## Phylogeny

Human AXL is classified within the tyrosine kinase (TK) group, receptor tyrosine kinase (RTK) class, TAM sub-family, where it clusters with TYRO3 and MERTK (Feneyrolles et al., 2014; Gajiwala et al., 2017). Orthologues are reported in Mus musculus, Rattus norvegicus and Danio rerio, indicating broad vertebrate conservation (Paccez et al., 2014; Zhu et al., 2019). Structural superposition of AXL and MERTK kinase domains yields an RMSD of ~0.8–0.9 Å, underscoring strong evolutionary conservation inside the TAM branch (Gajiwala et al., 2017).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O-phospho-L-tyrosine (Feneyrolles et al., 2014; Gajiwala et al., 2017).

## Cofactor Requirements

Catalytic activity requires divalent cations; purified kinase is active with Mg²⁺ or Mn²⁺ (Myers et al., 2016).

## Substrate Specificity

High-throughput bacterial display defined a consensus NxxI/L-Y-ΦΦΦ (Φ = hydrophobic) motif. Preferred features include Leu/Ile at –1, hydrophobic residues at +1 to +5, and Asn at –5 to –3, whereas Lys/Arg are disfavoured. Experimentally validated substrates comprise FAK1 Y861, ACK1, SHP-2, CTNND1, TJP2, BCAR1, CBLB and CBLC. Autophosphorylation at Y779 generates a PI3K docking site (Creixell et al., 2023; Gajiwala et al., 2017).

## Structure

The ectodomain contains two Ig-like and two fibronectin type III modules, followed by a single-pass transmembrane helix, a juxtamembrane segment and a C-terminal kinase domain that harbours the TAM-signature KWIAIES sequence (Feneyrolles et al., 2014). The first crystal structure captured both inactive and active kinase conformers within one asymmetric unit; they differ in C-helix orientation and juxtamembrane packing (Gajiwala et al., 2017). Key catalytic elements include gatekeeper Thr683, canonical HRD and DFG motifs, a complete hydrophobic spine and an activation loop bearing Y779, Y821 and Y866. Juxtamembrane Leu526 stabilises the active state; L526A reduces catalytic turnover by ~50 % (Gajiwala et al., 2017). Hydrogen-deuterium exchange indicates higher intrinsic dynamics for AXL relative to MERTK, offering selectivity determinants for drug design (Gajiwala et al., 2017).

## Regulation

Post-translational modifications  
• Autophosphorylation on Y698, Y702, Y703, Y779, Y821 and Y866 (Feneyrolles et al., 2014).  
• Ubiquitination drives endocytosis and down-regulation (Zhu et al., 2019).  
• Ectodomain shedding by ADAM10/17 restricts surface levels (Myers et al., 2016).  
• HSP90 chaperoning stabilises the receptor (Levin et al., 2016).

Activation mechanisms  
• Ligand-dependent homodimerisation upon GAS6 binding in the presence of phosphatidylserine (Levin et al., 2016; Dagamajalu et al., 2021).  
• Ligand-independent activation via receptor overexpression, oxidative stress, or heterodimerisation with TYRO3, EGFR or MET (Myers et al., 2016; Levin et al., 2016).

Transcriptional/epigenetic control  
• Positive: SP1/3, mutant p53, YAP1, HIF-1 (Levin et al., 2016; Bhalla & Gerber, 2023).  
• Negative: promoter CpG methylation; miR-34a and miR-199a/b (Myers et al., 2016).

## Function

Expression is documented in endothelial and vascular smooth-muscle cells, Schwann cells, neurons, monocytes, platelets and many adult organs; overexpression is frequent in lung, breast, glioblastoma, melanoma and pancreatic cancers (Feneyrolles et al., 2014; Dagamajalu et al., 2021; Myers et al., 2016).

Upstream inputs  
Primary ligand GAS6, with additional specificity for TULP-1 and galectin-3. Crosstalk with EGFR, MET and TYRO3 supports bypass signalling (Myers et al., 2016; Levin et al., 2016).

Interactors and substrates  
SH2/SH3 adaptors (PIK3R1/2/3, GRB2, PLCG1, NCK2), phosphatase PTPN11, kinases SRC family, LCK, FAK1, ACK1, and E3 ligases CBLB/CBLC (Creixell et al., 2023; Dagamajalu et al., 2021).

Downstream pathways  
Activation of PI3K-AKT-mTOR, RAS-RAF-MEK-ERK, SRC/FAK, JAK/STAT and NF-κB cascades drives survival, proliferation, migration, EMT, angiogenesis, immune modulation and efferocytosis (Feneyrolles et al., 2014; Paccez et al., 2014; Levin et al., 2016).

## Inhibitors

• R428/BGB324 (bemcentinib) – selective nanomolar ATP-competitive inhibitor that blocks signalling and enhances chemosensitivity in vivo (Paccez et al., 2014; Danielli et al., 2024).  
• Macrocyclic inhibitor co-crystallised with AXL (Gajiwala et al., 2017).  
• S49076, 2-D08, UNC2025, SGI-7079 and UNC569 – sub-micromolar potency (Zhu et al., 2019).  
• Dasatinib suppresses SRC-dependent AXL phosphorylation clusters (Creixell et al., 2023).

## Other Comments

AXL overexpression, amplification or activating fusions correlate with metastasis, poor prognosis and resistance to EGFR inhibitors, chemotherapy and immune checkpoint blockade (Myers et al., 2016; Levin et al., 2016; Zhu et al., 2019). Dysregulated GAS6-AXL signalling is additionally implicated in fibrosis, chronic immune disorders and vascular pathologies (Dagamajalu et al., 2021).

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