# RIP2 is K63 polyubiquitinated

Jupe, S., Kufer, TA., Rittinger, K., Wong, E.

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.

17/10/2024

# 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. ↗

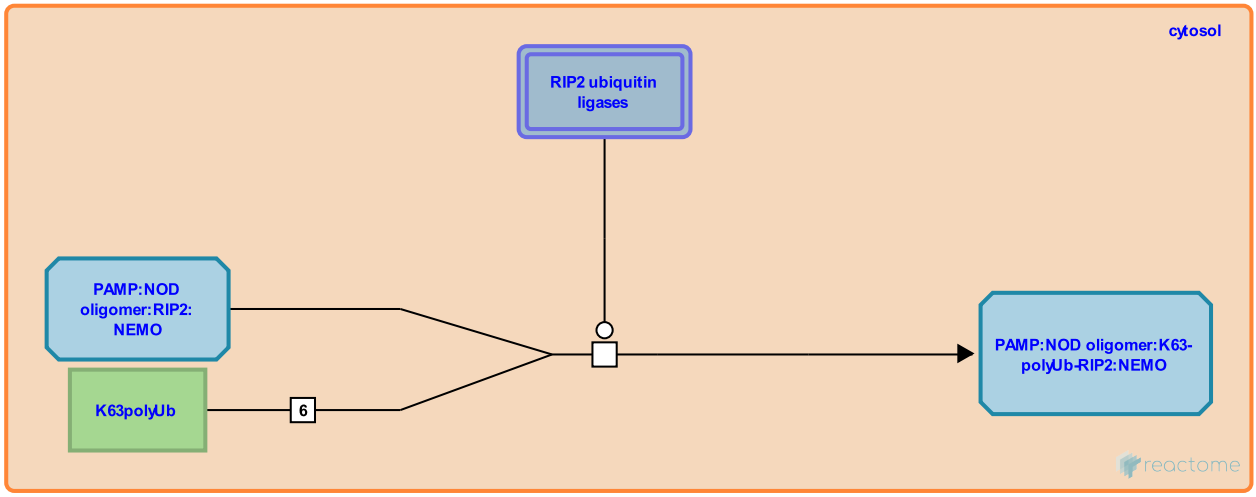
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

## RIP2 is K63 polyubiquitinated ↗

**Stable identifier:** R-HSA-688137

**Type:** transition

**Compartments:** cytosol




The close physical proximity of RIP2 proteins that results from NOD oligomerization triggers the conjugation of lysine (K)-63 linked polyubiquitin chains onto RIP2. Ubiquitination at K209 within the kinase domain was required for subsequent NFkappaB signaling (Hasegawa et al. 2008). The identity of the ubiquitin ligase responsible is an open question, with several candidates capable of RIP2 ubiquitination. TRAF6 has been reported as the ubiquitin ligase responsible (Yang et al. 2007) but subsequent reports suggest it is not responsible (see Tao et al. 2009 and Bertrand et al. 2009). Other candidates include the HECT-domain containing E3 ubiquitin ligase ITCH, which is able to K63 ubiquitinate RIP2 (at an undetermined site that is not K209) and is required for optimal NOD2:RIP2-induced p38 and JNK activation, while inhibiting NOD2:RIP2-induced NFkappaB activation (Tao et al. 2009). The Baculoviral IAP repeat-containing proteins (Birc/cIAP) 2 and 3 have also been shown capable of RIP2 ubiquitination and required for NOD2 signaling (Bertrand et al. 2009). It has been suggested that ITCH and a K209 E3 ligase compete for ubiquitination of RIP2, so that a subset of RIP2 becomes ubiquitinated on K209 to stimulate NEMO ubiquitination and subsequent NFkappaB activation while a second subset of RIP2 is polyubiquitinated by ITCH to activate JNK and p38 signaling (Tao et al. 2009).

## Literature references

Hasegawa, M., Nakano, H., Lucas, PC., Nunez, G., Fujimoto, Y., Inohara, N. et al. (2008). A critical role of RICK/RIP2 polyubiquitination in Nod-induced NF-kappaB activation. *EMBO J, 27*, 373-83. ↗

## Editions

| | | |
|---|---|---|
| 2010-04-22 | Authored | Jupe, S. |
| 2011-04-28 | Edited | Jupe, S. |
| 2011-04-28 | Reviewed | Kufer, TA. |
| 2011-06-06 | Reviewed | Rittinger, K., Wong, E. |