Chapter 17

PIGMENT EPITHELIUM-DERIVED FACTOR AND ANGIOGENESIS
Therapeutic Implications

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Abstract: Pigment epithelium-derived factor (PEDF), an extracellular glycoprotein of 50 kDa, is one of the main anti-angiogenic factors of the eye. Its main source is the retinal pigment epithelium, from which the mature protein is secreted in a polarized fashion toward the retina. PEDF is present at high concentrations in the interphotoreceptor matrix, the vitreous and the aqueous humor. Pathologies like retinopathy of prematurity, diabetic retinopathy and age-related macular degeneration lead to severe visual loss due to neovessel formation and are accompanied by decreases in PEDF levels during their active phase. Pathological generation of blood vessels is also a key component of the growth and spread of tumors. Two of the main steps in the process of angiogenesis are endothelial cell migration and proliferation. PEDF has been shown to inhibit both, and to induce apoptotic endothelial cell death. These observations have led to its use as an anti-angiogenic substance, not only in animal models of eye diseases but also in clinical trials. Viral-mediated gene transfer, genetically engineered cells, and protein delivery systems located in the periocular or intraocular compartments are used to deliver PEDF to its target. PEDF is well tolerated and targets only new vessel formation. This chapter discusses the effects of PEDF in angiogenic models and the different approaches used in its delivery for the treatment of angiogenic eye diseases.

1. INTRODUCTION

The development, morphogenesis and survival of the neural and vascular retina rely on growth, trophic and survival factors derived mostly from the adjacent retinal pigment epithelium (RPE). The RPE secretes pigment epithelium-derived factor (PEDF), which promotes neuronal differentiation
and survival in the retina. More importantly, PEDF inhibits retinal and choroidal angiogenesis.\(^1\) This interesting factor is deposited extracellularly in ocular compartments where it is a protector and barrier for vessel intrusion from the choroid into the neural retina. Its importance in the development, maintenance, and function of the retina is evident in animal models for inherited and light-induced retinal degeneration, ischemia-induced retina and laser-induced choroidal neovascularization, as well as in the inverse correlation between levels of PEDF protein in patients with diabetic retinopathy (DR), age-related macular degeneration (AMD) and progression of disease.\(^2\)-\(^{10}\) PEDF also protects neurons of the central nervous system (CNS) and prevents tumor growth and angiogenesis, broadening its effects to other systems (see below). These observations have increased interest in the use of PEDF for treatment of a diverse array of diseases involving defective neuronal differentiation, insufficient cell survival, pathological new blood vessel formation (as in retinitis pigmentosa, DR, and AMD). It has also been applied to diseases outside of the eye such as amyotrophic lateral sclerosis and rheumatoid arthritis, as well as in the prevention of tumor growth.

The main focus of this review will be to evaluate the effects of PEDF in angiogenic models \((in vitro\) and \(in vivo\)), the different approaches for its delivery, and how these can be applied to treat choroidal and retinal neovascularization.

2. **PEDF, A MEMBER OF THE SERPIN FAMILY**

Knowledge of the structure of a polypeptide contributes to the understanding of its function. Much of the information accumulated to date originates from the PEDF cDNA sequence, identified by Steele \textit{et al.}\(^{11}\) The human PEDF mRNA is \(~1.5\) kb in length, and analyses of its cDNA sequence predict that human PEDF is a unique gene and a member of the serine protease inhibitor (serpin) supergene family. Its longest open reading frame of 418 codons encodes a 46-kDa polypeptide with an asparagine glycosylation site at position 285-287 (Asn-Leu-Thr) and an N-terminal signal peptide associated with secreted proteins. The translated product has the expected molecular weight and undergoes modifications before and/or during secretion that include one Asn glycosylation, the loss of 20 N-terminal amino acids, and, in some cases, phosphorylation and/or N-acetylation or other post-translational modification at its N-terminal residue. The mature PEDF is a diffusible monomeric glycoprotein with an apparent molecular weight of \(~50,000\) on SDS-PAGE and a molecular radius not larger than 3.05 nm.\(^{12\text{-}15}\) It has an isoelectric point of 7.2-7.8,