Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 83

This document contains 1 pathway and 13 reactions (see Table of Contents)
PTEN protein stability is regulated by ubiquitin ligases, such as NEDD4, WWP2, STUB1 (CHIP), XIAP, MKRN1 and RNF146, which polyubiquitinate PTEN in response to different stimuli and thus target it for proteasome-mediated degradation (Wang et al. 2007, Van Themsche et al. 2009, Maddika et al. 2011, Ahmed et al. 2012, Lee et al. 2015, Li et al. 2015). Several ubiquitin proteases, such as USP13 and OTUD3, can remove polyubiquitin chains from PTEN and rescue it from degradation (Zhang et al. 2013, Yuan et al. 2015). TRIM27 (RFP) is an E3 ubiquitin ligase that polyubiquitinates PTEN on multiple lysines in the C2 domain of PTEN using K27 linkage between ubiquitin molecules. TRIM27 mediated ubiquitination inhibits PTEN lipid phosphatase activity, but does not affect PTEN protein localization or stability (Lee et al. 2013).

PTEN phosphorylation by the tyrosine kinase FRK (RAK) inhibits NEDD4 mediated polyubiquitination and subsequent degradation of PTEN, thus increasing PTEN half life. FRK mediated phosphorylation also increases PTEN enzymatic activity (Yim et al. 2009). Casein kinase 2 (CK2) mediated phosphorylation of the C-terminus of PTEN on multiple serine and threonine residues increases PTEN protein stability (Torres and Pulido 2001) but results in ~30% reduction in PTEN lipid phosphatase activity (Miller et al. 2002).

PREX2, a RAC1 guanine nucleotide exchange factor (GEF) can binds to PTEN and inhibit its catalytic activity (Fine et al. 2009).

**Literature references**


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NEDD4, WWP2, CHIP and XIAP polyubiquitinate PTEN

Location: Regulation of PTEN stability and activity

Stable identifier: R-HSA-6807134

Type: transition

Compartments: cytosol

Several ubiquitin ligases, including NEDD4 (Wang et al. 2007), STUB1 (CHIP) (Ahmed et al. 2012), WWP2 (Maddika et al. 2011) and XIAP (Van Themsche et al. 2009) can polyubiquitinate PTEN, targeting it for degradation.

Followed by: Proteasome degrades polyubiquitinated PTEN, USP13 and OTUD3 deubiquitinate PTEN

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AKT phosphorylates MKRN1

**Location:** Regulation of PTEN stability and activity

**Stable identifier:** R-HSA-8948757

**Type:** transition

**Compartments:** cytosol

AKT1 (and possibly AKT2 and AKT3), activated in response to EGF treatment, phosphorylates MKRN1, an E3 ubiquitin ligase, on serine residue S109. AKT-mediated phosphorylation results in stabilization of MKRN1, protecting it from ubiquitination and proteasome-mediated degradation (Lee et al. 2015).

**Followed by:** MKRN1 polyubiquitinates PTEN

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The C-terminal region of the E3 ubiquitin ligase MKRN1 interacts with PTEN and polyubiquitinates it on lysine residue K289, via K48 linkage. AKT-mediated phosphorylation of MKRN1 on serine residue S109 is a pre-requisite for MKRN1 stabilization and MKRN1-mediated ubiquitination of PTEN. MKRN1 is implicated as an oncogene in cervical cancer (Lee et al. 2015).

**Preceded by:** AKT phosphorylates MKRN1

**Followed by:** Proteasome degrades polyubiquitinated PTEN

**Literature references**

PTEN can bind tankyrases TNKS (TNKS1) and TNKS2. The interaction involves the tankyrase binding motif at the N-terminus of PTEN (RYQEDG). TNKS and TNKS2 poly-ADP-ribosylate (PARylate) PTEN on glutamic acid residues E40 and E150 and on aspartic acid residue D326. PTEN PARylation is a prerequisite for RNF146-mediated ubiquitination of PTEN (Li et al. 2015).

Followed by: RNF146 polyubiquitinates PARylated PTEN

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The E3 ubiquitin ligase RNF146 possesses a PAR recognition domain (WWE) which binds to PARylated PTEN. RNF146 polyubiquitinates PARylated PTEN, with lysine residues K342, K344 and K349 as major ubiquitination sites. RNF146-mediated ubiquitination targets PTEN for proteasome-mediated degradation (Li et al. 2015).

**Preceded by:** TNKS and TNKS2 PARylate PTEN

**Followed by:** Proteasome degrades polyubiquitinated PTEN

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Proteasome degrades polyubiquitinated PTEN

Location: Regulation of PTEN stability and activity

Stable identifier: R-HSA-8850992

Type: omitted

Compartments: cytosol

PTEN, polyubiquitinated by either NEDD4 (Wang et al. 2007), STUB1 (CHIP) (Ahmed et al. 2011), WWP2 (Maddika et al. 2011), XIAP (Van Themsche et al. 2009), MKRN1 (Lee et al. 2015) or RNF146 (Li et al. 2015), is degraded by the proteasome.

Preceded by: MKRN1 polyubiquitinates PTEN, NEDD4, WWP2, CHIP and XIAP polyubiquitinate PTEN, RNF146 polyubiquitinates PARylated PTEN

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Several ubiquitin proteases deubiquitinate polyubiquitinated PTEN. USP13 and OTUD3 prolong the half-life of PTEN by preventing its proteasome-mediated degradation. Loss of USP13 or OTUD3 expression promotes AKT activation and cancer aggressiveness (Zhang et al. 2013, Yuan et al. 2015).

**Preceded by:** NEDD4, WWP2, CHIP and XIAP polyubiquitinate PTEN

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PTEN binds FRK

Location: Regulation of PTEN stability and activity

Stable identifier: R-HSA-8847968

Type: binding

Compartments: cytosol

FRK (RAK), a SRC family member kinase, binds PTEN. The interaction involves the SH3 domain of FRK and the C2 domain of PTEN (Yim et al. 2009). Like other SRC family members, FRK is autophosphorylated on a C-terminal tyrosine residue Y387. FRK possesses a nuclear localization signal and is found in both nucleus and the cytosol (Cance et al. 1994).

Followed by: FRK phosphorylates PTEN

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FRK phosphorylates PTEN

Location: Regulation of PTEN stability and activity

Stable identifier: R-HSA-8847977

Type: transition

Compartments: cytosol

FRK tyrosine kinase (RAK) phosphorylates PTEN on tyrosine residue Y336. FRK-mediated phosphorylation inhibits NEDD4-mediated polyubiquitination and subsequent degradation of PTEN, thus increasing PTEN half-life. FRK-mediated phosphorylation also increases PTEN enzymatic activity (Yim et al. 2009).

Preceded by: PTEN binds FRK

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Casein kinase II phosphorylates PTEN

Location: Regulation of PTEN stability and activity

Stable identifier: R-HSA-8850945

Type: transition

Compartments: cytosol

Casein kinase II (CK2) constitutively phosphorylates the C-terminal tail of PTEN on serine and threonine residues S370, S380, T382, T383 and S385. S370 and S385 are the main CK2 phosphorylation sites in PTEN (Torres and Pulido 2001, Miller et al. 2002). CK2-mediated phosphorylation increases PTEN protein stability (Torres and Pulido 2001) but results in ~30% reduction in PTEN lipid phosphatase activity (Miller et al. 2002).

Followed by: PREX2 binds PTEN and inhibits it

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PREX2, a RAC1 guanine nucleotide exchange factor (GEF), binds to PTEN and inhibits its catalytic activity, resulting in enhanced PI3K/AKT signaling (Fine et al. 2009). The interaction involves the inositol polyphosphate 4-phosphatase domain and the pleckstrin homology (PH) domain of PREX2 and the PDZ binding domain, the phosphatase domain and the C2 domain of PTEN (Fine et al. 2009, Hodakoski et al. 2014). PREX2 binds both the unphosphorylated PTEN and PTEN phosphorylated at the C-terminal tail by casein kinase II, but inhibits the lipid phosphatase activity of phosphorylated PTEN only (Hodakoski et al. 2014). The GEF activity of PREX2 is not needed for PTEN inhibition (Fine et al. 2009).

PREX2 is frequently overexpressed in breast and prostate cancer (Fine et al. 2009) and mutated in melanoma (Berger et al. 2012).

**Preceded by:** Casein kinase II phosphorylates PTEN

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TRIM27 binds PTEN

**Location:** Regulation of PTEN stability and activity

**Stable identifier:** R-HSA-8850997

**Type:** binding

**Compartments:** cytosol

TRIM27 (RFP) binds PTEN. The interaction involves the C-terminal RFP domain of TRIM27 and the C-terminal tail of PTEN (Lee et al. 2013).

**Followed by:** TRIM27 polyubiquitinates PTEN

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**TRIM27 polyubiquitinates PTEN**

**Location:** Regulation of PTEN stability and activity

**Stable identifier:** R-HSA-8851011

**Type:** transition

**Compartments:** cytosol

TRIM27 (RFP) is an E3 ubiquitin ligase for PTEN. TRIM27 polyubiquitinates PTEN on multiple lysines in the C2 domain of PTEN using K27-linkage between ubiquitin molecules. TRIM27-mediated ubiquitination inhibits PTEN lipid phosphatase activity, but does not affect PTEN protein localization or stability (Lee et al. 2013).

**Preceded by:** TRIM27 binds PTEN

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