1. Phylogeny  
   Leukocyte tyrosine kinase (LTK), also known as TYK1 or protein tyrosine kinase 1, is a member of the receptor tyrosine kinase (RTK) superfamily that, based on available phylogenetic studies, is closely related to anaplastic lymphoma kinase (ALK). LTK appears to have evolved through gene duplication events that occurred during early vertebrate evolution, resulting in two closely related receptors that share substantial sequence similarity in their catalytic domains while diverging in their extracellular portions. Orthologs of LTK have been detected in a variety of vertebrate species including mammals, zebrafish, and amphibians, as well as in organisms such as the axolotl, where LTK has been implicated in pigment cell development. In phylogenetic analyses, LTK clusters within the ALK/LTK subfamily, and sequence comparisons further delineate conserved motifs in the kinase region that trace back to common ancestral RTKs present in jawed vertebrates (Wang2019evolutionaryanalysesguide pages 1-5, Rakshambikai2015typicalandatypical pages 6-9). Multiple lines of evidence indicate that LTK and ALK diverged from a common ancestor, and while ALK is predominantly associated with neural functions and oncogenic fusion events in cancers, LTK has retained a distinct set of functions in both the nervous system and in peripheral cell types such as pre-B lymphocytes (Christova2023ltkandalk pages 1-2, Wang2019evolutionaryanalysesguide pages 26-28). These evolutionary relationships place LTK within an evolutionarily conserved core set of receptor kinases that have maintained critical roles in cellular signaling since the early expansion of the vertebrate kinome (Wang2019evolutionaryanalysesguide pages 19-22).
2. Reaction Catalyzed  
   LTK catalyzes the transfer of a phosphate group from adenosine triphosphate (ATP) to specific tyrosine residues on substrate proteins. The reaction proceeds according to the classic mechanism for protein tyrosine kinases, in which ATP and a substrate protein with an accessible tyrosine hydroxyl group are converted into adenosine diphosphate (ADP), the phosphorylated substrate, and a proton. Notably, LTK has been reported to phosphorylate almost exclusively at the first tyrosine in the Y–x–x–x–Y–Y motif, thereby modifying its substrates in a highly defined manner (Brunner2023subcellularlocalizationand pages 61-63, Christova2023ltkandalk pages 1-2).
3. Cofactor Requirements  
   Like other protein kinases, LTK requires divalent metal ions as cofactors for its catalytic activity. Experimental evidence and comparative studies within the RTK family indicate that magnesium ions (Mg²⁺) are essential for coordinating ATP in the active site, thereby facilitating the proper orientation of the phosphate donor for the phosphoryl transfer reaction (Filis2023proteomewidedetectionand pages 1-2, Boubeva2011understandingtyrosinekinase pages 37-40).
4. Substrate Specificity  
   LTK displays substrate specificity consistent with other receptor tyrosine kinases; it preferentially recognizes substrates with a tyrosine-based motif. In particular, it has been reported to phosphorylate almost exclusively at the first tyrosine in a Y–x–x–x–Y–Y motif. This specificity is determined by both the sequence context flanking the target tyrosine and the three-dimensional organization of the kinase active site, which together ensure that the phosphate group is added selectively to tyrosine residues that conform to this consensus motif (Brunner2023subcellularlocalizationand pages 61-63, Rakshambikai2015typicalandatypical pages 6-9).
5. Structure  
   LTK is organized into three major domains: an extracellular domain (ECD), a single transmembrane domain, and an intracellular tyrosine kinase domain (TKD). The ECD is responsible for ligand recognition and binding; ligands such as ALKAL1 and ALKAL2 are known to trigger receptor activation upon binding to this portion (Christova2023ltkandalk pages 1-2). There is conflicting evidence regarding the precise sub-domain composition of the ECD. One set of findings indicates that the extracellular region may contain distinctive motifs such as a MAM domain that mediates homophilic interactions and lateral dimerization (Brunner2023subcellularlocalizationand pages 61-63), while other data report that, unlike ALK, LTK lacks both MAM and LDLa domains (Brunner2023subcellularlocalizationand pages 12-15). The transmembrane domain spans the cell membrane, anchoring the receptor and allowing for transmission of the extracellular signal to the cytoplasmic portion. Within the intracellular region, the TKD harbors the catalytic machinery necessary for phosphoryl transfer, including the ATP-binding pocket, catalytic loop, and activation segment. Experimentally derived studies have identified two NPXY motifs located around tyrosines 485 and 862 that serve as adaptor protein docking sites, and several phosphorylation sites, including the key residue tyrosine 672, which is indicative of receptor activation (Brunner2023subcellularlocalizationand pages 12-15, Brunner2023subcellularlocalizationand pages 35-39). In addition, post-translational modifications such as N- and O-linked glycosylations have been documented, with specific glycosylation sites at asparagine residues 257 and 412 affecting the receptor’s maturation and trafficking properties (Brunner2023subcellularlocalizationand pages 44-47, Brunner2023subcellularlocalizationand pages 50-54).
6. Regulation  
   The regulatory mechanisms governing LTK activity are multifaceted, relying on both extracellular signals and intrinsic post-translational modifications. Ligand binding to the ECD—most notably by secreted proteins ALKAL1 and ALKAL2—induces receptor dimerization, which in turn promotes autophosphorylation of critical tyrosine residues within the intracellular TKD. Phosphorylation at tyrosine 672 is one such modification that marks the active state of the kinase (Brunner2023subcellularlocalizationand pages 35-39, Christova2023ltkandalk pages 20-21). In neuronal cells, LTK has also been shown to physically interact with the insulin-like growth factor 1 receptor (IGF1R), phosphorylating it and thereby inhibiting its cell surface expression and downstream signaling via the PI3K pathway; this regulatory cross-talk is important for maintaining neuronal polarity and proper cortical migration (Christova2023ltkandalk pages 9-11, Christova2023ltkandalk pages 13-15, Christova2023ltkandalk pages 21-21). Glycosylation is another layer of regulation for LTK; specific N-linked glycosylation events at asparagine residues such as N257 and N412 modulate the receptor’s transit from the endoplasmic reticulum (ER) to the Golgi apparatus and eventually to the plasma membrane. Experimental manipulation of these glycosylation sites has demonstrated that the extent and pattern of glycosylation can influence both the molecular weight of LTK as observed on immunoblots and its overall activation state (Brunner2023subcellularlocalizationand pages 44-47, Brunner2023subcellularlocalizationand pages 50-54). Moreover, LTK has been implicated in the regulation of the secretory pathway itself by interacting with proteins involved in ER export, such as Sec12, and with cargo receptors like ERGIC-53, thereby linking its kinase activity to the regulation of intracellular protein trafficking (Brunner2023subcellularlocalizationand pages 20-24, Brunner2023subcellularlocalizationand pages 47-50). In addition to these positive regulatory mechanisms, pharmacological inhibitors such as Crizotinib and Ceritinib have been shown to suppress LTK autophosphorylation and downstream signaling, indicating that its kinase activity can also be modulated in a therapeutic context (Izumi2021theclip1–ltkfusion pages 4-6).
7. Function  
   LTK functions as a receptor tyrosine kinase that transduces extracellular signals into discrete intracellular responses. Upon ligand binding by ALKAL1 or ALKAL2 at the cell surface, LTK becomes activated through dimerization followed by autophosphorylation, leading to the initiation of downstream signaling cascades such as the mitogen-activated protein kinase (MAPK) pathway. This signaling output is associated with the promotion of cell growth, neurite outgrowth, and cell survival as demonstrated in experimental studies using chimeric receptor constructs (Christova2023ltkandalk pages 1-2, Izumi2021theclip1–ltkfusion pages 1-3). In neuronal cells, LTK plays a regulatory role by interfering with insulin-like growth factor 1 receptor (IGF1R) activity; its phosphorylation of IGF1R decreases the receptor’s cell surface localization and attenuates PI3K signaling, a mechanism that is critical for maintaining proper neuronal polarity and directing cortical migration (Christova2023ltkandalk pages 9-11, Christova2023ltkandalk pages 13-15, Christova2023ltkandalk pages 21-21). In addition to its roles in neural development, LTK is expressed in pre-B lymphocytes, where it may contribute to immune cell function via similar mechanisms of signal transduction. Regulation of the secretory pathway is another key aspect of LTK function; the receptor has been implicated in controlling ER export site formation and the efficient trafficking of cargo proteins through the ER–Golgi network (Brunner2023subcellularlocalizationand pages 15-20, Brunner2023subcellularlocalizationand pages 47-50). Furthermore, oncogenic variants of LTK, such as fusion proteins involving CLIP1–LTK, have been identified in non‐small‐cell lung cancer, where constitutive kinase activation leads to enhanced proliferation and survival of cancer cells (Izumi2021theclip1–ltkfusion pages 1-3). In other model organisms, such as zebrafish and axolotl, LTK has been linked to the specification of pigment cell lineages, particularly the development of iridophores, indicating that its biological roles extend to diverse developmental processes (Lopes2008leukocytetyrosinekinase pages 2-3, Kabangu2023leukocytetyrosinekinase pages 1-3).
8. Other Comments  
   Several inhibitors that were originally developed for the targeting of ALK have demonstrated efficacy against LTK or its oncogenic fusion variants. For instance, lorlatinib has been shown to effectively inhibit the kinase activity of the CLIP1–LTK fusion protein, leading to reduced proliferation of transformed cells in non‐small‐cell lung cancer models (Izumi2021theclip1–ltkfusion pages 24-26, Izumi2021theclip1–ltkfusion pages 8-10). In addition, Crizotinib and Ceritinib have been employed in experimental settings to block LTK autophosphorylation and downstream signaling, indicating their potential usability in therapeutic strategies aimed at modulating LTK function (Brunner2023subcellularlocalizationand pages 15-20). Disease associations for LTK are varied; beyond its involvement in cancer via fusion events, genetic association data collected from platforms such as OpenTargets link LTK to conditions including type 2 diabetes mellitus, albuminuria, and phenotypes related to drug use measurement, underscoring its clinical relevance in both oncological and metabolic contexts (OpenTargets Search: -LTK). In addition, certain polymorphisms such as the R42Q mutation, which has been observed in a short isoform of LTK, have been documented in subsets of patients with multiple myeloma, further illustrating the diversity of LTK’s involvement in disease states (Brunner2023subcellularlocalizationand pages 44-47).
9. References
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