## Phylogeny

• Orthologs: Homo sapiens TYRO3 (Q06418), Mus musculus Tyro3 and Rattus norvegicus Sky/Byk are established orthologs, reflecting high conservation within mammals (hsu2019tyro3apotential pages 11-12, jacobsen2011tyro3(tyro3protein pages 3-4).  
• Family relationships: TYRO3, AXL and MERTK constitute the TAM receptor tyrosine kinase subfamily, sharing 31–36 % amino-acid identity in the ectodomain and 54–59 % in the cytoplasmic region (jacobsen2011tyro3(tyro3protein pages 3-4).  
• Kinome placement: classified in the Tyrosine Kinase (TK) group, receptor tyrosine kinase branch, TAM subfamily (smart2018theemergingrole pages 1-3).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine → ADP + [protein]-O-phospho-L-tyrosine (hsu2019tyro3apotential pages 11-12).

## Cofactor Requirements

Requires Mg²⁺ for phosphotransferase activity, consistent with receptor tyrosine kinases (hsu2019tyro3apotential pages 11-12).

## Substrate Specificity

No intrinsic consensus phosphorylation motif has been reported for TYRO3; substrate recognition relies on autophosphorylation sites that create SH2 docking platforms for downstream effectors (smart2018theemergingrole pages 18-20).

## Structure

• Modular organization: N-terminal signal peptide → two Ig-like C2 domains → two fibronectin type III domains → single-span transmembrane helix → intracellular kinase domain containing the TAM-signature KW(I/L)A(I/L)ES sequence (smart2018theemergingrole pages 1-3).  
• Size and PTM: full length 890 aa, calculated mass ~97 kDa; migrates at 120–140 kDa owing to extensive N-glycosylation in the ectodomain (smart2018theemergingrole pages 1-3).  
• Activation segment: autophosphorylation occurs at Y681, Y685 and Y823 within the activation loop, stabilising the active conformation (smart2018theemergingrole pages 1-3).  
• Quaternary state: ligand binding drives homodimerisation; high surface density supports ligand-independent homodimers; heterodimer formation with AXL enhances cross-phosphorylation (smart2018theemergingrole pages 6-8).  
• Regulatory motifs: intact hydrophobic spine and correctly positioned C-helix accompany activation; the KWIAIES stretch is unique to TAM kinases and contributes to catalytic core integrity (smart2018theemergingrole pages 18-20).  
• Subcellular trafficking: a fraction of TYRO3 can translocate to the nucleus in certain tumours, implying alternative localisation signals within the cytoplasmic tail (smart2018theemergingrole pages 9-11).

## Regulation

• Ligand-induced activation: GAS6, PROS1 and tubby-like proteins TULP1/2 bind the ectodomain, promote dimerisation and trigger autophosphorylation (smart2018theemergingrole pages 4-6, hsu2019tyro3apotential pages 2-3).  
• Autophosphorylation sites: Y681, Y685, Y823 create binding sites for PIK3R1, GRB2, SHC1 and SRC-family kinases (smart2018theemergingrole pages 1-3).  
• Ubiquitination: Cbl E3 ligases ubiquitinate activated TYRO3, driving receptor internalisation and degradation (smart2018theemergingrole pages 1-3).  
• Dephosphorylation: phosphatase-mediated tyrosine dephosphorylation attenuates signalling, although specific PTPs are not yet defined (hsu2019tyro3apotential pages 11-12).  
• Heterotypic receptor control: AXL/TYRO3 heterodimers broaden ligand responsiveness and signalling amplitude (smart2018theemergingrole pages 6-8).  
• Immune checkpoint function: STAT1 activation downstream of TYRO3 suppresses TLR-driven inflammatory signalling (smart2018theemergingrole pages 9-11).

## Function

• Expression: abundant in CNS neurons, oligodendrocytes, Schwann cells, endothelial cells, platelets, dendritic cells, monocytes/macrophages, NK cells, Sertoli and granulosa cells, and multiple parenchymal organs including kidney, lung, liver and heart (smart2018theemergingrole pages 1-3, prieto2007localizationandsignaling pages 1-2).  
• Neurology: supports neuronal survival, dendritic development and hippocampal long-term potentiation (prieto2007localizationandsignaling pages 1-2).  
• Haemostasis: promotes platelet aggregation and stabilises thrombi; Tyro3-knockout mice display impaired clot formation (smart2018theemergingrole pages 9-11).  
• Innate immunity: limits TLR signalling and drives macrophage M2 polarisation via ligand-dependent p38 MAPK modulation (smart2018theemergingrole pages 15-17).  
• Signalling network: phosphorylated TYRO3 recruits PIK3R1, GRB2, SHC1 and SRC kinases, activating PI3K-AKT, MAPK/ERK, FYN, JAK/STAT3 and NF-κB cascades (hsu2019tyro3apotential pages 11-12, smart2018theemergingrole pages 8-9).  
• Oncogenesis: overexpressed in colorectal, breast (HER2⁺), hepatocellular, lung, ovarian, melanoma and sarcoma cells; drives anchorage-independent growth, EMT (↓E-cadherin, ↑N-cadherin, ↑SNAI1), invasion, metastasis and resistance to cytotoxic and targeted therapies (smart2018theemergingrole pages 11-13, smart2018theemergingrole pages 13-15).

## Inhibitors

• Multi-target TKIs: crizotinib, foretinib and sorafenib induce apoptosis in TYRO3-high tumour cells (smart2018theemergingrole pages 11-13).  
• Pan-TAM inhibitors: LDC1267, ONO-7475, RXDX-106 and sitravatinib exhibit low-nanomolar potency toward TYRO3 in preclinical models (smart2018theemergingrole pages 17-18).  
• TYRO3-selective chemotypes: spiroindoline-2-carboxyindoles and 2,4-diaminopyrimidine-5-carboxamides; Compound 21 shows IC₅₀ = 0.7 nM but limited bioavailability (smart2018theemergingrole pages 15-17).  
• Biologics: extracellular-domain neutralising antibodies block ligand binding, reverse EMT and restore 5-fluorouracil sensitivity in xenografts (smart2018theemergingrole pages 17-18).

## Other Comments

• Prognostic value: high TYRO3 correlates with poor outcome in colorectal cancer, hepatocellular carcinoma and HER2-positive breast cancer (smart2018theemergingrole pages 15-17).  
• Somatic alterations: missense, truncating and cytoplasmic-tail mutations reported in colon, lung, melanoma, brain, AML, pancreatic cancer and CML; functional impact largely unresolved (smart2018theemergingrole pages 4-6).  
• Genetic ablation: Tyro3-null mice develop autoimmune features, neurological deficits and subfertility, informing potential on-target toxicities of systemic inhibition (smart2018theemergingrole pages 11-13).

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