Metallothioneins bind metals

Atrian, S., May, B.

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

29/12/2022

https://reactome.org
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


Reactome database release: 83

This document contains 1 pathway and 27 reactions (see Table of Contents)
Metallothioneins bind metals

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


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MT1A binds zinc

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5661217

Type: binding

Compartments: cytosol

The MT1A metallothionein binds 7 zinc(II) atoms, 3 at the N-terminal beta domain and 4 at the C-terminal alpha domain (Sunderland et al. 2012). Binding is non-cooperative (Sunderland et al. 2012) and occurs via thiolate bonds between zinc and cysteine residues of the protein. MT1A binds 5 atoms of zinc before clustering of the zinc occurs (Summers et al. 2013). The 2 remaining zinc atoms bind MT1A with significantly less affinity (Summers et al. 2013).

Literature references


Editions

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MT1A binds cadmium

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5661219

Type: binding

Compartments: cytosol

Inferred from: Mt1 binds cadmium (Mus musculus)

MT1A binds 7 atoms of cadmium(II), 3 atoms at the N-terminal beta domain and 4 atoms at the C-terminal alpha domain (Rigby Duncan et al. 2008, Sunderland and Stillman 2008, Sutherland et al. 2012). A fifth cadmium atom bound to the alpha domain may be an intermediate formed during metal exchange (Rigby Duncan et al. 2008). Binding of cadmium is non-cooperative (Rigby Duncan and Stillman 2007, Sunderland and Stillman 2008). As inferred from mouse Mt1, MT1A may show less preference for zinc compared with cadmium and may therefore serve more than other metallothionein isoforms to detoxify cadmium.

Literature references


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MT1A binds arsenic

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5661230

Type: binding

Compartments: cytosol


Literature references


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MT1B binds zinc

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662603

Type: binding

Compartments: cytosol

Inferred from: MT1A binds zinc (Homo sapiens)

As inferred from MT1A, the metallothionein MT1B binds 7 atoms of zinc(II) non-cooperatively.

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MT1B binds cadmium

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662610

Type: binding

Compartments: cytosol

Inferred from: MT1A binds cadmium (Homo sapiens)

As inferred from MT1A, the metallothionein MT1B binds 7 atoms of cadmium(II) non-cooperatively.

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MT1E binds zinc

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662614

Type: binding

Compartments: cytosol

Inferred from: MT1A binds zinc (Homo sapiens)

As inferred from MT1A, the metallothionein MT1E binds 7 atoms of zinc(II) non-cooperatively.

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https://reactome.org
MT1E binds cadmium

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662595

Type: binding

Compartments: cytosol

Inferred from: MT1A binds cadmium (Homo sapiens)

As inferred from MT1A, the metallothionein MT1E binds 7 atoms of cadmium(II) non-cooperatively.

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https://reactome.org
**MT1F binds zinc**

**Location:** Metallothioneins bind metals

**Stable identifier:** R-HSA-5662623

**Type:** binding

**Compartments:** cytosol

**Inferred from:** MT1A binds zinc (Homo sapiens)

As inferred from MT1A, the metallothionein MT1F binds 7 atoms of zinc(II) non-cooperatively.

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https://reactome.org
**MT1F binds cadmium**

**Location:** Metallothioneins bind metals

**Stable identifier:** R-HSA-5662596

**Type:** binding

**Compartments:** cytosol

**Inferred from:** MT1A binds cadmium (Homo sapiens)

As inferred from MT1A, the metallothionein MT1F binds 7 atoms of cadmium(II) non-cooperatively.

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[https://reactome.org](https://reactome.org)
MT1G binds zinc

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662618

Type: binding

Compartments: cytosol

Inferred from: MT1A binds zinc (Homo sapiens)

As inferred from MT1A, the metallothionein MT1G binds 7 atoms of zinc(II) non-cooperatively.

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https://reactome.org
MT1G binds cadmium ➔

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662617

Type: binding

Compartments: cytosol

Inferred from: MT1A binds cadmium (Homo sapiens)

As inferred from MT1A, the metallothionein MT1G binds 7 atoms of cadmium(II) non-cooperatively.

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https://reactome.org
MT1H binds zinc

**Location:** Metallothioneins bind metals

**Stable identifier:** R-HSA-5662619

**Type:** binding

**Compartments:** cytosol

**Inferred from:** MT1A binds zinc (Homo sapiens)

As inferred from MT1A, the metallothionein MT1H binds 7 atoms of zinc(II) non-cooperatively.

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**MT1H binds cadmium**

**Location:** Metallothioneins bind metals

**Stable identifier:** R-HSA-5662597

**Type:** binding

**Compartments:** cytosol

**Inferred from:** MT1A binds cadmium (Homo sapiens)

As inferred from MT1A, the metallothionein MT1H binds 7 atoms of cadmium(II) non-cooperatively.

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May, B.

Atrian, S.
MT1M binds zinc

**Location:** Metallothioneins bind metals

**Stable identifier:** R-HSA-5662621

**Type:** binding

**Compartments:** cytosol

**Inferred from:** MT1A binds zinc (Homo sapiens)

As inferred from MT1A, the metallothionein MT1M binds 7 atoms of zinc(II) non-cooperatively.

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MT1M binds cadmium

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662599

Type: binding

Compartments: cytosol

Inferred from: MT1A binds cadmium (Homo sapiens)

As inferred from MT1A, the metallothionein MT1M binds 7 atoms of cadmium(II) non-cooperatively.

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MT1X binds zinc

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662615

Type: binding

Compartments: cytosol

Inferred from: MT1A binds zinc (Homo sapiens)

As inferred from MT1A, the metallothionein MT1X binds 7 atoms of zinc(II) non-cooperatively.

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MT1X binds cadmium

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662622

Type: binding

Compartments: cytosol

Inferred from: MT1A binds cadmium (Homo sapiens)

As inferred from MT1A, metallothionein MT1X binds 7 atoms of cadmium(II) non-cooperatively.

Editions

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The metallothionein MT2A binds 7 atoms of zinc(II) in two clusters, one at the N-terminal beta domain and one at the C-terminal alpha domain (Stillman et al. 2000, Yang et al. 2007). The cluster at the alpha domain is more stable than the cluster at the beta domain, making the beta domain a better zinc donor (Jiang et al. 2000). Each cluster assembles independently (Jiang et al. 2000).

**Literature references**


**Editions**

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https://reactome.org
The metallothionein MT2A binds 7 atoms of cadmium(II), a cluster of 4 atoms at the alpha domain at the C-terminus and a cluster of 3 atoms at the beta domain at the N-terminus (Pan et al. 1999).

**Literature references**


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MT2A binds copper

**Location:** Metallothioneins bind metals

**Stable identifier:** R-HSA-5662986

**Type:** binding

**Compartments:** cytosol

The metallothionein MT2A binds 10 atoms of copper(I). Complexes with up to 12 atoms of Cu+ are observed, however the predominant form appears to be MT2A:10Cu+ (Banci et al. 2010, Chung et al. 2010). Metallothioneins and CuZn-SOD have the highest affinities of cellular proteins for copper(I), but metallothioneins are incapable of removing copper from other cellular enzymes (Banci et al. 2010).

**Literature references**


MT3 binds zinc

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662606

Type: binding

Compartments: cytosol

The metallothionein MT3 binds 7 zinc(II) atoms in 2 clusters, one cluster of 4 atoms at the C-terminal alpha domain and one cluster of 3 atoms at the N-terminal beta domain (Eriste et al. 2003, Knipp et al. 2005, Meloni et al. 2007, Meloni et al. 2008, Meloni et al. 2009, Wu et al. 2014). Though MT3 has a lower overall affinity for zinc than MT2A does (Palumaa et al. 2005), MT3 is capable of binding an additional zinc atom with a binding constant of 100 micromolar (Eriste et al. 2003, Palumaa et al. 2005, Meloni et al. 2009). Stoichiometries up to MT3:11Zn2+ have been observed but the MT3:7Zn2+ form is more stable and predominates (Palumaa et al. 2002, Eriste et al. 2003, Palumaa et al.).

Followed by: MT3 exchanges zinc for copper

Literature references


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https://reactome.org
MT3 binds cadmium

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662620

Type: binding

Compartments: cytosol


Literature references


Editions

2015-01-10  Authored, Edited  May, B.
2015-09-19  Reviewed  Atrian, S.
MT3 binds copper

**Location:** Metallothioneins bind metals

**Stable identifier:** R-HSA-5663002

**Type:** binding

**Compartments:** cytosol

**Inferred from:** Mt3 binds copper (Mus musculus)

The metallothionein MT3 is able to bind 12 copper(I) atoms when fully saturated (Roschitzki et al. 2002). Initially, 4 copper(I) atoms bind to each of the alpha and beta domains followed by the binding of 4 more copper(I) atoms. As inferred from the mouse homolog, MT3 exhibits a Cu-thionein character stronger than that of the MT1 and MT2 isoforms and it displays a high capacity to bind Cu+ provided that this occurs in a non-oxidative milieux.

**Literature references**


**Editions**

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MT3 exchanges zinc for copper

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662613

Type: omitted

Compartments: cytosol

MT3:Zn2+ releases 3 zinc ions and binds 4 copper ions at the N-terminal beta domain (Roschitszi et al. 2003, Meloni et al. 2007, Meloni et al. 2008). By this mechanism MT3 is able to scavenge free copper ions and swap metal with an aggregated amyloid beta:copper(II) complex and a alpha-synuclein:copper(II) complex and thereby abolish production of reactive oxygen species (Meloni et al. 2008, Meloni and Vasak 2011, Pedersen et al. 2012, Luo et al. 2013). The copper ions are divalent (copper(II), Cu2+) before binding but univalent (copper(I), Cu1+) after binding (Meloni et al. 2008).

Preceded by: MT3 binds zinc

Literature references


MT4 binds zinc

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662653

Type: binding

Compartments: cytosol

Inferred from: Mt4 binds zinc (Mus musculus)

As inferred from the mouse homolog, MT4 binds 7 atoms of zinc(II).

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MT4 binds cadmium

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662649

Type: binding

Compartments: cytosol

Inferred from: Mt4 binds cadmium (Mus musculus)

As inferred from the mouse homolog, MT4 binds 7 atoms of cadmium(II).

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MT4 binds copper

Location: Metallothioneins bind metals

Stable identifier: R-HSA-5662647

Type: binding

Compartments: cytosol

Inferred from: Mt4 binds copper (Mus musculus)

As inferred from the mouse homolog, MT4 binds 10 atoms of copper(I).

Literature references


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  - MT1E binds cadmium
  - MT1F binds zinc
  - MT1F binds cadmium
  - MT1G binds zinc
  - MT1G binds cadmium
  - MT1H binds zinc
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  - MT1M binds zinc
  - MT1M binds cadmium
  - MT1X binds zinc
  - MT1X binds cadmium
  - MT2A binds zinc
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  - MT2A binds copper
  - MT3 binds zinc
  - MT3 binds cadmium
  - MT3 binds copper
  - MT3 exchanges zinc for copper
  - MT4 binds zinc
  - MT4 binds cadmium
  - MT4 binds copper