Orlic-Milacic, M., Tsoulfas, P.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

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01/06/2019
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: 68

This document contains 6 pathways and 1 reaction (see Table of Contents)

In the absence of its ligand, NTRK3 functions as a dependence receptor and triggers BAX and CASP9-dependent cell death (Tauszig-Delamasure et al. 2007, Ichim et al. 2013).

NTRK3 was reported to activate STAT3 through JAK2, but the exact mechanism has not been elucidated (Kim et al. 2016). NTRK3 was reported to interact with the adaptor protein SH2B2, but the biological role of this interaction has not been determined (Qian et al. 1998).

Receptor protein tyrosine phosphatases PTPRO and PTPRS (PTPsigma) negatively regulate NTRK3 signaling by dephosphorylating NTRK3 (Beltran et al. 2003, Faux et al. 2007, Hower et al. 2009, Tchetchelnitski et al. 2014). In addition to dephosphorylation of NTRK3 in-cis, the extracellular domain of pre-synaptic PTPRS can bind in-trans to extracellular domain of post-synaptic NTRK3, contributing to synapse formation (Takahashi et al. 2011, Coles et al. 2014).

Literature references


Editions

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NTRK3 (TRKC) is activated by binding to its ligand neurotrophin-3 (NTF3, also known as NT-3). Ligand binding induces dimerization of NTRK3 and trans-autophosphorylation of dimerized receptors on conserved tyrosine residues in the cytoplasmic tail. Autophosphorylated tyrosines serve as docking sites for binding of adaptor proteins that mediate downstream signaling (Lamballe et al. 1991, Philo et al. 1994, Tsoulfas et al. 1996, Huang and Reichardt 2001, Werner et al. 2014).

**Literature references**


Activated NTRK3 signals through PLCG1

**Location:** Signaling by NTRK3 (TRKC)

**Stable identifier:** R-HSA-9034793

The receptor tyrosine kinase NTRK3 (TRKC), when activated by its ligand NTF3 (NT-3), induces PLCG1 phosphorylation, triggering PLCG1 signaling (Marsh and Palfrey 1996, Yuen and Mobley 1999).

**Literature references**


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Activated NTRK3 signals through RAS

**Location:** Signaling by NTRK3 (TRKC)

**Stable identifier:** R-HSA-9034864

Upon activation by NTF3 (NT-3), the receptor tyrosine kinase NTRK3 (TRKC) triggers RAS signaling through adaptor proteins SHC1 and GRB2 (Marsh and Palfrey 1996, Gunn-Moore et al. 1997, Yuen and Mobley 1999). ERK activation downstream of NTRK3 may increase cell motility through WAVE. The mechanism is not known (Gromnitza et al. 2018).

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Activated NTRK3 signals through PI3K

**Location:** Signaling by NTRK3 (TRKC)

**Stable identifier:** R-HSA-9603381

The PI3K complex, composed of PIK3R1 and PIK3CA, co-immunoprecipitates with NTRK3 (TRKC), activated by NTF3 (NT-3) treatment (Yuen and Mobley 1999). Activation of NTRK3 correlates with activating phosphorylation of AKT, the main mediator of PI3K signaling (Tognon et al. 2001, Jin et al. 2008), and is dependent on PI3K activity (Tognon et al. 2001). NTRK3-mediated activation of PI3K signaling depends on SRC activation and the adaptor protein IRS1, but the exact mechanism is not known (Morrison et al. 2002, Lannon et al. 2004, Jin et al. 2008).

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https://reactome.org
When neuronal cells are deprived of the NTRK3 (TRKC) ligand NTF3 (NT-3), NTRK3 functions as a dependence receptor, promoting apoptosis. The pro-apoptotic activity of NTRK3 is implicated in proper nervous system development, by dictating the number of surviving sensory neurons (Tauszig-Delamasure et al. 2007). In the absence of its ligand, NTRK3 undergoes caspase-dependent cleavage (Tauszig-Delamasure et al. 2007), resulting in release of the NTRK3 killer fragment (KF). The NTRK3 KF, in complex with NELFB (COBRA1), inserts into the mitochondrial membrane, promoting cytochrome c release and apoptosome-mediated apoptosis (Ichim et al. 2013).

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Protein tyrosine phosphatases dephosphorylate NTRK3

**Location:** Signaling by NTRK3 (TRKC)

**Stable identifier:** R-HSA-9603719

**Type:** uncertain

**Compartments:** cytosol, plasma membrane

**Inferred from:** PTPRO dephosphorylate NTRK3 (Gallus gallus), PTPRS dephosphorylates Ntrk3 (Gallus gallus)

Receptor protein tyrosine phosphatases PTPRO and PTPRS (PTPsigma) are co-expressed with NTRK3 (TRKC) in a large portion of NTRK3 positive neurons. Recombinant PTPRO (Beltran et al. 2003, Hower et al. 2009, Tchetchelnitski et al. 2014) and PTPRS (Faux et al. 2007, Tchetchelnitski et al. 2014) are both able to bind NTRK3 and promote NTRK3 dephosphorylation, thus attenuating NTRK3 signaling. The precise mechanism has not been elucidated.

In addition to interaction between PTPRS and NTRK3 in-cis, extracellular domain of pre-synaptic PTPRS can bind in-trans to extracellular domain of post-synaptic NTRK3, contributing to synapse formation (Takahashi et al. 2011, Coles et al. 2014).

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