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Short Review

Pigment epithelium-derived factor in lipid metabolic disorders

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ABSTRACT

Pigment epithelium-derived factor (PEDF) is a secreted glycoprotein that has anti-angiogenic, anti-proliferative, neurotrophic and immunomodulatory properties. PEDF has recently emerged as a critical metabolic regulatory protein since the discovery of its modulatory activities in the lipolytic pathway by binding to adipose triglyceride lipase (ATGL). Despite being beneficial in maintaining the homeostasis of hepatic lipid accumulation, PEDF has been uncovered an unfavorable role associated with insulin resistance. The molecular events that connect these two apparent distinct observations have been controversial and remained largely unknown. Therefore in this short review, we attempt to summarize the current findings of PEDF regarding its lipid metabolic functions and provide perspectives in identifying PEDF as a potential therapeutic target in lipid disorders.

Pigment epithelium-derived factor (PEDF), encoded by the *serpinf1* gene, is a secreted glycoprotein that belongs to the serine protease inhibitor superfamily although it does not have any anti-proteolytic activity [1]. Research on PEDF began around early 1990s when PEDF was first identified in the conditioned media of human fetal retinal pigment epithelial cells (hence its name) as a neurotrophic factor for retinoblastoma cells [2,3]. Nearly a decade later, an important discovery showing PEDF as a potent inhibitor of angiogenesis (guarding ocular function) sparked the area of research of its anti-tumor properties [4]. Numerous models have been established to link decreased PEDF expression to increased tumor-associated vasculature. In fact, PEDF is also growth inhibitory as deficiency of PEDF causes epithelial hyperplasia in several organs [4,5]. Poorly differentiated tumors are often characterized by loss of PEDF [6,7]. Recently, PEDF has received much attention for its metabolic regulatory activity. This short review will specifically summarize

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the proposed mechanisms by which PEDF modulates lipid metabolism.

PEDF biochemistry

The PEDF gene, *serpinf1*, is located on chromosome 17p13 in humans, encoding an approximately 50 kDa protein with 418 amino acids in length (including a 20-amino acid signal peptide) [8]. The protease-sensitive serpin signature sequence is located near the C-terminus but however lacks the conformational change when cleaved as is observed in a typical inhibitory serpin [1,9]. PEDF is expressed in most tissues examined, with more prominent levels in the liver, testis, uterus, adipose tissue and skeletal muscle. As a secreted soluble protein, PEDF can also be detected in body fluids such as blood, tears, cerebrospinal fluids and aqueous/vitreous humour [10–14].

PEDF is known as a multifunctional protein. The molecular mechanisms by which PEDF exerts its diverse biological activities remain largely unidentified and are thought to be based on the interactions with different cell surface receptors that trigger distinct signaling pathways. A number of putative PEDF binding partners have been characterized so far, including membrane-bound phospholipase adipose triglyceride lipase (ATGL), laminin receptor, a cell-surface F1-ATP synthase, Wnt co-receptor LRP6, and more recently characterized PLXDC1/PLXDC2 receptors [15–19]. PEDF has also been shown to bind extracellular matrix (ECM) components such as heparin/heparan sulfate proteoglycans, collagens and hyaluronan [20–22]. The amino acids involved in these interactions have been mapped on human PEDF [Fig. 1]. These binding properties may contribute to retainment of PEDF in the ECM to facilitate its anti-tumor/antiangiogenic effects. Furthermore, studies have also revealed two functional epitopes: a 34-mer peptide (residues 44–77), which confers anti-angiogenic and apoptotic properties, and a 44-mer peptide (residues 78–121), which exhibits neurotrophic activity [23,24]. An even shorter peptide derived from the 34-mer designated as P18 (residues 60–77) has been proved to be more effective in blocking angiogenesis and tumor xenograft growth [Fig. 1] [25]. PEDF can be phosphorylated at specific serines by casein kinase 2 and protein kinase A [Fig. 1] [26]. Differential phosphorylation at these sites acts as a molecular switch to regulate the biological activity. Phosphomimetic mutants of PEDF have been shown to contain enhanced anti-angiogenic potency as an anti-tumor agent [27].

PEDF in hepatic lipid metabolism

As described earlier, liver is one of the highest PEDF producing organs. Despite its abundance, the functional role of PEDF has not been fully resolved. Being a powerful anti-angiogenic agent, PEDF has been shown to be crucial in the development and maintenance of hepatic vascular architecture [28]. In that regard, PEDF can have immense therapeutic implications for treatment of hepatocellular carcinoma (HCC), a typical hypervascular tumor. Indeed, a number of preclinical cancer models have provided evidence that PEDF administration by various means can inhibit tumor vasculature or metastasis from other organs [29–31]. However, research on a direct anti-tumor effect on HCC gives more divergent results, which depend a lot upon cell models used and receptor compositions [32,33].

The metabolic role of PEDF was first established in knockout animals in which PEDF deficient mice demonstrated liver steatosis, with an accompanying increase in body mass and visceral fat deposition [34]. PEDF null hepatocytes had pronounced accumulation of triglyceride compared to age-matched wild-type controls; this increase could be rescued by treatment with recombinant PEDF. Reduced PEDF levels and elevated hepatic triglyceride content have also been associated in an animal model and clinical cases of ethanol-induced steatosis. Ethanol exposure creates a hypoxic environment and induces activity of metalloproteinases-2 and -9, which in turn deplete PEDF via proteolytic degradation [35]. Conversely, overexpression of PEDF via adenoviral delivery has been shown to ameliorate hepatic lipid accumulation in a non-alcoholic fatty liver disease model, at least in part, by reduction of oxidative stress [36].

The mechanisms by which PEDF deficiency leads to lipid accumulation is thought to be due to decreased activity of ATGL. ATGL is the enzyme that specifically removes the first fatty acid in the step-wise triglyceride hydrolysis. PEDF has been shown to bind avidly to ATGL [18] and co-localize at the surface of adiposomes in hepatocytes [34]. Interestingly, ATGL-null mice also exhibit enlarged fat deposit and triglyceride accumulation in the liver and multiple other tissues, similar to what is observed in PEDF knockouts [37]. Many of

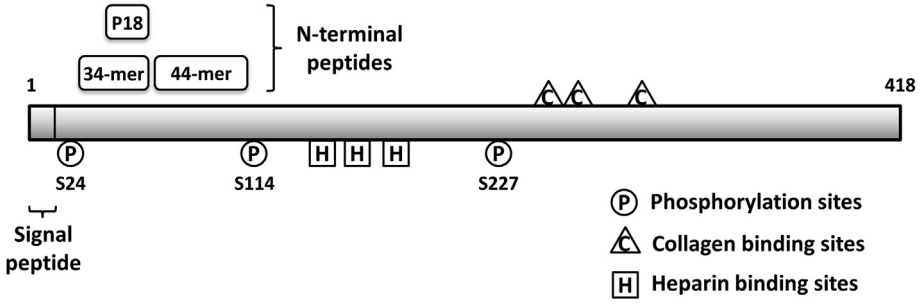

Fig. 1 **Schematic representation displaying functional peptides and key amino acid residues of PEDF.** The anti-angiogenic 34-mer, P18, and the neurotrophic 44-mer are marked. Phosphorylation sites, collagen and heparin binding sites are also indicated.