Signaling by Non-Receptor Tyrosine Kinases

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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


Reactome database release: 70

This document contains 2 pathways (see Table of Contents)
In addition to receptor tyrosine kinases, the human genome encodes at least 32 non-receptor tyrosine kinases (non-RTKs). These cytosolic tyrosine kinases lack a transmembrane domain but are recruited into signal transduction cascades through interaction with other plasma-bound receptors, which may or may not themselves have intrinsic catalytic activity. In this way, non-RTKs essentially function as an (additional) enzymatic subunit of the signaling complex and contribute to many of the same downstream signaling pathways. The non-RTKs can be grouped into 9 families (ABL, SYK, JAK, TEC, FAK, ACK, SRC, BRK/PTK6 and CSK) based on their domain structure (reviewed in Neet and Hunter, 1996).

Literature references

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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