

ALPK1 phosphorylates TIFA

Gillespie, ME., Shamovsky, V., Shao, F.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](#). For more information see our [license](#).

27/04/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics*, 33, 3461-3467. [↗](#)
- Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res*, 46, D649-D655. [↗](#)
- Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology*, 14, e1005968. [↗](#)

Reactome database release: 88

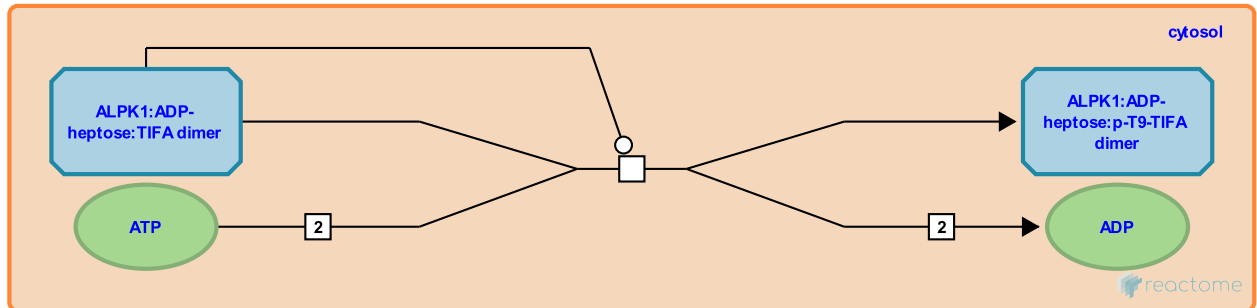
This document contains 1 reaction ([see Table of Contents](#))

ALPK1 phosphorylates TIFA ↗

Stable identifier: R-HSA-9645535

Type: transition

Compartments: cytosol



TRAF-interacting protein with a forkhead-associated (FHA) domain (TIFA) was reported to trigger NF-kappa B mediated inflammatory responses to *Helicobacter pylori*, *Shigella flexneri*, *Yersinia pseudotuberculosis* infections (Gall A et al. 2017; Milivojevic M et al. 2017; Gaudet RG et al. 2017; García-Weber D et al. 2018; Zhou P et al. 2018). During infection, ADP-heptose-activated alpha protein kinase 1 (ALPK1) binds and phosphorylates TIFA at threonine 9 (T9) (Zhou P et al. 2018). Defective NF- κ B activation in TIFA $-/-$ human embryonic kidney 293T (HEK293T) cells was restored by wild-type TIFA but not by the non-phosphorylatable T9A TIFA variant upon *H. pylori*, *S. flexneri*, *Y. pseudotuberculosis* infections (Zimmermann S et al. 2017; Gaudet RG et al. 2017; Zhou P et al. 2018). Moreover, T9A TIFA variant was unable to oligomerize preventing the *S. flexneri*-induced formation of the TIFA:TRAF6:TAK1-Ub complex in TIFA $-/-$ HEK293T cells (Gaudet RG et al. 2015, 2017). Unphosphorylated TIFA is thought to exist as an intrinsic dimer in solution (Huang CC et al. 2012). When T9 is phosphorylated, this is recognized by the FHA domain of other TIFA dimers leading to its oligomerization (Huang CC et al. 2012). Oligomerized TIFA promotes activation of an innate immune response by inducing the oligomerization and polyubiquitination of TRAF6, which leads to the activation of TAK1 (MAP3K7) and IKK (Ea CK et al. 2004).

Literature references

Wang, DC., Lu, S., Li, P., Dong, N., Zamyatina, A., Borio, A. et al. (2018). Alpha-kinase 1 is a cytosolic innate immune receptor for bacterial ADP-heptose. *Nature*, 561, 122-126. ↗

Editions

| | | |
|------------|----------|----------------|
| 2019-05-17 | Authored | Shamovsky, V. |
| 2019-06-03 | Reviewed | Gillespie, ME. |
| 2019-07-08 | Reviewed | Shao, F. |
| 2019-08-09 | Edited | Shamovsky, V. |