## Phylogeny

DSTYK is a single-copy kinase conserved in vertebrates (Homo sapiens, Mus musculus, Rattus norvegicus, Gallus gallus, Danio rerio) (Peng et al., 2006; Unknown Authors, 2014; Sun et al., 2020). Sequence homology places it in the receptor-interacting protein kinase (RIPK) family within the tyrosine-kinase-like (TKL) branch of the human kinome (Dong et al., 2025).

## Reaction Catalyzed

ATP + L-Ser/Thr/Tyr-[protein] ⇌ ADP + H⁺ + O-phospho-L-Ser/Thr/Tyr-[protein] (Peng et al., 2006).

## Cofactor Requirements

No divalent metal ion requirement has been reported (Dong et al., 2025).

## Substrate Specificity

• Site-specific phosphorylation of STING at Ser366 (Dong et al., 2025).  
• Phosphorylation of β-catenin at unidentified residues in vitro (Zhong et al., 2021).  
A global consensus motif has not been defined.

## Structure

The protein contains two cysteine-rich N-terminal non-catalytic regions (NCR1, NCR2) followed by a divergent eukaryotic protein kinase domain spanning residues 652–906 (Peng et al., 2006; Sun et al., 2020). No experimental or predicted 3-D structures are currently available (Dong et al., 2025). Canonical VAIK, HRD and DFG motifs are inferred by homology. Kinase-dead mutants K681A and D777A retain STING binding and endosomal localisation but lack catalytic activity (Dong et al., 2025).

## Regulation

• Phosphorylation of DSTYK by TBK1 enhances its ability to phosphorylate STING at late endosomes (Dong et al., 2025).  
• Electrophoretic mobility shifts indicate additional, unmapped post-translational modifications (Unknown Authors, 2014).  
• Constitutively localises to Rab7/LAMP1-positive late endosomes; this localisation is independent of catalytic activity (Dong et al., 2025).  
• Binding to STING is maintained in kinase-inactive mutants, separating docking from catalysis (Dong et al., 2025).

## Function

Expression: Highly expressed in innate immune cells (NK cells, dendritic cells, macrophages, neutrophils) and in several human cell lines including HEK293, HeLa, THP-1, A549, HT1080 and Hep-G2 (Dong et al., 2025).

Innate immunity: At late endosomes DSTYK phosphorylates STING-Ser366, promoting downstream activation of TBK1, IRF3 and NF-κB, thereby driving IFNB, ISG and pro-inflammatory cytokine expression during DNA-virus infection (Dong et al., 2025).

Cell death: Over-expression triggers both caspase-dependent and caspase-independent death pathways (Dong et al., 2025).

Wnt signalling / metabolism: Phosphorylates β-catenin, reduces its accumulation and represses Axin2, c-Myc, cyclin D1 and LDHA, limiting lung adenocarcinoma growth and stemness (Zhong et al., 2021).

ERK pathway: Somatic Met296Ile mutation increases ERK1/2 activity and tumour invasiveness in solitary fibrous tumour/hemangiopericytoma (Tang et al., 2019).

## Other Comments

Disease associations:  
• Heterozygous splice-site or missense variants cause autosomal dominant congenital anomalies of the kidney and urinary tract (Sanna-Cherchi et al., 2013).  
• Missense variant Leu91Met linked to hereditary spastic paraparesis with lower urinary-tract dysfunction (Vidic et al., 2021).  
• Loss-of-function alleles in zebrafish produce scoliosis-like vertebral malformations via mTORC1/TFEB dysregulation (Sun et al., 2020).  
• Kinase-domain ablation in mice impairs spatial learning and memory without major neurodevelopmental defects (Unknown Authors, 2014).  
• Cancer relevance: Met296Ile drives intraspinal dissemination of solitary fibrous tumour/hemangiopericytoma (Tang et al., 2019); reduced DSTYK expression suppresses lung adenocarcinoma via β-catenin regulation (Zhong et al., 2021).

No specific small-molecule or biologic inhibitors have been reported (Dong et al., 2025).

## References

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