Protein: Tyrosine-protein kinase receptor UFO (AXL)  
UniProt ID: P30530

## Phylogeny

Human AXL belongs to the Tyrosine Kinase (TK) group, Receptor Tyrosine Kinase (RTK) class, TAM subfamily together with TYRO3 and MERTK, as defined in the canonical human kinome classification (feneyrolles2014axlkinaseas pages 1-3, gajiwala2017theaxlkinase pages 12-13). Orthologs are documented in Mus musculus, Rattus norvegicus and Danio rerio, demonstrating conservation across vertebrates (paccez2014thereceptortyrosine pages 1-6, zhu2019axlreceptortyrosine pages 16-16). Structural superposition of AXL and MERTK kinase domains yields an RMSD of ~0.8–0.9 Å, indicating high evolutionary conservation within the TAM family (gajiwala2017theaxlkinase pages 3-4).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine → ADP + [protein]-O-phospho-L-tyrosine (feneyrolles2014axlkinaseas pages 1-3, gajiwala2017theaxlkinase pages 3-4).

## Cofactor Requirements

Catalytic activity requires divalent cations; purified human AXL kinase domain is active in the presence of Mg²⁺ or Mn²⁺ (myers2016axlinhibitorsin pages 1-4).

## Substrate Specificity

High-throughput bacterial display mapping shows a preference for hydrophobic residues at +1 to +5 (Φ), leucine or isoleucine at –1, and asparagine at –5 to –3 relative to the phosphorylated tyrosine, whereas lysine/arginine are disfavoured; consensus motif: NxxI/L-Y-ΦΦΦ (creixell2023dissectingsignalingregulators pages 20-23). Directly validated substrates include FAK1 Y861, ACK1, SHP-2, CTNND1, TJP2, BCAR1, CBLB and CBLC (creixell2023dissectingsignalingregulators pages 20-23). Autophosphorylation at Y779 creates a PI3K docking site, underscoring context-specific substrate selection (gajiwala2017theaxlkinase pages 3-4).

## Structure

Domain organisation: two N-terminal immunoglobulin-like domains followed by two fibronectin type III domains form the ectodomain; a single-pass transmembrane helix precedes a juxtamembrane segment and a C-terminal kinase domain containing the TAM-signature KWIAIES motif (feneyrolles2014axlkinaseas pages 1-3).  
3D architecture: the first crystal structure of the human kinase domain bound to a macrocyclic inhibitor captures both an inactive and an active molecule within the asymmetric unit, distinguished by C-helix orientation and juxtamembrane packing (gajiwala2017theaxlkinase pages 11-12). Catalytic features include gatekeeper Thr683, canonical HRD and DFG motifs, a fully assembled hydrophobic spine and an activation loop harbouring Y779, Y821 and Y866 (gajiwala2017theaxlkinase pages 3-4). Juxtamembrane Leu526 stabilises the active conformation; the L526A mutation halves catalytic turnover and reduces autophosphorylation (gajiwala2017theaxlkinase pages 3-4). Hydrogen-deuterium exchange shows higher conformational dynamics for AXL relative to MERTK, offering exploitable selectivity determinants (gajiwala2017theaxlkinase pages 24-25).

## Regulation

Post-translational modifications  
• Autophosphorylation: Y698, Y702, Y703, Y779, Y821, Y866; Y866 can serve as an inhibitory site (feneyrolles2014axlkinaseas pages 1-3).  
• Ubiquitination promotes endocytosis and down-regulation (zhu2019axlreceptortyrosine pages 16-16).  
• Ectodomain shedding by ADAM10/ADAM17 limits surface abundance (myers2016axlinhibitorsin pages 1-4).  
• HSP90 chaperoning stabilises the receptor (levin2016axlreceptoraxis pages 1-3).

Activation mechanisms  
• Ligand-dependent homodimerisation upon GAS6 binding in the presence of phosphatidylserine (levin2016axlreceptoraxis pages 1-3, dagamajalu2021apathwaymap pages 1-2).  
• Ligand-independent activation via receptor overexpression, oxidative stress, or heterodimerisation with TYRO3, EGFR or MET (myers2016axlinhibitorsin pages 4-8, levin2016axlreceptoraxis pages 1-3).

Transcriptional/epigenetic control  
• Positive regulators: SP1, SP3, mutant p53, YAP1, HIF-1 (levin2016axlreceptoraxis pages 1-3, bhalla2023axlinhibitorsstatus pages 1-3).  
• Negative regulators: promoter CpG methylation; miR-34a and miR-199a/b mediated mRNA degradation (myers2016axlinhibitorsin pages 4-8).

## Function

Expression: detectable in endothelial cells, vascular smooth-muscle, Schwann cells, neurons, monocytes, platelets and multiple adult organs; frequently overexpressed in lung, breast, glioblastoma, melanoma and pancreatic cancers (feneyrolles2014axlkinaseas pages 1-3, dagamajalu2021apathwaymap pages 4-5, myers2016axlinhibitorsin pages 4-8).

Upstream inputs  
• Primary ligand GAS6; additional ligands TULP-1 and galectin-3 bind selectively to AXL (myers2016axlinhibitorsin pages 4-8).  
• Crosstalk with EGFR, MET and TYRO3 facilitates bypass signalling (myers2016axlinhibitorsin pages 4-8, levin2016axlreceptoraxis pages 1-3).

Interactors and substrates  
• SH2/SH3 adaptors: PIK3R1/2/3, GRB2, PLCG1, NCK2 (dagamajalu2021apathwaymap pages 4-5).  
• Phosphatase: PTPN11 (dagamajalu2021apathwaymap pages 4-5).  
• Kinases: SRC family, LCK, FAK1, ACK1 (creixell2023dissectingsignalingregulators pages 20-23, dagamajalu2021apathwaymap pages 4-5).  
• E3 ligases: CBLB, CBLC (creixell2023dissectingsignalingregulators pages 20-23).

Downstream pathways  
Activation of PI3K-AKT-mTOR, RAS-RAF-MEK-ERK, SRC/FAK, JAK/STAT and NF-κB cascades governs survival, proliferation, migration, epithelial-mesenchymal transition, angiogenesis, immune modulation and efferocytosis (feneyrolles2014axlkinaseas pages 1-3, paccez2014thereceptortyrosine pages 16-21, levin2016axlreceptoraxis pages 1-3).

## Inhibitors

• R428/BGB324 (bemcentinib) – selective nanomolar AXL inhibitor that blocks downstream signalling and enhances chemosensitivity in vivo (paccez2014thereceptortyrosine pages 16-21, danielli2024evaluationofthe pages 13-13).  
• Macrocyclic inhibitor captured in the AXL crystal structure, stabilising the active conformation (gajiwala2017theaxlkinase pages 12-13).  
• S49076 (ATP-competitive MET/AXL/FGFR inhibitor), 2-D08, UNC2025, SGI-7079 and UNC569 show sub-micromolar AXL potency (zhu2019axlreceptortyrosine pages 9-10).  
• Dasatinib suppresses SRC-dependent AXL phosphorylation clusters C2/C3 (creixell2023dissectingsignalingregulators pages 17-20).

## Other Comments

AXL overexpression, gene amplification or activating fusions correlate with metastasis, poor prognosis and resistance to EGFR inhibitors, chemotherapy and immune checkpoint blockade in multiple solid tumours (myers2016axlinhibitorsin pages 4-8, levin2016axlreceptoraxis pages 1-3, zhu2019axlreceptortyrosine pages 16-16). The L526A juxtamembrane mutation impairs catalytic activity by ~50 % (gajiwala2017theaxlkinase pages 3-4). Dysregulated GAS6-AXL signalling is additionally implicated in fibrosis, chronic immune disorders and vascular pathologies (dagamajalu2021apathwaymap pages 1-2).

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