Gene Section
Mini Review

WWP1 (WW domain containing E3 ubiquitin protein ligase 1)

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Identity
Hugo: WWP1
Other names: AIP5 (Atropin-1-interacting protein 5); Tiul1 (TGIF-interacting ubiquitin ligase 1)
Location: 8q21.3

DNA/RNA

Description
The WWP1 gene encompasses 26 exons which span approximatively 142 kb of DNA. BAC clone RPCI-459L5 contains the complete human WWP1 genome sequence.

Transcription
WWP1 mRNA is strongly or modestly expressed in human heart, muscle, placenta, kidney, liver, pancreas and testis (Mosser et al., 1998; Komuro et al., 2004). The size of the WWP1 mRNA is about 4.2 kb (Chen et al., 2007). There are multiple splicing isoforms in the breast cancer cell line T47D (Flasza et al., 2002). The open reading frame for the full length WWP1 gene is 2766 bp. The transcription is increased by TGFβ (Chen et al., 2007).

Protein

Description
922 amino acids; approximatively 110 kDa protein; The C2 domain at N-terminus is responsible for calcium-dependent phospholipid binding. The four WW domains in the middle are responsible for protein-protein interaction with PY motifs. The HECT domain at the C-terminus is responsible for the ubiquitin transfer. The Cystein 890 is the catalytic center. The underlined WWP1 substrates do not have a PY motif (PPXY). A smaller WWP1 protein isoform was detected in two prostate cancer cell lines PC-3 and LAPC-4 (Chen et al., 2007a).
Protein structure: The HECT domain of WWP1 (see Figure 2C.) (Verdecia et al., 2003).

Figure 1. Boxes represent exons.
Figure 2A: WWP1 protein.

Figure 2B: Exogenous WWP1 expression in the 22Rv1 prostate cancer cell line was detected under a confocal microscopy. The endosomes are indicated by GFP-Rab5.

Figure 2C: Protein structure of WWP1.
**Expression**

The WWP1 protein is lowly expressed in normal prostate and breast but is frequently upregulated in prostate and breast cancers due to the gene amplification.

**Localisation**

Predominately on membrane structures in cytoplasm and occasionally in nucleus (see Figure 2B.).

**Function**

WWP1 is an E3 ubiquitin ligase. WWP1 negatively regulates the transforming growth factor-beta (TGF-b) signaling by targeting its molecular components, including TGF-beta receptor 1 (TbR1) (Komuro et al., 2004), Smad2 (Seo et al., 2004), and Smad4 (Moren et al., 2005) for ubiquitin mediated degradation.

In addition, WWP1 has been reported to target the epithelial Na+ channel (ENaC) (Malbert-Colas et al., 2003), Notch (Shaye and Greenwald, 2005), Runx2 (Jones et al., 2006; Shen et al., 2006), KLF2 (Zhang et al., 2004), and KLF5 (Ren et al., 2005) for ubiquitin-mediated proteolysis.

Recently, WWP1 has been demonstrated to inhibit p53 activity through exporting p53 from the nucleus after ubiquitination (Laine and Ronai, 2007). Overall, WWP1 may play a pro-survival role in several tumor types including breast (Ren et al., 2007b) and prostate (Ren et al., 2007a). WWP1 has also shown to promote virus budding (Martin-Serrano et al., 2005; Heidecker et al., 2007).

**Homology**

WWP1 belongs to the C2-WW-HECT E3 family which contains 8 other members (Chen and Matesic, 2007). The WWP1 gene is highly-conserved among species (from human to c. elegant).

**Mutations**

**Somatic**

The WWP1 gene is rarely mutated in human prostate cancer (Chen et al., 2007a). Two sequence alterations were detected in prostate cancer xenografts. One was 2393A→T (Glu798Val) in CWR91 and the other was 721A→T (Thr241Ser) in LuCaP35. Additionally, some mutations in the HECT domain decrease the E3 ligase activity (Verdecia et al., 2003).

**Implicated in**

**Prostate cancer**

**Disease**

The WWP1 gene is amplified in 31-44% prostate cancer cell lines/xenografts/tumors. Consistently, the WWP1 mRNA and protein is up-regulated in these samples compared to immortalized prostate epithelial cell lines. WWP1 knock-down increases the TGFb-induced CDK inhibitor p15 expression and decreases PC-3 prostate cancer cell growth in vitro. These results suggest that WWP1 may be an oncogene in prostate cancer.

**Breast cancer**

**Disease**

The WWP1 gene is amplified in 41-51% breast cancer cell lines/tumors. Consistently, the WWP1 mRNA and protein is up-regulated in breast cancer cells compared to immortalized breast epithelial cell lines. WWP1 knock-down induces growth arrest and apoptosis in MCF7 and HCC1500 breast cancer cell lines. Forced expression of WWP1 promotes MCF10A and 184B5 immortalized breast epithelial cell proliferation in an E3 ligase independent manner.

![Figure 3. WWP1 protein expression in normal breast epithelial cells and breast cancer cells by immunohistochemical staining.](image-url)
References


This article should be referenced as such: