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Review

PELP1: A review of PELP1 interactions, signaling, and biology ☆

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ABSTRACT

Proline, glutamic acid, and leucine rich protein 1 (PELP1) is a large multi-domain protein that has been shown to modulate an increasing number of pathways and biological processes. The first reports describing the cloning and characterization of PELP1 showed that it was an estrogen receptor coactivator. PELP1 has now been shown to be a coregulator for a growing number of transcription factors. Furthermore, recent reports have shown that PELP1 is a member of chromatin remodeling complexes. In addition to PELP1 nuclear functions, it has been shown to have cytoplasmic signaling functions as well. In the cytoplasm PELP1 acts as a scaffold molecule and mediates rapid signaling from growth factor and hormone receptors. PELP1 signaling ultimately plays a role in cancer biology by increasing proliferation and metastasis, among other cellular processes. Here we will review (1) the cloning and characterization of PELP1 expression, (2) interacting proteins, (3) PELP1 signaling, and (4) PELP1-mediated biology.

Contents

Abbreviations: AIB1, amplified in breast cancer 1; AR, androgen receptor; BCAS3, breast carcinoma amplified sequence 3; CBP, CREB binding protein; ChIP, chromatin immunoprecipitation; E2, estradiol; ER, estrogen receptor; ERRα, estrogen-related receptor alpha; FHL2, four and a half LIM domains 2; GR, glucocorticoid receptor; HDAC, histone deacetylase; IHC, immunohistochemistry; ILK1, integrin-linked kinase 1; KDM1, lysine-specific histone demethylase 1; LIM domain, Lin-1, Isl-1, and Mec-3 domain; MNAR, Modulator of Nongenomic Activity of ER; PELP1, proline, glutamic acid and leucine rich protein 1; RXR, retinoid X receptor; SH2, c-Src homology domain 2; SH3, c-Src homology domain 3; STAT3, signal transducer and activator or transcription 3; TIF2, transcriptional mediators/intermediary factor 2.

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1. Identification

PELP1 was first identified as a 160 kDa protein in a screen for Src homology 2 (SH2) domain-binding proteins (Park et al., 1995). In a subsequent study, a HeLa cell library was screened based on the peptide sequence of p160, and a cDNA clone that contained an open reading frame of 3846 bp was obtained. p160 was named proline, glutamic acid, and leucine rich protein 1 (PELP1), based on the high abundance of these amino acids in the protein. While PELP1 contains 10 LXXLL motifs and several other motifs common to transcriptional regulators, the overall protein structure is not homologous to other known proteins (Vadlamudi et al., 2001).

Shortly after the initial report describing the cloning and characterization of PELP1 (Vadlamudi et al., 2001), Wong and colleagues reported the cloning of Modulator of Nongenomic Activity of ER (MNAR). MNAR was identified by a GST-pull down approach using the ERβ ligand-binding domain (ERβ-LBD) as bait. In this study, whole cell extracts from MCF-7 cells, untreated or stimulated with estrogen, were incubated with GST-ERβ-LBD, and proteins that bound to ERβ in a ligand dependent manner were identified by mass spectrometry-based peptide microsequencing. This manuscript was later retracted due to irreproducibility of some of the signaling data (Wong et al., 2009). Peptide sequences isolated from a 120 kDa protein were homologous to PELP1, but the cloned gene was not 100% identical. The published PELP1 sequence contained an additional 435-bp region and a number of amino acid substitutions within highly GC-rich and repetitive amino acid regions (Balasenthil and Vadlamudi, 2003). To determine if PELP1 and MNAR were similar proteins encoded from the same gene or actually the same protein, the PELP1 cDNA was resequenced and it was found that the amino acid differences between MNAR and PELP1 were the result of sequencing errors. It was also determined that the extra 435-bp present in the PELP1 cDNA was the result of cloning an immature transcript containing an unspliced intron, and therefore PELP1 and MNAR are in fact the same protein (Balasenthil and Vadlamudi, 2003).

2. PELP1 expression

2.1. Normal tissue and development

PELP1 expression has been examined in normal tissues, during central nervous system and mammary gland development, and in cancer. The initial report describing the cloning of PELP1 found that it was differentially expressed in human tissues with the highest expression observed in testis, mammary gland, brain, skeletal muscle and lung tissue (Vadlamudi et al., 2001). In the mouse, PELP1 expression was observed in the hypothalamus, testis, ovary, uterus, adrenal gland, lung, pituitary, mammary gland, cerebellum and spleen, and immunohistochemistry showed that cytoplasmic and nuclear subcellular localization varied depending on the tissue type. During murine mammary gland development, PELP1 expression was found to be elevated during pregnancy and then reduced during lactation (Vadlamudi et al., 2001).

Estrogen and ERs have been shown to play a significant role in the development of the central nervous system (Beyer, 1999; McEwen and Alves, 1999). Since PELP1 was first identified as an ER coactivator there have been a number of studies specifically examining PELP1 expression in the mouse, rat, and monkey brain (Khan et al., 2006, 2005; Pawlak and Beyer, 2005). In BALB/c mice, PELP1 expression gradually declined in the midbrain and hypothalamus between embryonic day 15 and postnatal day 15, while remaining fairly constant in the cortex (Pawlak and Beyer, 2005). PELP1 expression was also found in primary neuronal and astroglial cell cultures from the mouse striatum and midbrain (Pawlak and Beyer, 2005). In the rat, PELP1 was cloned from the hypothalamus and found to be 86% homologous to human PELP1, containing a glutamic acid rich region, and LXXLL and PXXP motifs. PELP1 was found expressed in many regions of the rat brain with intense IHC staining in the hypothalamus, cerebral cortex, hippocampus, amygdala, and cerebellum (Khan et al., 2005). Similar PELP1 expression patterns were observed in the monkey brain (Khan et al., 2006). Interestingly, PELP1 and ER colocalized in many, but not all, rat neuronal tissues (Khan et al., 2005). However, PELP1 and the glucocorticoid receptor (GR) showed an absolute colocalization in the monkey and rat brain, suggesting that PELP1 may modulate GR activity in the brain (Khan et al., 2006).

While PELP1 does appear to play a role in mammary gland and brain development, it is not known if PELP1 expression is essential for the development of these organs or embryonic development in general. A PELP1 knockout mouse would provide additional information on the role of PELP1 in development, and tissue specific knockout of PELP1 (mammary epithelial cells, neuronal cells, etc.) would also help delineate the role of PELP1 in disease progression. To our knowledge these mouse models have not been developed.

2.2. Cancer

PELP1 expression has been shown to be dysregulated in many different types of cancer, with PELP1 expression in breast cancer being the most frequently reported. The first report describing cloning and characterization found that PELP1 was overexpressed in a handful of breast tumors compared to the normal adjacent tissue (Vadlamudi et al., 2001). This report also showed differential expression of PELP1 protein in a series of 9 breast cancer cell lines. MCF-7 cells appeared to have the highest expression, while T47D and MDA-453 cells had low to no expression. Subsequent studies in breast tumor samples have shown that PELP1 is overexpressed in 60–80% of breast tumors (Habashy et al., 2010; Vadlamudi et al., 2005b). High PELP1 expression has been shown to be associated with tumor grade (Habashy et al., 2010; Kumar et al., 2009; Rajhans et al., 2007), proliferation (Habashy et al., 2010; Kumar et al., 2009), node positive invasive breast cancer and distant metastasis (Habashy et al., 2010; Rajhans et al., 2007), and a decrease in breast cancer specific survival and disease free survival (Habashy et al., 2010). Interestingly, in the study with the largest number invasive breast cancers high PELP1 expression was inversely associated with ER, PR, AR and luminal cytokeratins, and positively associated with basal cytokeratins and p53 expression (Habashy et al., 2010). PELP1 has also been reported to display aberrant localization in some breast tumors; while PELP1 is found localized to the nucleus in normal breast tissue, cytoplasmic localization has been observed in a significant number of invasive breast cancers (Kumar et al., 2009; Vadlamudi et al., 2005b). Analysis of recurrence free survival in ER-positive patients indicates that patients with high cytoplasmic PELP1 responded poorly to tamoxifen treatment, while those with low levels of cytoplasmic PELP1 responded well (Kumar et al., 2009). Together, these reports suggest that PELP1 expression may play a significant role in both ER-positive and ER-negative breast cancer. It is likely that in ER-positive breast cancer the predominate role of PELP1 is enhancing ER extra-nuclear and nuclear actions, while in ER-negative breast cancer PELP1 is enhancing growth factor signaling pathways and promoting permissive transcriptional regulation through chromatin remodeling (see Section 4).

Increased PELP1 expression has also been reported in female cancers of the reproductive tract, in particular endometrial and ovarian. In endometrial cancer PELP1 was expressed in all 60 endometrial tumors tested, and alterations in subcellular localization were observed. Strong cytoplasmic staining was found in over