the retina, as demonstrated in numerous studies in vitro and in vivo. The therapeutic potential for PEDF is clear, and future preclinical studies towards the generation of PEDF-based drugs will prove beneficial towards treating retinal diseases.

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