

TNF:TNFR1:TRADD:TRAF2:K63polyUb- RIPK1:BIRC2,3:LUBAC recruits IKKA:IKB- KB:IKBK

Franjkić, T., Gillespie, ME., Munitić, I., Shamovsky, V., Tu, H., Wajant, H.

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](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://reactome.org/licenses/).

09/05/2024

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

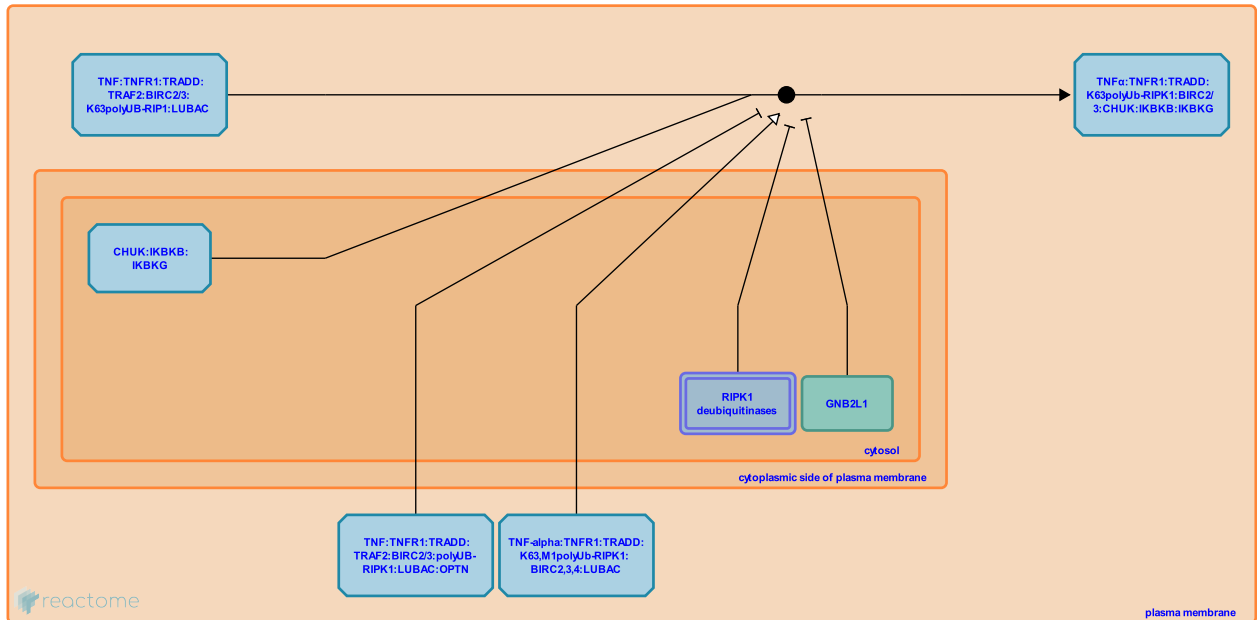
This document contains 1 reaction ([see Table of Contents](#))

TNF:TNFR1:TRADD:TRAF2:K63polyUb-RIPK1:BIRC2,3:LUBAC recruits IKKA:IKB-KB:IKBKG ↗

Stable identifier: R-HSA-5357776

Type: binding

Compartments: plasma membrane, cytosol



K63-polyubiquitinated RIPK1 binds to IKBKG (NEMO), resulting in the recruitment of the IKK complex to the TNF-alpha receptor 1 (TNFR1) signaling complex (Ea CK et al. 2006).

In addition, the linear polyubiquitination has been implicated in the NF-kappa-B activation. The linear ubiquitin chain assembly complex (LUBAC) ligase consisting of HOIL-1L, HOIP, and SHARPIN, specifically generates linear polyubiquitin chains (Kirisako T et al. 2006; Walczak H et al. 2012). IKBKG (NEMO), a regulatory component of the I κ B kinase (IKK) complex, is a substrate of LUBAC. LUBAC-mediated IKBKG ubiquitination enhances IKBKG interaction with the TNFR1 complex and stabilizes this protein complex to promote activation of NF-kappa-B (Haas TL et al. 2009).

Structural analysis revealed that NPL4 zinc finger 1 (NZF1) of HOIP can simultaneously bind both leucine zipper domains of NEMO (IKBKG) and ubiquitin and that both interactions are involved in the TNF alpha-mediated NF-kappa-B activation (Fujita H et al. 2014). In addition, NEMO (IKBKG) ubiquitination required RING-between-RING (RBR) domain of HOIL-1L (Smit JJ et al. 2013)

Literature references

Deng, L., Chen, ZJ., Pineda, G., Xia, ZP., Ea, CK. (2006). Activation of IKK by TNFalpha requires site-specific ubiquitination of RIP1 and polyubiquitin binding by NEMO. *Mol Cell*, 22, 245-57. ↗

Editions

| | | |
|------------|----------|----------------|
| 2015-02-15 | Edited | Shamovsky, V. |
| 2015-03-12 | Reviewed | Gillespie, ME. |
| 2015-05-12 | Authored | Shamovsky, V. |
| 2015-08-25 | Reviewed | Wajant, H. |
| 2022-10-31 | Reviewed | Tu, H. |
| 2023-02-14 | Reviewed | Munitić, I. |
| 2023-03-01 | Reviewed | Franjkić, T. |