## Phylogeny

Member of the tyrosine-kinase (TK) group, TRK subfamily; paralogues are NTRK2 (TRKB) and NTRK3 (TRKC) (Cocco et al., 2018, pp. 1-3). Orthologues are retained throughout vertebrates (human, mouse, rat, zebrafish, medaka, stickleback, sea lamprey), reflecting high conservation after the first and second whole-genome duplications (Brunet et al., 2016, pp. 6-7). In large-scale TK domain trees, the TRK subfamily clusters with DDR, ROR and MUSK receptor families (Brunet et al., 2016, pp. 3-4).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (Micro RNA-mediated regulation …, 2009, pp. 26-30).

## Cofactor Requirements

Requires divalent cations (Mg²⁺ or Mn²⁺) for ATP coordination (TRAF4 and castration-resistant prostate cancer, 2016, p. 27).

## Substrate Specificity

Autophosphorylation sites include Y676, Y680, Y681 (activation loop), Y496 (juxtamembrane NPXY motif) and Y791 (C-terminal PLCγ docking site) (Cocco et al., 2018, pp. 3-4). Phospho-Y496 recruits PTB-domain adaptors SHC1 and FRS2, illustrating preference for NPXY-containing motifs (Cocco et al., 2018, pp. 3-4). Motif profiling indicates selectivity for an acidic residue at –2 and a hydrophobic residue at +1 relative to the target Tyr (Structural and functional alterations …, 2020, pp. 25-28).

## Structure

Single-pass type I membrane protein (≈ 790-796 aa): signal peptide → three leucine-rich repeats flanked by cysteine clusters (C1, C2) → two Ig-like domains → transmembrane helix → juxtamembrane segment → bilobed TK domain → short C-terminal tail (Cocco et al., 2018, pp. 3-4). The mature, N-glycosylated receptor migrates at ~140 kDa (Cocco et al., 2018, pp. 3-4). The kinase domain contains the canonical VAIK, HRD and DFG motifs; Y674-Y675 (human numbering) lie in the activation loop and form part of the hydrophobic regulatory spine (TRAF4 and castration-resistant prostate cancer, 2016, p. 27).

## Regulation

Post-translational: autophosphorylation at Y676/Y680/Y681 enables full catalytic activity; Y496 phosphorylation creates SHC/FRS2 docking sites, while Y791 phosphorylation recruits PLCγ1 (Cocco et al., 2018, pp. 3-4). Lys63-linked polyubiquitination by CBL promotes internalisation and down-regulation (TRAF4 and castration-resistant prostate cancer, 2016, p. 27).  
Allosteric/contextual: nerve growth factor (NGF)–induced homodimerisation drives trans-phosphorylation (Small-molecule modulation …, 2024, pp. 11-15). Co-receptor p75^NTR modulates ligand affinity, turnover and signalling bias (Cocco et al., 2018, pp. 4-6). Alternative splicing generates isoforms TRKA I, TRKA II and constitutively active TRKA III that lacks Ig domains (Cocco et al., 2018, pp. 6-7).

## Function

Highly expressed in sympathetic, trigeminal and dorsal-root-ganglion neurons and in central cholinergic neurons; minimal expression in most non-neuronal tissues (Structural and functional alterations …, 2020, pp. 25-28). NGF binding promotes neuronal survival and differentiation, whereas NT-3 supports axonal extension via NTRK1 (Small-molecule modulation …, 2024, pp. 11-15). Key downstream cascades include:  
• SHC/FRS2-GRB2-SOS → RAS-RAF-MEK-ERK (neuronal differentiation) (Cocco et al., 2018, pp. 4-6).  
• SHC/GAB1 or direct p85 binding → PI3K-AKT (cell survival) (Diaz, 2016, pp. 34-37).  
• Y791-PLCγ1 → PKC pathway (neurite outgrowth) (Cocco et al., 2018, pp. 4-6).  
Interacting partners encompass SH2B1/2, IRS1/2, GRB2, SHP2 and SRC-family kinases (Cocco et al., 2018, pp. 6-7).

## Inhibitors

Clinically approved pan-TRK inhibitors larotrectinib and entrectinib bind the kinase domain with nanomolar potency; CEP-751 and lestaurtinib show pre-clinical activity (Cocco et al., 2018, pp. 6-7, 24-27). Resistance mutations arise within the kinase domain under drug pressure (Cocco et al., 2018, pp. 24-27).

## Other Comments

Loss-of-function variants (e.g., G571R) cause congenital insensitivity to pain with anhidrosis (Cocco et al., 2018, pp. 24-27). Oncogenic fusions retaining the kinase domain (e.g., TPM3-NTRK1, TPR-NTRK1) drive constitutive signalling in diverse tumours; the paralogous ETV6-NTRK3 fusion is well characterised (Cocco et al., 2018, pp. 20-21). Constitutively active splice variant TRKA III contributes to neuroblastoma (Cocco et al., 2018, pp. 6-7). Over-expression correlates with aggressive behaviour in several solid tumours via MAPK and PI3K pathway activation (Cocco et al., 2018, pp. 6-7).

## 9. References

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