1. Phylogeny  
   ALK (Anaplastic Lymphoma Kinase) is a receptor tyrosine kinase that belongs to the insulin receptor superfamily and is most closely related to leukocyte tyrosine kinase (LTK). Sequence comparisons indicate that ALK shares approximately 47% similarity with the insulin receptor and about 50% similarity with LTK, placing it squarely within a subgroup of RTKs that are evolutionarily conserved across vertebrates. Orthologs of ALK have been identified in mammals, birds, and other higher vertebrates, underscoring its important role in neural development and signaling. This evolutionary conservation reflects its early emergence during metazoan evolution and its preservation as a crucial mediator of neuronal differentiation and signal transduction (alam2021investigatingalkinhibitors pages 29-33, jr2013anaplasticlymphomakinase pages 2-3).
2. Reaction Catalyzed  
   ALK catalyzes the transfer of the γ-phosphate group from ATP to tyrosine residues on substrate proteins. The chemical reaction can be summarized as follows:  
     ATP + [protein]-tyrosine → ADP + [protein]-phosphotyrosine + H⁺  
   This phosphorylation reaction is a hallmark of protein tyrosine kinases and serves to modulate downstream signaling pathways that influence cell proliferation, differentiation, and survival (jr2013anaplasticlymphomakinase pages 2-3, alam2021investigatingalkinhibitors pages 40-45).
3. Cofactor Requirements  
   The catalytic activity of ALK is dependent on divalent metal ions, specifically Mg²⁺. Magnesium ions coordinate with the ATP molecule within the active site, thereby facilitating the proper positioning of ATP for the efficient transfer of the phosphate group to substrate tyrosine residues (taft2017ayeastbasedassay pages 13-22).
4. Substrate Specificity  
   ALK exhibits substrate specificity typical of receptor tyrosine kinases, preferentially phosphorylating tyrosine residues on proteins that are central to signaling pathways governing neuronal development and oncogenic transformation. Although a consensus phosphorylation motif for ALK substrates has not been exhaustively defined in the available literature, its activity is directed toward substrates that play key roles in downstream cascades including the RAS–MAPK, PI3K–AKT, and JAK–STAT pathways. In pathological contexts such as neuroblastoma and ALK‐positive lung cancer, aberrant ALK activation results in increased phosphorylation of substrates that drive cell proliferation and survival (jr2013anaplasticlymphomakinase pages 1-2, alam2021investigatingalkinhibitors pages 36-40).
5. Structure  
   ALK is a type I transmembrane receptor that comprises approximately 1620 amino acids. It is organized into three major domains: an extracellular ligand-binding region, a single transmembrane helix, and an intracellular catalytic tyrosine kinase domain.  
    • The extracellular domain contains two MAM (meprin/A5-protein/PTPµ) domains, which are thought to mediate homophilic cell–cell interactions and contribute to receptor dimerization. In addition, an LDL receptor class A (LDLa) domain and a glycine‐rich (GR) region are present; these domains are implicated in ligand binding and possibly in modulating receptor conformation upon ligand engagement. Notably, ALK undergoes extensive N-linked glycosylation that increases its apparent molecular weight in its mature form to approximately 200 kDa, well above the predicted mass based solely on its amino acid sequence (alam2021investigatingalkinhibitors pages 29-33, jr2013anaplasticlymphomakinase pages 2-3).  
    • The transmembrane segment is a short hydrophobic region, roughly 21 amino acids in length, that anchors ALK in the plasma membrane while orienting its extracellular domain for ligand interaction and its intracellular domain for signal transduction.  
    • The intracellular region is dominated by a tyrosine kinase domain that spans approximately 561 amino acids. This kinase domain is organized into a smaller N-terminal lobe, which features a glycine-rich loop involved in ATP binding, and a larger C-terminal lobe that contains the catalytic and activation loops. Critical structural features of the kinase domain include the αC-helix, which forms a salt bridge with a conserved lysine residue essential for ATP binding, and the activation loop, which harbors a DFG motif. Conformational shifts of the DFG motif (the “DFG-in” active and “DFG-out” inactive conformations) regulate catalytic activity. In addition, conserved motifs such as the HRD motif of the catalytic loop and the hydrophobic regulatory (R) and catalytic (C) spines are essential for the proper orientation of catalytic residues and for the stabilization of the active conformation (alam2021investigatingalkinhibitors pages 33-36, jr2013anaplasticlymphomakinase pages 4-5, huang2018anaplasticlymphomakinase pages 5-7).  
   Ligand binding to the extracellular domain induces receptor dimerization, which is mechanically transduced to the intracellular domain, resulting in trans-autophosphorylation of specific tyrosine residues and full activation of the kinase (alam2021investigatingalkinhibitors pages 33-36).
6. Regulation  
   The activity of ALK is tightly controlled by multiple regulatory mechanisms. Activation commences with ligand binding to the extracellular domain, predominantly by ALKAL2 (also known as Augmentor β), which has been shown to be a potent agonist. This interaction induces receptor dimerization, leading to a conformational rearrangement that permits autophosphorylation of key tyrosine residues within the intracellular kinase domain. Autophosphorylation, particularly within the activation loop (for example, phosphorylation of tyrosine residue Y1283), is pivotal for alleviating the autoinhibited state and fully activating the kinase (alam2021investigatingalkinhibitors pages 29-33, alam2021investigatingalkinhibitors pages 75-77).  
   Post-translational modifications further regulate ALK activity. For instance, the extracellular domain is subject to extensive N-linked glycosylation, which is critical for proper folding, stability, receptor trafficking, and ligand responsiveness. In addition, proteolytic cleavage events can generate truncated receptor forms that might have distinct localization or signaling properties (huang2018anaplasticlymphomakinase pages 7-10, jr2013anaplasticlymphomakinase pages 2-3).  
   Activating mutations within the kinase domain, such as those affecting residues F1174, R1275, and F1245, have been identified in neuroblastoma and other cancers. These mutations can alter the conformation of the kinase domain, favoring the active state independent of ligand stimulation and leading to uncontrolled signaling. Moreover, formation of ALK fusion proteins (e.g., EML4-ALK), in which the ALK kinase domain is aberrantly joined to a partner protein that provides a dimerization motif, results in constitutive, ligand-independent kinase activation that drives oncogenesis (alam2021investigatingalkinhibitors pages 29-33, jr2013anaplasticlymphomakinase pages 13-14, jr2013anaplasticlymphomakinase pages 26-27).
7. Function  
   ALK is primarily expressed during nervous system development and is detectable in specific regions of both the central and peripheral nervous systems. Its normal physiological role is to mediate processes such as neuronal proliferation, differentiation, and migration. The receptor transduces extracellular signals—following binding of its potent ligand ALKAL2—into intracellular responses by activating downstream signaling cascades including the RAS–MAPK, PI3K–AKT, JAK–STAT, and PLC-γ pathways. Through these pathways, ALK influences gene expression, cell survival, and synaptic connectivity during neurogenesis (huang2018anaplasticlymphomakinase pages 1-5, alam2021investigatingalkinhibitors pages 40-45).  
   In addition to its developmental functions, ALK has been implicated in metabolic regulation. In hypothalamic neurons, ALK functions as a key regulator of energy homeostasis by modulating energy expenditure, suppressing white adipose tissue lipolysis, and adjusting sympathetic tone. This role as a “thinness protein” contributes to resistance to weight gain, further underscoring its physiological significance (information provided in the Protein Function description).  
   Pathologically, aberrant activation of ALK, whether through gene mutations, overexpression, or gene fusions (such as EML4-ALK in non‐small cell lung cancer or NPM-ALK in anaplastic large-cell lymphoma), leads to constitutive signaling that promotes oncogenesis. ALK-driven malignancies are characterized by enhanced cellular proliferation, survival, and metastatic potential, making this kinase a critical target for precision oncology (jr2013anaplasticlymphomakinase pages 1-2, jr2013anaplasticlymphomakinase pages 13-14, alam2021investigatingalkinhibitors pages 40-45).
8. Other Comments  
   Several small molecule inhibitors have been developed to target ALK’s aberrant kinase activity in cancer. The first approved inhibitor, crizotinib, is an ATP-competitive agent that has demonstrated clinical efficacy in ALK-positive non-small cell lung cancer; subsequent inhibitors such as ceritinib, alectinib, brigatinib, and lorlatinib have been introduced to address resistance emerging from mutations within the kinase domain (jr2013anaplasticlymphomakinase pages 16-17, attwood2021trendsinkinase pages 3-4).  
   Notable activating mutations within ALK—especially those at residues F1174, R1275, and F1245—are associated with constitutive kinase activity and adverse clinical outcomes in neuroblastoma, thereby informing mutation‐specific therapeutic strategies. In addition, noncanonical regulatory mechanisms, including alternative transcription initiation and proteolytic cleavage, contribute to the production of distinct ALK isoforms that may have differential activities and subcellular localizations. These multifaceted regulatory layers further underscore the complexity of ALK’s role in both normal physiology and disease, and they serve as potential additional targets for therapeutic intervention (alam2021investigatingalkinhibitors pages 29-33, jr2013anaplasticlymphomakinase pages 7-9, huang2018anaplasticlymphomakinase pages 7-10).
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