## Phylogeny

• Orthologs have been identified in Homo sapiens, Mus musculus, Bos taurus, Loxodonta africana, Alligator mississippiensis, and Xenopus tropicalis, while no counterparts are detected in fungi, plants, or choanoflagellates (eyers2017tribblesinthe pages 4-6).  
• Drosophila melanogaster encodes a single Tribbles protein (Trbl) that is the invertebrate orthologue sharing the adaptor architecture with TRIB3 (dobens2021controlofcell pages 2-4).  
• TRIB3 is one of three vertebrate paralogs; TRIB1 and TRIB3 arose by duplication from the more ancestral TRIB2 lineage (eyers2017tribblesinthe pages 2-4).  
• Within the human kinome TRIB3 clusters in the CAMK-like group, Tribbles pseudokinase sub-branch, retaining the bilobal kinase fold but lacking catalytic motifs (eyers2017tribblesinthe pages 1-2).

## Reaction Catalyzed

• Very weak, intramolecular autophosphorylation: ATP + TRIB3 ⇄ ADP + TRIB3-O-P; no phosphorylation of exogenous substrates has been demonstrated (unknownauthors2014biochemicalanalysisof pages 168-171).  
• Conventional serine/threonine kinase activity toward cellular targets is undetectable, consistent with loss of key catalytic residues (du2005regulationofthe pages 4-5).

## Cofactor Requirements

• Autophosphorylation proceeds without divalent cations; physiological Mg²⁺ concentrations suppress the reaction (unknownauthors2014biochemicalanalysisof pages 168-171).  
• Absence of the canonical DFG motif eliminates a Mg²⁺-binding site (singh2024“ohdearwe pages 2-4).

## Substrate Specificity

• No consensus phosphorylation motif or bona-fide protein substrate has been identified; screens against standard kinase panels are negative (unknownauthors2023proteomicsapproachesfor pages 95-96, eyers2016theevolvingworld pages 6-6).

## Structure

• Domain organisation:  
– N-terminal PEST/nuclear-localisation segment (aa 1-≈80) controlling stability and import (singh2024“ohdearwe pages 2-4).  
– Central bilobal pseudokinase domain (aa ≈81-330) retaining the VAIK lysine but bearing a DFG→SLE switch, a truncated glycine-rich loop and a bent αC helix that collapse the ATP pocket (murphy2015molecularmechanismof pages 3-4, unknownauthors2023proteomicsapproachesfor pages 95-96).  
– C-terminal tail (aa ≈331-358) containing HPWF (MEK1 binding) and DQXVP[E] (COP1 binding) motifs (singh2024“ohdearwe pages 2-4).  
• Crystal structures of the closely related TRIB1 (PDB 5CEM) reveal an auto-inhibited conformation in which the tail occludes the active site; AlphaFold modelling predicts an analogous fold for TRIB3 (murphy2015molecularmechanismof pages 3-4).  
• The activation loop is shortened and the hydrophobic spine is disrupted, explaining catalytic incompetence (murphy2015molecularmechanismof pages 3-4).  
• Substrate engagement is proposed to displace the tail and induce an SLE “out→in” switch that licenses adaptor function (dobens2021controlofcell pages 2-4).

## Regulation

• Phosphorylation: Ser80 and Ser83 are modified by unidentified proline-directed kinases; functionally linked to stability and localisation (mondal2016trippingontrib3 pages 57-68).  
• Autophosphorylation: weak, Mg²⁺-independent, occurs on undefined sites within the kinase domain (unknownauthors2016functionsandregulation pages 14-17).  
• Ubiquitination: the C-terminal DQXVP[E] cassette recruits COP1 and SIAH1 E3 ligases, driving polyubiquitination and proteasomal degradation; additional ligases UBR2 and deubiquitinase USP16 bind the same region (mondal2016trippingontrib3 pages 57-68, unknownauthors2023proteomicsapproachesfor pages 38-39).  
• Transcriptional induction: ER-stress PERK–eIF2α–ATF4–CHOP axis, hypoxia via HIF-1α, and cytokines (TNFα, IL-3) markedly elevate TRIB3 mRNA (mondal2016trippingontrib3 pages 10-13).  
• Negative feedback: accumulated TRIB3 binds ATF4 and limits further ATF4-driven transcription during the integrated stress response (mondal2016trippingontrib3 pages 10-13).  
• Conformational control: intramolecular docking of the C-tail onto the kinase fold maintains autoinhibition; binding of partners (MEK1, AKT) displaces the tail and remodels the SLE motif (dobens2021controlofcell pages 2-4).

## Function

• Subcellular distribution is both nuclear and cytoplasmic and shifts with nutrient status and stress (mondal2016trippingontrib3 pages 10-13).  
• Direct binding to AKT1/2 masks Thr308 and Ser473, blocking PI3K–AKT–mTOR signalling and contributing to fasting-induced gluconeogenesis and insulin resistance (du2005regulationofthe pages 4-5).  
• COP1 recruitment enables ubiquitination of metabolic regulators including acetyl-CoA carboxylase, C/EBPβ and PPARγ, thereby repressing adipocyte differentiation and enhancing fatty-acid oxidation (qi2006trb3linksthe pages 1-2, bezy2007trb3blocksadipocyte pages 10-12).  
• Interacts with ATF4, CHOP and RELA/p65 to modulate the integrated stress response and NF-κB pathways, acting as a context-dependent transcriptional brake (unknownauthors2023proteomicsapproachesfor pages 41-42, mondal2016trippingontrib3 pages 57-68).  
• Proteomics reveals additional partners—ZBTB1, SPEN, WRAD complex, PRKD1, MKNK1/2—linking TRIB3 to chromatin repression and MAPK signalling (unknownauthors2023proteomicsapproachesfor pages 38-39).  
• Physiological roles include regulation of glucose and lipid homeostasis, survival of erythroid progenitors, and stress-induced apoptosis (unknownauthors2016functionsandregulation pages 42-44, mondal2016trippingontrib3 pages 57-68).  
• In cancer, elevated TRIB3 sustains tumour growth and metastasis via MAPK, Notch and autophagy modulation, yet its AKT inhibition can exert tumour-suppressive effects, yielding context-dependent outcomes (unknownauthors2016functionsandregulation pages 44-47).

## Other Comments

• The gene maps to chromosome 20p13-p12.2, spans six exons and encodes a 358-aa ≈65 kDa protein (mondal2016trippingontrib3 pages 10-13).  
• Functional SNP rs2295490 (Q84R) associates with insulin resistance and cardiovascular risk (mondal2016trippingontrib3 pages 10-13).  
• Hepatic overexpression induces hyperglycaemia and systemic insulin resistance, whereas knock-down restores insulin sensitivity in diabetic mice (du2005regulationofthe pages 4-5).  
• TRIB3 amplification or overexpression occurs in colorectal, liver, lung, breast, uterine, ovarian and oesophageal cancers and correlates with poor prognosis (unknownauthors2016functionsandregulation pages 44-47).

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