## Phylogeny

MuSK belongs to the receptor tyrosine kinase (RTK) group of the human kinome and forms a muscle-restricted branch that is most closely related to the ROR subfamily (Manning et al., 2002; Valenzuela et al., 1995). Primary-sequence conservation is high across vertebrates (e.g., 94 % identity with rat MuSK; 97 % within the kinase domain) and extends to Torpedo californica electric-organ RTK, underscoring strong evolutionary conservation (Valenzuela et al., 1995).

## Reaction Catalyzed

ATP + protein-L-tyrosine ⇌ ADP + protein-L-tyrosine-phosphate (Duong-Ly & Peterson, 2013).

## Cofactor Requirements

Catalysis requires a divalent metal ion; Mg²⁺ (and, interchangeably, Mn²⁺) coordinates the ATP γ-phosphate in the active site (Duong-Ly & Peterson, 2013).

## Substrate Specificity

Peptide-array profiling places MuSK in an RTK cluster that favours hydrophobic residues (Ile/Leu) at positions −1 and +3 relative to the target tyrosine while disfavoring acidic residues at +3 (Yaron-Barir et al., 2024).

## Structure

• Ectodomain: four Ig-like domains followed by a Frizzled-type cysteine-rich domain; Ig1–Ig2 crystal structure resolved at 2.2 Å (PDB 2IEP) (Stiegler et al., 2006).  
• Single-pass transmembrane helix (Valenzuela et al., 1995).  
• Cytoplasmic region: juxtamembrane segment containing Tyr553 (NPXY) and a catalytic domain with activation-loop Tyr750/Tyr754/Tyr755 (Hubbard & Gnanasambandan, 2013).

Key 3-D features  
– Ig1 dimerisation interface (Met48, Leu83, Ile96); mutations block agrin-dependent activation (Stiegler et al., 2006).  
– Surface disulfide Cys98–Cys112 stabilises Ig1 folding (Stiegler et al., 2006).  
– Unphosphorylated kinase domain adopts an autoinhibited conformation; phosphorylation of Tyr750/754/755 converts it to the active state (Hubbard & Gnanasambandan, 2013).  
– Phospho-Tyr553 recruits the PTB adaptor Dok7 to juxtapose two kinase domains and promote activation-loop phosphorylation (Hubbard & Gnanasambandan, 2013).

## Regulation

Post-translational modifications  
• Autophosphorylation at Tyr553 enables Dok7 binding and downstream signalling (Herbst & Burden, 2000).  
• Activation-loop phosphorylation of Tyr750, Tyr754 and Tyr755 is required for full catalytic activity (Hubbard & Gnanasambandan, 2013).  
• Additional regulated sites include Tyr576, Tyr599, Ser678, Ser751 and Tyr755 (Budayeva et al., 2022; Prömer et al., 2025).  
• Ser751 is a CaMK2β target in vitro, but this modification is dispensable for MuSK activation in vivo (Prömer et al., 2025).  
• N-linked glycosylation of extracellular domains modulates agrin responsiveness; deglycosylation abolishes signalling (Glass et al., 1996).

Allosteric/ligand control  
• Neural agrin binds LRP4, forming a complex that clusters MuSK and triggers basal autophosphorylation (Hubbard & Gnanasambandan, 2013).  
• Dok7 interaction with pTyr553 stabilises MuSK dimers and drives activation-loop phosphorylation (Hubbard & Gnanasambandan, 2013).

## Function

Expression  
MuSK is selectively expressed in skeletal muscle, up-regulated during myoblast-to-myotube differentiation, and concentrated at the postsynaptic membrane of the neuromuscular junction (DeChiara et al., 1996; Valenzuela et al., 1995).

Upstream inputs  
– Neural agrin via LRP4 (DeChiara et al., 1996).  
– Basal Wnt binding to the cysteine-rich domain (Hubbard & Gnanasambandan, 2013).

Downstream partners and pathways  
– PTB adaptor Dok7 (Hubbard & Gnanasambandan, 2013).  
– Crk/Crk-L, Abl1 and Src kinases, Rapsyn, Dishevelled-1, PAK1, Rac1 and Cdc42 mediate acetylcholine-receptor (AChR) clustering and cytoskeletal remodelling (Fish & Fallon, 2020; Wang et al., 2007).  
– Phosphorylation of Rab10, Rab35 and related Rab GTPases links MuSK to vesicular trafficking (Budayeva et al., 2022).

Physiological roles  
MuSK initiates and maintains AChR clustering, postsynaptic gene expression and cytoskeletal organisation essential for neuromuscular transmission; genetic ablation prevents embryonic neuromuscular junction (NMJ) formation and signalling deficits cause progressive synaptic fragmentation and muscle weakness (DeChiara et al., 1996; Fish & Fallon, 2020).

## Other Comments

IgG4 autoantibodies against MuSK produce a subset of myasthenia gravis by interfering with agrin/LRP4-dependent activation, and inherited loss-of-function mutations in MU​SK or DOK7 cause congenital myasthenic syndromes (Hubbard & Gnanasambandan, 2013).

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