## Phylogeny

TRRAP/Tra1 is universally conserved in eukaryotes; orthologues are found in Saccharomyces cerevisiae (Tra1), Schizosaccharomyces pombe (Tra1) and Mus musculus (Trrap), and no surveyed genome lacks a TRRAP gene (Unknown Authors, 2018, pp. 164-167; Unknown Authors, 2021, pp. 20-22, 36-40).  
Within the kinome it belongs to the phosphatidylinositol-3-kinase-related kinase (PIKK) family and forms the sole, conserved pseudoPIKK branch (Elías-Villalobos et al., 2019, pp. 6-9). DNA-PKcs is its closest paralogue, reflecting an ancient gene-duplication event that preceded divergence of the catalytically active ATM/ATR/mTOR/DNA-PKcs/SMG1 clades (Elías-Villalobos et al., 2019, pp. 12-17). Loss of the canonical VAIK, HRD and DFG motifs underlies its catalytic inactivation (Elías-Villalobos et al., 2019, pp. 6-9).

## Reaction Catalyzed

Protein-OH + ATP → Protein-O-P + ADP  
No phosphoryl-transfer is detected because all essential catalytic residues are missing (Elías-Villalobos et al., 2019, pp. 25-30).

## Cofactor Requirements

Neither Mg²⁺/Mn²⁺ nor ATP binding has been observed; the protein is catalytically inactive (Elías-Villalobos et al., 2019, pp. 25-30; Unknown Authors, 2021, pp. 131-135).

## Substrate Specificity

No phosphorylation consensus motif or enzymatic substrate specificity has been assigned owing to the absence of kinase activity (Unknown Authors, 2021, pp. 131-135).

## Structure

• N-terminal α-solenoid containing ~60–70 HEAT/TPR repeats that form Finger, Ring and Clasp sub-domains for partner binding (Elías-Villalobos et al., 2019, pp. 25-30; Unknown Authors, 2021, pp. 36-40).  
• Central FAT domain (~15 TPR repeats) supports the C-terminal head (Unknown Authors, 2021, pp. 22-26).  
• C-terminal PI3K-like pseudokinase domain with FRB, LBE and PRD insertions; adopts the two-lobe kinase fold but lacks the catalytic Lys, Asp and DFG triad and has a partially occluded cleft (Unknown Authors, 2021, pp. 131-135; Wang et al., 2018, pp. 6-7).  
• FATC tail folds into a hydrophobic pocket of the kinase lobe, stabilising the structure (Unknown Authors, 2021, pp. 131-135).  
• Cryo-EM and AlphaFold models reveal a “diamond-ring” topology in which the HEAT solenoid encircles a compact FAT-KIN head, creating a rigid scaffold (Elías-Villalobos et al., 2019, pp. 25-30; Unknown Authors, 2021, pp. 40-43).  
• Regulatory elements: an extended, stabilised activation loop and a displaced PRD keep the active-site non-productive (Wang et al., 2018, pp. 6-7).

## Regulation

• Folding and nuclear stability depend on the HSP90–R2TP–TTT chaperone system; depletion of TELO2, TTI1 or TTI2 destabilises TRRAP and reduces its transcriptional output (Unknown Authors, 2018, pp. 76-79, 167-170).  
• Complex selection: Spt20 mediates incorporation into SAGA, whereas Eaf5/Eaf1 promote mutually exclusive engagement with NuA4/TIP60 (Elías-Villalobos et al., 2019, pp. 9-12; Unknown Authors, 2021, pp. 143-147).  
• Limited hinge motions between HEAT solenoid and FAT domain accommodate partner subunits without activating the pseudokinase (Unknown Authors, 2021, pp. 135-139).  
• Post-translational modifications of TRRAP itself have not been mapped (Elías-Villalobos et al., 2019, pp. 17-21).

## Function

• Serves as a scaffold subunit of SAGA/STAGA, PCAF and NuA4/TIP60 histone acetyltransferase complexes, nucleating HAT and deubiquitinase modules (Knutson & Hahn, 2011, pp. 1-2; Elías-Villalobos et al., 2019, pp. 1-6).  
• Acts as a co-activator for DNA-bound transcription factors such as c-MYC, E2F1, p53, Sp1 and adenoviral E1A, enhancing histone H4/H2A acetylation at target promoters (Yin & Wang, 2021, pp. 1-3; Elías-Villalobos et al., 2019, pp. 17-21).  
• Supports oncogenic MYC programmes; depletion in colorectal cancer cells down-regulates MYC targets and de-represses interferon-stimulated genes (Unknown Authors, 2018, pp. 164-170).  
• Contributes to DNA-damage response and telomere maintenance through its role in TIP60 (Unknown Authors, 2021, pp. 20-22).  
• Expression: nuclear, ubiquitous and essential; complete loss is embryonic lethal in mice (Unknown Authors, 2021, pp. 36-40).  
• Key partners include the TTT chaperone triad, Spt20 (SAGA), Eaf1/Eaf5 (NuA4) and multiple transcription activators (Knutson & Hahn, 2011, pp. 12-13; Unknown Authors, 2021, pp. 135-139).

## Other Comments

Somatic missense mutations cluster on HEAT and FAT surfaces that mediate complex assembly, potentially compromising co-activator integrity (Wang et al., 2018, pp. 6-7; Unknown Authors, 2021, pp. 131-135). TRRAP overexpression or activity is required in several tumour types (colorectal, breast and others), highlighting its value as a non-enzymatic therapeutic target (Unknown Authors, 2018, pp. 167-170; Wang et al., 2018, pp. 6-7).

## 9. References

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