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PELP1: Structure, biological function and clinical significance

Gangadhara Reddy Sareddy, Ratna K. Vadlamudi *

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

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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.

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Abbreviations: AP1, activator protein 1; AR, androgen receptor; CBP, CREB- 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 domains 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 κB; NR, nuclear receptor; PELP1, proline-, glutamic acid-, and leucine-rich protein1; 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; SENP3, 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.

* Corresponding author.
E-mail address: vadlamudi@uthscsa.edu (R.K. Vadlamudi).

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1. Introduction

Human proline-, glutamic acid-, and Leucine-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, rat, 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. 2001). 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., 2001). PELP1 is an estrogen receptor (ESR) target gene. 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. 2001). PELP1 is present within several sub-compartments of the nucleus, including the chromatin, nucleoplasm, and nuclear matrix (Nair et al. 2004). 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.

2. PELP1 structure

PELP1 protein contains 10 nuclear receptor (NR)-interacting boxes (LXXLL motifs) that facilitate its interactions with nuclear receptors (Vadlamudi et al., 2001). 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., 2004; Nair et al. 2004). 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).

3. 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 (GSK3β) phosphorylate PELP1 at Thr745 and Ser1059 in the brain and it play a role in its stability (Sareddy 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.

4. 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 (ERRα) (Rajhans et al., 2008) progesterone receptor (PR) (Daniel et al., 2015), glucocorticoid

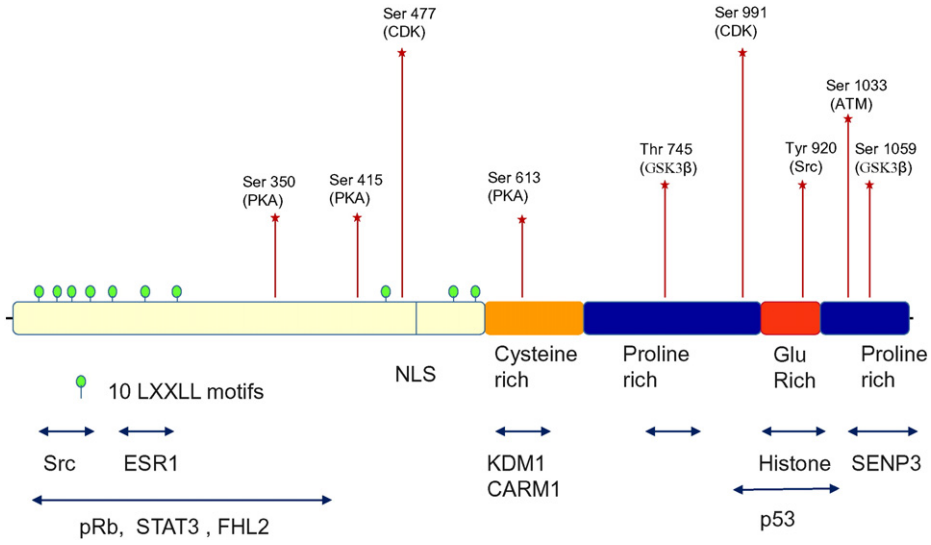

Fig. 1. Schematic representation of PELP1 domains that are important for its scaffolding functions. PELP1 contain 10 LXXLL motifs that facilitate its interactions with nuclear receptors (NRs). PELP1 contain multiple SH2, SH3, binding sites that facilitate its interactions with Src and p85 subunit of 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.

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