1. Phylogeny  
   NTRK3, also known as TrkC, is a member of the neurotrophin receptor tyrosine kinase family that includes two other paralogous proteins, TrkA (encoded by NTRK1) and TrkB (encoded by NTRK2) (vaishnavi2015trkingdownan pages 2-4). Orthologs of NTRK3 are widely distributed among vertebrates, and its amino acid sequence, especially within the intracellular kinase domain, is highly conserved across mammalian, avian, amphibian, and piscine species (amatu2019tropomyosinreceptorkinase pages 1-2). Within the kinome, NTRK3 falls into the receptor tyrosine kinase (RTK) superfamily and specifically the Trk subfamily, which has been evolutionarily maintained due to its critical role in neurotrophin-mediated signaling (vaishnavi2015trkingdownan pages 2-4). Comparative phylogenetic analyses have demonstrated that the structure and function of NTRK3 have been preserved during vertebrate evolution, indicating that the neurotrophin-3 (NT-3) binding function and downstream regulatory roles represent an evolutionarily ancient mechanism for controlling neuronal differentiation and survival (amatu2019tropomyosinreceptorkinase pages 1-2).
2. Reaction Catalyzed  
   NTRK3 is a receptor tyrosine kinase that catalyzes the transfer of the gamma-phosphate from ATP to specific tyrosine residues on target proteins. The canonical reaction is represented as follows:  
     ATP + [protein]-tyrosine → ADP + [protein]-phosphotyrosine + H⁺  
   In the context of NTRK3, ligand binding by NT-3 induces receptor dimerization and leads to trans-autophosphorylation of critical tyrosine residues on the intracellular domain. This phosphorylation event serves both to activate the receptor’s own kinase activity and to create binding sites for downstream adaptor proteins that mediate signaling through pathways such as phosphatidylinositol 3-kinase (PI3K)/AKT and mitogen-activated protein kinase (MAPK) (amatu2019tropomyosinreceptorkinase pages 2-3, jin2020rolesoftrkc pages 1-3). The autophosphorylation reaction is an essential early step in transducing extracellular NT-3 binding into intracellular biochemical signals that ultimately regulate cellular processes like survival and differentiation (lannon2004investigationsintothe pages 181-183).
3. Cofactor Requirements  
   The kinase activity of NTRK3 is dependent on ATP serving as the phosphate donor, and this catalytic process is facilitated by the presence of divalent cations, most notably Mg²⁺. Mg²⁺ acts as a cofactor by coordinating with ATP in the active site of the kinase domain, thereby enabling proper positioning of the γ-phosphate for transfer onto substrate tyrosine residues (amatu2019tropomyosinreceptorkinase pages 2-3, cocco2018ntrkfusionpositivecancers pages 4-6). The requirement for Mg²⁺ is characteristic of most protein kinases and is essential for stabilizing the transition state during phosphoryl transfer. Although additional cofactors such as Mn²⁺ may sometimes substitute under in vitro conditions, physiological activity is primarily dependent on Mg²⁺ (jiang2021developmentofsmallmolecule pages 3-5).
4. Substrate Specificity  
   NTRK3 exhibits substrate specificity typical of receptor tyrosine kinases by targeting tyrosine residues for phosphorylation. Upon NT-3 binding, NTRK3 autophosphorylates on specific intracellular tyrosine residues, which in the case of TrkC include sites such as Y705, Y709, and Y710. These phosphorylated residues serve as docking sites for SH2 domain–containing adaptor proteins, including members such as SHC and FRS2, and for enzymes such as phospholipase Cγ (PLCγ) (amatu2019tropomyosinreceptorkinase pages 2-3). The consensus substrate motif recognized by NTRK3 has not been defined with the same granularity as some other kinases; however, its selectivity is largely determined by the positioning of specific tyrosine residues within the autophosphorylation loop and the surrounding sequence context that facilitates the recruitment of downstream signaling molecules (jin2020rolesoftrkc pages 1-3, vaishnavi2015trkingdownan pages 18-19). Through this mechanism, the specificity of NTRK3 ensures that its activation precisely stimulates critical signaling pathways such as the PI3K/AKT cascade for cell survival and the MAPK pathway for differentiation and proliferation, thereby converting an extracellular growth signal into a coordinated intracellular response (cocco2018ntrkfusionpositivecancers pages 3-4).
5. Structure  
   NTRK3 is a transmembrane receptor tyrosine kinase composed of three principal regions: a large extracellular ligand-binding domain, a hydrophobic transmembrane helix, and an intracellular catalytic domain. The extracellular region is characterized by a complex arrangement of structural motifs including cysteine-rich clusters, multiple leucine-rich repeats, and immunoglobulin-like (Ig) domains. These structural elements are responsible for high-affinity binding to its cognate ligand, NT-3, and play a critical role in determining ligand specificity (amatu2019tropomyosinreceptorkinase pages 1-2, amatu2019tropomyosinreceptorkinase pages 7-8).  
   The transmembrane domain is typically a single α-helical segment that anchors the receptor in the cell membrane, ensuring proper spatial positioning for signal transduction. This region is highly conserved among RTKs and contributes primarily to the structural integrity of the receptor rather than to enzymatic catalysis (vaishnavi2015trkingdownan pages 2-4).  
   The intracellular portion harbors the highly conserved tyrosine kinase domain, which adopts a bilobal structure composed of a smaller N-terminal lobe predominantly formed of β-sheets and a larger C-terminal lobe that is largely helical. Connecting these lobes is a flexible hinge region that allows for the dynamic movement necessary during catalysis. Within the kinase domain, several motifs are critical for catalytic activity and regulation. Notably, the activation loop—a segment that undergoes conformational changes upon autophosphorylation—contains key tyrosine residues (e.g., Y705, Y709, Y710) whose phosphorylation is essential for full kinase activation (takahashi2011postsynaptictrkcand pages 7-8, jin2020rolesoftrkc pages 1-3). In addition, the conserved DFG (Asp-Phe-Gly) motif, located at the beginning of the activation loop, is pivotal in defining the active (DFG-in) and inactive (DFG-out) conformations of the enzyme, thus serving as a regulatory switch for its catalytic activity (jiang2021developmentofsmallmolecule pages 3-5).  
   Alternative splicing of NTRK3 can result in multiple isoforms, including full-length receptors containing the intracellular kinase domain and truncated variants that lack catalytic activity. The truncated forms, though devoid of kinase function, may still participate in cell adhesion and synaptogenic signaling mechanisms, as reported in studies highlighting non-catalytic roles for TrkC in synapse formation (takahashi2011postsynaptictrkcand pages 13-14, amatu2019tropomyosinreceptorkinase pages 8-9). Structural investigations using crystallography and computational models have further revealed the spatial organization of the kinase active site, including the hydrophobic spine and C-helix, which are critical for regulatory conformational changes during activation (jiang2021developmentofsmallmolecule pages 3-5, cocco2018ntrkfusionpositivecancers pages 3-4). These studies collectively underscore the modular design of NTRK3, wherein discrete structural domains mediate ligand recognition, membrane integration, and enzyme catalysis, thereby ensuring precise control over receptor activation and downstream signaling.
6. Regulation  
   The regulatory mechanisms of NTRK3 encompass multiple layers of control that modulate its activation and signal transduction properties. Under normal physiological conditions, binding of NT-3 to the extracellular domain of NTRK3 induces receptor dimerization, which in turn triggers autophosphorylation of specific tyrosine residues within the intracellular kinase domain (amatu2019tropomyosinreceptorkinase pages 2-3, jin2020rolesoftrkc pages 1-3). This phosphorylation event not only activates the kinase but also creates docking sites for a variety of adaptor proteins that initiate downstream signaling cascades such as the PI3K/AKT and MAPK pathways.  
   Alternative splicing contributes significantly to the regulation of NTRK3 by generating distinct isoforms. Some isoforms retain the full kinase domain and are capable of mediating classical tyrosine phosphorylation-dependent signaling, while others are truncated and lack catalytic activity. The non-catalytic variants, which may be highly expressed during specific developmental stages such as synaptogenesis, have been implicated in modulating cell adhesion and synaptic organization independent of NT-3 binding (amatu2019tropomyosinreceptorkinase pages 8-9, takahashi2011postsynaptictrkcand pages 7-8).  
   In addition to ligand-induced activation, NTRK3 is subject to regulation by post-translational modifications. Autophosphorylation of key tyrosine residues (e.g., Y705, Y709, Y710) is required not only for kinase activation but also for the recruitment of downstream signaling molecules such as SHC and PLCγ, which further propagates the signal (amatu2019tropomyosinreceptorkinase pages 2-3, jin2020rolesoftrkc pages 1-3). There is also evidence suggesting that ubiquitination and subsequent receptor internalization may play roles in terminating or modulating NTRK3 signaling, although detailed mechanistic insights into these processes remain less well characterized in the current literature (cocco2018ntrkfusionpositivecancers pages 20-21).  
   In pathological settings, particularly in oncogenesis, regulatory control of NTRK3 is disrupted by gene fusions, most notably the ETV6-NTRK3 fusion. This fusion event results in the constitutive dimerization of the receptor’s kinase domain—driven by the dimerization motifs contributed by the fusion partner—leading to ligand-independent, persistent signaling through proliferative and survival pathways (martin2006theroleof pages 52-57, jin2020rolesoftrkc pages 14-16). Such aberrant regulation is a hallmark of several pediatric and adult malignancies, where the loss of normal ligand dependency contributes to uncontrolled cell growth (vaishnavi2015trkingdownan pages 18-19). Moreover, point mutations and alternative splicing events that affect the phosphorylation sites or the conformation of the kinase domain can further influence the regulatory status of NTRK3, thereby altering its signaling output (jin2020rolesoftrkc pages 12-14, amatu2019tropomyosinreceptorkinase pages 8-9). Collectively, these regulatory mechanisms ensure that NTRK3 signaling is tightly controlled under normal conditions, while their disruption contributes to disease phenotypes.
7. Function  
   NTRK3 plays an essential role in mediating the effects of neurotrophin-3 (NT-3) in the nervous system, as well as influencing processes in non-neuronal tissues. In the nervous system, NT-3 binding to NTRK3 triggers a cascade of intracellular events that promote neuronal survival, differentiation, and synaptic formation. The activation of NTRK3 leads to the stimulation of the PI3K/AKT pathway, which provides anti-apoptotic signals, and the MAPK pathway, which is involved in promoting differentiation and neurite outgrowth (amatu2019tropomyosinreceptorkinase pages 2-3, jin2020rolesoftrkc pages 1-3). This signaling not only supports the survival of sensory neurons but is also critically involved in processes such as memory formation, proprioception, and nociception (amatu2019tropomyosinreceptorkinase pages 8-9).  
   Beyond the nervous system, NTRK3 has been implicated in heart development and vascular regulation. Experimental studies in animal models suggest that disruption of NTRK3 signaling can result in structural cardiac abnormalities and defects in neuromuscular connectivity, underscoring its role in both neuronal and cardiac development (amatu2019tropomyosinreceptorkinase pages 8-9).  
   At the cellular level, NTRK3 activation regulates a broad range of downstream signaling molecules through its phosphorylated tyrosine docking sites. These interactions lead to the assembly of multiprotein signaling complexes that integrate signals from the extracellular milieu with cellular processes including gene transcription, protein synthesis, and cytoskeletal organization (vaishnavi2015trkingdownan pages 18-19, jin2020rolesoftrkc pages 1-3). In addition, the receptor’s capacity to undergo alternative splicing results in isoforms that exert distinct functional outputs. For example, non-catalytic NTRK3 isoforms have been shown to participate in excitatory synapse formation by functioning as synaptogenic adhesion molecules independent of their kinase activity, thereby contributing to the precise organization of neural circuits (takahashi2011postsynaptictrkcand pages 13-14, takahashi2011postsynaptictrkcand pages 7-8).  
   In oncogenic contexts, aberrations in NTRK3 are often observed through gene fusions, such as the ETV6-NTRK3 fusion, which confers constitutive kinase activity that bypasses normal regulatory mechanisms. This ligand-independent activation drives persistent proliferative and survival signaling via cascades such as PI3K/AKT and Ras/MAPK, thereby contributing to tumorigenesis in diverse malignancies including congenital fibrosarcoma, secretory breast carcinoma, and other solid tumors (martin2006theroleof pages 52-57, jin2020rolesoftrkc pages 14-16, cocco2018ntrkfusionpositivecancers pages 27-31). The role of NTRK3 fusions as oncogenic drivers makes the receptor a critical target in precision oncology, and its inhibition by small molecule therapeutics has been shown to induce apoptosis and inhibit tumor growth in preclinical models (vaishnavi2015trkingdownan pages 18-19, cocco2018ntrkfusionpositivecancers pages 20-21).  
   The integration of NTRK3 signaling with other cellular pathways further exemplifies its importance in normal and pathological states. The recruitment of adaptor proteins such as Shc and IRS, and the subsequent activation of downstream kinases, illustrates the receptor’s central role as a signaling hub that coordinates responses to extracellular cues (jin2020rolesoftrkc pages 1-3, amatu2019tropomyosinreceptorkinase pages 2-3). This multifaceted function underlines the fundamental contributions of NTRK3 to neurodevelopment, as well as its potential for dysregulation in cancer.
8. Other Comments  
   Targeted inhibition of NTRK3, particularly in the context of gene fusions, represents a significant therapeutic advancement in oncology. Several small-molecule inhibitors, including larotrectinib and entrectinib, have received regulatory approval for the treatment of tumors harboring NTRK gene fusions, with demonstrated efficacy across a wide range of histologies (vaishnavi2015trkingdownan pages 18-19, cocco2018ntrkfusionpositivecancers pages 20-21). In addition, emerging resistance due to secondary mutations in the kinase domain—such as solvent-front mutations (e.g., G623R)—has prompted the development of next-generation inhibitors designed to overcome these obstacles (jin2020rolesoftrkc pages 14-16, cocco2018ntrkfusionpositivecancers pages 31-34).  
   Beyond its role in cancer, the function of NTRK3 in the nervous system suggests that modulation of its activity may have implications for the treatment of neurodegenerative and neurodevelopmental disorders. However, therapeutic interventions aimed at NTRK3 must balance the need to inhibit oncogenic signaling with the preservation of its normal physiological functions in neuronal survival and differentiation (amatu2019tropomyosinreceptorkinase pages 2-3, takahashi2011postsynaptictrkcand pages 13-14).  
   The existence of multiple receptor isoforms resulting from alternative splicing further complicates the functional landscape of NTRK3, as truncated variants lacking kinase activity may serve as dominant negative regulators or mediate non-catalytic signaling roles, particularly in synapse formation and neuronal connectivity (takahashi2011postsynaptictrkcand pages 7-8, amatu2019tropomyosinreceptorkinase pages 8-9).  
   Overall, the comprehensive nomenclature and functional profile of NTRK3 underscores its significance as a receptor tyrosine kinase central to neurotrophin–mediated signal transduction, with critical roles in both developmental biology and oncogenesis. Its structural complexity, precise regulation via ligand binding and post‐translational modifications, and involvement in major signaling cascades justify its status as a key therapeutic target in precision medicine (vaishnavi2015trkingdownan pages 6-7, jin2021developmentofsmallmolecule pages 17-18).

References

1. (amatu2019tropomyosinreceptorkinase pages 2-3): A. Amatu, A. Sartore-Bianchi, K. Bencardino, E. G. Pizzutilo, F. Tosi, and S. Siena. Tropomyosin receptor kinase (trk) biology and the role of ntrk gene fusions in cancer. Annals of Oncology, 30:viii5-viii15, Nov 2019. URL: https://doi.org/10.1093/annonc/mdz383, doi:10.1093/annonc/mdz383. This article has 313 citations and is from a highest quality peer-reviewed journal.
2. (amatu2019tropomyosinreceptorkinase pages 8-9): A. Amatu, A. Sartore-Bianchi, K. Bencardino, E. G. Pizzutilo, F. Tosi, and S. Siena. Tropomyosin receptor kinase (trk) biology and the role of ntrk gene fusions in cancer. Annals of Oncology, 30:viii5-viii15, Nov 2019. URL: https://doi.org/10.1093/annonc/mdz383, doi:10.1093/annonc/mdz383. This article has 313 citations and is from a highest quality peer-reviewed journal.
3. (jiang2021developmentofsmallmolecule pages 3-5): Tingting Jiang, Guan Wang, Yao Liu, Lu Feng, Meng Wang, Jie Liu, Yi Chen, and Ouyang Liang. Development of small-molecule tropomyosin receptor kinase (trk) inhibitors for ntrk fusion cancers. Acta Pharmaceutica Sinica B, 11:355-372, Feb 2021. URL: https://doi.org/10.1016/j.apsb.2020.05.004, doi:10.1016/j.apsb.2020.05.004. This article has 111 citations and is from a peer-reviewed journal.
4. (jin2020rolesoftrkc pages 1-3): W Jin. Roles of trkc signaling in the regulation of tumorigenicity and metastasis of cancer. Cancers, Jan 2020. URL: https://doi.org/10.3390/cancers12010147, doi:10.3390/cancers12010147. This article has 39 citations and is from a peer-reviewed journal.
5. (jin2020rolesoftrkc pages 12-14): W Jin. Roles of trkc signaling in the regulation of tumorigenicity and metastasis of cancer. Cancers, Jan 2020. URL: https://doi.org/10.3390/cancers12010147, doi:10.3390/cancers12010147. This article has 39 citations and is from a peer-reviewed journal.
6. (jin2020rolesoftrkc pages 14-16): W Jin. Roles of trkc signaling in the regulation of tumorigenicity and metastasis of cancer. Cancers, Jan 2020. URL: https://doi.org/10.3390/cancers12010147, doi:10.3390/cancers12010147. This article has 39 citations and is from a peer-reviewed journal.
7. (martin2006theroleof pages 52-57): Matthew J. Martin. The role of the insulin-like growth factor signaling axis in etv6-ntrk3- mediated anchorage-independent growth and transformation. Unknown journal, 2006. URL: https://doi.org/10.14288/1.0100488, doi:10.14288/1.0100488. This article has 0 citations.
8. (takahashi2011postsynaptictrkcand pages 13-14): Hideto Takahashi, Pamela Arstikaitis, Tuhina Prasad, Thomas E. Bartlett, Y. T. Wang, T. Murphy, and A. Craig. Postsynaptic trkc and presynaptic ptpσ function as a bidirectional excitatory synaptic organizing complex. Neuron, 69:287-303, Jan 2011. URL: https://doi.org/10.1016/j.neuron.2010.12.024, doi:10.1016/j.neuron.2010.12.024. This article has 231 citations and is from a highest quality peer-reviewed journal.
9. (vaishnavi2015trkingdownan pages 18-19): Aria Vaishnavi, Anh T. Le, and Robert C. Doebele. Trking down an old oncogene in a new era of targeted therapy. Cancer Discovery, 5:25-34, Jan 2015. URL: https://doi.org/10.1158/2159-8290.cd-14-0765, doi:10.1158/2159-8290.cd-14-0765. This article has 695 citations and is from a highest quality peer-reviewed journal.
10. (vaishnavi2015trkingdownan pages 2-4): Aria Vaishnavi, Anh T. Le, and Robert C. Doebele. Trking down an old oncogene in a new era of targeted therapy. Cancer Discovery, 5:25-34, Jan 2015. URL: https://doi.org/10.1158/2159-8290.cd-14-0765, doi:10.1158/2159-8290.cd-14-0765. This article has 695 citations and is from a highest quality peer-reviewed journal.
11. (amatu2019tropomyosinreceptorkinase pages 1-2): A. Amatu, A. Sartore-Bianchi, K. Bencardino, E. G. Pizzutilo, F. Tosi, and S. Siena. Tropomyosin receptor kinase (trk) biology and the role of ntrk gene fusions in cancer. Annals of Oncology, 30:viii5-viii15, Nov 2019. URL: https://doi.org/10.1093/annonc/mdz383, doi:10.1093/annonc/mdz383. This article has 313 citations and is from a highest quality peer-reviewed journal.
12. (amatu2019tropomyosinreceptorkinase pages 7-8): A. Amatu, A. Sartore-Bianchi, K. Bencardino, E. G. Pizzutilo, F. Tosi, and S. Siena. Tropomyosin receptor kinase (trk) biology and the role of ntrk gene fusions in cancer. Annals of Oncology, 30:viii5-viii15, Nov 2019. URL: https://doi.org/10.1093/annonc/mdz383, doi:10.1093/annonc/mdz383. This article has 313 citations and is from a highest quality peer-reviewed journal.
13. (cocco2018ntrkfusionpositivecancers pages 20-21): Emiliano Cocco, Maurizio Scaltriti, and Alexander Drilon. Ntrk fusion-positive cancers and trk inhibitor therapy. Nature Reviews Clinical Oncology, 15:731-747, Oct 2018. URL: https://doi.org/10.1038/s41571-018-0113-0, doi:10.1038/s41571-018-0113-0. This article has 1442 citations and is from a domain leading peer-reviewed journal.
14. (cocco2018ntrkfusionpositivecancers pages 27-31): Emiliano Cocco, Maurizio Scaltriti, and Alexander Drilon. Ntrk fusion-positive cancers and trk inhibitor therapy. Nature Reviews Clinical Oncology, 15:731-747, Oct 2018. URL: https://doi.org/10.1038/s41571-018-0113-0, doi:10.1038/s41571-018-0113-0. This article has 1442 citations and is from a domain leading peer-reviewed journal.
15. (cocco2018ntrkfusionpositivecancers pages 3-4): Emiliano Cocco, Maurizio Scaltriti, and Alexander Drilon. Ntrk fusion-positive cancers and trk inhibitor therapy. Nature Reviews Clinical Oncology, 15:731-747, Oct 2018. URL: https://doi.org/10.1038/s41571-018-0113-0, doi:10.1038/s41571-018-0113-0. This article has 1442 citations and is from a domain leading peer-reviewed journal.
16. (cocco2018ntrkfusionpositivecancers pages 31-34): Emiliano Cocco, Maurizio Scaltriti, and Alexander Drilon. Ntrk fusion-positive cancers and trk inhibitor therapy. Nature Reviews Clinical Oncology, 15:731-747, Oct 2018. URL: https://doi.org/10.1038/s41571-018-0113-0, doi:10.1038/s41571-018-0113-0. This article has 1442 citations and is from a domain leading peer-reviewed journal.
17. (cocco2018ntrkfusionpositivecancers pages 4-6): Emiliano Cocco, Maurizio Scaltriti, and Alexander Drilon. Ntrk fusion-positive cancers and trk inhibitor therapy. Nature Reviews Clinical Oncology, 15:731-747, Oct 2018. URL: https://doi.org/10.1038/s41571-018-0113-0, doi:10.1038/s41571-018-0113-0. This article has 1442 citations and is from a domain leading peer-reviewed journal.
18. (lannon2004investigationsintothe pages 181-183): Investigations into the cellular pathways underlying ETV6-NTRK3-mediated transformation
19. (takahashi2011postsynaptictrkcand pages 7-8): Hideto Takahashi, Pamela Arstikaitis, Tuhina Prasad, Thomas E. Bartlett, Y. T. Wang, T. Murphy, and A. Craig. Postsynaptic trkc and presynaptic ptpσ function as a bidirectional excitatory synaptic organizing complex. Neuron, 69:287-303, Jan 2011. URL: https://doi.org/10.1016/j.neuron.2010.12.024, doi:10.1016/j.neuron.2010.12.024. This article has 231 citations and is from a highest quality peer-reviewed journal.
20. (vaishnavi2015trkingdownan pages 6-7): Aria Vaishnavi, Anh T. Le, and Robert C. Doebele. Trking down an old oncogene in a new era of targeted therapy. Cancer Discovery, 5:25-34, Jan 2015. URL: https://doi.org/10.1158/2159-8290.cd-14-0765, doi:10.1158/2159-8290.cd-14-0765. This article has 695 citations and is from a highest quality peer-reviewed journal.