## Phylogeny

PAN3 orthologs are found throughout eukaryotes, including humans, mouse, *Drosophila*, *Caenorhabditis elegans*, *Xenopus*, *Neurospora crassa*, *Chaetomium thermophilum*, and the yeasts *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* (Brown et al., 1996; Verma et al., 2024; Wolf et al., 2014). The protein contains a kinase-like fold but lacks the catalytic residues required for phosphotransfer and is therefore classified as a pseudokinase; accordingly, it is omitted from kinome catalogues (Christie et al., 2013; Verma et al., 2024).

## Reaction Catalyzed

Within the heterotrimeric PAN2-PAN3 complex, PAN2 is the catalytic subunit, and the assembled enzyme removes adenosine residues from the 3′ poly(A) tail of mRNA in a 3′→5′ exonucleolytic reaction:

poly(A)ₙ + H₂O → poly(A)ₙ₋₁ + AMP (Martin & Coller, 2014; Schäfer et al., 2019).

## Cofactor Requirements

Deadenylation by the PAN2-PAN3 complex requires divalent metal ions, typically Mg²⁺ (Unknown Authors, 2020a). The PAN3 pseudokinase domain binds ATP, although it is catalytically inactive (Wolf et al., 2014; Unknown Authors, 2014).

## Substrate Specificity

The complex selectively targets the 3′ poly(A) tail of mRNAs (Wolf et al., 2014; Unknown Authors, 2020b). PAN3 enhances specificity through:  
• a PAM2 motif that interacts with poly(A)-binding protein (PABP), tethering the enzyme to polyadenylated transcripts (Mangus et al., 2004; Wolf et al., 2014);  
• a CCCH-type zinc-finger that contacts poly(A) RNA directly (Verma et al., 2024; Unknown Authors, 2020a).  
The stacked helical conformation of pure poly(A) is preferred; incorporation of guanosines into the tail strongly inhibits deadenylation (Tang et al., 2019; Unknown Authors, 2020a).

## Structure

PAN3 contains an N-terminal intrinsically disordered region with a CCCH zinc finger and PAM2 motif, a central pseudokinase (PK) domain, an intervening coiled-coil (CC) region, and a C-terminal knob (CK) domain (Wolf et al., 2014; Unknown Authors, 2014). The CC mediates formation of an asymmetric PAN3 homodimer; one such dimer associates with a single PAN2 molecule to form the active heterotrimer (Schäfer, 2014; Zhang et al., 2023). Dimerization also creates a tryptophan-binding pocket for GW182/TNRC6 proteins (Christie et al., 2013). The PK domain adopts the canonical bilobal kinase fold but lacks the catalytic Lys-Asp pair (Christie et al., 2013).

## Regulation

PAN3 is subject to multisite phosphorylation. In yeast, Pho85-Pcl1 phosphorylates T57 and S252 of Pan3p; in mammals, Cdk5 phosphorylates PAN3 (Unknown Authors, 1980; Verma et al., 2024). Phosphorylation modulates PABP binding and subcellular localization: hypophosphorylated variants accumulate in cytoplasmic P-bodies, whereas hyper-phosphorylated mimetics relocalize to the nucleus (Unknown Authors, 1980). ATP binding to the pseudokinase domain further influences complex stability and activity (Schäfer, 2014; Christie et al., 2013).

## Function

PAN3 acts as the regulatory subunit of the cytoplasmic PAN deadenylase, localizing to P-bodies where it:  
• recruits PAN2 to polyadenylated mRNAs via PAM2–PABP and zinc-finger–RNA contacts (Wolf et al., 2014);  
• engages GW182/TNRC6 proteins, linking the complex to miRNA-mediated silencing (Christie et al., 2013);  
• interacts with Dun1 kinase and the RNA-binding protein MEX3 (Wolf et al., 2014; Unknown Authors, 2020c).  
In *S. cerevisiae*, deletion of PAN3 abolishes PAN activity, lengthens poly(A) tails, and renders cells sensitive to nocodazole (Brown et al., 1996; Verma et al., 2024). In mammalian cells, PAN3 maintains spindle integrity and supports survival under microtubule stress (Verma et al., 2024).

## Other Comments

No disease-linked PAN3 mutations are reported in the cited literature. Mutations in the ATP-binding pocket impair mRNA decay, and mutations that disrupt PAN2 binding abolish deadenylation (Christie et al., 2013).

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