## Phylogeny

Orthologs of STYK1 are present across jawed vertebrates, including fish, amphibians, birds and mammals (brunet2016wholegenomeduplications pages 4-5).  
The gene was lost in the lizard Anolis carolinensis, whereas two paralogs are retained in turtles and birds (liu2017identificationandcharacterization pages 9-11).  
Maximum-likelihood trees place human STYK1 as a distinct receptor tyrosine kinase subfamily that arose during the first two vertebrate whole-genome duplications (brunet2016wholegenomeduplications pages 4-5).  
Hidden-Markov-model annotation assigns STYK1 to the SuRTK106 subfamily most closely related to the VEGFR/PDGFR/RET/FGFR/Tie lineage despite secondary extracellular domain reduction (filis2023proteomewidedetectionand pages 2-4).

## Reaction Catalyzed

ATP + [protein]-L-tyrosine ⇌ ADP + [protein]-O-phospho-L-tyrosine (ye2003isolationandcharacterization pages 1-2).

## Cofactor Requirements

Receptor tyrosine kinases require a divalent cation such as Mg²⁺ for catalysis, a dependency expected for STYK1 (gu2006designandevaluation pages 7-8).

## Substrate Specificity

STYK1 phosphorylates the catalytic subunit PIK3C3 on tyrosine residues within the autophagy-specific class III phosphatidylinositol 3-kinase complex I (zhou2020styk1promotesautophagy pages 14-17).  
The kinase increases serine phosphorylation of BECN1 in the same complex (zhou2020styk1promotesautophagy pages 9-11).  
A kinome-wide peptide-array survey did not report an intrinsic consensus motif for STYK1 (yaronbarir2024theintrinsicsubstrate pages 1-2).

## Structure

STYK1 contains a truncated extracellular segment (<30 aa), a single transmembrane helix (~residues 37–59) and an intracellular kinase domain spanning residues 116–378 (ye2003isolationandcharacterization pages 2-6).  
Its glycine-rich loop is an atypical CSGSCG-K motif (ye2003isolationandcharacterization pages 6-6).  
Catalytic Lys147 and Glu157 form the conserved Lys–Glu pair that anchors ATP (ye2003isolationandcharacterization pages 2-6).  
The HRD motif is replaced by HGDVAARN in subdomain VIb (ye2003isolationandcharacterization pages 6-6).  
Phosphorylation of Tyr191 within the activation segment promotes homodimerisation and activation (zhou2020styk1promotesautophagy pages 14-17).  
Mutation K147R abolishes ATP binding and catalytic activity (zhou2020styk1promotesautophagy pages 9-11).  
Homology modelling predicts a canonical bilobal kinase fold with an intact regulatory spine; no experimental crystal structure is available (zhou2020styk1promotesautophagy pages 9-11).

## Regulation

Autophosphorylation of Tyr191 strengthens dimer formation and enhances binding to ATG14, BECN1 and PIK3C3 (zhou2020styk1promotesautophagy pages 14-17).  
EGFR phosphorylates STYK1 at Tyr356, an event blocked by erlotinib or gefitinib (zhou2022phosphorylatedstyk1restrains pages 7-10).  
AMPK phosphorylates Ser304 following EGFR-TKI treatment (zhou2022phosphorylatedstyk1restrains pages 7-10).  
C-terminal Tyr417 acts as an autoinhibitory site; its removal increases mitogenic signalling (hou2015nokmediatedmitogenic pages 9-10).  
Constitutive homodimerisation via transmembrane and kinase domains is required for full activity (zhou2020styk1promotesautophagy pages 14-17).

## Function

STYK1 mRNA is expressed broadly, with highest levels in brain, placenta and prostate (ye2003isolationandcharacterization pages 1-2).  
Overexpression occurs in lung, estrogen-receptor-negative breast, castration-resistant prostate, ovarian, colorectal cancers and acute leukaemia (hou2015nokmediatedmitogenic pages 9-10).  
High transcript levels associate with chemotherapy non-response in acute leukaemia (nirasawa2014significanceofserine pages 5-8).  
STYK1 promotes assembly of the PtdIns3K-C1 complex, elevates PIK3C3 lipid-kinase activity and accelerates autophagosome formation (zhou2020styk1promotesautophagy pages 20-21).  
The kinase activates MAPK and PI3K/Akt pathways, leading to GSK-3β Ser9 phosphorylation (hu2015serinethreoninetyrosine pages 4-5).  
By relieving EGFR-mediated autophagy inhibition, STYK1 modulates sensitivity of non-small-cell lung cancer cells to EGFR-targeted therapy (zhou2022phosphorylatedstyk1restrains pages 7-10).

## Inhibitors

No peer-reviewed small-molecule or biological inhibitors that directly target STYK1 catalytic activity have been reported (nirasawa2014significanceofserine pages 5-8).

## Other Comments

STYK1 functions as an oncogene that promotes tumour invasion and metastasis in vivo (hou2015nokmediatedmitogenic pages 9-10).  
High STYK1 expression predicts poor prognosis in colorectal cancer (hu2015serinethreoninetyrosine pages 4-5).  
Cancer-associated variants P302L and V395I diminish STYK1-mediated mitogenic signalling (hou2015nokmediatedmitogenic pages 9-10).  
The kinase-dead mutant K147R fails to promote autophagy (zhou2020styk1promotesautophagy pages 9-11).

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