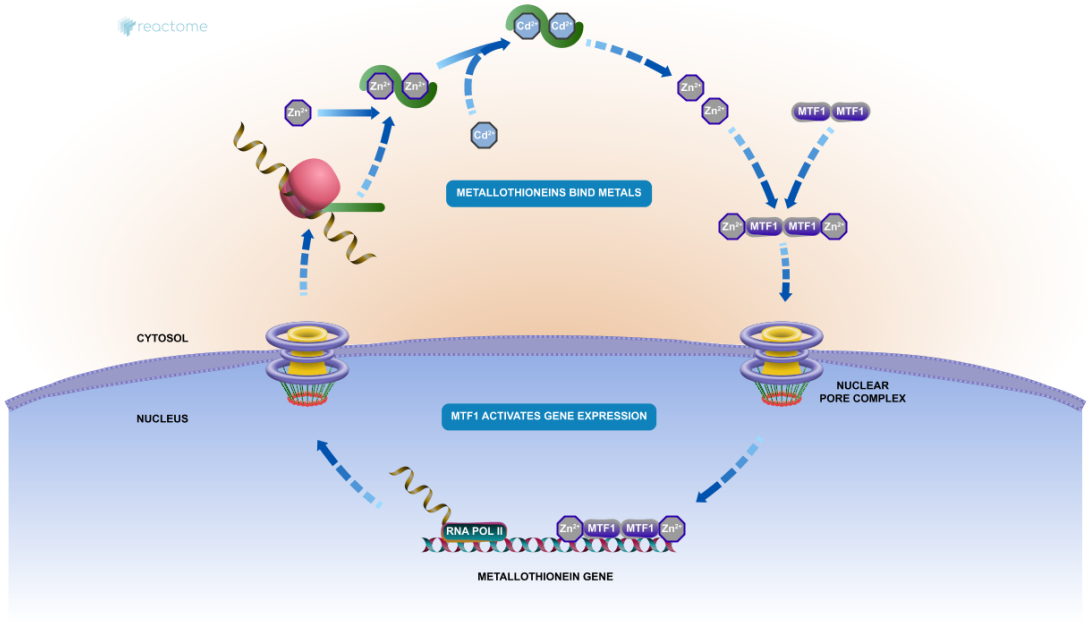
Response to metal ions



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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.

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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. ↗

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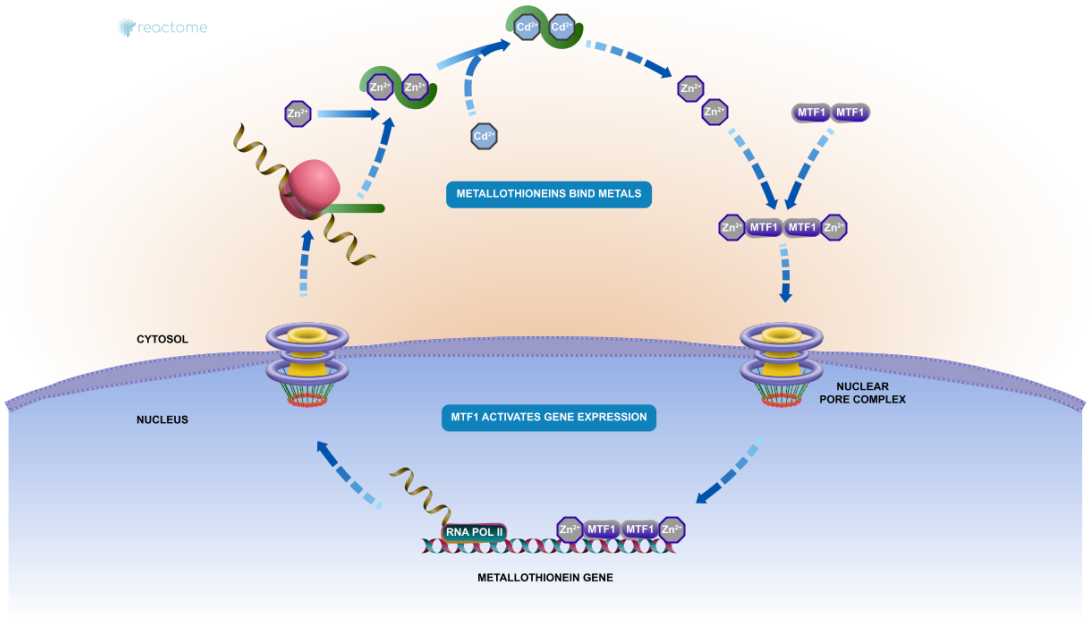
Reactome database release: 77

This document contains 3 pathways (see Table of Contents)

Response to metal ions

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

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

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

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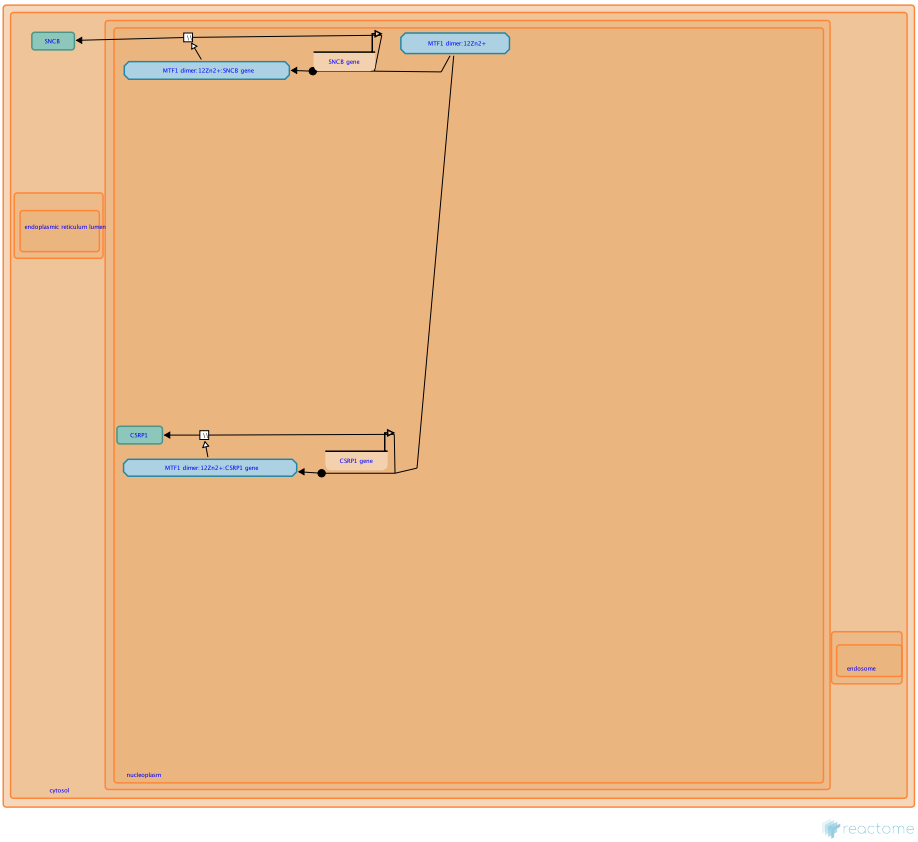
Editions

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

MTF1 activates gene expression ↗

Location: Response to metal ions

Stable identifier: R-HSA-5660489



The MTF1:zinc complex in the nucleus binds Metal Response Elements (MREs), DNA containing the core consensus sequence 5'-TGCRCNC-3', and activates or represses transcription depending on the context of the MRE (reviewed in Laity and Andrews 2007, Jackson et al. 2008, Gunther et al. 2012, Grzywacz et al. 2015). The 6 zinc fingers of each MTF1 monomer have different affinities for zinc and evidence from the mouse homolog indicates that different concentrations of zinc, and hence different metal loads in MTF1, activate different subsets of target genes (Wang et al. 2004, Dong et al. 2015). Genes activated by MTF1 include those encoding metallothioneins, zinc transporters, and stress-response proteins (Hardyman et al. 2016).

Literature references

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

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

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Editions

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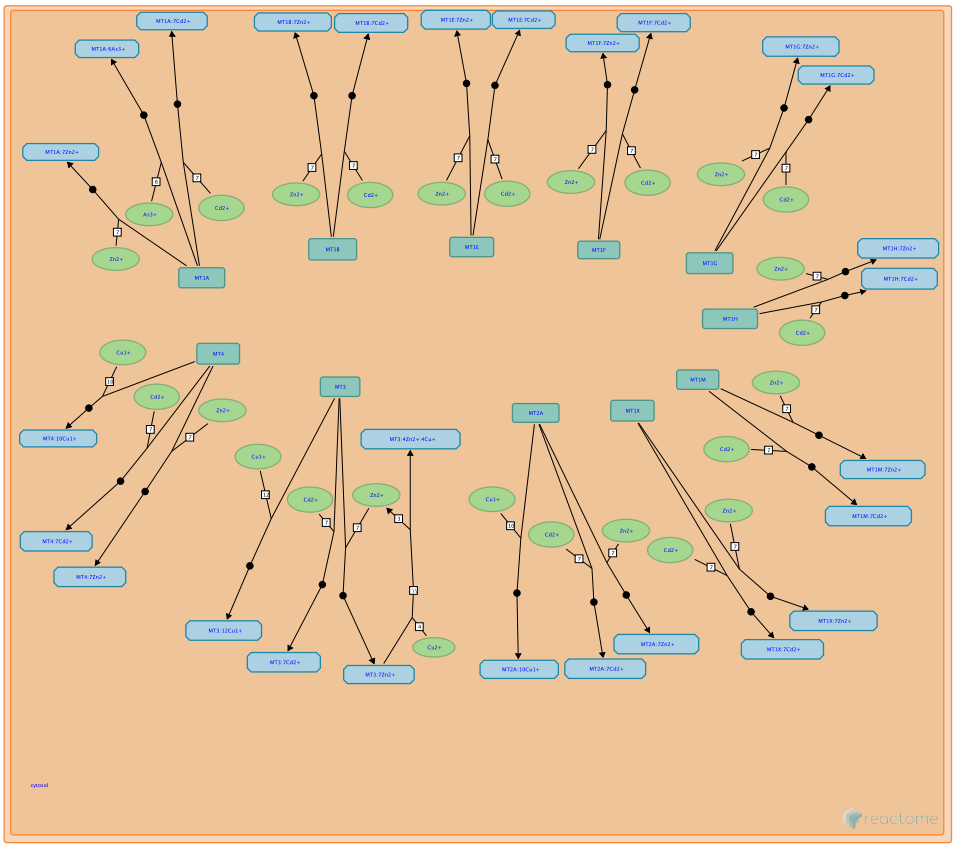
Metallothioneins bind metals ↗

Location: Response to metal ions

Stable identifier: R-HSA-5661231



Metallothioneins are highly conserved, cysteine-rich proteins that bind metals via thiolate bonds (recent general reviews in Capdevila et al. 2012, Blindauer et al. 2014, reviews of mammalian metallothioneins in Miles et al. 2000, Maret 2011, Vasak and Meloni 2011, Thirumoorthy et al. 2001, Babula et al. 2012). Mammals contain 4 general metallothionein isoforms (MT1,2,3,4). The MT1 isoform has radiated in primates to 8 or 9 functional proteins (depending on classification of MT1L). Each mammalian metallothionein binds a total of 7 divalent metal ions in two clusters, the alpha and beta clusters. Though the functions of metallothioneins have not been fully elucidated, they appear to participate in detoxifying heavy metals (reviewed in Sharma et al. 2013), storing and transporting zinc, and redox biochemistry. Metallothioneins interact with many other cellular proteins, with most interactions involving proteins of the central nervous system (reviewed in Atrian and Capdevila 2013).

Literature references

Miles, AT., Hawksworth, GM., Beattie, JH., Rodilla, V. (2000). Induction, regulation, degradation, and biological significance of mammalian metallothioneins. *Crit. Rev. Biochem. Mol. Biol., 35*, 35-70. ↗

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