1. Phylogeny  
   AXL is a receptor tyrosine kinase that is a member of the TAM family, which comprises TYRO3, AXL, and MERTK, and is evolutionarily conserved across vertebrate species (OpenTargets Search: -AXL). Its orthologs can be identified in mammals and other vertebrates, which supports its fundamental role in processes such as immune regulation and cell signaling across evolution (bhanumathy2021proteintyrosinekinases pages 1-2). Based on comprehensive kinome studies by Manning and colleagues, AXL falls within a distinct subgroup of receptor tyrosine kinases that emerged during vertebrate evolution, and its conservation from lower vertebrates to humans underscores its involvement in critical cellular functions (OpenTargets Search: -AXL). In summary, the phylogenetic context of AXL is defined by its grouping with the TAM receptors in the broader RTK superfamily, and its widespread ortholog distribution points to an ancient and essential role in cellular regulation (bhanumathy2021proteintyrosinekinases pages 1-2).
2. Reaction Catalyzed  
   AXL catalyzes a phosphorylation reaction in which the γ-phosphate group of ATP is transferred to specific tyrosine residues on target substrate proteins, thereby converting ATP to ADP and resulting in the formation of a phosphorylated protein plus a proton (OpenTargets Search: -AXL). This general kinase reaction can be represented as: ATP + [protein]-tyrosine → ADP + [protein]-phosphotyrosine + H⁺, a process that underlies the signal transduction functions of AXL (bhanumathy2021proteintyrosinekinases pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of AXL, as with most protein kinases, requires the presence of divalent cations, with magnesium ions (Mg²⁺) serving as the essential cofactor necessary for ATP binding and proper alignment of the phosphate group during the phosphoryl transfer reaction (OpenTargets Search: -AXL). Mg²⁺ acts by stabilizing the negative charges of ATP and facilitating the coordination of residues in the active site of the kinase domain, a requirement that is consistent across many tyrosine kinases (bhanumathy2021proteintyrosinekinases pages 1-2).
4. Substrate Specificity  
   AXL exhibits substrate specificity that is characterized by the phosphorylation of specific tyrosine residues on a set of downstream signaling proteins. The substrates of AXL include the regulatory subunits of phosphoinositide 3‐kinase—PIK3R1, PIK3R2, and PIK3R3—as well as adaptor and effector proteins such as GRB2, PLCG1, LCK, and PTPN11, all of which contribute to the propagation of intracellular signaling (OpenTargets Search: -AXL). Additional candidate substrates include molecules involved in feedback and regulatory processes, such as CBL, NCK2, SOCS1, and TNS2, whose phosphorylation events facilitate further modulation of cell survival pathways (bhanumathy2021proteintyrosinekinases pages 1-2). The recognition of substrate proteins is determined by the structure of the AXL kinase domain, and although a strict consensus phosphorylation motif for AXL has not been fully delineated in the available literature, its diverse substrate repertoire suggests that the receptor is capable of phosphorylating substrates that possess accessible tyrosine residues within specific protein–protein interaction contexts (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 15-16).
5. Structure  
   AXL is a type I transmembrane protein whose domain organization can be divided into three major regions. At the N-terminus, the extracellular domain comprises two immunoglobulin-like (Ig-like) domains and two fibronectin type III (FNIII) repeats, which together mediate the binding of its principal ligand, growth arrest–specific protein 6 (GAS6) (OpenTargets Search: -AXL). This extracellular architecture is critical for ligand recognition and subsequent receptor dimerization. Following the extracellular region is a single transmembrane helix that anchors AXL in the plasma membrane, providing a conduit for signal transduction from the extracellular milieu to the intracellular compartment (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 15-16). The intracellular part of AXL contains the tyrosine kinase domain, which is organized into a bilobal structure typical of protein kinases; it includes an N-terminal lobe largely comprising β–sheets, a C-terminal lobe dominated by α–helices, and a well‐defined catalytic cleft where ATP binds (bhanumathy2021proteintyrosinekinases pages 1-2).  
   Within the kinase domain, key catalytic and regulatory features are present: an activation loop that undergoes conformational changes upon autophosphorylation, a conserved DFG motif that coordinates the magnesium ion, and a C-helix that plays a significant role in ATP positioning and substrate orientation (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 15-16). AXL also contains autophosphorylation sites, such as tyrosine 702, which are critical for its full activation and serve as docking sites for downstream signaling molecules (OpenTargets Search: -AXL). These structural elements are in line with the canonical architecture of receptor tyrosine kinases and are essential for both catalytic activity and regulation of the receptor’s signaling output (bhanumathy2021proteintyrosinekinases pages 1-2).
6. Regulation  
   The activity of AXL is predominantly regulated at the level of its extracellular ligand interactions and subsequent receptor dimerization. Binding of the vitamin K–dependent ligand GAS6 to the extracellular domain of AXL induces receptor dimerization, which in turn triggers autophosphorylation of key tyrosine residues within the intracellular kinase domain; this autophosphorylation event is necessary for the recruitment of downstream signaling molecules (OpenTargets Search: -AXL). In addition to ligand binding, proteolytic cleavage of AXL’s extracellular domain by metalloproteinases such as ADAM10 and ADAM17 can release a soluble form (sAXL) into the extracellular space, an event that modulates the overall cellular levels of membrane-bound AXL and serves as a putative biomarker for disease progression in certain cancers (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 15-16). Post-translational modifications – including ubiquitination – further influence receptor internalization and degradation, thereby providing additional layers of regulation that fine-tune signal intensity (OpenTargets Search: -AXL). Moreover, AXL’s phosphorylation status is modulated by interactions with other kinases and adaptor proteins, ensuring that the balance between activation and inhibition is maintained under physiological conditions (bhanumathy2021proteintyrosinekinases pages 1-2).
7. Function  
   AXL functions as a receptor tyrosine kinase that transduces extracellular signals into intracellular responses, thereby regulating a variety of physiological processes. Upon binding to GAS6, AXL dimerizes and autophosphorylates, leading to the recruitment and activation of diverse downstream signaling molecules, including the PI3-kinase subunits (PIK3R1, PIK3R2, PIK3R3), GRB2, PLCG1, LCK, and PTPN11; these events culminate in the activation of the AKT kinase pathway (OpenTargets Search: -AXL). Through this signaling cascade, AXL promotes cell survival, proliferation, migration, and differentiation, which are vital processes in normal tissue homeostasis as well as in pathological states such as cancer (katoh2020precisionmedicinefor pages 8-9). In endothelial cells, AXL-mediated signaling contributes to cell survival during acidification by preventing apoptosis, whereas in immune cells it is critical for optimal cytokine signaling during the development of natural killer cells (OpenTargets Search: -AXL). Additionally, AXL is involved in hepatic regeneration and has been implicated in the survival of gonadotropin-releasing hormone neurons, indicating its widespread influence on cellular physiology (katoh2020precisionmedicinefor pages 8-9). In oncogenic contexts, overexpression and aberrant activation of AXL are associated with enhanced tumor cell migration, invasion, and therapy resistance; its activity is thus linked to aggressive tumor phenotypes in a range of cancers (OpenTargets Search: -AXL).
8. Other Comments  
   AXL is recognized as an oncogene, and its overexpression has been reported in several human malignancies, including acute myeloid leukemia, melanoma, non-small cell lung cancer, and others, where it is often correlated with poor prognosis and resistance to targeted therapies (katoh2020precisionmedicinefor pages 8-9). Owing to its central role in promoting pro-survival and migratory signals, AXL has emerged as a promising therapeutic target. Several inhibitors have been developed that target the kinase activity of AXL; for example, the small molecule inhibitor BGB324 (bemcentinib) has shown promising preclinical and early clinical results in overcoming resistance mechanisms in cancer (moonmuang2023theroleof pages 14-15). In addition, antibody-based therapeutics and antibody–drug conjugates aimed at AXL are under investigation to selectively suppress AXL-mediated oncogenic pathways (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 1-2). The development of selective inhibitors is guided by detailed kinase selectivity profiling using kinome-wide assays, ensuring that potential drugs achieve a favorable balance between potency and selectivity (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 5-6). Furthermore, soluble AXL (sAXL) generated through proteolytic shedding has garnered attention as a non-invasive biomarker for disease progression and therapeutic response, particularly in the context of metastatic cancers (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 6-7). These aspects underscore the importance of AXL not only as a regulatory node in normal signaling but also as a critical target in oncology drug discovery (katoh2020precisionmedicinefor pages 8-9).
9. References
10. OpenTargets Search: -AXL. Buniello, A. et al. (2025). Open Targets Platform: facilitating therapeutic hypotheses building in drug discovery. Nucleic Acids Research.
11. bhanumathy2021proteintyrosinekinases pages 1-2. Kalpana K. Bhanumathy, Amrutha Balagopal, Frederick S. Vizeacoumar, et al. (2021). Protein tyrosine kinases: their roles and their targeting in leukemia. Cancers, 13:184.
12. liu2017identificationandcharacterization pages 8-9. Ake Liu, Funan He, and Xun Gu. (2017). Identification and characterization of tyrosine kinases in anole lizard indicate the conserved tyrosine kinase repertoire in vertebrates. Molecular Genetics and Genomics, 292:1405-1418.
13. moonmuang2023theroleof pages 14-15. Sutpirat Moonmuang, Apichat Tantraworasin, Santhasiri Orrapin, et al. (2023). The role of proteomics and phosphoproteomics in the discovery of therapeutic targets and biomarkers in acquired EGFR-TKI-resistant non-small cell lung cancer. International Journal of Molecular Sciences, 24:4827.
14. szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 1-2, 15-16, 5-6, 6-7. István Szabadkai, Robert Torka, Rita Garamvölgyi, et al. (2018). Discovery of n-[4-(quinolin-4-yloxy)phenyl]benzenesulfonamides as novel AXL kinase inhibitors. Journal of Medicinal Chemistry, 61:6277-6292.
15. katoh2020precisionmedicinefor pages 8-9. Masuko Katoh and Masaru Katoh. (2020). Precision medicine for human cancers with Notch signaling dysregulation (review). International Journal of Molecular Medicine, 45:279-297.

References

1. (OpenTargets Search: -AXL): Open Targets Query (-AXL, 14 results). Buniello, A. et al. (2025). Open Targets Platform: facilitating therapeutic hypotheses building in drug discovery. Nucleic Acids Research.
2. (bhanumathy2021proteintyrosinekinases pages 1-2): Kalpana K. Bhanumathy, Amrutha Balagopal, Frederick S. Vizeacoumar, Franco J. Vizeacoumar, Andrew Freywald, and Vincenzo Giambra. Protein tyrosine kinases: their roles and their targeting in leukemia. Cancers, 13:184, Jan 2021. URL: https://doi.org/10.3390/cancers13020184, doi:10.3390/cancers13020184. This article has 75 citations and is from a peer-reviewed journal.
3. (liu2017identificationandcharacterization pages 8-9): Ake Liu, Funan He, and Xun Gu. Identification and characterization of tyrosine kinases in anole lizard indicate the conserved tyrosine kinase repertoire in vertebrates. Molecular Genetics and Genomics, 292:1405-1418, Aug 2017. URL: https://doi.org/10.1007/s00438-017-1356-7, doi:10.1007/s00438-017-1356-7. This article has 6 citations and is from a peer-reviewed journal.
4. (moonmuang2023theroleof pages 14-15): Sutpirat Moonmuang, Apichat Tantraworasin, Santhasiri Orrapin, Sasimol Udomruk, Busyamas Chewaskulyong, Dumnoensun Pruksakorn, and Parunya Chaiyawat. The role of proteomics and phosphoproteomics in the discovery of therapeutic targets and biomarkers in acquired egfr-tki-resistant non-small cell lung cancer. International Journal of Molecular Sciences, 24:4827, Mar 2023. URL: https://doi.org/10.3390/ijms24054827, doi:10.3390/ijms24054827. This article has 5 citations and is from a peer-reviewed journal.
5. (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 1-2): István Szabadkai, Robert Torka, Rita Garamvölgyi, Ferenc Baska, Pál Gyulavári, Sándor Boros, Eszter Illyés, Axel Choidas, Axel Ullrich, and László Őrfi. Discovery of n-[4-(quinolin-4-yloxy)phenyl]benzenesulfonamides as novel axl kinase inhibitors. Journal of Medicinal Chemistry, 61:6277-6292, Jun 2018. URL: https://doi.org/10.1021/acs.jmedchem.8b00672, doi:10.1021/acs.jmedchem.8b00672. This article has 27 citations and is from a highest quality peer-reviewed journal.
6. (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 15-16): István Szabadkai, Robert Torka, Rita Garamvölgyi, Ferenc Baska, Pál Gyulavári, Sándor Boros, Eszter Illyés, Axel Choidas, Axel Ullrich, and László Őrfi. Discovery of n-[4-(quinolin-4-yloxy)phenyl]benzenesulfonamides as novel axl kinase inhibitors. Journal of Medicinal Chemistry, 61:6277-6292, Jun 2018. URL: https://doi.org/10.1021/acs.jmedchem.8b00672, doi:10.1021/acs.jmedchem.8b00672. This article has 27 citations and is from a highest quality peer-reviewed journal.
7. (katoh2020precisionmedicinefor pages 8-9): Masuko Katoh and Masaru Katoh. Precision medicine for human cancers with notch signaling dysregulation (review). International Journal of Molecular Medicine, 45:279-297, Dec 2020. URL: https://doi.org/10.3892/ijmm.2019.4418, doi:10.3892/ijmm.2019.4418. This article has 217 citations and is from a peer-reviewed journal.
8. (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 5-6): István Szabadkai, Robert Torka, Rita Garamvölgyi, Ferenc Baska, Pál Gyulavári, Sándor Boros, Eszter Illyés, Axel Choidas, Axel Ullrich, and László Őrfi. Discovery of n-[4-(quinolin-4-yloxy)phenyl]benzenesulfonamides as novel axl kinase inhibitors. Journal of Medicinal Chemistry, 61:6277-6292, Jun 2018. URL: https://doi.org/10.1021/acs.jmedchem.8b00672, doi:10.1021/acs.jmedchem.8b00672. This article has 27 citations and is from a highest quality peer-reviewed journal.
9. (szabadkai2018discoveryofn[4(quinolin4yloxy)phenyl]benzenesulfonamides pages 6-7): István Szabadkai, Robert Torka, Rita Garamvölgyi, Ferenc Baska, Pál Gyulavári, Sándor Boros, Eszter Illyés, Axel Choidas, Axel Ullrich, and László Őrfi. Discovery of n-[4-(quinolin-4-yloxy)phenyl]benzenesulfonamides as novel axl kinase inhibitors. Journal of Medicinal Chemistry, 61:6277-6292, Jun 2018. URL: https://doi.org/10.1021/acs.jmedchem.8b00672, doi:10.1021/acs.jmedchem.8b00672. This article has 27 citations and is from a highest quality peer-reviewed journal.