Phosphorylation of IRF-3/IRF7 and their release from the activated TLR3 complex

Fitzgerald, KA., Gay, NJ., Gillespie, ME., Masci, A M., Shamovsky, V., de Bono, B.

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

29/09/2022

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. ↗

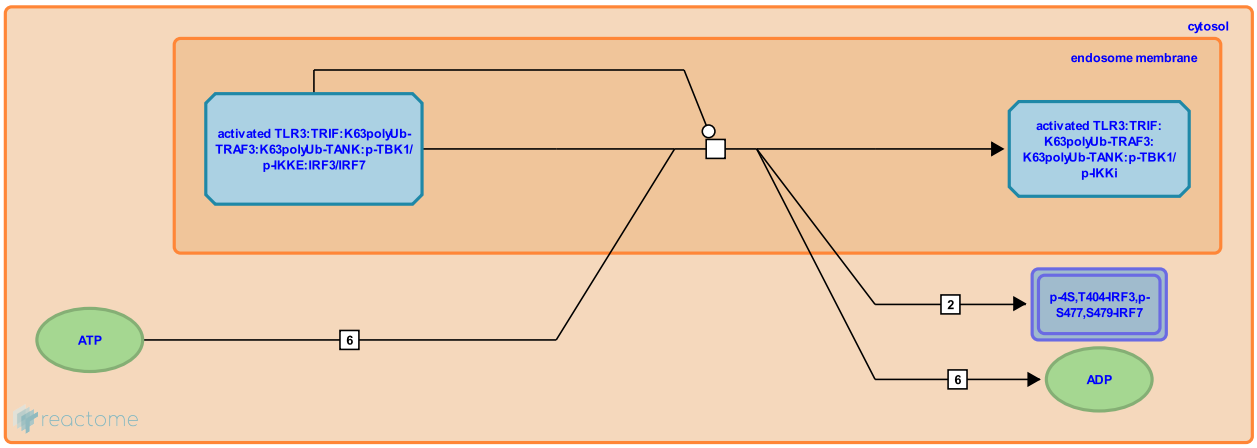
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Phosphorylation of IRF-3/IRF7 and their release from the activated TLR3 complex

Stable identifier: R-HSA-9013978

Type: transition

Compartments: endosome membrane, cytosol



Human IRF3 is activated through a two step phosphorylation in the C-terminal domain mediated by TBK1 and/or IKKi. It requires Ser386 and/or Ser385 (site 1) and a cluster of serine/threonine residues between Ser396 and Ser405 (site 2) (Panne et al. 2007). Phosphorylated residues at site 2 alleviate autoinhibition to allow interaction with CBP (CREB-binding protein) and facilitate phosphorylation at site 1. Phosphorylation at site 1 is required for IRF3 dimerization.

IRF3 and IRF7 transcription factors possess distinct structural characteristics; IRF7 is phosphorylated on Ser477 and Ser479 residues (Lin R et al. 2000). TRAF6 mediated ubiquitination of IRF7 is also required and essential for IRF7 phosphorylation and activation. The K-63 linked ubiquitination occurs on the last three C-terminal lysine sites (positions 444, 446, and 452) of human IRF7 independently of its C-terminal functional phosphorylation sites.(Ning et al. 2008).

Literature references

Coyle, AJ., Faia, KL., Fitzgerald, KA., Liao, SM., Rowe, DC., Latz, E. et al. (2003). IKKepsilon and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol, 4*, 491-6.

McWhirter, SM., Maniatis, T., Harrison, SC., Panne, D. (2007). Interferon regulatory factor 3 is regulated by a dual phosphorylation-dependent switch. *J Biol Chem, 282*, 22816-22.

Fujita, T., Inagaki, F., Takahashi, K., Yoneyama, M., Mori, M., Ito, T. (2004). Identification of Ser-386 of interferon regulatory factor 3 as critical. *J Biol Chem, 279*, 9698-702.

Editions

2005-08-16	Authored	de Bono, B.
2006-04-24	Reviewed	Gay, NJ.
2010-11-30	Reviewed	Gillespie, ME.
2012-11-13	Reviewed	Fitzgerald, KA.
2014-05-16	Reviewed	Masci, A M.
2014-05-16	Edited	Shamovsky, V.