1. Phylogeny  
   Tyrosine‐protein kinase STYK1 (also known as SuRTK106 or NOK) is phylogenetically classified as a receptor‐type kinase within the protein tyrosine kinase (RTK) superfamily. Comparative sequence analyses position STYK1 among a group of RTKs that share similarity with members of the platelet‐derived growth factor and fibroblast growth factor receptor families, even though its extracellular region is notably reduced relative to classical RTKs (brunet2016wholegenomeduplications pages 4-5, chen2014clinicopathologicfeaturesand pages 1-2). Phylogenetic reconstruction based on the conserved kinase domain indicates that STYK1 is evolutionarily conserved across vertebrate species, with orthologs detectable in amphibians (e.g., Xenopus tropicalis) and mammals (ye2003isolationandcharacterization pages 1-2, kwon2019tracingtheevolution pages 117-121). Gene duplication events associated with early vertebrate whole genome duplications contributed to the diversification of the receptor tyrosine kinase repertoire, and STYK1 appears as one member emerging from these duplications (brunet2016wholegenomeduplications pages 3-4). Recent computational phylogenetic studies that integrate kinase domain motifs have further grouped STYK1 within a subset of RTK‐related pseudokinases, a categorization that emphasizes conserved but noncanonical catalytic motifs (kwon2019tracingtheevolutiona pages 19-23, liu2017identificationandcharacterization pages 8-9).
2. Reaction Catalyzed  
   STYK1 catalyzes the transfer of a phosphate moiety from ATP to the hydroxyl group of target proteins, with a preference for tyrosine residues, thereby converting ATP into ADP and producing a phospho‐modified substrate as follows:  
   ATP + [protein]–tyrosine → ADP + [protein]–phosphotyrosine + H⁺ (chen2014clinicopathologicfeaturesand pages 1-2, ye2003isolationandcharacterization pages 1-2).
3. Cofactor Requirements  
   The catalytic activity of STYK1 is dependent upon the presence of divalent metal ions. In common with other protein kinases, STYK1 requires Mg²⁺ as a cofactor to stabilize ATP binding and to facilitate the phosphotransfer reaction (ye2003isolationandcharacterization pages 2-6, chen2014clinicopathologicfeaturesand pages 1-2).
4. Substrate Specificity  
   While a definitive consensus phosphorylation motif for STYK1 has not been unequivocally established in the literature provided, experimental evidence indicates that STYK1 phosphorylates proteins involved in key oncogenic pathways. Functional studies have linked its kinase activity to the phosphorylation of targets that participate in MAP kinase and phosphatidylinositol 3’-kinase (PI3K) signaling cascades, with substrates including Akt and glycogen synthase kinase 3 beta (GSK-3β) among those reported (chen2014clinicopathologicfeaturesand pages 6-7, jackson2009aberrantstyk1expression pages 1-2). In addition, regulatory effects on autophagy have been associated with phosphorylation events affecting components of the PI3K complex, although the precise substrate motif for STYK1 remains to be fully delineated (chen2014clinicopathologicfeaturesand pages 7-7, tsuji…diagnosticrelevanceof pages 4-5).
5. Structure  
   STYK1 is a 422–amino acid receptor‐type protein kinase that exhibits a modular domain arrangement. It comprises a markedly small extracellular domain, a single transmembrane helix, and an intracellular catalytic domain. The extracellular domain is considerably truncated when compared with typical RTKs, a feature that has been highlighted in phylogenetic analyses and is thought to underlie unique regulatory properties (brunet2016wholegenomeduplications pages 4-5, tsuji…diagnosticrelevanceof pages 4-5). The transmembrane segment is characterized by a long stretch of hydrophobic residues (e.g., the predicted sequence PTLLVTI-FLILLGVI) that facilitates membrane anchoring (ye2003isolationandcharacterization pages 6-6). The intracellular domain, spanning approximately amino acids 116–378, adopts a bilobal kinase fold similar to that observed in other RTKs; the N-terminal lobe contains a partially conserved glycine-rich loop (CSGSCG) with a conserved lysine residue (K147) essential for ATP coordination, while the C-terminal lobe harbors the catalytic loop and activation segments (bailey2014biochemicalanalysisof pages 75-78, ye2003isolationandcharacterization pages 2-6). Deviations from canonical kinase motifs—such as the substitution of the second metal-binding aspartate in the DFG motif with a glycine—have been documented, and these atypical features are often associated with kinase domains classified as pseudokinases (bailey2014biochemicalanalysisof pages 75-78, ye2003isolationandcharacterization pages 6-6). Structural studies, including experimental data and homology modeling, indicate that the key catalytic and regulatory elements such as the activation loop, the C-helix, and the hydrophobic spine are maintained, albeit with modifications that may influence catalytic efficiency (boubeva2011understandingtyrosinekinase pages 37-40, zhou2020styk1promotesautophagy pages 9-11). Additionally, the intracellular domain has been shown to mediate dimerization, an event that is critical for proper regulatory control of kinase activity (zhou2020styk1promotesautophagy pages 9-11, zhou2022phosphorylatedstyk1restrains pages 7-10).
6. Regulation  
   STYK1 is regulated through a series of phosphorylation events and conformational changes within its intracellular domain. Phosphorylation by upstream kinases is central to its modulation. For instance, phosphorylation at tyrosine 356, catalyzed by activated EGFR, has been reported to enhance the binding of STYK1 to EGFR, thereby influencing downstream signaling through the MAPK and PI3K pathways (zhou2022phosphorylatedstyk1restrains pages 10-12, zhou2022phosphorylatedstyk1restrains pages 7-7). In parallel, serine 304 on STYK1 is phosphorylated by AMPK in response to specific stimuli such as EGFR tyrosine kinase inhibitor treatment, which modulates autophagic flux and drug sensitivity in non‐small cell lung cancer (NSCLC) cells (zhou2022phosphorylatedstyk1restrains pages 10-12, zhou2022phosphorylatedstyk1restrains pages 12-13). An autoinhibitory tyrosine residue at position 417 has also been identified and is implicated in dampening kinase activity through intramolecular inhibition (jackson2009aberrantstyk1expression pages 7-7). In addition to these phosphorylation events, the intracellular kinase domain facilitates dimerization, a process that further regulates its catalytic function and contributes to complex formation with interacting partners (zhou2020styk1promotesautophagy pages 9-11, zhou2022phosphorylatedstyk1restrains pages 3-7). Moreover, estrogen-related signaling through the G-protein–coupled receptor GPR30 has been shown to influence STYK1 mRNA levels in ovarian cancer cells, though the corresponding changes in protein levels appear less pronounced (jackson2009aberrantstyk1expression pages 1-2).
7. Function  
   STYK1 exhibits strong transforming capabilities when overexpressed and has been implicated in tumor cell invasion and metastatic dissemination. Its kinase activity is associated with the activation of major signaling cascades, notably the MAP kinase and phosphatidylinositol 3’-kinase pathways, which are critical for cell proliferation and survival (chen2014clinicopathologicfeaturesand pages 1-2, chen2014clinicopathologicfeaturesand pages 6-7). Elevated levels of STYK1 correlate with aggressive clinical behavior in several malignancies, including non-small cell lung cancer, ovarian cancer, and breast cancer; in these contexts, STYK1 expression has been linked to poor survival outcomes and enhanced metastatic potential (jackson2009aberrantstyk1expression pages 1-2, tsuji…diagnosticrelevanceof pages 4-5, chen2014clinicopathologicfeaturesand pages 7-7). Functional studies have demonstrated its role in modulating autophagy; by attenuating epidermal growth factor receptor (EGFR)-mediated inhibition of autophagy, STYK1 contributes to the regulation of cell survival pathways that impact sensitivity to EGFR-targeted therapies (zhou2022phosphorylatedstyk1restrains pages 2-3, zhou2022phosphorylatedstyk1restrains pages 7-10). These findings underscore the involvement of STYK1 as a signaling integrator that not only transduces extracellular cues but also influences intracellular homeostasis via regulation of autophagic processes.
8. Other Comments  
   Experimental suppression of STYK1 expression via siRNA approaches has resulted in decreased tumorigenic potential in cell culture models and reduced tumor growth in xenograft studies, reinforcing its designation as an oncogenic factor and a potential therapeutic target (tsuji…diagnosticrelevanceof pages 4-5, chen2014clinicopathologicfeaturesand pages 3-6). While no small molecule inhibitors specific for STYK1 have yet been validated, its regulatory interaction with EGFR and involvement in autophagy modulation highlight prospective strategies (zhou2022phosphorylatedstyk1restrains pages 12-13, jackson2009aberrantstyk1expression pages 7-7). Disease associations include a strong correlation between STYK1 overexpression and unfavorable clinical outcomes in non-small cell lung cancer, ovarian cancer, and other malignancies, emphasizing its relevance in cancer biology. The aberrant expression and phosphorylation patterns observed across various tumor types support continued investigation into STYK1 as a candidate for therapeutic intervention.
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