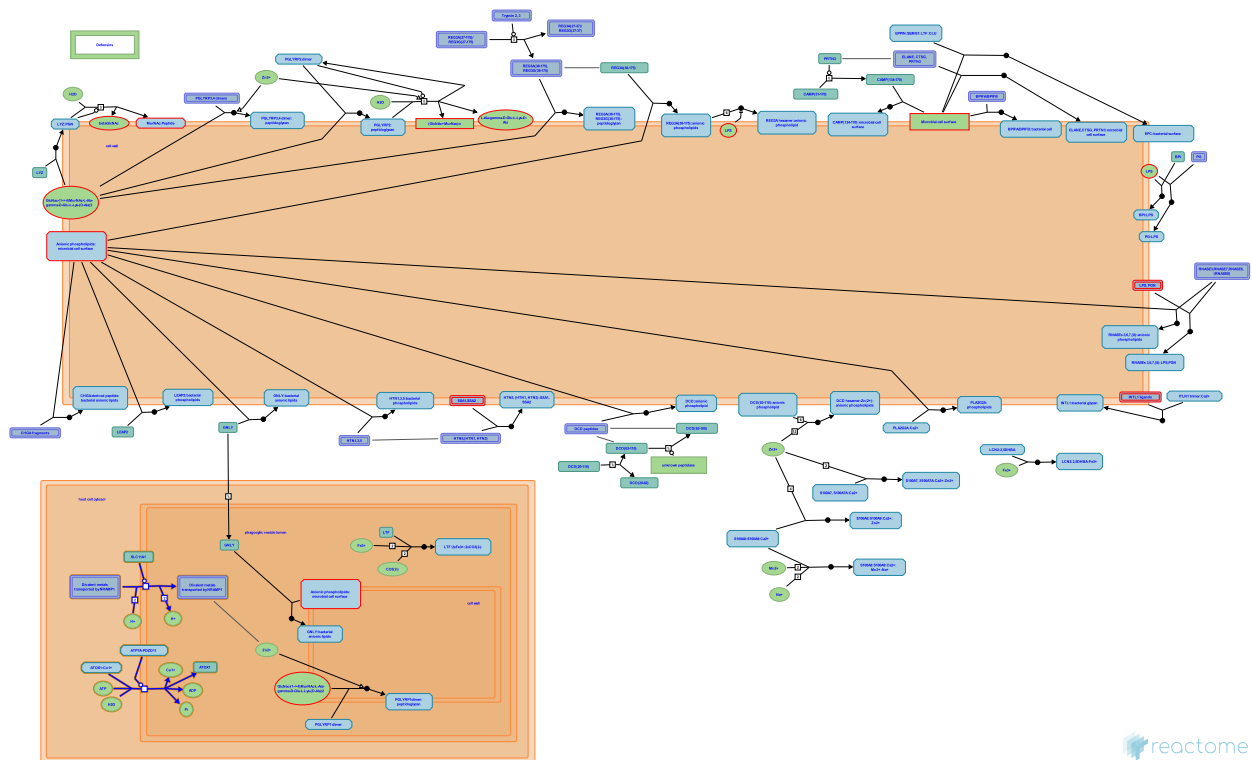


# Ion influx/efflux at host-pathogen interface



Hains, DS., He, L., Jassal, B., Jupe, S., Shamovsky, V.

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

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of [Creative Commons Attribution 4.0 International \(CC BY 4.0\) License](https://creativecommons.org/licenses/by/4.0/). For more information see our [license](https://reactome.org/licenses/).

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](https://reactome.org/textbook/).

30/04/2024

## 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

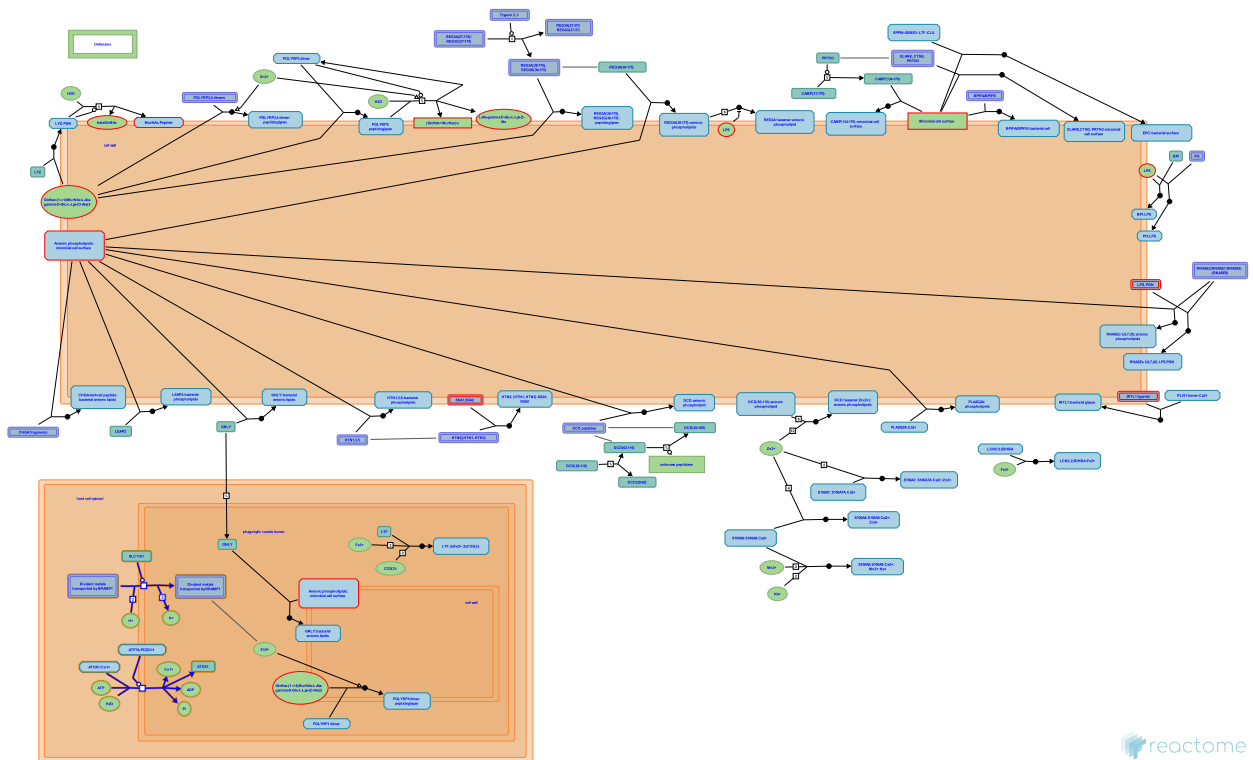
- Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics*, 18, 142. [↗](#)
- Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). 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 1 pathway and 2 reactions ([see Table of Contents](#))

# Ion influx/efflux at host-pathogen interface ↗

Stable identifier: R-HSA-6803544



reactome

Essential metal ions act as co-factors that enable enzymes to catalyse a wider range of chemical transformations than would be achievable using solely organic catalysts. The precise metal requirements of organisms vary between species, environmental niches, metabolic states and circadian rhythms.

Metals are required cofactors for numerous processes that are essential to both pathogen and host. They are coordinated in enzymes responsible for DNA replication and transcription, relief from oxidative stress, and cellular respiration. However, excess transition metals can be toxic due to their ability to cause spontaneous redox cycling and disrupt normal metabolic processes. Vertebrates have evolved intricate mechanisms to limit the availability of some crucial metals while concurrently flooding sites of infection with antimicrobial concentrations of other metals. Both pathogens and hosts have complex regulatory systems for metal homeostasis. Understanding these provides strategies for fighting pathogens, either by excluding essential metals from the microbes, by delivery of excess metals to cause toxicity, or by complexing metals in microorganisms.

## Literature references

Guengerich, FP. (2015). Introduction: Metals in Biology: METALS AT THE HOST-PATHOGEN INTERFACE. *J. Biol. Chem.*, 290, 18943-4. ↗

Skaar, EP., Becker, KW. (2014). Metal limitation and toxicity at the interface between host and pathogen. *FEMS Microbiol. Rev.*, 38, 1235-49. ↗

## Editions

2015-10-05	Authored	Shamovsky, V.
2016-04-15	Reviewed	Jupe, S.
2016-08-02	Reviewed	Hains, DS.
2016-08-15	Edited	Shamovsky, V.

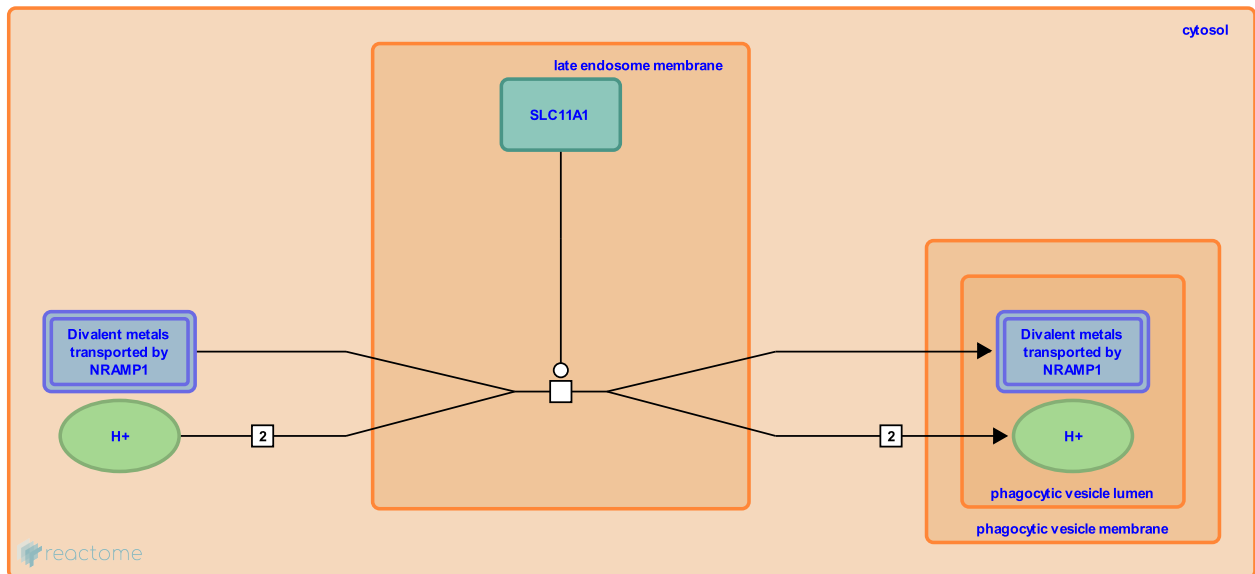
# NRAMP1 transports divalent metal ions across phagosomal membranes of macrophages ↗

**Location:** Ion influx/efflux at host-pathogen interface

**Stable identifier:** R-HSA-435171

**Type:** transition

**Compartments:** late endosome membrane, phagocytic vesicle lumen, cytosol



Natural resistance-associated macrophage proteins (NRAMPs) regulate macrophage activation for antimicrobial activity against intracellular pathogens. They do this by mediating divalent metal ion transport across macrophage membranes and the subsequent use of these ions in the Fenton/and or Haber–Weiss reactions of free radical formation.

The human gene SLC11A1 encodes NRAMP1 (Kishi F, 2004; Kishi F and Nobumoto M, 1995) which can utilize the protonmotive force to mediate divalent iron ( $\text{Fe}^{2+}$ ), zinc ( $\text{Zn}^{2+}$ ) and manganese ( $\text{Mn}^{2+}$ ) influx to or efflux from phagosomes.

## Literature references

Kishi, F., Nobumoto, M. (1995). Identification of natural resistance-associated macrophage protein in peripheral blood lymphocytes. *Immunol Lett*, 47, 93-6. ↗

Kishi, F. (1994). Isolation and characterization of human Nramp cDNA. *Biochem Biophys Res Commun*, 204, 1074-80. ↗

## Editions

2009-08-21	Edited	Jassal, B.
2009-09-07	Authored	Jassal, B.
2009-11-12	Reviewed	He, L.

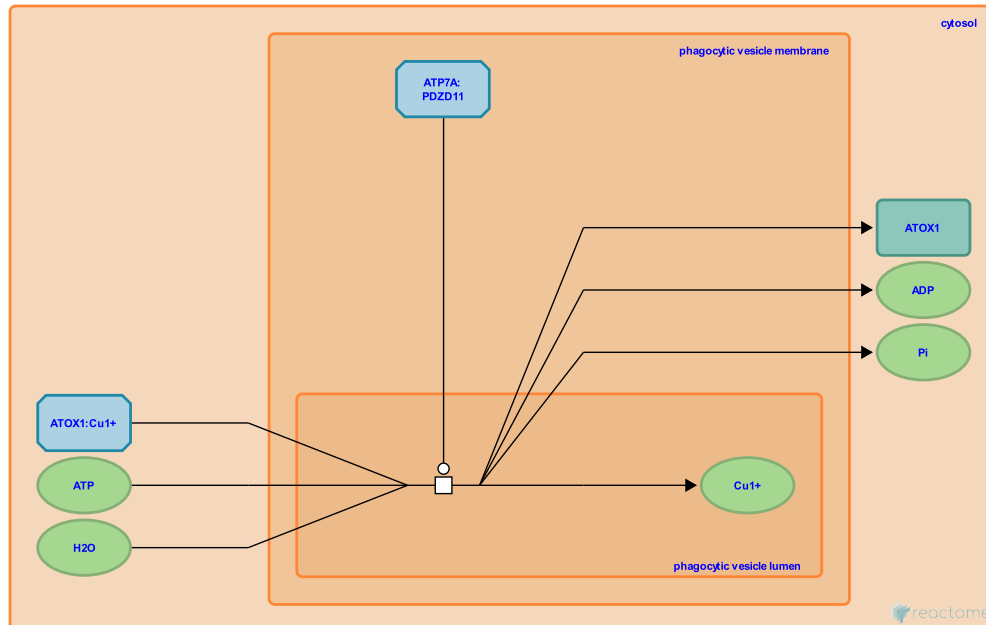
## ATP7A transports cytosolic Cu<sup>2+</sup> to phagosomal lumen ↗

**Location:** Ion influx/efflux at host-pathogen interface

**Stable identifier:** R-HSA-6803545

**Type:** transition

**Compartments:** phagocytic vesicle lumen, phagocytic vesicle membrane, cytosol



Copper is an essential cofactor of key metabolic enzymes (Linder MC & Hazegh-Azam M 1996). Under normal conditions, the biosynthetic incorporation of copper into secreted and plasma membrane-bound proteins requires activity of the copper-transporting P1B-type ATPases (Cu-ATPases), ATP7A and ATP7B (Camakaris J et al. 1999; La Fontaine S & Mercer JF 2007; Lutsenko S et al. 2007). The Cu-ATPases also export excess copper from the cell and thus critically contribute to the homeostatic control of copper (Camakaris J et al. 1999; La Fontaine S & Mercer JF 2007). However, during bacterial infection phagocytic cells accumulate copper Cu(I) in cytoplasmic vesicles that partially fuse with the phagolysosome, attacking invading microbes with toxic levels of Cu (Festa RA & Thiele DJ 2012). The accumulation of Cu(I) in the phagosome may be dependent upon the trafficking of ATP7A to the membranes of these vesicles (Fu Y et al. 2014). Silencing of ATP7A expression in mouse RAW264.7 macrophages attenuated bacterial killing, suggesting a role for ATP7A-dependent copper transport in the bactericidal activity of macrophages (White C et al. 2009). Copper toxicity targets iron-sulfur containing proteins via iron displacement from solvent-exposed iron-sulfur clusters (Macomber L & Imlay JA 2009; Chillappagari S et al. 2010; Djoko KY & McEwan AG 2013). Copper resistance has been shown to be required for virulence in two animal models of mycobacterial infection (Wolschendorf F et al. 2011; Shi X et al. 2014).

Mutations in the gene encoding ATP7A results in a severe copper-deficiency known as Menkes disease (Kaler SG 2011).

### Literature references

- McEwan, AG., Ong, CL., Walker, MJ., Djoko, KY. (2015). The Role of Copper and Zinc Toxicity in Innate Immune Defense against Bacterial Pathogens. *J. Biol. Chem.*, 290, 18954-61. ↗
- Festa, RA., Thiele, DJ. (2012). Copper at the front line of the host-pathogen battle. *PLoS Pathog.*, 8, e1002887. ↗
- Hodgkinson, V., Petris, MJ. (2012). Copper homeostasis at the host-pathogen interface. *J. Biol. Chem.*, 287, 13549-55. ↗

## Editions

2015-10-05	Authored	Shamovsky, V.
2016-04-15	Reviewed	Jupe, S.
2016-08-02	Reviewed	Hains, DS.
2016-08-15	Edited	Shamovsky, V.

# Table of Contents

Introduction	1
☒ Ion influx/efflux at host-pathogen interface	2
↳ NRAMP1 transports divalent metal ions across phagosomal membranes of macrophages	3
↳ ATP7A transports cytosolic Cu <sup>2+</sup> to phagosomal lumen	4
Table of Contents	6