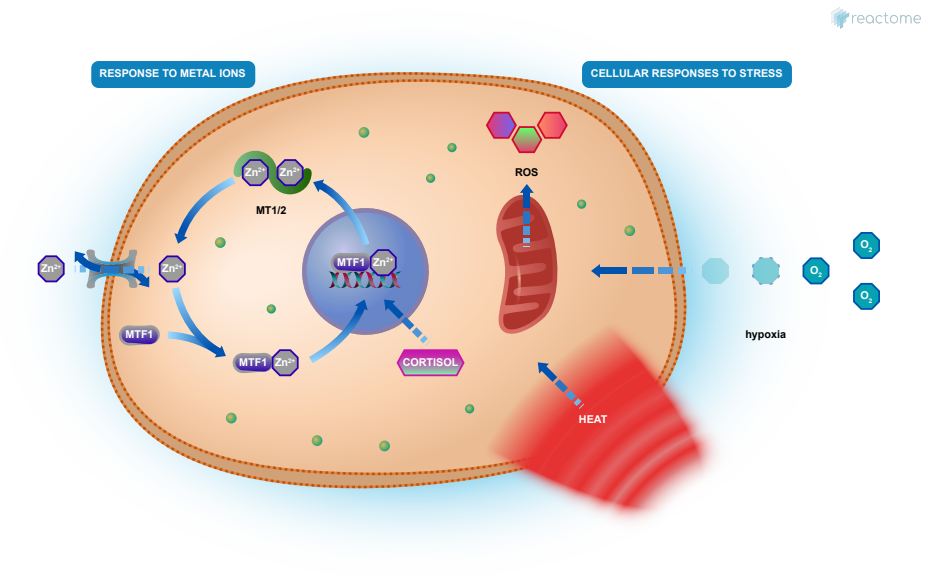
Cellular responses to stimuli



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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. ↗

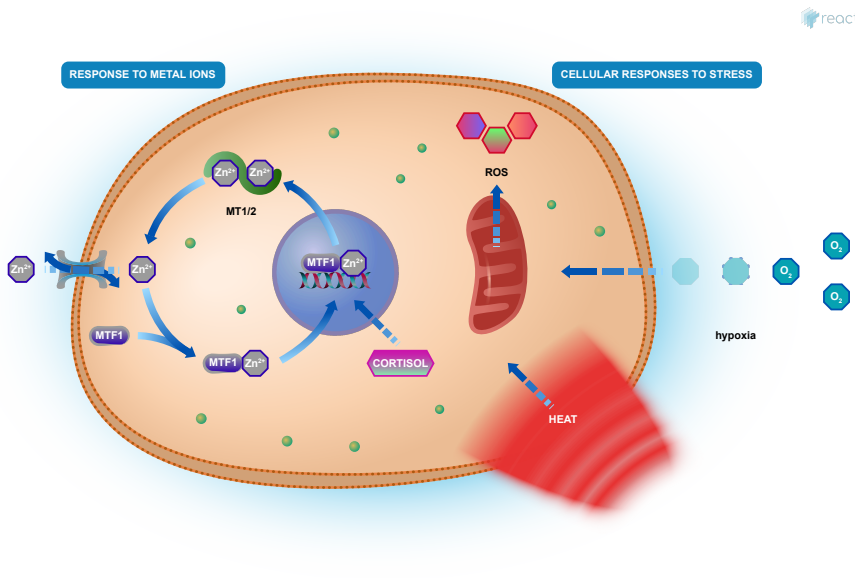
Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Reactome database release: 88

This document contains 3 pathways (see Table of Contents)

Cellular responses to stimuli ↗

Stable identifier: R-HSA-8953897



Individual cells detect and respond to diverse external molecular and physical signals. Appropriate responses to these signals are essential for normal development, maintenance of homeostasis in mature tissues, and effective defensive responses to potentially noxious agents (Kultz 2005). It is convenient, if somewhat arbitrary, to distinguish responses to signals involved in development and homeostasis from ones involved in stress responses, and that classification is followed here, with **macroautophagy** and **responses to metal ions** classified as responses to normal external stimuli, while responses to hypoxia, reactive oxygen species, and heat, and the process of cellular senescence are classified as **stress responses**. Signaling cascades are integral components of all of these response mechanisms but because of their number and diversity, they are grouped in a separate signal transduction superpathway in Reactome.

Literature references

Kültz, D. (2005). Molecular and evolutionary basis of the cellular stress response. *Annu. Rev. Physiol., 67*, 225-57. ↗

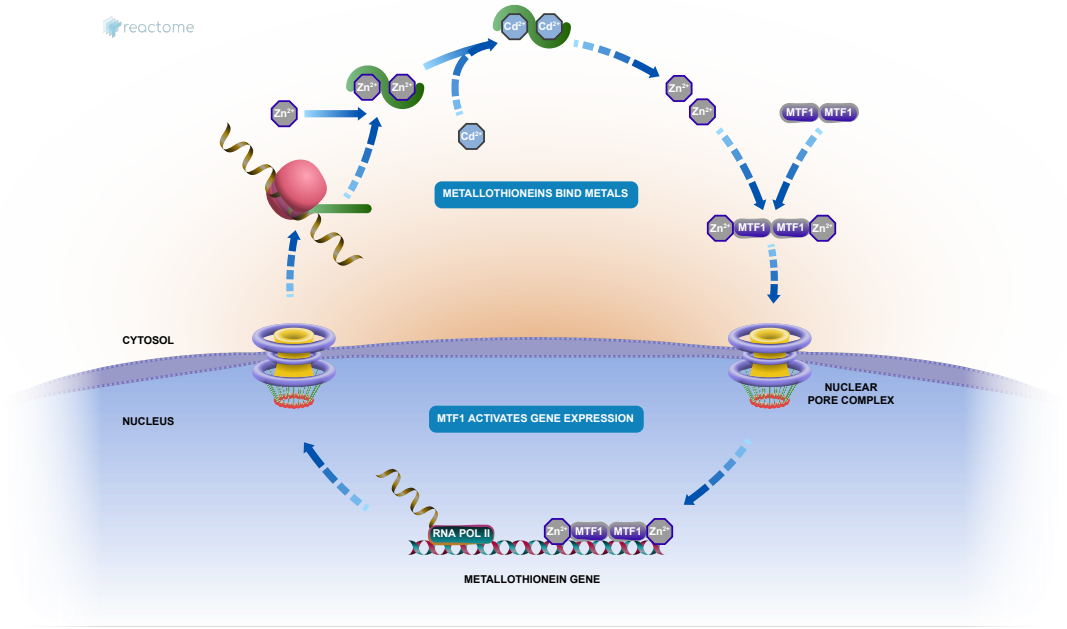
Editions

2012-05-20	Reviewed	D'Eustachio, P.
2015-05-13	Reviewed	Tooze, SA.
2015-09-03	Reviewed	Klionsky, DJ.
2015-09-19	Reviewed	Atrian, S.
2016-12-30	Authored, Edited	D'Eustachio, P.

Response to metal ions

Location: Cellular responses to stimuli

Stable identifier: R-HSA-5660526



Though metals such as zinc, copper, and iron are required as cofactors for cellular enzymes they can also catalyze damaging metal substitution or unspecific redox reactions if they are not sequestered. The transcription factor MTF1 directs the major cellular response to zinc, cadmium, and copper. MTF1 activates gene expression to up-regulate genes encoding proteins, such as metallothioneins and glutamate-cysteine ligase (GCLC), involved in sequestering metals. MTF1 represses gene expression to down-regulate genes encoding transporters that import the metals into the cell (reviewed in Laity and Andrews 2007, Jackson et al. 2008, Günther et al. 2012, Dong et al. 2015). During activation MTF1 in the cytosol binds zinc ions and is translocated into the nucleus, where it binds metal response elements in the promoters of target genes. Activation of MTF1 by cadmium and copper appears to be indirect as these metals displace zinc from metallothioneins and the displaced zinc then binds MTF1.
Metallothioneins bind metals and participate in detoxifying heavy metals, storing and transporting zinc, and redox biochemistry.

Literature references

Jackson, KA., Coneyworth, LJ., Valentine, RA., Ford, D., Mathers, JC. (2008). Mechanisms of mammalian zinc-regulated gene expression. *Biochem. Soc. Trans., 36*, 1262-6.

Wang, Q., Dou, Y., Dong, G., Chen, H., Qi, M. (2015). Balance between metallothionein and metal response element binding transcription factor 1 is mediated by zinc ions (review). *Mol Med Rep, 11*, 1582-6.

Andrews, GK., Laity, JH. (2007). Understanding the mechanisms of zinc-sensing by metal-response element binding transcription factor-1 (MTF-1). *Arch. Biochem. Biophys., 463*, 201-10.

Lindert, U., Günther, V., Schaffner, W. (2012). The taste of heavy metals: gene regulation by MTF-1. *Biochim. Biophys. Acta, 1823*, 1416-25.

Editions

2014-12-28	Authored, Edited	May, B.
2015-09-19	Reviewed	Atrian, S.

Cellular responses to stress ↗

Location: Cellular responses to stimuli

Stable identifier: R-HSA-2262752

Cells are subject to external molecular and physical stresses such as foreign molecules that perturb metabolic or signaling processes, and changes in temperature or pH. Cells are also subject to internal molecular stresses such as production of reactive metabolic byproducts. The ability of cells and tissues to modulate molecular processes in response to such stresses is essential to the maintenance of tissue homeostasis (Kultz 2005). Specific stress-related processes annotated here are **cellular response to hypoxia**, **cellular response to heat stress**, **cellular senescence**, **HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand**, **response of EIF2AK1 (HRI) to heme deficiency**, **heme signaling**, **cellular response to chemical stress**, **cellular response to starvation**, and **unfolded protein response**.

Literature references

Kültz, D. (2005). Molecular and evolutionary basis of the cellular stress response. *Annu. Rev. Physiol., 67*, 225-57. ↗

Editions

2012-05-20	Reviewed	D'Eustachio, P.
2012-05-20	Authored, Edited	Matthews, L.
2024-02-28	Reviewed	Matthews, L.

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