Signaling by PTK6

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31/05/2020
**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: 72

This document contains 10 pathways (see Table of Contents)
PTK6 (BRK) is an oncogenic non-receptor tyrosine kinase that functions downstream of ERBB2 (HER2) (Xiang et al. 2008, Peng et al. 2015) and other receptor tyrosine kinases, such as EGFR (Kamalati et al. 1996) and MET (Castro and Lange 2010). Since ERBB2 forms heterodimers with EGFR and since MET can heterodimerize with both ERBB2 and EGFR (Tanizaki et al. 2011), it is not clear if MET and EGFR activate PTK6 directly or act through ERBB2. Levels of PTK6 increase under hypoxic conditions (Regan Anderson et al. 2013, Pires et al. 2014). The kinase activity of PTK6 is negatively regulated by PTPN1 phosphatase (Fan et al. 2013) and SRMS kinase (Fan et al. 2015), as well as the STAT3 target SOCS3 (Gao et al. 2012). PTK6 activates STAT3-mediated transcription (Ikeda et al. 2009, Ikeda et al. 2010) and may also activate STAT5-mediated transcription (Ikeda et al. 2011). PTK6 promotes cell motility and migration by regulating the activity of RHO GTPases RAC1 (Chen et al. 2004) and RHOA (Shen et al. 2008), and possibly by affecting motility-related kinesins (Lukong and Richard 2008). PTK6 crosstalks with AKT1 (Zhang et al. 2005, Zheng et al. 2010) and RAS signaling cascades (Shen et al. 2008, Ono et al. 2014) and may be involved in MAPK7 (ERK5) activation (Ostrander et al. 2007, Zheng et al. 2012). PTK6 enhances EGFR signaling by inhibiting EGFR down-regulation (Kang et al. 2010, Li et al. 2012, Kang and Lee 2013). PTK6 may also enhance signaling by IGF1R (Fan et al. 2013) and ERBB3 (Kamalati et al. 2000).

PTK6 promotes cell cycle progression by phosphorylating and inactivating CDK inhibitor CDKN1B (p27) (Patel et al. 2015).

PTK6 activity is upregulated in osteopontin (OPN or SPP1)-mediated signaling, leading to increased VEGF expression via PTK6/NF-kappaB/ATF4 signaling path. PTK6 may therefore play a role in VEGF-dependent tumor angiogenesis (Chakraborty et al. 2008).

PTK6 binds and phosphorylates several nuclear RNA-binding proteins, including SAM68 family members (KHDRSB1, KHDRSB2 and KHDRSB3) (Derry et al. 2000, Haegebarth et al. 2004, Lukong et al. 2005) and
SFPQ (PSF) (Lukong et al. 2009). The biological role of PTK6 in RNA processing is not known.

For a review of PTK6 function, please refer to Goel and Lukong 2015.

**Literature references**


**Editions**

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Levels of PTK6 increase under hypoxic conditions due to direct transcriptional regulation of PTK6 gene by hypoxia inducible transcription factors (HIFs) (Regan Anderson et al. 2013). PTK6 protein levels are also rapidly stabilized in hypoxic conditions in a HIF-independent manner (Pires et al. 2014). It has also been shown that PTK6 is ubiquitinated in normoxic conditions by a so far unknown E3 ligase (Pires et al. 2014).

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PTK6 (BRK) is activated downstream of ERBB2 (HER) (Xiang et al. 2008, Peng et al. 2015) and other receptor tyrosine kinases, such as EGFR (Kamalati et al. 1996) and MET (Castro and Lange 2010). However, it is not clear if MET and EGFR activate PTK6 directly or act through ERBB2, since it is known that ERBB2 forms heterodimers with EGFR (Spivak-Kroizman et al. 1992), and MET can heterodimerize with both EGFR and ERBB2 (Tanizaki et al. 2011).

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PTK6 Activates STAT3

**Location:** Signaling by PTK6

**Stable identifier:** R-HSA-8849474

PTK6-mediated phosphorylation activates STAT3 transcription factor via STAP2 adapter protein. STAT3 transcriptional target SOCS3 is a negative regulator of PTK6 and inhibits PTK6-mediated phosphorylation of STAT3, thus creating a negative feedback loop (Liu et al. 2006, Ikeda et al. 2009, Ikeda et al. 2010). PTK6 may also activate STAT5-mediated transcription (Ikeda et al. 2011).

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PTK6 promotes cell cycle progression by phosphorylating and inactivating CDK inhibitor CDKN1B (p27) (Patel et al. 2015). PTK6 also negatively modulates CDKN1B expression via regulation of the activity of the FOXO3 (FOXO3A) transcription factor (Chan and Nimnual 2010).

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PTK6 Regulates RHO GTPases, RAS GTPase and MAP kinases

Location: Signaling by PTK6

Stable identifier: R-HSA-8849471

PTK6 promotes cell motility and migration by regulating the activity of RHO GTPases RAC1 (Chen et al. 2004) and RHOA (Shen et al. 2008). PTK6 inhibits RAS GTPase activating protein RASA1 (Shen et al. 2008) and may be involved in MAPK7 (ERK5) activation (Ostrander et al. 2007, Zheng et al. 2012).

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PTK6 Regulates RTKs and Their Effectors AKT1 and DOK1

**Location:** Signaling by PTK6

**Stable identifier:** R-HSA-8849469

PTK6 enhances EGFR signaling by inhibiting EGFR down-regulation (Kang et al. 2010, Li et al. 2012, Kang and Lee 2013). PTK6 may also enhance signaling by other receptor tyrosine kinases (RTKs), such as IGF1R (Fan et al. 2013) and ERBB3 (Kamalati et al. 2000).

PTK6 affects AKT1 activation (Zhang et al. 2005, Zheng et al. 2010) and targets negative regulator of RTKs, DOK1, for degradation (Miah et al. 2014).

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PTK6 promotes HIF1A stabilization

**Location:** Signaling by PTK6

**Stable identifier:** R-HSA-8857538

HBEGF-stimulated formation of EGFR heterodimers with GPNMB triggers PTK6-mediated phosphorylation and stabilization of the hypoxia inducible factor 1 alpha (HIF1A) under normoxic conditions. This process depends on the presence of a long non-coding RNA LINC01139 (LINK-A) (Lin et al. 2016).

**Literature references**

The kinase activity of PTK6 is negatively regulated by both PTPN1 phosphatase (Fan et al. 2013), which dephosphorylates tyrosine Y342 of PTK6, and SRMS kinase (Fan et al. 2015), which phosphorylates PTK6 on tyrosine residue Y447.

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