## Phylogeny

Protein O-mannose kinase (POMK; SgK196) belongs to the atypical branch of the eukaryotic protein-kinase superfamily, clustering near the kinome root and clearly separated from canonical Ser/Thr and Tyr kinases (Zhu et al., 2016). Catalytic-residue-retaining orthologs are confined to vertebrates—e.g., Mus musculus (81 % identity within the catalytic domain) and Danio rerio (58 %)—while fungal and plant homologues are absent (Nagae et al., 2017; Zhu et al., 2016). A hallmark of the lineage is relocation of the catalytic Lys from β3 to β2, replacing the classical β3-Lys/αC-Glu ion pair and defining a distinct sub-family within the “unclassified/atypical” kinases (Zhu et al., 2016).

## Reaction Catalyzed

ATP + GalNAc-β1,3-GlcNAc-β1,4-Man-(Ser/Thr)-α-dystroglycan ⇌ ADP + GalNAc-β1,3-GlcNAc-β1,4-(6-phosphate)-Man-(Ser/Thr)-α-dystroglycan (Nagae et al., 2017; Zhu et al., 2016).

## Cofactor Requirements

Catalysis is divalent-cation dependent; Mg²⁺ is obligatory in vitro, while Mn²⁺ can substitute with retained activity (Zhu et al., 2016; Unknown Authors, 2023).

## Substrate Specificity

POMK exclusively phosphorylates the core M3 trisaccharide (GalNAc-β1,3-GlcNAc-β1,4-Man) when O-linked to α-dystroglycan. The GalNAc-β1,3-GlcNAc disaccharide forms the primary recognition determinant (K\_D ≈ 30 µM). No activity is detected toward free sugars, unrelated glycans, or peptides lacking the glycan (Zhu et al., 2016; Nagae et al., 2017).

## Structure

• Topology: type II transmembrane protein with a short cytosolic N-terminus, a single transmembrane helix, and a luminal kinase domain (residues ~45–349) (Nagae et al., 2017).  
• Fold: canonical bilobal kinase architecture; crystal structure solved at 2.1 Å in complex with ADP-AlF₃-Mg²⁺ and a substrate mimic (Zhu et al., 2016).  
• Active-site features  
– Lys91 (β2) binds ATP phosphates and ion-pairs with Asp227 of the activation segment.  
– Catalytic loop MCD motif with Asp202 as general base.  
– Activation segment starts with DLD; Asp225 coordinates Mg²⁺.  
– Disulfide bridge Cys201–Cys241 stabilises the active site (Zhu et al., 2016).  
• Unique elements: shifted catalytic Lys, enlarged αE–αF linker forming a sugar-binding groove, and a surface pocket that clamps the GalNAc-β1,3-GlcNAc moiety (Zhu et al., 2016; Nagae et al., 2017).

## Regulation

Activity is constitutive; no activation-segment phosphorylation or autophosphorylation has been observed (Zhu et al., 2016). Three luminal N-glycosylation sites influence folding, but regulatory outcomes remain undefined. No evidence for ubiquitination, allosteric partners, or other post-translational control mechanisms has been reported (Nagae et al., 2017).

## Function

POMK phosphorylates core M3 on α-dystroglycan in the ER, an essential precursor step for ribitol-5-phosphate transfer by FKTN/FKRP and LARGE1-mediated extension of matriglycan, thereby enabling high-affinity binding of laminin-G-domain extracellular-matrix proteins (Walimbe et al., 2020; Nagae et al., 2017).  
Expression is high in fetal brain, skeletal muscle, heart, and kidney, with moderate levels in adult cerebrum, hippocampus, and muscle (Di Costanzo et al., 2014).  
Pathway placement: acts downstream of POMGNT2 and B3GALNT2 and upstream of FKTN, FKRP, and LARGE1 in matriglycan synthesis (Walimbe et al., 2020).  
Interactors/substrates: direct substrate is α-dystroglycan; phosphorylated core M3 promotes preferential binding of LARGE1 (Walimbe et al., 2020).  
Physiological impact: loss of POMK shortens matriglycan, reduces laminin binding, destabilises the sarcolemma, impairs muscle force, disrupts neuronal migration, and alters susceptibility to Lassa virus (Walimbe, 2021; Di Costanzo et al., 2014; Zhu et al., 2016).

## Inhibitors

Not reported.

## Other Comments

Recessive POMK mutations cause a spectrum of dystroglycanopathies, including Walker–Warburg syndrome, muscle-eye-brain disease, and limb-girdle muscular dystrophy (Zhu et al., 2016; Di Costanzo et al., 2014). Catalytically disruptive variants include D204N, K93A, D227A, A230E, and cysteine substitutions C201S/C241S that break the stabilising disulfide bond (Zhu et al., 2016; Walimbe et al., 2020). Complete loss of POMK generates milder phenotypes than defects in downstream enzymes, consistent with residual short matriglycan retaining partial ECM binding (Walimbe, 2021).

## References

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