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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

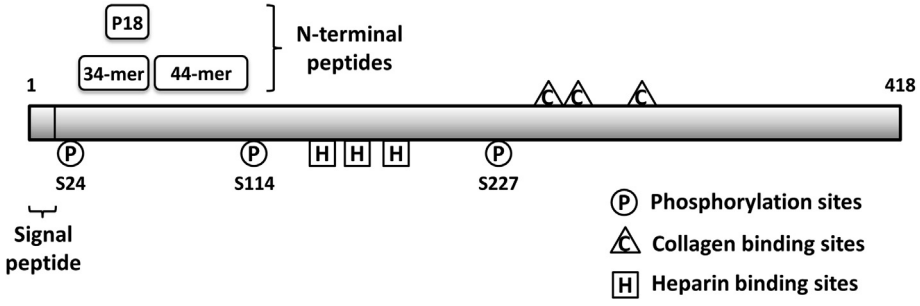

Fig. 1 **Schematic representation displaying functional peptides and key amino acid residues of PEDF.** The anti-angiogenic 34-mer, P18, and the neurotrophic 44-mer are marked. Phosphorylation sites, collagen and heparin binding sites are also indicated.

the established functions of PEDF have been shown to be through ATGL, suggesting dependency of ATGL activity on PEDF levels [38,39]. Downstream action of PEDF in hepatic lipid metabolism has yet to be determined. One study has revealed an interaction between PEDF and PPARα *in vitro*, thereby regulating PPARα transactivation [40]. As PEDF is a secreted glycoprotein, whether this interaction occurs in a more physiologically relevant condition needs further validation. However, PEDF indeed has a nuclear localization motif and its nuclear presence have been documented [41,42]. Further investigation may be facilitated to elucidate the relationship between PEDF localization and biological function.

PEDF in the adipose tissue

PEDF is also highly expressed by adipose tissue. In fact, PEDF is one of the most abundant proteins secreted by human primary adipocytes, which may be regarded as a major source for the circulating levels [43]. The expression pattern of PEDF during adipogenic differentiation remains a controversy. While a number of studies have shown a decrease in PEDF mRNA and protein during differentiation in 3T3-L1 preadipocytes [44,45] and adipose-derived stem cells [46], others have shown a differentiation dependent increase [43]. This discrepancy has not been resolved except for the knowledge that these assays were conducted in cells from different species. Despite these differences in findings, studies have revealed that exposure of adipose tissue to PEDF stimulates lipolysis, in accordance with its role in triglyceride catabolism in the liver [47,48]. In addition, recombinant and adenoviral PEDF attenuate adipogenic differentiation of 3T3-L1 preadipocytes, as evidenced by down-regulation of adipocyte markers and decreased lipid accumulation. PEDF also promotes osteoblast differentiation of mesenchymal stem cells [46]. Interestingly, the inhibition by PEDF is only effective at early stages of differentiation, allowing suppression of early ERK1/2 and subsequent C/EBP-β activation [45]. These results may explain why as studies have reported PEDF elevation in metabolic disorders [49], no apparent physiological effect on adipogenesis and body fat content can be observed. A recent report has demonstrated that adipose tissue-specific overexpression of PEDF only enhances adipocyte lipolysis but has no effect on local vascularization and systemic adiposity [50]. Additional functions of PEDF in adipose tissue need to be further elucidated.

PEDF and insulin resistance

Based on what is described above, we know that PEDF is a potentially beneficial metabolic regulatory protein and may be an appropriate candidate for drug development. However, the implications of PEDF in insulin resistance make therapeutic applications less feasible and require further characterization. The role of PEDF in insulin resistance and metabolic disorders is not well understood and remains largely controversial. Circulating levels of PEDF have been found to be elevated in various metabolic disorders such as obesity, type 2 diabetes [51], polycystic ovarian syndrome [52] and metabolic syndrome [49,53]. In contrast, PEDF levels decrease significantly after weight loss [54]. Some researchers conclude that the elevation of PEDF may act as a counter measure against obesity-related metabolic derangement while some suggest otherwise. Whether PEDF is the cause or effect of impaired metabolism remains debated.

In an HCC cell line Hep3B, PEDF has been shown to improve insulin resistance in cells exposed to advanced glycation end products (AGEs), reactive derivatives associated with several vascular and neurological complications in diabetic patients. PEDF blocks AGE-induced activation of Rac-1 GTPase and subsequent phosphorylation of insulin receptor substrate-1 (IRS-1) at serine-307, JNK, c-Jun and IκB kinase. JNK is an inhibitory serine/threonine kinase that phosphorylates IRS-1, which in turn interferes with the interaction between IRS-1 and insulin receptor, thus preventing tyrosine phosphorylation of IRS-1. PEDF also inhibits AGE-dependent decrease in IRS-1 tyrosine phosphorylation, thereby increasing the association of p85 subunit of phosphatidylinositol 3-kinase (PI3K) with IRS-1, causing glycogen synthesis in the presence of insulin [55]. Moreover, PEDF administration ameliorates AGE-induced platelet activation and shortened tail vein bleeding time in diabetic rats and protects against early phase of experimental diabetic retinopathy. These effects may result from an outcome of anti-oxidative properties through suppression of NADPH oxidase-driven superoxide generation [56,57]. PEDF null mice recapitulate features of metabolic syndrome including increased adiposity, liver steatosis, impaired glucose tolerance, and increased circulating pro-inflammatory metabolites. PEDF deficient hepatocytes treated with recombinant PEDF protein can suppress IL-1β-mediated stress mediators such as JNK and p38 by normalizing IRS-1 and Akt signaling [58]. These findings identify the role of PEDF in maintaining homeostasis in metabolic syndrome.

In contrast with the effect on hepatocytes and diabetic retinopathy, the link between PEDF and insulin resistance has been established in an extensive series of cellular and animal studies. In human and mouse adipocytes and human skeletal muscle cells, PEDF causes insulin resistance [43]. Prolonged PEDF exposure in lean mice reduces insulin sensitivity. This decrease is accompanied by activation of pro-inflammatory kinases JNK and ERK1/2 in the muscle and adipose tissue, which in turn attenuates insulin signaling. Insulin sensitivity is enhanced after administration of a PEDF neutralizing antibody to obese mice over 5 days while skeletal muscle and liver triglyceride content is decreased [47]. These results suggest a causal role of PEDF in obesity-induced insulin resistance. To pharmacologically alleviate insulin resistance that involves PEDF, Yang and coworkers have found that rosiglitazone, a thiazolidinedione (TZD) family of diabetes medication often used as an insulin sensitizer, inhibits PEDF expression and secretion, with an improvement of insulin resistance [59]. Metformin, another common diabetes medication, also has a lowering effect on serum PEDF levels and ameliorates insulin resistance via increased AMP activated protein kinase (AMPK) activation [60]. However, clinical studies using metformin suggest more divergent outcomes [61].

The underlying mechanisms behind these apparently distinct observations are not clear. One possible explanation is

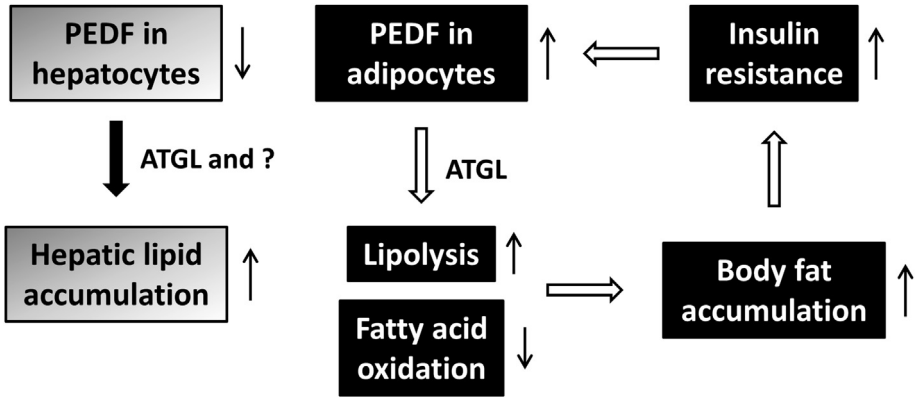

Fig. 2 **Distinct functions of PEDF in lipid metabolic disorders.** On one hand, PEDF exerts its anti-inflammatory and anti-oxidative properties in maintaining the homeostasis of hepatic lipid accumulation. On the other hand, increased PEDF in adipose tissue has the potential to initiate a cascade of events that may eventually lead to insulin resistance.

that these observations may have been made under different cellular contexts. As described in the previous section, ATGL, the putative PEDF receptor, is a triglyceride lipase that is critical in lipid homeostasis. ATGL null mice exhibit several phenotypes that are very similar to PEDF knockouts. However, a recent study using ATGL null mice has shown that many of the metabolic actions exerted by PEDF administration, including increased adipose tissue lipolysis, suppression of skeletal muscle fatty acid oxidation and insulin resistance, are diminished [38]. Hence the adverse effects of PEDF on insulin actions are dependent upon the presence of ATGL. Moreover, PEDF itself can attenuate ATGL protein accumulation via proteasomal degradation in adipocytes, adding another level of regulation [48]. Therefore, dysregulation of the PEDF-ATGL interaction may result in insulin resistance, as seen in type 2 diabetes and other conditions characterized by elevated circulating PEDF levels. An anti-inflammatory or anti-oxidative effect of PEDF described in hepatocytes and other cell types may reflect relatively low abundance of ATGL (although present) in these tissues compared with the adipocytes. PEDF may also transmit these signals via different binding partners other than ATGL and this requires further studies to confirm.

Concluding remarks

PEDF is a multifunctional protein that is produced by various tissues and released in soluble form in the circulation. Through interactions with multiple binding receptors, PEDF can initiate a wide range of cellular responses that regulate angiogenesis, proliferation, differentiation, energy metabolism, inflammation and oxidative stress. It has also been implicated in a variety of chronic diseases, including cancer, metabolic syndrome and vascular diseases.

In terms of therapeutic potential, the majority of the pre-clinical models demonstrate a beneficial outcome such as amelioration of ocular neovascular disease [62] and inhibition of tumor progression. However, the role of PEDF in glucose and lipid metabolism remains largely uncertain as clinical studies reveal positive correlations between serum PEDF levels and several major metabolic disorders. While PEDF shows anti-inflammatory and anti-oxidative properties in various systems, increased PEDF, via ATGL, promotes adipocyte lipolysis and decreases the capacities of skeletal muscle to oxidize fatty acids, leading to ectopic accumulation of excessive fatty acids and their metabolites and eventually insulin resistance. As prolonged insulin exposure promotes PEDF production by adipocytes [43], a feed-forward vicious circle can be initiated and ultimately contribute to development of metabolic disorders such as type 2 diabetes [Fig. 2]. Therefore in order to make PEDF a successful drug without unwanted secondary effects, generation of small active peptides that confer distinct functions may be a way to go. The crystal structure of PEDF provides information regarding important amino acid residues or epitopes responsible for receptor binding and the diverse biological activities that have been identified [9]. Including the 34-mer, 44-mer and P18 described in the previous section, more PEDF peptide mimetics have been produced to test their efficacy for treatment of different clinical conditions. Optimization of these active peptides/fragments to maintain strong biological activity and bioavailability needs immediate efforts. Studies on PEDF binding partners will further extend our knowledge of the underlying mechanisms that can lead to better treatment strategies.

Conflicts of interest

The authors have no conflict of interest to declare regarding this manuscript.

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