Published in final edited form as:

Gene. 2016 July 1; 585(1): 128–134. doi:10.1016/j.gene.2016.03.017.

PELP1: Structure, biological function and clinical significance

Gangadhara Reddy Sareddy and Ratna K. Vadlamudi*

Department of Obstetrics and Gynecology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas 78229

Abstract

Proline-, glutamic acid-, and leucine-rich protein 1 (PELP1) is a scaffolding protein that functions as a coregulator of several transcription factors and nuclear receptors. Notably, the PELP1 protein has a histone-binding domain, recognizes histone modifications and interacts with several chromatin-modifying complexes. PELP1 serves as a substrate of multitude of kinases, and phosphorylation regulates its functions in various complexes. Further, PELP1 plays essential roles in several pathways including hormonal signaling, cell cycle progression, ribosomal biogenesis, and the DNA damage response. PELP1 expression is upregulated in several cancers, its deregulation contributes to therapy resistance, and it is a prognostic biomarker for breast cancer survival. Recent evidence suggests that PELP1 represents a novel therapeutic target for many hormonal cancers. In this review, we summarized the emerging biological properties and functions of PELP1.

Key Words and Molecules

Nuclear receptor; estrogen receptor; transcriptional activation; hormonal action; signal transduction; coregulator; PELP1

Introduction

Human Proline-, Glutamic acid-, and Geucine-rich Protein 1 (PELP1) map to the chromosomal region 17p13.2 and encodes a protein of 1130 aa. PELP1 gene is highly conserved across species including mouse, rats, dog, cow, and chimpanzee. PELP1 is expressed in a wide variety of tissues; the highest levels of expression are found in the brain, testes, ovaries, and uterus (Greger et al 2005; Khan et al 2005; Pawlak and Beyer 2005; Vadlamudi et al 2001b). There are two PELP1 isoforms: a long isoform of 3.8 Kb and a short isoform of 3.4 Kb. The long isoform has an extra intron (435 bp) inframe. The short isoform lacks this intron and is widely expressed in many cells, including cancer cells (Balasenthil and Vadlamudi 2003). PELP1 expression is developmentally regulated in the mammary glands (Vadlamudi et al 2001a). PELP1 is an estrogen receptor (ESR) target gene.

*Correspondence: vadlamudi@uthscsa.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

The PELP1 promoter has two estrogen-response element (ERE) half sites and is similarly upregulated by both ESR1 and ESR2 (Mishra et al 2004). PELP1 contains a central consensus nuclear localization sequence and exhibits both cytoplasmic and nuclear localization depending on the tissue (Vadlamudi et al 2001b). PELP1 is present within several sub-compartments of the nucleus, including the chromatin, nucleoplasm, and nuclear matrix (Nair et al 2004a). In this review, we summarized the emerging biological properties and functions of PELP1 and mostly focused on the functions of short isoform that is commonly expressed in normal and cancer cells.

PELP1 structure

PELP1 protein contains 10 nuclear receptor (NR)-interacting boxes (LXXLL motifs) that facilitate its interactions with nuclear receptors (Vadlamudi et al 2001a). A unique feature of PELP1 is the presence of an unusual stretch of 70 acidic amino acids in the C-terminus that functions as a histone-binding region (Choi et al 2004a; Nair et al 2004a). PELP1 contains several consensus PXXP motifs that facilitate its interactions with proteins containing Src homology 3 (SH3) domains. The PELP1 sequence further contains several conserved protein-protein interaction motifs that bind to forkhead-associated (FHA), Src homology 2 (SH2), SH3, PDZ, and WW domains. PELP1 also has two nucleolar domains (Nuc 202) that play an important role in PELP1-mediated ribosomal functions (Gonugunta et al 2011).

PELP1 post-translational modifications

PELP1 is phosphorylated by hormonal and growth factor signals and thus has potential to couple physiological signals to nuclear receptors and transcriptional factors. Epidermal growth factor (EGF) signaling promotes tyrosine as well as serine phosphorylation of PELP1 (Vadlamudi et al 2005b). Growth factors promote phosphorylation of PELP1 via protein kinase A (PKA) at Ser350, Ser415, and Ser613 (Nagpal et al 2008). Glycogen synthase kinase 3 β (GSK3 β) phosphorylate PELP1 at Thr745 and Ser1059 in the brain and it play a role in its stability (Sareddy GR et al 2015). CDKs phosphorylate PELP1 at Ser477 and Ser991 in a cell cycle-dependent manner (Nair et al 2010a). DNA damage induced kinases (ATM, ATR) phosphorylates PELP1 on Ser1033. (Nair et al 2014). Phosphorylation of PELP1 seems to be the key regulatory mechanism that controls its localization, modulates its interactions with adaptor proteins, alter its stability depending on the site of phosphorylation and may function as a sensor of the physiologic signals by connecting them to nuclear receptors.

PELP1 Interactome

PELP1 interacts and functions as a coregulator of several NRs, including ESR1 (Vadlamudi et al., 2001), ESR2 (Vadlamudi et al 2004), estrogen-related receptor α (ERR α) (Rajhans et al 2008) progesterone receptor (PR) (Daniel et al 2015), glucocorticoid receptor (GR) (Kayahara et al 2008), androgen receptor (AR) (Nair et al 2007), retinoid X receptor (RXR) (Singh et al 2006). PELP1 also functions as a coregulator of several other transcription factors, including activator protein 1 (AP1), specificity protein 1 (SP1), nuclear factor κ B (NF- κ B) (Choi et al 2004a), signal transducer and activator of transcription (STAT3)

(Manavathi et al 2005) and four and a half LIM protein 2 (FHL2) (Nair et al 2007). The LXXLL motifs present in PELP1 are implicated for its interaction with liganded steroid receptors. However, PELP1 is also able to interact with unliganded steroid receptors and other transcription factors suggesting additional protein-protein interactions other than LXXLL motifs may also play a role in PELP1 interactions.

In addition to nuclear receptors and transcription factors, PELP1 is shown to interact with several key players of cell cycle progression, including retinoblastoma protein (pRb) (Balasenthil and Vadlamudi 2003), cyclin-dependent kinase 2 (CDK2), and -4 (CDK4) (Nair et al 2010a), E2F1 (Krishnan et al 2015) and p53 (Krishnan et al 2015) (Nair et al 2014). PELP1 also interacts with several kinases including c-Src (Chakravarty et al 2010a), phosphoinositide 3-kinase (PI3K) (Dimple et al 2008), epidermal growth factor receptor (EGFR) (Vadlamudi et al 2005c), integrin-linked kinase (ILK1) (Chakravarty et al 2010a), mechanistic target of rapamycin (mTOR) (Gonugunta et al 2014b) and GSK3 β (Sareddy GR et al 2015). PELP1 interactions with cell cycle and growth factor signaling components suggest its potential role as a mediator of hormonal signaling cross talk with cell cycle machinery.

PELP1 also interacts with several components of chromatin-modifying complexes, including CBP/p300 (Vadlamudi et al 2001a), histone deacetylase 2 (Choi et al 2004a; Vadlamudi et al 2001b), histones (Choi et al 2004a; Nair et al 2004a), Sumo-2, (Rosendorff et al 2006), lysine-specific demethylase 1A (KDM1A) (Nair et al 2010c), protein arginine methyltransferases (PRMT) (Mann et al 2014a), coactivator-associated arginine methyltransferase 1 (CARM1) (Mann et al 2013). Global mass spectrometry studies identified PELP1 as a stable component of the LAS1L, TEX10, and SENP3 complex (Malovannaya et al 2011) and the Five Friends of Methylated Chtop (5FMC) complex (Fanis et al 2012). Using proteomics, PELP1 was also identified as a DACH1-binding protein (Popov et al 2009). Collectively, these emerging findings suggest that PELP1 lacks known enzymatic activity and functions as a scaffolding protein coupling various proteins to transcription factors and nuclear receptors.

Biological functions of PELP1

Genomic functions

PELP1 interacts with and functions as a coactivator of a number of transcription factors, including ESR1, ESR2, AR, E2F and STAT3 (Girard et al 2013; Vadlamudi and Kumar 2007a). RNA sequencing (RNA-seq) studies using breast cancer cells identified 318 genes as PELP1-regulated genes, and many of which are involved in breast cancer progression (Mann et al 2014b). Chromatin immune precipitation studies showed that PELP1 recruit to the promoters of ESR1, AR, E2F, and STAT target genes (Girard et al 2014; Gonugunta et al 2014a; Ravindranathan et al 2015). PELP1 interacts with GR in the nucleus and regulates GR transactivation in a manner depending on the cell type, and PELP1 is capable of regulating both AF1 and AF2 functions of the GR (Kayahara et al 2008). PELP1 facilitates E2-induced AR signaling by forming a protein complex with AR and ESR2 on the DNA, leading to the proliferation of PCa cells in the absence of androgen, allowing for cross talk between these steroid receptors (Yang et al 2012). PELP1 regulates the expression of several

genes involved in the epithelial mesenchymal transition (EMT) (Chakravarty et al 2011a; Roy et al 2012a). It modulates the expression of metastasis-influencing microRNAs (miR-200a and miR-141) and regulates their expression by recruiting chromatin modifier histone deacetylase 2 (HDAC2) (Roy et al 2014). Collectively, these findings suggest that PELP1 functions as a coregulator of many nuclear receptors, contribute to activation of their genes. Further, cellular concentration of nuclear receptors may affect how PELP1 interact with and modulate functions of nuclear receptors.

Extra-nuclear functions

PELP1 acts as a scaffolding protein coupling the ESR1 with Src kinase, leading to activation of the ESR1–Src–MAPK pathway (Vadlamudi et al 2005c). PELP1 is required for optimal activation of ESR1 extranuclear actions (Chakravarty et al 2010a). It facilitates E2 and growth factor–mediated activation of PI3K in the cytosolic compartment (Dimple et al 2008). Growth factor signals promote PELP1 interactions with STAT3 and PELP1-mediated genomic and non-genomic functions play a role in the growth factor-mediated STAT3 transactivation functions (Manavathi et al 2005). Hepatocyte growth factor-regulated tyrosine kinase substrate (HRS) is a novel PELP1-binding protein that sequesters PELP1 in the cytoplasm, leading to the activation of MAPK (Rayala et al 2006). PELP1 modulates the ESR1–Src–ILK1 signaling to promote cytoskeletal rearrangements, motility and metastasis (Chakravarty et al 2010b). PELP1 also interacts with mTOR and activates its downstream signaling (Gonugunta et al 2014b).

Cell cycle

Estrogens induce proliferation of ESR1-positive breast epithelial cells by stimulating G₁/S transition (Foster et al 2001). PELP1 is a novel substrate of CDKs, and is sequentially phosphorylated by the CDK4/cyclin D1, CDK2/cyclin E and CDK2/cyclin A complexes (Nair et al 2010b). PELP1 couples E2 signaling to the E2F axis, and CDK phosphorylation plays a key role in the PELP1 oncogenic functions (Nair et al 2010b). PELP1 regulates the biologically relevant process of meiosis and participates in maintaining meiotic arrest via interactions with G beta-gamma (Gβγ) and AR (Haas et al 2005). EGF can promote PELP1 phosphorylation at CDK sites (Olsen et al 2006). Studies using inducible transgenic mice model revealed that PELP1 regulates expression of a number of known ESR1 target genes involved in cellular proliferation including cyclin D1 and CDKs, and that PELP1 was hyper-phosphorylated at its CDK phosphorylation site, suggesting an autocrine loop involving the CDK–cyclin D1–PELP1 axis in promoting mammary tumorigenesis (Cortez et al 2014).

Chromatin modifications

PELP1 interacts with and recruits a number of epigenetic modifiers in the target chromatin and facilitates activation of number genes involved in cell proliferation and cancer progression (Nair et al 2010d). PELP1 interacts with KDM1 and alters the substrate specificity of KDM1 from H3K4 to H3K9. Effective demethylation of dimethyl H3K9 by KDM1 requires a KDM1–ESR1–PELP1 functional complex (Nair et al 2010c). Since PELP1 expression is deregulated in cancer, PELP1 ability to modulate KDM1 substrate specificity has the potential to alter histone methylation at ESR1 target genes, contributing to hormone-driven tumor progression. PELP1 functionally interacts with the arginine

methyltransferase CARM1, and the PELP1–CARM1 interactions synergistically enhance ESR1 transactivation and PELP1 status determines histone H3 arginine methylation code at ESR1 target gene promoters (Mann et al 2013). PELP1 functions as the core component of 5FMC, and provides a mechanistic link between arginine methylation and (de)sumoylation in the control of transcriptional activity (Fanis et al 2012). PELP1 interacts with LAS1L and SENP3, components of the MLL1–WDR5 supercomplex involved in chromatin remodeling. Further, PELP1 in pancreatic cancer cells is glutaminated by polyglutamylase TTLL4 and these post translational modifications play a role in coordination of chromatin remodeling by PELP1 (Kashiwaya et al 2010).

Reader of Histones

PELP1 is a unique NR coregulator that contains a histone binding domain and interacts with histones. Initial studies suggested that PELP1 participates in chromatin remodeling activity via displacement of histone H1 in cancer cells (Nair et al 2004b). Subsequent studies showed that the PELP1 histone binding domain also recognizes the hypoacetylated histones H3 and H4 and prevents them from becoming substrates of histone acetyltransferase. These studies suggested that PELP1 maintains the hypoacetylated state of histones at the target genomic site, and ER binding reverses its role to hyperacetylate histones (Choi et al 2004b). Using histone peptide arrays, it was demonstrated that PELP1 uniquely recognizes histones modified by arginine and lysine dimethylation (Mann et al 2013). MacroH2A1 is a histone variant that plays a role in transcriptional repression. Recent studies identified PELP1 as a ligand-independent macrodomain-interacting factor and the co-recruitment of macroH2A1 and PELP1 is suggested to cooperatively regulate gene expression outcomes (Hussey et al 2014).

DNA Damage Response

p53 is an important transcription factor and tumor suppressor that plays a critical role in DNA damage response (DDR), including cell cycle arrest, repair, or apoptosis. PELP1 is phosphorylated by DDR kinases, and this phosphorylation of PELP1 is important for p53 coactivation functions. PELP1-depleted p53 (wild-type) breast cancer cells were less sensitive to various genotoxic agents, including etoposide, camptothecin or gamma-radiation (Nair et al 2014). PELP1 also interacts with MTP53, regulates its recruitment, and alters MTP53 target gene expression. PELP1 knockdown decreased cell survival and increased apoptosis upon genotoxic stress. Mechanistic studies revealed that PELP1 depletion contributes to increased stability of E2F1, a transcription factor that regulates both cell cycle and apoptosis in a context-dependent manner (Krishnan et al 2015).

RNA Splicing

Recent data indicates that PELP1 oncogenic functions involve alternative splicing, leading to the activation of unique pathways that support tumor progression. RNA-seq analysis also revealed that PELP1 regulates the expression of several genes involved in alternative splicing, and the PELP1-regulated genome includes several uniquely spliced isoforms. PELP1 binds RNA with a preference to poly-C, co-localizes with the splicing factor SC35 at nuclear speckles, and participates in alternative splicing. Further, PELP1 interacts with the arginine methyltransferase PRMT6 and modifies its functions (Mann et al 2014a).

Ribosome biogenesis

PELP1 plays a critical role in ribosomal biogenesis. The SENP3-associated complex comprising PELP1, TEX10 and WDR18 is involved in maturation and nucleolar release of the large ribosomal subunit. The PELP1-associated factor LAS1L is a SENP3-sensitive target of SUMO and SUMO conjugation/deconjugation determines the nucleolar partitioning of PELP1 complex (Finkbeiner et al 2011). Additional studies confirmed that LAS1L interacts with Rix1 complex (that contain PELP1, TEX10, and WDR18) along with NOL9 and SENP3, and that PELP1 is required for optimal 60S ribosomal subunit synthesis (Castle et al 2012). PELP1 is localized in the nucleolus and is needed for the active ribosomal RNA transcription. The phosphorylation of PELP1 by CDK also plays an important role in PELP1 nucleolar localization (Gonugunta et al 2011).

Neuronal functions

PELP1 is widely expressed in many regions of brain, including the hippocampus, hypothalamus, and cerebral cortex (Brann et al 2008). Subcellular localization studies revealed that PELP1 is highly localized in the cell nucleus of neurons and has some cytoplasm localization (Khan et al 2006). PELP1 interacts with ESR1, Src, PI3K and GSK3 β in the brain. Using forebrain-specific PELP1 knockout mice, it was shown that PELP1 is essential for E2-mediated extranuclear signaling (including activation of ERK and Akt) and anti-apoptotic effects (such as the attenuation of JNK signaling and the increase in phosphorylation of GSK3 β following global cerebral ischemia (GCI) (Sareddy GR et al 2015).

Functions of PELP1 in Cancer

PELP1 is a proto-oncogene (Rajhans et al 2007) and functions as a critical coregulatory protein that provides cancer cells with a distinct growth and survival advantage (Gonugunta et al 2014a; Ravindranathan et al 2015). Overexpression of PELP1 in the mammary gland using transgenic mice model contributed to mammary gland carcinoma, further supporting its oncogenic potential *in vivo* (Cortez et al 2014). PELP1 oncogenic signaling is implicated in progression of several cancers including breast (Krishnan et al 2015; Zhang et al 2015), endometrial (Vadlamudi et al 2004) ovarian (Chakravarty 2008), salivary (Vadlamudi et al 2005a), prostate (Yang et al 2012), lung (Slowikowski et al 2015), pancreas (Kashiwaya et al 2010) and colon (Ning et al 2014).

Metastasis

PELP1 interacts with various enzymes that modulate the cytoskeleton, cell migration and metastasis. Invasive breast neoplasms and metastatic tumors have increased PELP1 expression compared to node-negative specimens (Rajhans et al 2007). PELP1-mediated ESR1 extranuclear actions via ESR1–Src–PELP1–ILK1 pathway play a critical role in ESR1-positive metastasis (Chakravarty et al 2010a). PELP1 is also shown to play a role in ESR1-negative metastasis. PELP1 knockdown reduced the *in vivo* metastatic potential of ESR1-negative breast cancer cells and significantly reduced lung metastatic nodules in a xenograft assay (Roy et al 2012b). PELP1 downregulation substantially reduced cell proliferation, migration and invasion of endometrial cancer cells (Wan and Li 2012).

Hormonal therapy resistance

Deregulation of PELP1 signaling contributes to hormonal therapy resistance (Gonugunta et al 2014a; Vadlamudi and Kumar 2007b). Tumor PELP1 mRNA expression is associated with estrogen levels in breast cancer, suggesting a potentially important role of PELP1 in ESR1-breast cancer growth *in vivo* (Flageng et al 2015). In a subset of tumors, PELP1 is localized in the cytoplasm alone, and altered localization of PELP1 contributes to tamoxifen resistance via excessive activation of AKT pathway (Vadlamudi et al 2005c). Using PELP1-cyto transgenic mouse model, it was demonstrated that altered localization of PELP1 promotes tamoxifen therapy resistance (Kumar et al 2009). A recent study showed that cytoplasmic PELP1 induces signaling pathways that converge on $ERR\gamma$ to promote cell survival in the presence of tamoxifen (Girard et al 2015). AR, PELP1, and Src form constitutive complexes in prostate neoplasm model cells that exhibit androgen independence, and activation of the Src/MAPK kinase pathway is implicated in androgen independence (Unni et al 2004). In therapy resistant cells, Src axis couples ESR1 with PELP1 and pharmacological inhibition of Src using dasatinib substantially inhibited the growth of therapy resistant MCF7-PELP1 model cells (Vallabhaneni et al 2011).

Autophagy

Autophagy plays a critical role in the management of cellular homeostasis under various stress conditions. PELP1 and its interacting protein HRS is shown to be co-recruited to the autophagosomes in the presence of resveratrol. Since PELP1 expression is dysregulated in human cancers, these findings highlight the significance of the autophagic selective degradation of PELP1 following resveratrol (or other phytoestrogens) treatment in developing future strategies to use resveratrol under cancer prevention and therapeutic settings (Ohshiro et al 2007; Ohshiro et al 2008; Raz et al 2008).

Prognostic significance of PELP1

Performing PELP1 immunohistochemistry on invasive breast cancers biopsies from 1,162 patients it was demonstrated that PELP1 expression is an independent prognostic predictor of shorter breast cancer-specific survival and disease-free interval, and its expression is useful in assessing the clinical outcome of patients with ESR1-positive breast cancer (Habashy et al 2010). PELP1 expression is also shown to have diagnostic utility for metastatic triple negative breast cancer (Dang et al 2015), and PELP1/Ki-67 double high expression in tumors is an independent prognostic factor for predicting a poor outcome for patients with triple negative breast cancer (TNBC) (Zhang et al 2015). Patients whose tumors had high levels of cytoplasmic PELP1 responded poorly to tamoxifen than patients whose tumors had low levels of cytoplasmic PELP1 (Kumar et al 2009). PELP1 phosphorylation at the ATM target site was significantly greater in the TNBC tumors than in the other subtypes of breast cancer and in the normal tissues (Krishnan et al 2015). The PELP1 transcript and protein increase in non-small cell lung cancer and correlates with stage (Slowikowski et al 2015). Studies using ovarian tumor tissue arrays revealed that PELP1 is over expressed twofold to threefold in 60% of ovarian neoplasia (Dimple et al 2008). PELP1 localization and/or $ERR\gamma$ activation is suggested as a potential biomarkers for tamoxifen responsiveness (Girard et al 2015). PELP1 may play a role in the pathogenesis and

progression of astrocytic tumors and its status has utility as a prognostic biomarker (Kefalopoulou et al 2012). DACH1 expression is lost in human breast cancer, which functions as an endogenous inhibitor of ESR1 function. Loss of DACH1 allows PELP1 to serve as an ESR1 coactivator, and the DACH1–PELP1 axis has potential to serve as a biomarker of poor prognosis (Popov et al 2009). ESR2 and PELP1 axis is shown to be involved in colorectal tumorigenesis and might have prognostic significance (Grivas et al 2009). PELP1 is identified as one of the potential biomarkers that may play important roles in pediatric asthma initiation (Xu 2014).

Therapeutic Targeting of PELP1

Treatment of breast and ovarian cancer xenografts with liposomal PELP1–siRNA–DOPC formulations revealed that knockdown of PELP1 significantly reduced the tumor growth in both models (Chakravarty et al 2011b; Cortez et al 2012). These results provided initial proof that PELP1 is a potential therapeutic target. Since no direct inhibitor of PELP1 is currently available, an alternative strategy would be to target PELP1 downstream targets. The CDK2 inhibitor roscovitine preferentially down regulates the expression of ESR1 and PELP1. Results from these studies supported that inhibition of CDK2 activity has the potential to abrogate the growth of PELP1-driven, hormonal therapy–resistant cells (Nair et al 2011). The mTOR-targeting drugs rapamycin and AZD8055 significantly reduced proliferation of PELP1-overexpressed breast cancer cells in both *in vitro* and *in vivo* xenograft tumor models, suggesting that mTOR inhibitor(s) may be effective chemotherapeutic agents for downregulating PELP1 oncogenic functions (Gonugunta et al 2014b). A recent study showed that liganded PR-B enhances the proliferative responses to estradiol and IGF1 via scaffolding of ESR1–PELP1–IGF1R-containing complexes. Therefore, PR antagonists may have therapeutic utility in treating a subset of PELP1-deregulated luminal ESR1, PR positive breast cancer (Daniel et al 2015). Targeting PELP1-mediated epigenetic alterations through inhibition of KDM1 (Bennani-Baiti 2012; Cortez et al 2012) and the arginine methyltransferases (Mann et al 2013) could be a promising cancer therapeutic for blocking PELP1. PELP1 interacts with several NRs via LXXLL motifs, and disruption of these interactions may have therapeutic value. A recent study showed feasibility of this approach using a small molecule peptidomimetic (D2) that abrogated androgen-induced proliferation of prostate cancer cells by interfering with the PELP1 interactions with AR (Ravindranathan et al 2013). These findings provide evidence that targeting NR–PELP1 interactions using peptidomimetics is a viable approach; however, further tuning of these molecules is needed to tailor therapies to specific NR–PELP1 interactions (Ravindranathan et al 2013). Recent studies suggested that targeting PELP1 could enhance the chemotherapeutic response of TNBC through the inhibition of cell cycle progression and activation of apoptosis. Accordingly, depletion of PELP1 via siRNA increased the expression of E2F1 target genes and reduced TNBC cell survival in response to genotoxic agents. These findings suggest that PELP1 is an important molecular target in TNBC, and that PELP1-targeted therapies may enhance response to chemotherapies (Krishnan et al 2015).

Concluding Remarks

The proto-oncogene PELP1 is a critical coregulator that interacts with multiple nuclear receptors and other transcription factors, provides cancer cells with a distinct growth and survival advantage. PELP1 plays roles in many processes that influence cancer progression including cell cycle, ribosome biogenesis, chromatin modifications, DNA damage response, histone methylation, and RNA splicing. PELP1 overexpression has been reported in many cancers, and is prognostically linked to shorter breast cancer-specific survival, therapy resistance, and metastasis. Collectively, these data support a central role for PELP1 and its direct protein-protein interactions in cancer progression. Since PELP1 lacks known enzymatic activity, there is a critical need for the development of therapeutic agents that interfere with PELP1 interactions with various signaling complexes to block the progression of PELP1-driven cancers. Recently, feasibility of such approach was demonstrated by developing an inhibitor that block PELP1 interactions with AR. Further, development of small molecular inhibitors that block PELP1 interactions with several of its effector molecules and nuclear receptors will likely have an important role in cancer treatment either as a monotherapy and or in combination with current therapies. The evolving evidence connecting PELP1 to histone modifications and epigenetic enzymes also suggests that drugs targeting epigenetic modifier enzymes may represent novel target for treating PELP1 deregulated tumors.

Acknowledgments

This review and the corresponding Gene Wiki article are written as part of the Gene WikiReview series-a series resulting from a collaboration between the journal GENE and the Gene Wiki Initiative. The Gene Wiki Initiative is supported by National Institutes of Health (GM089820). Additional support for Gene Wiki Reviews is provided by Elsevier, the Publisher of GENE. Vadlamudi research program was supported by the NIH/NCI grant NIH-CA178499 and CPRIT grant DP150096 The corresponding Gene Wiki entry for this review can be found here: <https://en.wikipedia.org/wiki/PELP-1>

Abbreviations

AP1	Activator protein 1
AR	Androgen receptor
CBP	CRE-binding protein-binding protein
CDK	cyclin-dependent kinase
DDR	DNA damage response
E2F	E2F Transcription Factor 1
EGF	epidermal growth factor
EGFR	EGF receptor
ESR1	estrogen receptor alpha
ESR2	Estrogen receptor beta
ERRα	estrogen-related receptor α

FHA	forkhead-associated
FHL2	four and a half LIM protein 2
GR	glucocorticoid receptor
GSK3β	Glycogen Synthase Kinase 3 Beta
HDAC2	histone deacetylase 2
HRS	hepatocyte growth factor-regulated tyrosine kinase substrate
ILK	integrin-linked kinase
KDM1A	lysine-specific demethylase 1A
MLL	myeloid/lymphoid or mixed-lineage leukemia
MAPK	mitogen-activated protein kinase
MiR	microRNA
NF-κB	nuclear factor κ B
NR	nuclear receptor
PELP1	proline-, glutamic acid-, and leucine-rich protein
PI3K	phosphatidylinositol-3 kinase
PKA	protein kinase A
PPAR	peroxisome proliferator-activated receptor
PR	progesterone receptor
pRb	retinoblastoma protein
RA	retinoic acid
RXR	retinoid X receptor
SEN3	SUMO1/sentrin/SMT3 specific peptidase 3
SH	Src homology
SP1	specificity protein 1 (SP1)
STAT	signal transducer and activator of transcription
TNBC	Triple negative breast cancer
TTLL4	Tubulin Tyrosine Ligase-Like Family Member 4

References

- Balasenthil S, Vadlamudi RK. Functional interactions between the estrogen receptor coactivator PELP1/MNAR and retinoblastoma protein. *J Biol Chem.* 2003; 278:22119–22127. [PubMed: 12682072]
- Bennani-Baiti IM. Integration of ERalpha-PELP1-HER2 signaling by LSD1 (KDM1A/AOF2) offers combinatorial therapeutic opportunities to circumventing hormone resistance in breast cancer. *Breast Cancer Res.* 2012; 14:112. [PubMed: 22992372]

- Brann DW, Zhang QG, Wang RM, Mahesh VB, Vadlamudi RK. PELP1-a novel estrogen receptor-interacting protein. *Mol Cell Endocrinol.* 2008; 290:2–7. [PubMed: 18571832]
- Castle CD, Cassimere EK, Denicourt C. LAS1L interacts with the mammalian Rix1 complex to regulate ribosome biogenesis. *Mol Biol Cell.* 2012; 23:716–728. [PubMed: 22190735]
- Chakravarty D, Nair SS, Santhamma B, Nair BC, Wang L, Bandyopadhyay A, Agyin JK, Brann D, Sun LZ, Yeh IT, Lee FY, Tekmal RR, Kumar R, Vadlamudi RK. Extranuclear functions of ER impact invasive migration and metastasis by breast cancer cells. *Cancer Res.* 2010a; 70:4092–4101. [PubMed: 20460518]
- Chakravarty D, Roy SS, Babu CR, Dandamudi R, Curiel TJ, Vivas-Mejia P, Lopez-Berestein G, Sood AK, Vadlamudi RK. Therapeutic Targeting of PELP1 Prevents Ovarian Cancer Growth and Metastasis. *Clin Cancer Res.* 2011a; 17:2250–2259. [PubMed: 21421858]
- Choi YB, Ko JK, Shin J. The transcriptional corepressor, PELP1, recruits HDAC2 and masks histones using two separate domains. *J Biol Chem.* 2004a; 279:50930–50941. [PubMed: 15456770]
- Cortez V, Mann M, Tekmal S, Suzuki T, Miyata N, Rodriguez-Aguayo C, Lopez-Berestein G, Sood AK, Vadlamudi RK. Targeting the PELP1-KDM1 axis as a potential therapeutic strategy for breast cancer. *Breast Cancer Res.* 2012; 14:R108. [PubMed: 22812534]
- Cortez V, Samayoa C, Zamora A, Martinez L, Tekmal RR, Vadlamudi RK. PELP1 overexpression in the mouse mammary gland results in the development of hyperplasia and carcinoma. *Cancer Res.* 2014; 74:7395–7405. [PubMed: 25377474]
- Dang DN, Raj G, Sarode V, Molberg KH, Vadlamudi RK, Peng Y. Significantly increased PELP1 protein expression in primary and metastatic triple-negative breast carcinoma: comparison with GATA3 expression and PELP1's potential role in triple-negative breast carcinoma. *Hum Pathol.* 2015 in press.
- Daniel AR, Gaviglio AL, Knutson TP, Ostrander JH, D'Assoro AB, Ravindranathan P, Peng Y, Raj GV, Yee D, Lange CA. Progesterone receptor-B enhances estrogen responsiveness of breast cancer cells via scaffolding P. *Oncogene.* 2015; 34:506–515. [PubMed: 24469035]
- Dimple C, Nair SS, Rajhans R, Pitcheswara PR, Liu J, Balasenthil S, Le XF, Burow ME, Auersperg N, Tekmal RR, Broaddus RR, Vadlamudi RK. Role of PELP1/MNAR signaling in ovarian tumorigenesis. *Cancer Res.* 2008; 68:4902–4909. [PubMed: 18559538]
- Fanis P, Gillemans N, Aghajani-refah A, Pourfarzad F, Demmers J, Esteghamat F, Vadlamudi RK, Grosveld F, Philipsen S, van Dijk TB. Five friends of methylated chromatin target of protein-arginine-methyltransferase[prmt]-1 (chtpp), a complex linking arginine methylation to desumoylation. *Mol Cell Proteomics.* 2012; 11:1263–1273. [PubMed: 22872859]
- Finkbeiner E, Haindl M, Muller S. The SUMO system controls nucleolar partitioning of a novel mammalian ribosome biogenesis complex. *EMBO J.* 2011; 30:1067–1078. [PubMed: 21326211]
- Flageng MH, Knappskog S, Gjerde J, Lonning PE, Mellgren G. Estrogens Correlate with PELP1 Expression in ER Positive Breast Cancer. *PLoS One.* 2015; 10:e0134351. [PubMed: 26247365]
- Foster JS, Henley DC, Bukovsky A, Seth P, Wimalasena J. Multifaceted regulation of cell cycle progression by estrogen: regulation of Cdk inhibitors and Cdc25A independent of cyclin D1-Cdk4 function. *Mol Cell Biol.* 2001; 21:794–810. [PubMed: 11154267]
- Girard BJ, Daniel AR, Lange CA, Ostrander JH. PELP1: a review of PELP1 interactions, signaling, and biology. *Mol Cell Endocrinol.* 2014; 382:642–651. [PubMed: 23933151]
- Girard BJ, Regan Anderson TM, Welch SL, Nicely J, Seewaldt VL, Ostrander JH. Cytoplasmic PELP1 and ERRgamma protect human mammary epithelial cells from Tam-induced cell death. *PLoS One.* 2015; 10:e0121206. [PubMed: 25789479]
- Gonugunta VK, Miao L, Sareddy GR, Ravindranathan P, Vadlamudi R, Raj GV. The social network of PELP1 and its implications in breast and prostate cancers. *Endocr Relat Cancer.* 2014a; 21:T79–T86. [PubMed: 24859989]
- Gonugunta VK, Nair BC, Rajhans R, Sareddy GR, Nair SS, Vadlamudi RK. Regulation of rDNA transcription by proto-oncogene PELP1. *PLoS One.* 2011; 6:e21095. [PubMed: 21695158]
- Gonugunta VK, Sareddy GR, Krishnan SR, Cortez V, Roy SS, Tekmal RR, Vadlamudi RK. Inhibition of mTOR signaling reduces PELP1-mediated tumor growth and therapy resistance. *Mol Cancer Ther.* 2014b; 13:1578–1588. [PubMed: 24688046]

- Greger JG, Guo Y, Henderson R, Ross JF, Cheskis BJ. Characterization of MNAR expression. *Steroids*. 2005; 71:317–22. [PubMed: 16297421]
- Grivas PD, Tzelepi V, Sotiropoulou-Bonikou G, Kefalopoulou Z, Papavassiliou AG, Kalofonos H. Expression of ERalpha, ERbeta and co-regulator PELP1/MNAR in colorectal cancer: prognostic significance and clinicopathologic correlations. *Cell Oncol*. 2009; 31:235–247. [PubMed: 19478391]
- Haas D, White SN, Lutz LB, Rasar M, Hammes SR. The modulator of nongenomic actions of the estrogen receptor (MNAR) regulates transcription-independent androgen receptor-mediated signaling: evidence that MNAR participates in G protein-regulated meiosis in *Xenopus laevis* oocytes. *Mol Endocrinol*. 2005; 19:2035–2046. [PubMed: 15831520]
- Habashy HO, Powe DG, Rakha EA, Ball G, Macmillan RD, Green AR, Ellis IO. The prognostic significance of PELP1 expression in invasive breast cancer with emphasis on the ER-positive luminal-like subtype. *Breast Cancer Res Treat*. 2010; 120:603–612. [PubMed: 19495959]
- Hussey KM, Chen H, Yang C, Park E, Hah N, Erdjument-Bromage H, Tempst P, Gamble MJ, Kraus WL. The histone variant MacroH2A1 regulates target gene expression in part by recruiting the transcriptional coregulator PELP1. *Mol Cell Biol*. 2014; 34:2437–2449. [PubMed: 24752897]
- Kashiwaya K, Nakagawa H, Hosokawa M, Mochizuki Y, Ueda K, Piao L, Chung S, Hamamoto R, Eguchi H, Ohigashi H, Ishikawa O, Janke C, Shinomura Y, Nakamura Y. Involvement of the tubulin tyrosine ligase-like family member 4 polyglutamylase in PELP1 polyglutamylation and chromatin remodeling in pancreatic cancer cells. *Cancer Res*. 2010; 70:4024–4033. [PubMed: 20442285]
- Kayahara M, Ohanian J, Ohanian V, Berry A, Vadlamudi R, Ray DW. MNAR functionally interacts with both NH2- and COOH-terminal GR domains to modulate transactivation. *Am J Physiol Endocrinol Metab*. 2008; 295:E1047–E1055. [PubMed: 18682536]
- Kefalopoulou Z, Tzelepi V, Zolota V, Grivas PD, Christopoulos C, Kalofonos H, Maraziotis T, Sotiropoulou-Bonikou G. Prognostic value of novel biomarkers in astrocytic brain tumors: nuclear receptor co-regulators AIB1, TIF2, and PELP1 are associated with high tumor grade and worse patient prognosis. *J Neurooncol*. 2012; 106:23–31. [PubMed: 21735116]
- Khan MM, Hadman M, De Sevilla LM, Mahesh VB, Buccafusco J, Hill WD, Brann DW. Cloning, distribution, and colocalization of MNAR/PELP1 with glucocorticoid receptors in primate and nonprimate brain. *Neuroendocrinology*. 2006; 84:317–329. [PubMed: 17142998]
- Khan MM, Hadman M, Wakade C, De Sevilla LM, Dhandapani KM, Mahesh VB, Vadlamudi RK, Brann DW. Cloning, expression, and localization of MNAR/PELP1 in rodent brain: colocalization in estrogen receptor-alpha- but not in gonadotropin-releasing hormone-positive neurons. *Endocrinology*. 2005; 146:5215–5227. [PubMed: 16141397]
- Krishnan SR, Nair BC, Sareddy GR, Roy SS, Natarajan M, Suzuki T, Peng Y, Raj G, Vadlamudi RK. Novel role of PELP1 in regulating chemotherapy response in mutant p53-expressing triple negative breast cancer cells. *Breast Cancer Res Treat*. 2015; 150:487–499. [PubMed: 25788226]
- Kumar R, Zhang H, Holm C, Vadlamudi RK, Landberg G, Rayala SK. Extranuclear coactivator signaling confers insensitivity to tamoxifen. *Clin Cancer Res*. 2009; 15:4123–4130. [PubMed: 19470742]
- Malovannaya A, Lanz RB, Jung SY, Bulynko Y, Le NT, Chan DW, Ding C, Shi Y, Yucer N, Krenciute G, Kim BJ, Li C, Chen R, Li W, Wang Y, O'Malley BW, Qin J. Analysis of the human endogenous coregulator complexome. *Cell*. 2011; 145:787–799. [PubMed: 21620140]
- Manavathi B, Nair SS, Wang RA, Kumar R, Vadlamudi RK. Proline-, glutamic acid-, and leucine-rich protein-1 is essential in growth factor regulation of signal transducers and activators of transcription 3 activation. *Cancer Res*. 2005; 65:5571–5577. [PubMed: 15994929]
- Mann M, Cortez V, Vadlamudi R. PELP1 oncogenic functions involve CARM1 regulation. *Carcinogenesis*. 2013; 34:1468–1475. [PubMed: 23486015]
- Mann M, Zou Y, Chen Y, Brann D, Vadlamudi R. PELP1 oncogenic functions involve alternative splicing via PRMT6. *Mol Oncol*. 2014a; 8:389–400. [PubMed: 24447537]
- Mishra SK, Balasenthil S, Nguyen D, Vadlamudi RK. Cloning and functional characterization of PELP1/MNAR promoter. *Gene*. 2004; 330:115–122. [PubMed: 15087130]

- Nagpal JK, Nair S, Chakravarty D, Rajhans R, Pothana S, Brann DW, Tekmal RR, Vadlamudi RK. Growth factor regulation of estrogen receptor coregulator PELP1 functions via Protein Kinase A pathway. *Mol Cancer Res.* 2008; 6:851–861. [PubMed: 18505929]
- Nair BC, Krishnan SR, Sareddy GR, Mann M, Xu B, Natarajan M, Hasty P, Brann D, Tekmal RR, Vadlamudi RK. Proline, glutamic acid and leucine-rich protein-1 is essential for optimal p53-mediated DNA damage response. *Cell Death Differ.* 2014; 21:1409–1418. [PubMed: 24786831]
- Nair BC, Nair SS, Chakravarty D, Challa R, Manavathi B, Yew PR, Kumar R, Tekmal RR, Vadlamudi RK. Cyclin-dependent kinase-mediated phosphorylation plays a critical role in the oncogenic functions of PELP1. *Cancer Res.* 2010a; 70:7166–7175. [PubMed: 20807815]
- Nair BC, Vallabhaneni S, Tekmal RR, Vadlamudi RK. Roscovitine confers tumor suppressive effect on therapy-resistant breast tumor cells. *Breast Cancer Res.* 2011; 13:R80. [PubMed: 21834972]
- Nair SS, Guo Z, Mueller JM, Koochekpour S, Qiu Y, Tekmal RR, Schule R, Kung HJ, Kumar R, Vadlamudi RK. Proline-, glutamic acid-, and leucine-rich protein-1/modulator of nongenomic activity of estrogen receptor enhances androgen receptor functions through LIM-only coactivator, four-and-a-half LIM-only protein 2. *Mol Endocrinol.* 2007; 21:613–624. [PubMed: 17192406]
- Nair SS, Mishra SK, Yang Z, Balasenthil S, Kumar R, Vadlamudi RK. Potential role of a novel transcriptional coactivator PELP1 in histone H1 displacement in cancer cells. *Cancer Res.* 2004a; 64:6416–6423. [PubMed: 15374949]
- Nair SS, Nair BC, Cortez V, Chakravarty D, Metzger E, Schule R, Brann DW, Tekmal RR, Vadlamudi RK. PELP1 is a reader of histone H3 methylation that facilitates oestrogen receptor- α target gene activation by regulating lysine demethylase 1 specificity. *EMBO Rep.* 2010c; 11:438–444. [PubMed: 20448663]
- Ning Z, Zhang Y, Chen H, Wu J, Song T, Wu Q, Liu F. PELP1 suppression inhibits colorectal cancer through c-Src downregulation. *Oxid Med Cell Longev.* 2014; 2014:193523. [PubMed: 24967003]
- Ohshiro K, Rayala SK, El-Naggar AK, Kumar R. Delivery of cytoplasmic proteins to autophagosomes. *Autophagy.* 2008; 4:104–106. [PubMed: 18000392]
- Ohshiro K, Rayala SK, Kondo S, Gaur A, Vadlamudi RK, El-Naggar AK, Kumar R. Identifying the estrogen receptor coactivator PELP1 in autophagosomes. *Cancer Res.* 2007; 67:8164–8171. [PubMed: 17804729]
- Olsen JV, Blagoev B, Gnäd F, Macek B, Kumar C, Mortensen P, Mann M. Global, in vivo, and site-specific phosphorylation dynamics in signaling networks. *Cell.* 2006; 127:635–648. [PubMed: 17081983]
- Pawlak J, Beyer C. Developmental expression of MNAR mRNA in the mouse brain. *Cell Tissue Res.* 2005; 320:545–549. [PubMed: 15846512]
- Popov VM, Zhou J, Shirley LA, Quong J, Yeow WS, Wright JA, Wu K, Rui H, Vadlamudi RK, Jiang J, Kumar R, Wang C, Pestell RG. The cell fate determination factor DACH1 is expressed in estrogen receptor- α -positive breast cancer and represses estrogen receptor- α signaling. *Cancer Res.* 2009; 69:5752–5760. [PubMed: 19605405]
- Rajhans R, Nair HB, Nair SS, Cortez V, Ikuko K, Kirma NB, Zhou D, Holden AE, Brann DW, Chen S, Tekmal RR, Vadlamudi RK. Modulation of in situ estrogen synthesis by proline-, glutamic acid-, and leucine-rich protein-1: potential estrogen receptor autocrine signaling loop in breast cancer cells. *Mol Endocrinol.* 2008; 22:649–664. [PubMed: 18079323]
- Rajhans R, Nair S, Holden AH, Kumar R, Tekmal RR, Vadlamudi RK. Oncogenic potential of the nuclear receptor coregulator proline-, glutamic acid-, leucine-rich protein 1/modulator of the nongenomic actions of the estrogen receptor. *Cancer Res.* 2007; 67:5505–5512. [PubMed: 17545633]
- Ravindranathan P, Lange CA, Raj GV. Minireview: Deciphering the Cellular Functions of PELP1. *Mol Endocrinol.* 2015; 29:1222–1229. [PubMed: 26158753]
- Ravindranathan P, Lee TK, Yang L, Centenera MM, Butler L, Tilley WD, Hsieh JT, Ahn JM, Raj GV. Peptidomimetic targeting of critical androgen receptor-coregulator interactions in prostate cancer. *Nat Commun.* 2013; 4:1923. [PubMed: 23715282]
- Rayala SK, Hollander P, Balasenthil S, Molli PR, Bean AJ, Vadlamudi RK, Wang RA, Kumar R. Hepatocyte growth factor-regulated tyrosine kinase substrate (HRS) interacts with PELP1 and activates MAPK. *J Biol Chem.* 2006; 281:4395–4403. [PubMed: 16352611]

- Raz L, Khan MM, Mahesh VB, Vadlamudi RK, Brann DW. Rapid estrogen signaling in the brain. *Neurosignals*. 2008; 16:140–153. [PubMed: 18253054]
- Rosendorff A, Sakakibara S, Lu S, Kieff E, Xuan Y, DiBacco A, Shi Y, Shi Y, Gill G. NXP-2 association with SUMO-2 depends on lysines required for transcriptional repression. *Proc Natl Acad Sci U S A*. 2006; 103:5308–5313. [PubMed: 16567619]
- Roy S, Chakravarty D, Cortez V, De MK, Bandyopadhyay A, Ahn JM, Raj GV, Tekmal RR, Sun L, Vadlamudi RK. Significance of PELP1 in ER-negative breast cancer metastasis. *Mol Cancer Res*. 2012a; 10:25–33. [PubMed: 22086908]
- Roy SS, Gonugunta VK, Bandyopadhyay A, Rao MK, Goodall GJ, Sun LZ, Tekmal RR, Vadlamudi RK. Significance of PELP1/HDAC2/miR-200 regulatory network in EMT and metastasis of breast cancer. *Oncogene*. 2014; 33:3707–3716. [PubMed: 23975430]
- Sareddy GR, Zhang Q, Wang R, Scott E, OConner J, Chen Y, Vadlamudi R, Brann D. The Estrogen Receptor Co-Regulator Proline Glutamic Acid and Leucine Rich Protein 1 (PELP1) Mediates Estrogen Rapid Signaling and Neuroprotection in the Brain. *Proc Natl Acad Sci U S A*. 2014; 112:E6673–82. [PubMed: 26627258]
- Singh RR, Gururaj AE, Vadlamudi RK, Kumar R. 9-cis-retinoic acid up-regulates expression of transcriptional coregulator PELP1, a novel coactivator of the retinoid X receptor alpha pathway. *J Biol Chem*. 2006; 281:15394–15404. [PubMed: 16574651]
- Slowikowski BK, Galecki B, Dyszkiewicz W, Jagodzinski PP. Increased expression of proline-, glutamic acid- and leucine-rich protein PELP1 in non-small cell lung cancer. *Biomed Pharmacother*. 2015; 73:97–101. [PubMed: 26211588]
- Unni E, Sun S, Nan B, McPhaul MJ, Cheskis B, Mancini MA, Marcelli M. Changes in androgen receptor nongenotropic signaling correlate with transition of LNCaP cells to androgen independence. *Cancer Res*. 2004; 64:7156–7168. [PubMed: 15466214]
- Vadlamudi RK, Balasenthil S, Broaddus RR, Gustafsson JA, Kumar R. Dereglulation of estrogen receptor coactivator proline-, glutamic acid-, and leucine-rich protein-1/modulator of nongenomic activity of estrogen receptor in human endometrial tumors. *J Clin Endocrinol Metab*. 2004; 89:6130–6138. [PubMed: 15579769]
- Vadlamudi RK, Balasenthil S, Sahin AA, Kies M, Weber RS, Kumar R, El-Naggar AK. Novel estrogen receptor coactivator PELP1/MNAR gene and ERbeta expression in salivary duct adenocarcinoma: potential therapeutic targets. *Hum Pathol*. 2005a; 36:670–675. [PubMed: 16021574]
- Vadlamudi RK, Kumar R. Functional and biological properties of the nuclear receptor coregulator PELP1/MNAR. *Nucl Recept Signal*. 2007a; 5:e004. [PubMed: 17525794]
- Vadlamudi RK, Manavathi B, Balasenthil S, Nair SS, Yang Z, Sahin AA, Kumar R. Functional implications of altered subcellular localization of PELP1 in breast cancer cells. *Cancer Res*. 2005b; 65:7724–7732. [PubMed: 16140940]
- Vadlamudi RK, Wang RA, Mazumdar A, Kim Y, Shin J, Sahin A, Kumar R. Molecular cloning and characterization of PELP1, a novel human coregulator of estrogen receptor alpha. *J Biol Chem*. 2001a; 276:38272–38279. [PubMed: 11481323]
- Vallabhaneni S, Nair BC, Cortez V, Challa R, Chakravarty D, Tekmal RR, Vadlamudi RK. Significance of ER-*Src* axis in hormonal therapy resistance. *Breast Cancer Res Treat*. 2011; 130:377–385. [PubMed: 21184269]
- Wan J, Li X. PELP1/MNAR suppression inhibits proliferation and metastasis of endometrial carcinoma cells. *Oncol Rep*. 2012; 28:2035–2042. [PubMed: 22992812]
- Xu W. Expression data analysis to identify biomarkers associated with asthma in children. *Int J Genomics*. 2014; 2014:165175. [PubMed: 24790987]
- Yang L, Ravindranathan P, Ramanan M, Kapur P, Hammes SR, Hsieh JT, Raj GV. Central role for PELP1 in nonandrogenic activation of the androgen receptor in prostate cancer. *Mol Endocrinol*. 2012; 26:550–561. [PubMed: 22403175]
- Zhang Y, Dai J, McNamara KM, Bai B, Shi M, Chan MS, Liu M, Sasano H, Wang X, Li X, Liu L, Ma Y, Cao S, Xing Y, Zhao B, Song Y, Wang L. Prognostic significance of proline, glutamic acid, leucine rich protein 1 (PELP1) in triple-negative breast cancer: a retrospective study on 129 cases. *BMC Cancer*. 2015; 15:699. [PubMed: 26472563]

Figure 1.

Schematic representation of PELP1 domains that are important for its scaffolding functions. PELP1 contain 10 LXXLL motifs that facilitate its interactions with nuclear receptors (NRs). PELP1 contain multiple SH2, SH3, binding sites that facilitate its interactions with Src and p85 subunit of PI3K. PELP1 is phosphorylated by multiple kinases including CDKs, PKA, GSK3β, Src, EGFR, ATM and their phosphorylation regulate PELP1 oncogenic functions. Glu rich domain contain 70 acidic amino acids that facilitate PELP1 binding to histone. Proline rich domain confer additional specificity to Glu rich region. Bidirectional arrow indicate putative binding region of respective proteins.

Fig 2. Overview of PELP1 signaling

PELP1 interacts with and function as a coregulator of several nuclear receptors (NRs) including ESR1, PR, GR, AR and RXR. PELP1 facilitates chromatin modifications via interactions with several enzymes including KDM1A, PRMT, CARM1, and HDAC2. PELP1 interacts with and modulate functions of several key players in cell cycle progression including CDKs, pRb, E2F, and p53. PELP1 participate in NR extra-nuclear signaling by coupling NRs with cytosolic kinases such as Src, PI3K that contribute to activation of pathways such as MAPK and AKT. PELP1 play an active role in the ribosomal biogenesis via its interaction with TEX10-WDR18-SEN3 complex. Deregulation of PELP1 signaling contribute to alterations in tumor cell proliferation, apoptosis, metastasis and therapy resistance.