Trimerization of cytosolic HSF1

Pani, B., Shamovsky, V.

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

18/01/2021

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. ↗

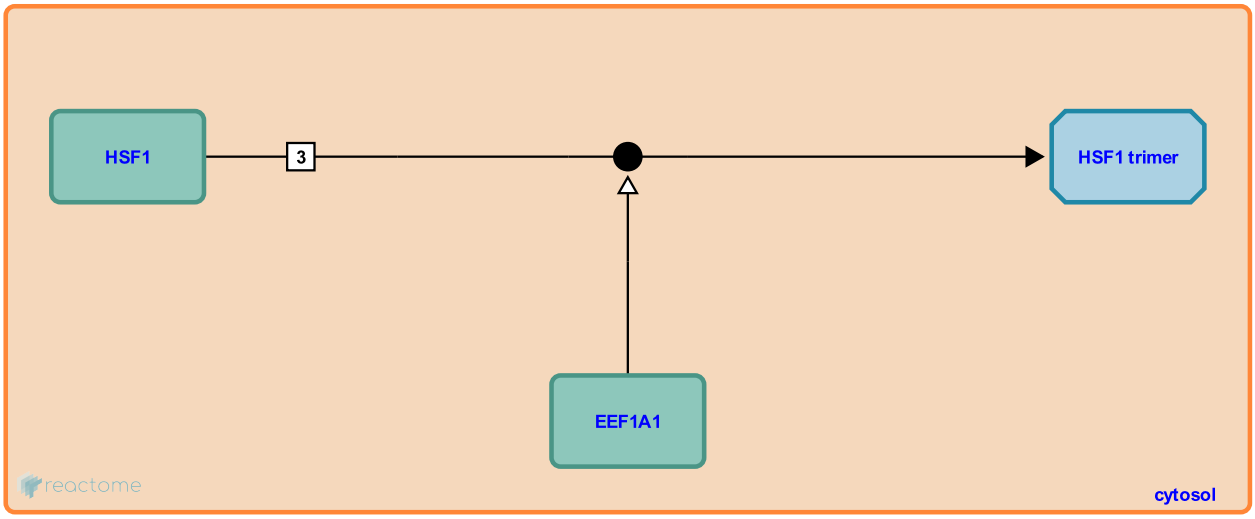
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Trimerization of cytosolic HSF1

Stable identifier: R-HSA-3371591

Type: binding

Compartments: cytosol



Accumulation of non-native or misfolded proteins upon cellular stress is believed to release monomeric HSF1 from chaperon regulatory proteins (Guo Y et al. 2001). The released HSF1 monomer is rapidly converted to a homotrimer (Baler R et al. 1993; Herbomel G et al 2013). Upon trimerization HSF1 undergoes significant conformational changes resulting in an assembly of a stable triple-stranded alpha-helical coiled-coil structure with the amino-terminal hydrophobic domains from individual monomeric units (Rabindran SK et al. 1993; Zuo J et al. 1994, 1995; Neef DW et al. 2013). Biochemical and structural analysis strongly suggest that the monomer-to-trimer transition is tightly regulated at several interdependent levels. Thus, HSPs and cofactors bind HSF1 monomers preventing trimerization (Zou J et al.1998; Guo Y et al. 2001). In addition, leucine zippers (LZ) in the trimerization domain (LZ1-LZ3) are thought to retain HSF1 in its inactive monomeric form by intramolecular coiled-coil interactions with LZ4 in the carboxyl-terminus of HSF1, while LZ interactions between trimerization domains of individual monomeric units facilitate homotrimerization (Rabindran SK et al. 1993; Zuo J et al. 1994, 1995; Neef DW et al. 2013). HSF1 flexible linker region between DNA binding domain and first LZ of the trimerization domain was also found to modulate the monomer-trimer equilibrium (Liu PCC and Thiele DJ 1999). Furthermore, intermolecular disulfide bonds between cysteine residues 36 and 103 were reported to stabilize HSF1 trimer, while intramolecular disulfide crosslink inhibited HSF1 oligomerization (Lu M et al. 2008, 2009). Moreover, redox regulatory mechanisms were shown to regulate thiol-disulfide exchange and the conformation and activity of mammalian HSF1 in response to stress (Manalo DJ et al. 2002; Ahn SG and Thiele DJ 2003).

A ribonucleoprotein complex containing translation elongation factor EEF1A1 (eEF1A) and a long non-coding RNA, HSR1 (heat shock RNA-1) was shown to mediate trimerization of HSF1 (Shamovsky I et al. 2006).

Literature references

Baler, R., Dahl, G., Voellmy, R. (1993). Activation of human heat shock genes is accompanied by oligomerization, modification, and rapid translocation of heat shock transcription factor HSF1. *Mol. Cell. Biol., 13*, 2486-96.

Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.