Signaling by NTRK2 (TRKB)

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31/10/2022
**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: 82  

This document contains 10 pathways (see Table of Contents)
NTRK2 (TRKB) belongs to the family of neurotrophin tyrosine kinase receptors, also known as NTRKs or TRKs. Besides NTRK2, the family includes NTRK1 (TRKA) and NTRK3 (TRKC). Similar to other receptor tyrosine kinases (RTKs), NTRK2 is activated by ligand binding to its extracellular domain. Ligand binding induces receptor dimerization, followed by trans-autophosphorylation of dimerized receptors on conserved tyrosine residues in the cytoplasmic region. Phosphorylated tyrosines in the intracellular domain of the receptor serve as docking sites for adapter proteins, triggering downstream signaling cascades. Brain-derived neurotrophic factor (BDNF) and neurotrophin-4 (NTF4, also known as NT-4) are two high affinity ligands for NTRK2. Neurotrophin-3 (NTF3, also known as NT-3), a high affinity ligand for NTRK3, binds to NTRK2 with low affinity and it is not clear if it the low level of activation of NTRK2 by NTF3 plays a physiologically relevant role. Nerve growth factor (NGF), a high affinity ligand for NTRK1, does not interact with NTRK2. NTRK2 activation triggers downstream RAS, PI3K, and PLCgamma signaling cascades, thought to be involved in neuronal development in both the peripheral (PNS) and central nervous system (CNS). In addition, NTRK2 plays an important, but poorly elucidated, role in long-term potentiation (LTP) and learning (reviewed by Minichiello 2009). NTRK2 may modify neuronal excitability and synaptic transmission by directly phosphorylating voltage gated channels (Rogalski et al. 2000).

It was recently demonstrated that the protein tyrosine phosphatase PTPN12 negatively regulates NTRK2 signaling and neurite outgrowth. In the presence of PTPN12, NTRK2 phosphorylation at tyrosine Y816 decreases. It has not yet been demonstrated that PTPN12 acts directly to dephosphorylate Y816 (and possibly other phosphotyrosines) of NTRK2 (Ambjorn et al. 2013).

Binding of SH2D1A (SAP) to NTRK2 attenuates NTRK2 trans autophosphorylation and downstream signaling through an unknown mechanism (Lo et al. 2005).
Little is known about downregulation of NTRK2 (TRKB) receptor via ubiquitin dependent pathways (Sanchez Sanchez and Arevalo 2017). CBL, a ubiquitin ligase involved in degradation of many receptor tyrosine kinases, was shown to ubiquitinate and, unexpectedly, increase stability of NTRK2 (Pandya et al. 2014). NTRK2 undergoes ubiquitination by the TRAF6 E3 ubiquitin ligase complex. While ubiquitination by the TRAF6 complex negatively regulates NTRK2 induced AKT activation, the effect of TRAF6 mediated ubiquitination on NTRK2 protein levels has not been examined (Jadhav et al. 2008).

Downregulation of the TRKB receptor may depend on the activating ligand, with BDNF inducing more rapid ubiquitination and degradation compared to NTF4 (NT4). NTRK2 undergoes both lysosome dependent and proteasome dependent degradation upon stimulation by BDNF, while stimulation by NTF4 may protect NTRK2 from the lysosome degradation route (Proenca et al. 2016).

**Literature references**


**Editions**

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BDNF activates NTRK2 (TRKB) signaling

Location: Signaling by NTRK2 (TRKB)

Stable identifier: R-HSA-9024909

Signaling by the neurotrophin receptor tyrosine kinase NTRK2 (TRKB) can be activated by binding to brain-derived neurotrophic factor (BDNF), which functions as a ligand for NTRK2 (Soppet et al. 1991, Klein et al. 1991). Binding to BDNF triggers NTRK2 dimerization (Ohira et al. 2001) and trans-autophosphorylation of NTRK2 dimers on conserved tyrosine residues in the cytoplasmic tail of the receptor (Guiton et al. 1994, Minichiello et al. 1998, McCarty and Feinstein 1999). Phosphorylated tyrosine residues subsequently serve as docking sites for recruitment of effector proteins that trigger downstream signaling cascades.

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### Editions

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Neurotrophin receptor tyrosine kinase NTRK2 (TRKB) is a low affinity receptor for neurotrophin-3 (NTF3, also known as NT-3) (Soppet et al. 1991). NTF3 predominantly functions as the ligand for the NTRK3 (TRKC) receptor (Marsh and Palfrey 1996). Binding to NTF3 can trigger NTRK2 dimerization (Ohira et al. 2001) and trans-autophosphorylation of NTRK2 dimers on conserved tyrosine residues in the cytoplasmic tail of the receptor (Middlemas et al. 1994). The efficacy of this process, however, is low in comparison to NTRK2 activation by BDNF and NTF3, and downstream signaling has not been studied.

**Literature references**


NTF4 activates NTRK2 (TRKB) signaling

**Location:** Signaling by NTRK2 (TRKB)

**Stable identifier:** R-HSA-9026357

Signaling by the neurotrophin receptor tyrosine kinase NTRK2 (TRKB) can be activated by binding to neurotrophin-4 (NTF4, also known as NT-4), which functions as a ligand for NTRK2 (Klein et al. 1992, Ip et al. 1993, Ohira et al. 2001). Binding to NTF4 triggers NTRK2 dimerization (Ohira et al. 2001) and trans-autophosphorylation of NTRK2 dimers on conserved tyrosine residues in the cytoplasmic tail of the receptor (Minichiello et al. 1998). Phosphorylated tyrosine residues subsequently serve as docking sites for recruitment of effector proteins that trigger downstream signaling cascades.

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Activated NTRK2 signals through RAS

Location: Signaling by NTRK2 (TRKB)

Stable identifier: R-HSA-9026519

Activation of the neurotrophin receptor NTRK2 (TRKB) by BDNF or NTF4 triggers downstream RAS signaling. The best studied mechanism for activation of RAS signaling downstream of NTRK2 is through SHC1-mediated recruitment of the GRB2:SOS1 complex, triggering SOS1-mediated guanine nucleotide exchange on RAS and formation of active RAS:GTP complexes (Minichiello et al. 1998, McCarthy and Feinstein 1999, Yuen and Mobley 1999).

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Activated NTRK2 signals through PLCG1

Location: Signaling by NTRK2 (TRKB)

Stable identifier: R-HSA-9026527


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Activated NTRK2 signals through PI3K

Location: Signaling by NTRK2 (TRKB)

Stable identifier: R-HSA-9028335

Neurotrophin receptor NTRK2 (TRKB), activated by BDNF or NTF4, activates PI3K, resulting in formation of the PIP3 secondary messenger. PIP3 activates AKT signaling, and AKT signaling activates mTOR signaling (Yuen and Mobley 1999, Cao et al. 2013).

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Adapter proteins FRS2 and FRS3 can both bind to the cytoplasmic tail of activated NTRK2 (TRKB) receptor, which is followed by NTRK2-mediated phosphorylation of FRS2 and FRS3. NTRK2 signaling through FRS3 has been poorly characterized (Easton et al. 1999, Yuen and Mobley 1999, Dixon et al. 2006, Zeng et al. 2014). Phosphorylated FRS2 is known to recruit GRB2 (presumably in complex with SOS1) and PTPN11 (SHP2) to activated NTRK2, leading to augmentation of RAS signaling (Easton et al. 1999, Easton 2006).

**Literature references**


Activated NTRK2 signals through FYN

**Location:** Signaling by NTRK2 (TRKB)

**Stable identifier:** R-HSA-9032500

In mouse brain, Fyn activation downstream of Bdnf-induced Ntrk2 (TrkB) signaling results in increased protein levels of AMPA receptor subunits Gria2 (GluR2), Gria3 (GluR3) and Gria1 (GluR1) without change in mRNA levels (Narisawa-Saito et al. 1999).

BDNF-mediated activation of NTRK2 increases phosphorylation of voltage gated sodium channels by FYN, resulting in decrease of sodium currents (Ahn et al. 2007).

FYN activation downstream of NTRK2 is implicated in olygodendrocyte myelination and contributes to BDNF-induced activation of ERK1/2 (MAPK3/1) through an unknown mechanism (Peckham et al. 2015).

Besides acting downstream of NTRK2, FYN and other SRC kinases, activated by other receptors such as GPCRs, may phosphorylate NTRK2 and enhance its catalytic activity (Rajagopal and Chao 2006, Huang and McNamara 2010).

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CDK5, in complex with its activator CDK5R1 (p35), binds to BDNF-activated NTRK2 (TRKB). NTRK2 promotes CDK5 catalytic activity by phosphorylating CDK5 at tyrosine residue Y15 (Cheung et al. 2007), although CDK5 can also be phosphorylated at Y15 independently of NTRK2 (Zhao et al. 2009). CDK5 phosphorylates serine residue S479 of NTRK2 (corresponds to S478 in mouse and rat) (Cheung et al. 2007, Zhao et al. 2009). Phosphorylation of NTRK2 at S479 is needed for BDNF-triggered dendritic growth (Cheung et al. 2007), hippocampal long-term potentiation (LTP) and spatial memory (Lai et al. 2012). These processes involve NTRK2-mediated activation of RHO GTPases RAC1 (Lai et al. 2012) and possibly CDC42 (Cheung et al. 2007). In cultured isolated neurons, phosphorylation at S479 affects localization of NTRK2 (Zhao et al. 2009), but this does not appear to be the case in vivo (Lai et al. 2012).

CDK5-mediated phosphorylation of NTRK2 was suggested to influence the level of AKT activity, downstream mTOR signaling and DLG4 (PSD-95) expression, but further elucidation is needed (Lai et al. 2012).

Signaling by TRKB and CDK5 plays a role in inflammation induced hypersensitivity to heat-triggered pain in rats (Zhang et al. 2014).

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