## Phylogeny

Anaplastic Lymphoma Kinase (ALK) is a receptor tyrosine kinase (RTK) classified within the insulin receptor (IR) superfamily (li2008developmentofanaplastic pages 3-5, roskoski2013anaplasticlymphomakinase pages 1-2, webb2009anaplasticlymphomakinase pages 1-3). According to kinome classifications, ALK is placed within the RTK group (manning2002theproteinkinase pages 3-3, li2008developmentofanaplastic pages 16-19). ALK is most closely related to leukocyte tyrosine kinase (LTK), forming a distinct subgroup within the IR superfamily (palmer2009anaplasticlymphomakinase pages 1-2, roskoski2013anaplasticlymphomakinase pages 3-4, huang2018anaplasticlymphomakinase pages 1-5).

Orthologs of ALK are conserved across species, underscoring its evolutionary importance in nervous system development (webb2009anaplasticlymphomakinase pages 3-4). Known orthologs include: - Murine ALK, which is located on chromosome 17, consists of 1,621 amino acids, and shares 87% sequence homology with human ALK (li2008developmentofanaplastic pages 3-5, palmer2009anaplasticlymphomakinase pages 2-3). - *Drosophila melanogaster* ALK (DAlk), which is involved in the development of gut musculature and neuronal circuits (li2008developmentofanaplastic pages 3-5, palmer2009anaplasticlymphomakinase pages 1-2). - *Caenorhabditis elegans* ortholog SCD-2, which participates in presynaptic neural differentiation and dauer formation signaling (li2008developmentofanaplastic pages 3-5, palmer2009anaplasticlymphomakinase pages 2-3). - Zebrafish possess two ALK family genes, ALK and LTK, which are involved in neural crest lineage development and pigmentation (palmer2009anaplasticlymphomakinase pages 2-3).

## Reaction Catalyzed

As a tyrosine kinase, ALK catalyzes the transfer of the γ-phosphate group from an ATP molecule to the hydroxyl group of tyrosine residues on protein substrates (huang2018anaplasticlymphomakinase pages 1-5, roskoski2017anaplasticlymphomakinase pages 11-16). ATP + a protein-L-tyrosine = ADP + a protein-L-tyrosine phosphate (lee2010crystalstructureof pages 1-2, roskoski2013anaplasticlymphomakinase pages 3-4).

## Cofactor Requirements

The catalytic activity of ALK requires Mg²⁺ ions as cofactors (roskoski2013anaplasticlymphomakinase pages 4-5). The enzyme utilizes two Mg²⁺ ions, which are coordinated by the DFG motif aspartate (D1270) and N1254, to properly position the phosphates of ATP for catalysis (roskoski2013anaplasticlymphomakinase pages 4-5, roskoski2017anaplasticlymphomakinase pages 16-20).

## Substrate Specificity

Analysis of ALK’s intrinsic substrate specificity reveals position-specific amino acid preferences that govern substrate recognition, particularly at positions -1 to +3 relative to the phosphoacceptor tyrosine (yaronbarir2024theintrinsicsubstrate pages 3-3). There is a predominant selection for aliphatic hydrophobic residues, such as isoleucine, at the -1 and +3 positions (yaronbarir2024theintrinsicsubstrate pages 3-3). Conversely, ALK shows a general disfavoring of serine at the -1 position and glutamate at the +3 position (yaronbarir2024theintrinsicsubstrate pages 3-3).

## Structure

The full-length human ALK protein is a single-chain receptor of 1620 amino acids (corte2018roleandtargeting pages 1-3). Post-translational N-glycosylation results in a mature protein of ~200–220 kDa (li2008developmentofanaplastic pages 3-5, webb2009anaplasticlymphomakinase pages 1-3).

**Domain Organization:** - **Extracellular Domain (ECD):** Comprises a signal peptide (1–18), two meprin/A5/PTPmu (MAM) domains (264–427 and 480–626), one low-density lipoprotein receptor class A (LDL-A) domain (453–471), and a glycine-rich region (816–940). The combination of two MAM domains and one LDL-A domain is a unique feature of ALK (huang2018anaplasticlymphomakinase pages 1-5, roskoski2013anaplasticlymphomakinase pages 3-4). The ECD contains binding sites for ligands midkine and pleiotrophin (li2008developmentofanaplastic pages 3-5). - **Transmembrane Domain (residues 1039–1059):** A single transmembrane helix that anchors ALK in the plasma membrane (roskoski2013anaplasticlymphomakinase pages 3-4). - **Intracellular Domain (ICD, residues 1060–1620):** Consists of a juxtamembrane region and the catalytic kinase domain (1116–1392) (roskoski2013anaplasticlymphomakinase pages 3-4, huang2018anaplasticlymphomakinase pages 1-5).

**3D Structure:** The kinase domain has a canonical bi-lobal architecture, with a smaller N-terminal lobe and a larger C-terminal lobe (roskoski2017anaplasticlymphomakinase pages 11-16, lee2010crystalstructureof pages 4-5). - **N-lobe:** Composed of a five-stranded β-sheet and the regulatory αC-helix (lee2010crystalstructureof pages 4-5). It contains the conserved GxGxxG P-loop, which binds ATP phosphates (roskoski2013anaplasticlymphomakinase pages 4-5). - **C-lobe:** Primarily helical, it contains the catalytic loop and the activation loop (lee2010crystalstructureof pages 4-5). The ATP-binding cleft is situated between the two lobes (roskoski2017anaplasticlymphomakinase pages 11-16). Crystal structures are available for the ALK catalytic domain in apo (PDB: 3L9P), ADP-bound (PDB: 3LCS), and staurosporine-bound (PDB: 3LCT) states (lee2010crystalstructureof pages 1-2).

**Key Catalytic and Regulatory Features:** - **Activation Loop (A-loop):** Spans residues 1270–1299 and starts with a DFG motif (lee2010crystalstructureof pages 4-5). It contains a key three-tyrosine autophosphorylation motif (Y¹²⁷⁸xxxY¹²⁸²Y¹²⁸³) (kong2019drugdiscoverytargeting pages 3-5, zhao2015anaplasticlymphomakinase pages 1-6). In its unphosphorylated, inactive state, a short helix within the A-loop (αAL) packs against the αC-helix, while the distal part of the loop obstructs the substrate-binding region (lee2010crystalstructureof pages 1-2). - **αC-helix:** Its position is critical for activity. In the active “αC-in” conformation, a salt bridge forms between Lys1150 (β3 strand) and Glu1167 (αC-helix) (roskoski2013anaplasticlymphomakinase pages 4-5, lee2010crystalstructureof pages 7-8). - **Hydrophobic Spines:** Conserved regulatory (R-spine) and catalytic (C-spine) motifs, composed of residues from both lobes, are crucial for maintaining the structural integrity of the active kinase conformation (kong2019drugdiscoverytargeting pages 3-5, roskoski2013anaplasticlymphomakinase pages 5-6). - **Catalytic Residues:** Features the HRDLAARN sequence in its catalytic loop, with Asp1249 serving as the catalytic base (roskoski2013anaplasticlymphomakinase pages 4-5). The kinase possesses a K/E/D/D catalytic signature, which includes Lys1150, Glu1167, Asp1270, and Asp1249 (kong2019drugdiscoverytargeting pages 3-5, roskoski2017anaplasticlymphomakinase pages 16-20).

## Regulation

ALK activity is principally regulated through ligand-induced dimerization, autophosphorylation, and dephosphorylation (corte2018roleandtargeting pages 1-3).

**Post-Translational Modifications:** - **Autophosphorylation:** Ligand-induced dimerization leads to trans-autophosphorylation of the three tyrosine residues (Tyr1278, Tyr1282, Tyr1283) in the activation loop, which is essential for full kinase activation (corte2018roleandtargeting pages 1-3, li2008developmentofanaplastic pages 3-5). ALK shows a preference for phosphorylating the first tyrosine (Tyr1278) in this motif (lee2010crystalstructureof pages 2-3). - **Dephosphorylation:** The receptor protein tyrosine phosphatases PTPRB and PTPRZ act as negative regulators by dephosphorylating ALK, leading to its inactivation (corte2018roleandtargeting pages 1-3, zhao2015anaplasticlymphomakinase pages 1-6). - **N-glycosylation:** The extracellular domain contains 16 consensus sites for N-glycosylation, which influences protein folding, quality control, and membrane anchoring (huang2018anaplasticlymphomakinase pages 7-10, li2008developmentofanaplastic pages 3-5). - **Cleavage:** The full-length 220 kDa ALK protein can be cleaved to produce a 140 kDa truncated variant. Additionally, the intracellular domain can be cleaved by caspase-3 during apoptosis (huang2018anaplasticlymphomakinase pages 7-10).

**Conformational Regulation:** The kinase domain switches between inactive and active conformations. In the inactive state, the A-loop adopts an inhibitory pose that blocks the substrate-binding site (lee2010crystalstructureof pages 1-2, lee2010crystalstructureof pages 2-3). Phosphorylation of the A-loop tyrosines induces a conformational change to an open, active state that allows substrate binding and catalysis (roskoski2017anaplasticlymphomakinase pages 16-20, lee2010crystalstructureof pages 8-9).

## Function

ALK is a receptor tyrosine kinase that plays an essential role in the development and differentiation of the central and peripheral nervous systems (roskoski2013anaplasticlymphomakinase pages 1-2, li2008developmentofanaplastic pages 3-5).

**Expression:** Under normal conditions, ALK mRNA is highly expressed in the adult human brain and is also present in the small intestine, testis, prostate, and colon (corte2018roleandtargeting pages 1-3, zhao2015anaplasticlymphomakinase pages 1-6). It is not expressed in lymphoid tissues or the lungs (corte2018roleandtargeting pages 1-3). During embryonic development, expression is primarily localized to the nervous system, including the hippocampus and spinal cord motor neurons (huang2018anaplasticlymphomakinase pages 1-5, webb2009anaplasticlymphomakinase pages 3-4).

**Signaling Pathways:** - **Upstream:** Known activating ligands for ALK include midkine (MK) and pleiotrophin (PTN), although they are not specific to ALK (corte2018roleandtargeting pages 1-3, li2008developmentofanaplastic pages 3-5). The *Drosophila* ortholog DAlk is activated by the ligand Jelly belly (Jeb) (li2008developmentofanaplastic pages 5-7). - **Downstream:** Upon activation, ALK phosphorylates intracellular substrates such as Insulin Receptor Substrate-1 (IRS-1), SHC, and Phospholipase C-gamma (PLC-γ), initiating multiple downstream signaling pathways (li2008developmentofanaplastic pages 3-5). These pathways include: - PLCγ (corte2018roleandtargeting pages 1-3) - JAK-STAT (corte2018roleandtargeting pages 1-3) - PI3K-AKT-mTOR (corte2018roleandtargeting pages 1-3) - RAS/MEK/ERK (MAPK) (corte2018roleandtargeting pages 1-3, kong2019drugdiscoverytargeting pages 3-5) - Sonic hedgehog (SHH) (corte2018roleandtargeting pages 1-3) These signaling cascades promote cell growth, transformation, and anti-apoptotic effects (corte2018roleandtargeting pages 1-3). ALK may also act as a dependence receptor, triggering apoptosis in the absence of a ligand (li2008developmentofanaplastic pages 3-5).

## Inhibitors

Several small-molecule inhibitors targeting the ATP-binding pocket of the ALK kinase domain have demonstrated clinical efficacy (corte2018roleandtargeting pages 1-3). These include crizotinib, ceritinib, and alectinib (corte2018roleandtargeting pages 1-3, huang2018anaplasticlymphomakinase pages 7-10). Crizotinib was the first such inhibitor to receive FDA approval for treating ALK-positive non-small cell lung cancer (roskoski2013anaplasticlymphomakinase pages 1-2).

## Other Comments

Aberrant ALK activation is a critical oncogenic driver in several malignancies, such as anaplastic large-cell lymphoma (ALCL), non-small cell lung cancer (NSCLC), neuroblastoma, and inflammatory myofibroblastic tumors (IMT) (corte2018roleandtargeting pages 1-3, huang2018anaplasticlymphomakinase pages 7-10).

**Mechanisms of Oncogenic Activation:** - **Chromosomal Rearrangements:** The most frequent mechanism of activation is through chromosomal translocations that create fusion proteins. These fusions cause ligand-independent dimerization and constitutive kinase activity (corte2018roleandtargeting pages 1-3, huang2018anaplasticlymphomakinase pages 7-10). The most prominent examples are NPM-ALK in ALCL and EML4-ALK in NSCLC (corte2018roleandtargeting pages 1-3). - **Activating Mutations:** Germline and somatic mutations are common in neuroblastoma, with mutational hotspots at residues F1174, F1245, and R1275 (huang2018anaplasticlymphomakinase pages 7-10). Mutations such as F1174L and R1275Q enhance kinase activity by destabilizing the inactive conformation (lee2010crystalstructureof pages 2-3). - **Gene Amplification and Overexpression:** Increased ALK gene copy number and protein overexpression are found in neuroblastoma and rhabdomyosarcomas (huang2018anaplasticlymphomakinase pages 7-10, kong2019drugdiscoverytargeting pages 3-5).

Acquired resistance to ALK inhibitors is a clinical challenge, often arising from secondary mutations within the ALK kinase domain or the activation of alternative bypass signaling pathways (roskoski2013anaplasticlymphomakinase pages 1-2, corte2018roleandtargeting pages 1-3).

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