Tumor Biol.
DOI 10.1007/s13277-016-5326-1

REVIEW

Signatures of prostate-derived Ets factor (PDEF) in cancer

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Received: 24 June 2016 / Accepted: 6 September 2016

Abstract The Ets proteins are a family of transcription factors characterized by an evolutionarily conserved DNA-binding domain and have diverse biological functions including tumor suppressor as well as tumor promoter functions. They are regulated via a complex and diverse number of mechanisms and control key cellular processes. Prostate-derived Ets transcription factor (PDEF), a unique member of the ETS family, is present in tissues with high epithelial content are hormone-regulated, such as prostate, breast, salivary glands, ovaries, colon, airways, and stomach tissues. PDEF (prostate-derived Ets factor) is also referred to as SPDEF (SAM pointed domain containing Ets transcription factor), PSE (mouse homolog), or hPSE (human PSE) in the literature and is the sole member of the PDEF ETS sub-family. The role of PDEF in cancer development is still not fully elucidated though. The present article focuses on the key findings about the PDEF's biological functions, interacting proteins, and its target genes. There is a strong urge to focus on the clinical studies in larger cohort, which elucidate the regulation of PDEF and its target genes, to determine the potential of PDEF as biomarker. Based on the studies discussed in the present article, one can anticipate that PDEF offers a great potential for developing therapeutics against cancer.

Keywords PDEF · SPDEF · PSE · Tumor suppressor · Cancer

Introduction

Gene regulation is one of the most critical puzzles in science. It maintains the integrity of cells and ensures proper cell survival and growth. When rattled, gene regulation can have horrendous effects on the cell(s), resulting in cell death or diseased states, such as cancer. The cells of higher organisms exhibit an incredible number of genetic responses, which are regulated by various transcription factors (TFs), which participate in most of the cellular mechanisms. Transcription factors further increase the level of genetic complexity in cellular machinery, and many TFs within the same family often work differently to affect the transcription and finally the function of a single gene. Given the function of TFs, along with other mechanisms of gene regulation, it is not surprising that cells are capable of doing so much with so few genes. In the present article, the role of a transcription factor viz prostate derived E-twenty-six (Ets) factor (PDEF) in cancer is discussed.

PDEF structure and distinct sites

Prostate-derived Ets factor (PDEF) is a member of the ETS family of transcription factors and has been intensely investigated for its role in cancer development and progression. The original ETS gene (v-Ets) was identified as a viral oncogene in the avian-transforming retrovirus E26 [1]. PDEF is also referred to as SPDEF (SAM pointed domain containing Ets transcription factor), PSE (mouse homolog), or hPSE (human PSE) in the literature and is the sole member of the PDEF ETS sub-family [2]; however, for consistency in this article, PDEF will be used only. Though a member of Ets factor, it is unique in many aspects compared to the other family members. (i) PDEF is described as an mRNA transcript, which is highly expressed in prostate tumor cells and regulates prostate-specific antigen gene expression. (ii) It has been demonstrated as an androgen receptor co-regulator. Another distinct feature includes its restricted expression in epithelial cells and has only been found in prostate, breast, colon, ovary, gastric, and airway epithelium [3–5]. Structurally, (iii) PDEF is unique as it contains a pointed domain (PD) in addition to the ETS

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Published online: 10 September 2016

domain; whereas, all other family members contain another conserved domain, either a repression domain (RD), a negative domain (ND), or a transcriptional activator domain (TAD) in addition to the ETS domain. (iv) The 88 amino acid ETS domain is located directly on the N-terminus. (v) The ETS domain of PDEF preferentially binds to GGAT sequences instead of the GGAA sequence preferentially preferred by other Ets proteins. (vi) PDEF also contains two putative PEST domains (a common feature of rapidly degraded proteins) and a number of phosphorylation sites [6–9].

ETS family members are regulated mostly by phosphorylation and other post-translational modifications (PTMs) have merely studied [9]. PDEF contains a number of potential phosphorylation sites; however, the only validated phosphorylation site is T50, located within the PX(S/T)P, mitogen-activated protein kinase (MAPK) consensus sequence [10]. Additional phosphorylation sites have been confirmed; however, the exact positions are not validated yet [11]. However, PI3-kinase phosphorylation consensus sequence has been shown to present in PDEF along with a potential protein kinase C site, two AKT, two tyrosine-kinase, and eight MAPK phosphorylation sites [7].

In addition, different studies have demonstrated that PDEF is regulated both at transcription and post-translation levels [9, 12, 13]. Findlay et al. (2008) have demonstrated that PDEF is regulated posttranscriptionally via two micro-RNAs (miRs), miR-204 and miR-510, by binding to the 30 UTR of PDEF and therefore prevent PDEF mRNA translation [14]. Additionally, levels of miR-204 and miR-510 are elevated and inversely correlate with the expression of PDEF as observed in both the breast and prostate tumor samples [13, 14]. Extensive research to determine the exact mechanism of the regulation of PDEF and its role in tumorigenesis is the need of the present hour.

PDEF and other partners in the play (binding proteins and target genes)

Binding proteins

PDEF, as a captain, has been shown to bind to various proteins and to regulate the functions of several genes, which act like as players, through which it sets the ground. Androgen receptor (AR) has been identified as the very first partner of PDEF. In LNCaP prostate cancer cells Oettgen et al. [7] have demonstrated, PDEF physically interacts with the DNA-binding domain of the AR to cooperatively enhance prostate-specific antigen (PSA) promoter activity. Chen et al. have demonstrated the importance of PDEF with another binding partner NKX-3.1 (a tumor suppressor gene encodes homedomain transcription factor) [15]. Their co-transfection analysis revealed that NKX-3.1 could abolish the transcriptional activation function of PDEF on the PSA promoter [15]. Using a yeast two hybrid system, Chen et al. have demonstrated that the interaction between PDEF and NKX-3.1 requires a part of homedomain and tyrosine-rich 21 amino acid sequence that lies at the Ct-terminal to the homedomain [16]. The RUNX transcription factors (RUNX1, RUNX2, and RUNX3) play essential roles in hematopoiesis, skeletal development, and cancer have also been demonstrated to interact with PDEF [17]. Chromatin immunoprecipitation (ChIP) analysis showed that RUNX1 is specifically bound to the PSA regulatory region in LNCaP cells. RUNX1 and RUNX2 activated the PSA regulatory region alone or cooperatively with PDEF [17].

Cho et al. (2009) did a thorough study to search the PDEF and its interacting proteins. In human breast cancer MDA-MB-231 cells, PDEF was transiently overexpressed and protein complexes were isolated by immunoprecipitation and PDEF-interacting proteins were analyzed by high throughput proteomic approach (LC-MS/MS) [18]. These authors identified 286 proteins in the PDEF-associated protein complex. They demonstrated that PDEF-interacting proteins are not only distributed in the nucleus, but also in the cytoplasm, as well as other subcellular compartments. PDEF was found to interact with a variety of proteins involved in cell cycle, DNA repair, cytoskeleton organization, mRNA processing, tRNA biosynthesis, etc. [18]. The data from Cho et al. (2009) pointed out that PDEF might be regulated by Erbb2 or EGFR-activated signaling pathways in breast cancer cells; however, more studies are needed in this direction.

A similar approach was applied to determine the PDEF-interacting protein in prostate cancer in PC3 human prostate cells. Sabherwal et al. (2012) have used iTRAQ labeling followed by mass spectrometric (MS) analysis to identify candidate proteins that are differentially expressed in prostate cancer cells with or without PDEF [19]. These authors have identified 115 proteins, of which 35 were upregulated and 80 were downregulated in the two sets of prostate cancer cells [19].

A number of different proteins have been identified as binding partners of PDEF; however, more studies are required to know the exact function and importance of these interactions. It will be interesting to know the exact function and sites of binding of these proteins, which can later be used for diagnostic and therapeutic purposes.

Target genes

As mentioned above, there are number of partners associated with PDEF. Because of this complexity and connectivity of various regulatory mechanisms, a number of roles have been emerging which demonstrate the complexity of PDEF in various pathologic and non-pathological states. Over the past decade, numerous genes have found to be regulated by PDEF. Most of PDEF's target genes are deregulated in the

Table 1 PDEF target genes and major findings

Gene(s)	Description	Cancer/cellular model	Main findings/observations	Reference
PSA	Increased levels of prostate-specific antigen (PSA) are a primary screening tool for prostate cancer.	Prostate cancer cell line	In vitro translated PDEF bound specifically and with high affinity to PSA promoter-derived ETS binding sites and therefore is an important regulator of prostate gland and/or prostate cancer development. This observation is the first among all which demonstrates that PSA is regulated by PDEF.	[7]
MMP-9 MMP-7	Central role in tumor progression, from angiogenesis, inflammatory processes to stromal remodeling, and ultimately metastasis	Breast and prostate cancer cell line	PDEF is a negative regulator of MMPs. Levels of PDEF is inversely correlated with MMP9 expression in prostate cancer and colorectal cancer, and this equation works vice versa.	[4, 11, 20]
Survivin	Survivin is an inhibitor of apoptosis.	Breast, ovarian, and prostate cancer	Survivin as a direct transcriptional target of PDEF, however précises site is not known. PDEF is a negative regulator of survivin transcription and therefore, expression of PDEF and survivin is inversely associated.	[13, 21, 22]
uPA and uPAR	The urokinase plasminogen activator (uPA) system represents a family of serine proteases that are involved in the degradation of basement membrane and the extracellular matrix, leading to tumor cell invasion and metastasis. High endogenous levels of uPA and uPAR are associated with advanced metastasis.	Breast cancer cell line	PDEF regulate the expression of uPA nad uPAR. uPA is a direct transcriptional target of PDEF and downregulates uPA; however, on the contrary, PDEF upregulate the expression of uPAR. This could be due to presence of a compensatory mechanism due to which PDEF-mediated loss of uPA to maintain signaling through the receptor. Interestingly, increased expression of uPAR is known to impair the urokinase system and therefore reduce the metastatic potential of cells in a breast cancer model.	[13, 23–25]
Maspin	Maspin is a type II tumor suppressor gene that is often downregulated during breast cancer progression.	Breast, prostate cancer cell line, and lung cancer	Loss of PDEF during tumor progression leads to the decreased expression of maspin, which results to increase tumor cell invasion and metastasis. Murine PDEF has been demonstrated to regulate the maspin promoter; therefore, PDEF is a positive regulator of maspin. However, no correlation was observed in maspin and PDEF expression was observed in lung cancer.	[23, 26–28]
p21	The p21/CIP1 protein is a negative regulator of cyclin-dependent kinase activity and therefore regulates progression through the cell cycle.	In vivo breast tumor xenograft model, breast cancer cell line	PDEF overexpression leads to an increase in p21/CIP1 by decreasing Cdk2 activity and cell proliferation. P21 is a direct target of PDEF. PDEF directly binds to the 2118 bp region of the p21 promoter to regulate p21 levels. In an in vivo breast tumor xenograft model, PDEF has been demonstrated to decreased tumor growth and increased tumor-free survival via regulation of p21.	[29]
p62	p62 is a multidomain protein implicated in a number of cellular functions, including cell survival apoptosis and autophagy.	Breast cancer cell line	PDEF upregulates p62 transcription by directly binding to the p62 promoter. PDEF upregulates p62 promoter activity through at least two sites. Moreover, proteasome inhibitor 1 (PS1) downregulates the PDEF-induced p62 promoter activation through one of these sites.	[30]
Slug	Slug is a regulator of the epithelial to mesenchymal transition (EMT) which helps in tumorigenic epithelial cells acquiring mesenchymal cell properties results in increased motility and invasion.	Breast and prostate cancer cell line	PDEF re-expression in prostate tumor cells reduces slug expression and results in inhibiting both invasion and migration. These observations reinforce the fact that PDEF is negative regulator of EMT, and therefore is a potential tumor suppressor.	[13]
VASP	Play an important role in linking signaling pathways to remodeling of the actin cytoskeleton. It localizes to the cellular	Breast cancer cell line	Gene ontology analysis identified VASP as putative PDEF target gene with biological associations with multiple critical pathways	[24]

Table 1 (continued)

Gene(s)	Description	Cancer/cellular model	Main findings/observations	Reference
	membrane and produces multiple non-functional lamellipodia thereby inhibiting cell migration		involved in metastatic cascade. These observations were validated in vitro and VASP is found to be upregulated by PDEF.	
LASP1	An actin-binding protein and involved in cytoskeletal reorganization	Breast cancer cell line	PDEF has reciprocal effects on *LASP1* gene expression in noninvasive and invasive breast cancer model as determined using bioinformatics tools. However, clinical evidence does not support this as no significant correlation was observed in LASP1 and PDEF expression in human breast tumor biopsies. Future studies are needed to know the exact association between PDEF and LASP1.	[24, 31]
Stathmin	An important regulatory protein of microtubule dynamics	Prostate cancer cell line	Stathmin was identified as PDEF target using iTRAQ-MS proteomic analysis. PDEF overexpression results in the downregulation of stathmin (STMN) suggesting that they are inversely correlated. Re-expression of STMN reversed the antitumor properties of PDEF in PDEF-overexpressing PC3 and CWR22rv1 prostate cancer cells. These results suggest that PDEF inhibit prostate cancer progression by transcriptional downregulation of oncogenic STMN expression.	[19]
DNA methylation	DNA methylation is an important regulator of gene transcription. Aberrant DNA methylation patterns —hypermethylation and hypomethylation compared to normal tissue— have been associated with a large number of human malignancies.	Breast and prostate cancer cell line	Effect of DNA methylation and histone modification on the expression of PDEF was studied in breast and prostate cancer cells using specific inhibitors. The inhibition of methylation increases the expression of PDEF in breast cancer cell, not in prostate cancer cells, suggesting selective functionality of PDEF in breast cancer cells. p21, a target gene of PDEF, positively correlates with PDEF expression following DNA methylation inhibition. Inhibition of methylation decreases proliferation rate of breast cancer cells. Other epigenetic alterations such as histone modifications were not observed in these breast cancer cells following treatment with specific HDAC inhibitors.	[32]
HOXB13	HOXB13 is a transcription factor with a home domain and has recently been demonstrated to promote prostate cancer invasion by reducing the level of intracellular zinc. HOXB13 is also abundant in castration-resistant prostate tumors.	Prostate cancer cell line	HOXB13 significantly targeted and suppressed the expression of the PDEF and therefore promote cell migration and invasion. HOXB13 counteracted the expression of PDEF target genes involved in the invasion of prostate cancer cells, namely MMP-9 and Survivin.	[33, 34]

PSA prostate-specific antigen, *MMP* matrix metalloproteinase, *VASP* vasodilator stimulated phosphoprotein, *uPA* urokinase type plasminogen activator, *uPAR* urokinase type plasminogen activator receptor

carcinogenesis process. Table 1 summarizes each target gene described to date and its relation to PDEF.

PDEF besides potential tumor suppressor

Most of the studies described above emphasize PDEF as a potential tumor suppressor; however, PDEF does have other functions in normal physiology. In non-pathological tissues, PDEF has been shown to play a role in cell differentiation. PDEF has been demonstrated to present in the subsets of epithelial cells lining the trachea, bronchi, and tracheal glands in mouse. It interacts with C-terminal domain of thyroid transcription factor 1 and activates expression of genes selectively expressed in airway epithelial cells (Sftpa, Scgb1a1, Foxj1, and Sox17), which results in the goblet cell differentiation and hyperplasia [35]. Extensive study by Chen et al. (2009) has demonstrated that PDEF controls a transcriptional program critical for pulmonary goblet cell differentiation in mice [36]. Overexpression of PDEF enhances

expression of genes regulating goblet cell differentiation and protein glycosylation, including forkhead box A3 (Foxa3), anterior gradient 2 (Agr2), and glucosaminyl (N-acetyl) transferase 3, mucin type (Gcnt3). In addition, differentiation defects in pulmonary goblet cells and in intestinal Paneth and goblet cells have been reported [5, 37].

Horst et al. (2010) in a mouse model have explored the physiologic function of PDEF in the stomach, where it is expressed to a significant level [38]. PDEF is expressed predominantly in mucous gland cells of the antrum and in mucous neck cells of the glandular corpus in mice. In PDEF, knockout mice develop profound mucosal hyperplasia of the gastric antrum in addition to the sub mucosal infiltration of inflammatory cells. The absence of PDEF impaired terminal maturation of antral mucous gland cells and reduced numbers of secretory granules [38]. These observations clearly pointed out the role of PDEF in terminal maturation of antral mucous gland cells to protect animals from gastric inflammation and resulting hyperplasia. Overall, studied discussion in this section clearly pointed that PDEF plays a critical role in regulating a transcriptional network mediating various physiological functions.

Concluding remarks

PDEF regulates many genes (as discusses above), which participate in various stages of tumor development. Some of the studies have mentioned PDEF as a potential biomarker of the disease [11, 22, 39] and correlate its expression with the various stages of cancer; however, studies with firm conclusions and in large study cohort are still lacking. While the majority of publications support the role of PDEF as a tumor suppressor in the early stages of tumor progression and in tumor metastasis, some reports raise concerns pointing to the opposite conclusions (for details please refer to [9]). The exact mechanism of loss of PDEF in advanced stages of tumor progression and the regulation of PDEF still remains enigmatic; however, knowing about the various aspects of this transcription factor, one would not hesitate to state that the PDEF is a unique molecule, which has potential to be a novel therapeutic and diagnostic target in cancer biology in the near future. Finally, more research is required focusing on the ways in which this crucial tumor suppressor can be utilized in cancer prevention, diagnosis, and treatment.

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