

# **PTEN Regulation**



🖗 reactome

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### 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.

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#### Literature references

- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. 7
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. A
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, *14*, e1005968. *オ*

This document contains 5 pathways (see Table of Contents)

#### PTEN Regulation 7

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reactome

PTEN is regulated at the level of gene transcription, mRNA translation, localization and protein stability.

Transcription of the PTEN gene is regulated at multiple levels. Epigenetic repression involves the recruitment of Mi-2/NuRD upon SALL4 binding to the PTEN promoter (Yang et al. 2008, Lu et al. 2009) or EVI1-mediated recruitment of the polycomb repressor complex (PRC) to the PTEN promoter (Song et al. 2009, Yoshimi et al. 2011). Transcriptional regulation is also elicited by negative regulators, including NR2E1:ATN1 (atrophin-1) complex, JUN (c-Jun), SNAIL and SLUG (Zhang et al. 2006, Vasudevan et al. 2007, Escriva et al. 2008, Uygur et al. 2015) and positive regulators such as TP53 (p53), MAF1, ATF2, EGR1 or PPARG (Stambolic et al. 2001, Virolle et al. 2001, Patel et al. 2001, Shen et al. 2006, Li et al. 2016).

MicroRNAs miR-26A1, miR-26A2, miR-22, miR-25, miR-302, miR-214, miR-17-5p, miR-19 and miR-205 bind PTEN mRNA and inhibit its translation into protein. These microRNAs are altered in cancer and can account for changes in PTEN levels (Meng et al. 2007, Xiao et al. 2008, Yang et al. 2008, Huse et al. 2009, Kim et al. 2010, Poliseno, Salmena, Riccardi et al. 2010, Cai et al. 2013). In addition, coding and non-coding RNAs can prevent microRNAs from binding to PTEN mRNA. These RNAs are termed competing endogenous RNAs or ceRNAs. Transcripts of the pseudogene PTENP1 and mRNAs transcribed from SERINC1, VAPA and CNOT6L genes exhibit this activity (Poliseno, Salmena, Zhang et al. 2010, Tay et al. 2011, Tay et al. 2014).

PTEN can translocate from the cytosol to the nucleus after undergoing monoubiquitination. PTEN's ability to localize to the nucleus contributes to its tumor suppressive role (Trotman et al. 2007). The ubiquitin protease USP7 (HAUSP) targets monoubiquitinated PTEN in the nucleus, resulting in PTEN deubiquitination and nuclear exclusion. PML, via an unknown mechanism that involves USP7- and PML-interacting protein DAXX, inhibits USP7-mediated deubiquitination of PTEN, thus promoting PTEN nuclear localization. Disruption of PML function in acute promyelocytic leukemia, through a chromosomal translocation that results in expression of a fusion protein PML-RARA, leads to aberrant PTEN localization (Song et al. 2008).

Several ubiquitin ligases, including NEDD4, WWP2, STUB1 (CHIP), RNF146, XIAP and MKRN1, polyubiquitinate PTEN and target it for proteasome-mediated degradation (Wang et al. 2007, Van Themsche et al. 2009, Ahmed et al. 2011, Maddika et al. 2011, Lee et al. 2015, Li et al. 2015). The ubiquitin proteases USP13 and OTUD3, frequently down-regulated in breast cancer, remove polyubiquitin chains from PTEN, thus preventing its degradation and increasing its half-life (Zhang et al. 2013, Yuan et al. 2015). The catalytic activity of PTEN is negatively regulated by PREX2 binding (Fine et al. 2009, Hodakoski et al. 2014) and TRIM27-mediated

ubiquitination (Lee et al. 2013), most likely through altered PTEN conformation.

In addition to ubiquitination, PTEN also undergoes SUMOylation (Gonzalez-Santamaria et al. 2012, Da Silva Ferrada et al. 2013, Lang et al. 2015, Leslie et al. 2016). SUMOylation of the C2 domain of PTEN may regulate PTEN association with the plasma membrane (Shenoy et al. 2012) as well as nuclear localization of PTEN (Bassi et al. 2013, Collaud et al. 2016). PIASx-alpha, a splicing isorom of E3 SUMO-protein ligase PIAS2 has been implicated in PTEN SUMOylation (Wang et al. 2014). SUMOylation of PTEN may be regulated by activated AKT (Lin et al. 2016). Reactions describing PTEN SUMOylation will be annotated when mechanistic details become available.

Phosphorylation affects the stability and activity of PTEN. FRK tyrosine kinase (RAK) phosphorylates PTEN on tyrosine residue Y336, which increases PTEN half-life by inhibiting NEDD4-mediated polyubiquitination and subsequent degradation of PTEN. FRK-mediated phosphorylation also increases PTEN enzymatic activity (Yim et al. 2009). Casein kinase II (CK2) constitutively phosphorylates the C-terminal tail of PTEN on serine and threonine residues S370, S380, T382, T383 and S385. 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).

PTEN localization and activity are affected by acetylation of its lysine residues (Okumura et al. 2006, Ikenoue et al. 2008, Meng et al. 2016). PTEN can undergo oxidation, which affects its function, but the mechanism is poorly understood (Tan et al. 2015, Shen et al. 2015, Verrastro et al. 2016).

#### Literature references

- Rameh, L., Varmeh, S., Sportoletti, P., Fornari, A., Loda, M., Poliseno, L. et al. (2010). Identification of the miR-106b~25 microRNA cluster as a proto-oncogenic PTEN-targeting intron that cooperates with its host gene MCM7 in transformation. *Sci Signal, 3*, ra29. 7
- Kern, PA., Keniry, M., Anderson, KE., Hawkins, PT., Mense, SM., Barrows, D. et al. (2014). Regulation of PTEN inhibition by the pleckstrin homology domain of P-REX2 during insulin signaling and glucose homeostasis. *Proc. Natl. Acad. Sci. U.S.A.*, 111, 155-60. *¬*
- Yang, L., Lin, C., Wang, W., Li, N., Chen, J., Songyang, Z. et al. (2015). Poly-ADP ribosylation of PTEN by tankyrases promotes PTEN degradation and tumor growth. *Genes Dev.*, 29, 157-70. ↗
- Pandolfi, PP., Carracedo, A., Egia, A., Song, MS., Teruya-Feldstein, J., Lo-Coco, F. et al. (2008). The deubiquitinylation and localization of PTEN are regulated by a HAUSP-PML network. *Nature*, 455, 813-7.
- Wang, J., Shen, YH., LeMaire, SA., Wang, XL., Coselli, JS., Gan, Y. et al. (2006). Up-regulation of PTEN (phosphatase and tensin homolog deleted on chromosome ten) mediates p38 MAPK stress signal-induced inhibition of insulin signaling. A cross-talk between stress signaling and insulin signaling in resistin-treated human endothelial cells. J. Biol. Chem., 281, 7727-36. *¬*

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#### **Regulation of PTEN gene transcription** *对*

#### **Location:** PTEN Regulation

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reactome

Transcription of the PTEN gene is regulated at multiple levels. Epigenetic repression involves the recruitment of Mi-2/NuRD upon SALL4 binding to the PTEN promoter (Yang et al. 2008, Lu et al. 2009) or EVI1-mediated recruitment of the polycomb repressor complex (PRC) to the PTEN promoter (Song et al. 2009, Yoshimi et al. 2011). Transcriptional regulation is also elicited by negative regulators, including NR2E1:ATN1 (atrophin-1) complex, JUN (c-Jun), SNAIL and SLUG (Zhang et al. 2006, Vasudevan et al. 2007, Escriva et al. 2008, Uygur et al. 2015) and positive regulators such as TP53 (p53), MAF1, ATF2, EGR1 or PPARG (Stambolic et al. 2001, Virolle et al. 2001, Patel et al. 2001, Shen et al. 2006, Li et al. 2016).

#### Literature references

- Sato, T., Nitta, E., Kitamura, T., Yoshimi, A., Shimabe, M., Yoshiki, Y. et al. (2011). Evi1 represses PTEN expression and activates PI3K/AKT/mTOR via interactions with polycomb proteins. *Blood*, *117*, 3617-28. *¬*
- Huang, WL., Li, J., Feng, Y., Xia, YF., Shi, QH., Tsao, SW. et al. (2009). The polycomb group protein Bmi-1 represses the tumor suppressor PTEN and induces epithelial-mesenchymal transition in human nasopharyngeal epithelial cells. J. Clin. Invest., 119, 3626-36.
- Zhang, CL., Zou, Y., Gage, FH., Evans, RM., Yu, RT. (2006). Nuclear receptor TLX prevents retinal dystrophy and recruits the corepressor atrophin1. *Genes Dev.*, 20, 1308-20.
- Gridley, T., Murray, SA., García de Herreros, A., Herranz, N., Dave, N., Virtanen, I. et al. (2008). Repression of PTEN phosphatase by Snail1 transcriptional factor during gamma radiation-induced apoptosis. *Mol. Cell. Biol., 28*, 1528-40. *¬*
- Stambolic, V., Sas, D., Benchimol, S., Snow, B., Jang, Y., MacPherson, D. et al. (2001). Regulation of PTEN transcription by p53. *Mol. Cell*, *8*, 317-25.

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#### **Regulation of PTEN mRNA translation ↗**

#### **Location:** PTEN Regulation

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reactome

MicroRNAs miR-17, miR-19a, miR-19b, miR-20a, miR-20b, miR-21, miR-22, miR-25, miR 26A1, miR 26A2, miR-93, miR-106a, miR-106b, miR 205, and miR 214 and bind PTEN mRNA and inhibit its translation into protein. These microRNAs are altered in cancer and can account for changes in PTEN levels. There is evidence that PTEN mRNA translation is also inhibited by other microRNAs, such as miR-302 and miR-26B, and these microRNAs will be annotated when additional experimental details become available (Meng et al. 2007, Xiao et al. 2008, Yang et al. 2008, Huse et al. 2009, Kim et al. 2010, Poliseno, Salmena, Riccardi et al. 2010, Zhang et al. 2010, Tay et al. 2011, Qu et al. 2012, Cai et al. 2013). In addition, coding and non coding RNAs can prevent microRNAs from binding to PTEN mRNA. These RNAs are termed competing endogenous RNAs or ceRNAs. Transcripts of the pseudogene PTENP1 and mRNAs transcribed from SERINC1, VAPA and CNOT6L genes exhibit this activity (Poliseno, Salmena, Zhang et al. 2010, Tay et al. 2011, Tay et al. 2014).

#### Literature references

- Cai, J., Huang, Y., Li, R., Yang, Y., Yuan, J., Fang, L. et al. (2013). miR-205 targets PTEN and PHLPP2 to augment AKT signaling and drive malignant phenotypes in non-small cell lung cancer. *Cancer Res.*, 73, 5402-15. *¬*
- Rameh, L., Varmeh, S., Sportoletti, P., Fornari, A., Loda, M., Poliseno, L. et al. (2010). Identification of the miR-106b~25 microRNA cluster as a proto-oncogenic PTEN-targeting intron that cooperates with its host gene MCM7 in transformation. *Sci Signal*, *3*, ra29. 7
- Kong, W., O'Donnell, JD., Kruk, PA., Zhao, JJ., He, L., Wenham, RM. et al. (2008). MicroRNA expression profiling in human ovarian cancer: miR-214 induces cell survival and cisplatin resistance by targeting PTEN. *Cancer Res., 68*, 425-33. ↗
- Weiss, D., Karreth, F., Tan, SM., Di Cunto, F., Rigoutsos, I., Provero, P. et al. (2011). Coding-independent regulation of the tumor suppressor PTEN by competing endogenous mRNAs. *Cell*, 147, 344-57.
- Park, PJ., Johnson, MD., Jiang, X., Kim, H., Huang, W., Pennicooke, B. (2010). Integrative genome analysis reveals an oncomir/oncogene cluster regulating glioblastoma survivorship. *Proc. Natl. Acad. Sci. U.S.A.*, 107, 2183-8.

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#### **Regulation of PTEN localization**

#### Location: PTEN Regulation

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reactome

When monoubiquitinated by E3 ubiquitin ligases XIAP and NEDD4, PTEN translocates from the cytosol to the nucleus (Trotman et al. 2007, Van Themsche et al. 2009). USP7 (HAUSP)-mediated deubiquitination of monoubiquitinated nuclear PTEN promotes relocalization of PTEN to the cytosol (Song et al. 2008).

#### Literature references

- Van Themsche, C., Parent, S., Leblanc, V., Asselin, E. (2009). X-linked inhibitor of apoptosis protein (XIAP) regulates PTEN ubiquitination, content, and compartmentalization. J. Biol. Chem., 284, 20462-6. 7
- Trotman, LC., Wang, X., Carver, BS., Jiang, X., Pavletich, NP., Tempst, P. et al. (2007). Ubiquitination regulates PTEN nuclear import and tumor suppression. *Cell*, 128, 141-56. *¬*
- Pandolfi, PP., Carracedo, A., Egia, A., Song, MS., Teruya-Feldstein, J., Lo-Coco, F. et al. (2008). The deubiquitinylation and localization of PTEN are regulated by a HAUSP-PML network. *Nature*, 455, 813-7.

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#### Regulation of PTEN stability and activity 7

#### **Location:** PTEN Regulation

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reactome

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 proteasomemediated 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

- Van Themsche, C., Parent, S., Leblanc, V., Asselin, E. (2009). X-linked inhibitor of apoptosis protein (XIAP) regulates PTEN ubiquitination, content, and compartmentalization. J. Biol. Chem., 284, 20462-6. 🛪
- Li, K., Dai, H., Lu, Y., Hu, R., Craven, RJ., Hennessy, BT. et al. (2009). Rak functions as a tumor suppressor by regulating PTEN protein stability and function. *Cancer Cell*, 15, 304-14.
- Pulido, R., Torres, J. (2001). The tumor suppressor PTEN is phosphorylated by the protein kinase CK2 at its C terminus. Implications for PTEN stability to proteasome-mediated degradation. J. Biol. Chem., 276, 993-8. 🛪
- Pokorny, JL., Palicharla, VR., Kavela, S., Chen, J., Maddika, S., Rani, N. et al. (2011). WWP2 is an E3 ubiquitin ligase for PTEN. *Nat. Cell Biol.*, 13, 728-33.

Hewitt, SM., Han, HJ., Lee, MS., Lee, C., Chung, JY., Kim, JH. et al. (2015). PI3K/AKT activation induces PTEN ubiquitination and destabilization accelerating tumourigenesis. *Nat Commun, 6*, 7769.

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