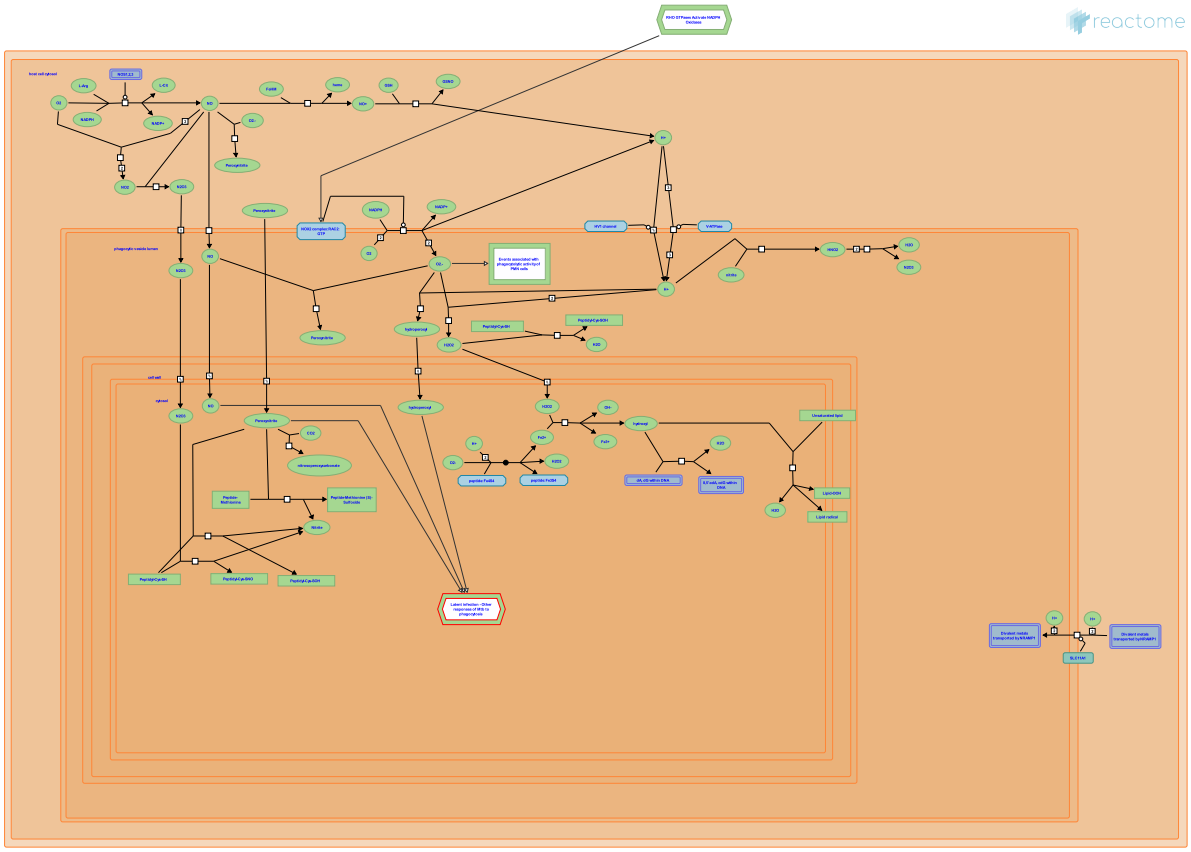
ROS and RNS production in phagocytes



Akkerman, JW., He, L., Jassal, B., Jupe, S., Kunapuli, SP., Nüsse, O., Shamovsky, V., Stephan, R., Warner, D.

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

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.

24/04/2024

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. ↗

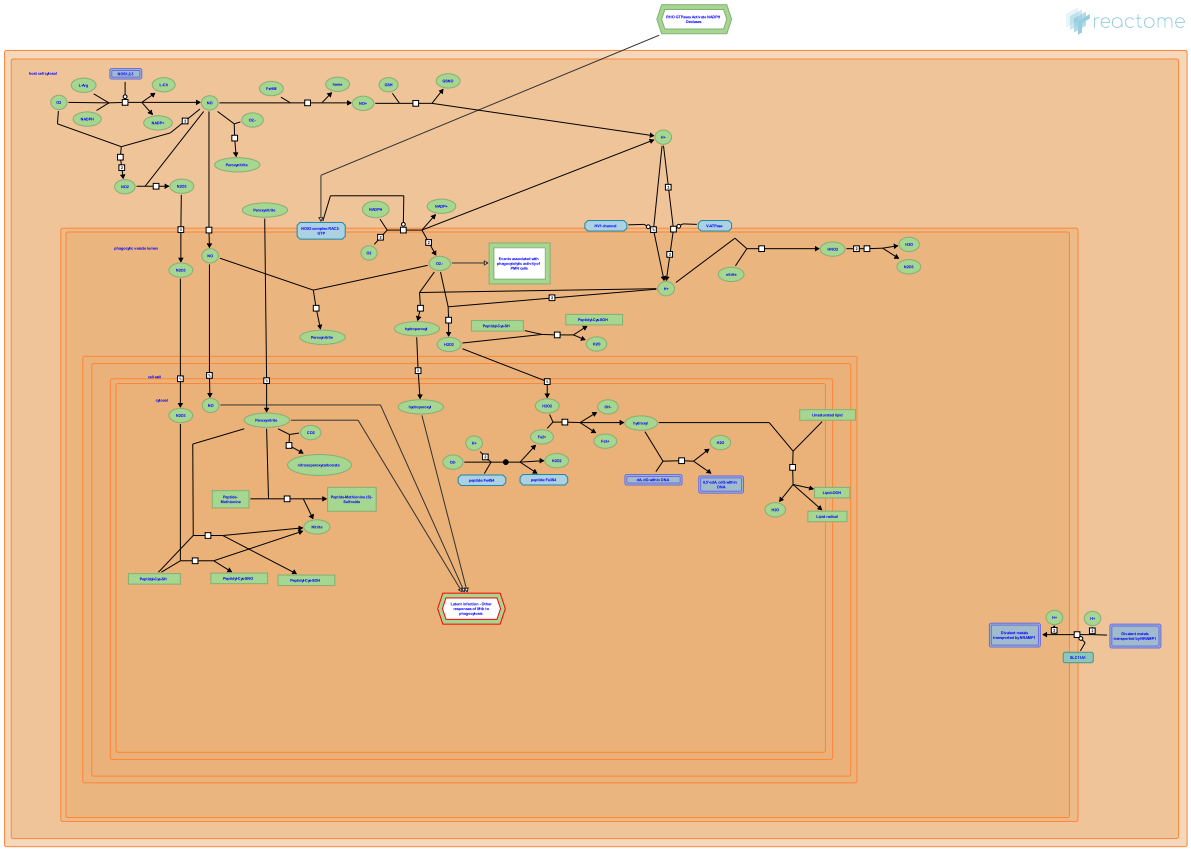
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

ROS and RNS production in phagocytes ↗

Stable identifier: R-HSA-1222556



The first line of defense against infectious agents involves an active recruitment of phagocytes to the site of infection. Recruited cells include polymorhonuclear (PMN) leukocytes (i.e., neutrophils) and monocytes/macrophages, which function together as innate immunity sentinels (Underhill DM & Ozinsky A 2002; Stuart LM & Ezekowitz RA 2005; Flannagan RS et al. 2012). Dendritic cells are also present, serving as important players in antigen presentation for ensuing adaptive responses (Savina A & Amigorena S 2007). These cell types are able to bind and engulf invading microbes into a membrane-enclosed vacuole - the phagosome, in a process termed phagocytosis. Phagocytosis can be defined as the receptor-mediated engulfment of particles greater than 0.5 micron in diameter. It is initiated by the cross-linking of host cell membrane receptors following engagement with their cognate ligands on the target surface (Underhill DM & Ozinsky A 2002; Stuart LM & Ezekowitz RA 2005; Flannagan RS et al. 2012). When engulfed by phagocytes, microorganisms are exposed to a number of host defense microbicidal events within the resulting phagosome. These include the production of reactive oxygen and nitrogen species (ROS and RNS, RONS) by specialized enzymes (Fang FC et al. 2004; Kohchi C et al. 2009; Gostner JM et al. 2013; Vatansever F et al. 2013). NADPH oxidase (NOX) complex consume oxygen to produce superoxide radical anion (O2.-) and hydrogen peroxide (H2O2) (Robinson et al. 2004). Induced NO synthase (iNOS) is involved in the production of NO, which is the primary source of all RNS in biological systems (Evans TG et al. 1996). The phagocyte NADPH oxidase and iNOS are expressed in both PMN and mononuclear phagocytes and both cell types have the capacity for phagosomal burst activity. However, the magnitude of ROS generation in neutrophils far exceeds that observed in macrophages (VanderVen BC et al. 2009). Macrophages are thought to produce considerably more RNS than neutrophils (Fang FC et al. 2004; Nathan & Shiloh 2000).

The presence of RONS characterized by a relatively low reactivity, such as H2O2, $O2^{\cdot-}$ or NO, has no deleterious effect on biological environment (Attia SM 2010; Weidinger A & and Kozlov AV 2015). Their activity is controlled by endogenous antioxidants (both enzymatic and non-enzymatic) that are induced by oxidative stress. However the relatively low reactive species can initiate a cascade of reactions to generate more damaging “secondary” species such as hydroxyl radical (•OH), singlet oxygen or peroxinitrite (Robinson JM 2008; Fang FC et al. 2004). These "secondary" RONS are extremely toxic causing irreversible damage to all classes of biomolecules (Weidinger A & and Kozlov AV 2015; Fang FC et al.

2004; Kohchi C et al. 2009; Gostner JM et al. 2013; Vatansever F et al. 2013).

Although macrophages and neutrophils use similar mechanisms for the internalization of targets, there are differences in how they perform phagocytosis and in the final outcome of the process (Tapper H & Grinstein S 1997; Vierira OV et al. 2002). Once formed, the phagosome undergoes an extensive maturation process whereby it develops into a microbicidal organelle able to eliminate the invading pathogen. Maturation involves re-modeling both the membrane of the phagosome and its luminal contents (Vierira OV et al. 2002). In macrophages, phagosome formation and maturation follows a series of strictly coordinated membrane fission/fusion events between the phagosome and compartments of the endo/lysosomal network gradually transforming the nascent phagosome into a phagolysosome, a degradative organelle endowed with potent microbicidal properties (Zimmerli S et al. 1996; Vierira OV et al. 2002). Neutrophils instead contain a large number of preformed granules such as azurophilic and specific granules that can rapidly fuse with phagosomes delivering antimicrobial substances (Karlsson A & Dahlgren C 2002; Naucler C et al. 2002; Nordenfelt P and Tapper H 2011). Phagosomal pH dynamics may also contribute to the maturation process by regulating membrane traffic events. The microbicidal activity of macrophages is characterized by progressive acidification of the lumen (down to pH 4–5) by the proton pumping vATPase. A low pH is a prerequisite for optimal enzymatic activity of most late endosomal/lysosomal hydrolases reported in macrophages. Neutrophil phagosome pH regulation differs significantly from what is observed in macrophages (Nordenfelt P and Tapper H 2011; Winterbourn CC et al. 2016). The massive activation of the oxidative burst is thought to result in early alkalization of neutrophil phagosomes which is linked to proton consumption during the generation of hydrogen peroxide (Segal AW et al. 1981; Levine AP et al. 2015). Other studies showed that neutrophil phagosome maintained neutral pH values before the pH gradually decreased (Jankowski A et al. 2002). Neutrophil phagosomes also exhibited a high proton leak, which was initiated upon activation of the NADPH oxidase, and this activation counteracted phagosomal acidification (Jankowski A et al. 2002).

The Reactome module describes ROS and RNS production by phagocytic cells. The module includes cell-type specific events, for example, myeloperoxidase (MPO)-mediated production of hypochlorous acid in neutrophils. It also highlights differences between phagosomal pH dynamics in neutrophils and macrophages. The module describes microbicidal activity of selective RONS such as hydroxyl radical or peroxynitrite. However, detection of any of these species in the phagosomal environment is subject to many uncertainties (Nüsse O 2011; Erard M et al. 2018). The mechanisms by which reactive oxygen/nitrogen species kill pathogens in phagocytic immune cells are still not fully understood.

Literature references

Cosio, G., Grinstein, S., Flannagan, RS. (2009). Antimicrobial mechanisms of phagocytes and bacterial evasion strategies. *Nat Rev Microbiol, 7*, 355-66. ↗

Yang, Y., Werner, J., Karakhanova, S., Bazhin, AV. (2013). Reactive oxygen species in the immune system. *Int. Rev. Immunol., 32*, 249-70. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.
2018-11-07	Reviewed	Nüsse, O.
2018-11-07	Edited, Revised	Shamovsky, V.

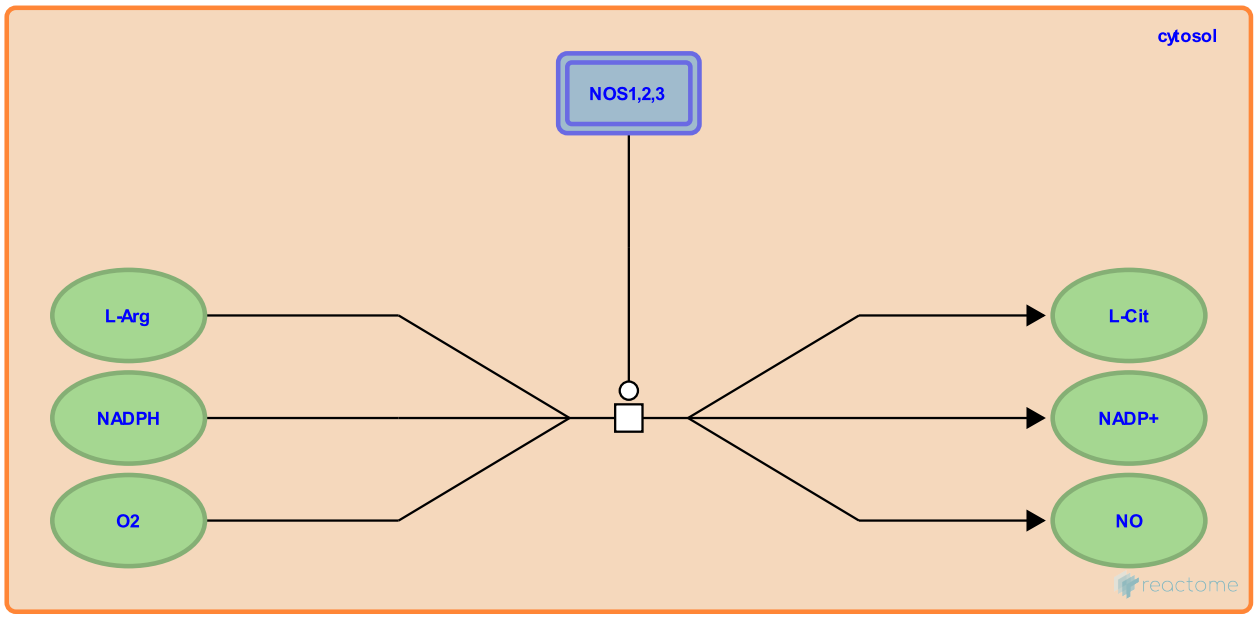
Nitric Oxide Synthase (NOS) produces Nitric Oxide (NO) ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-418436

Type: transition

Compartments: cytosol



Nitric oxide synthase (NOS) produces NO from L-arginine. There are three isoforms of NOS, endothelial, neuronal and inducible (eNOS, nNOS, and iNOS) (Alderton WK et al. 2001). The three isozymes are regulated differentially. eNOS and nNOS, which are constitutively expressed in certain cells, are activated by he binding of calcium (Ca2+) and calmodulin (Alderton WK et al. 2001; Feng C 2012). iNOS is induced in response to immunostimulatory signals and once synthesized, iNos is constitutively active (Alderton WK et al. 2001; Aktan F 2004; Pautz A et al. 2010). NO produced by NOS acts as a signalling molecule by diffusing across cell membranes to activate soluble guanylate cyclase (sGC).

Followed by: Superoxide and nitric oxide react to peroxynitrite in the phagosome, Nitric oxide oxidizes to nitrosyl ion, Nitric oxide diffuses into the phagosome, Superoxide and nitric oxide react to peroxynitrite

Literature references

Marletta, MA., Derbyshire, ER. (2009). Biochemistry of soluble guanylate cyclase. *Handb Exp Pharmacol*, 17-31. ↗

Editions

2009-06-03	Authored	Akkerman, JW.
2010-06-07	Edited	Jupe, S.
2010-06-07	Reviewed	Kunapuli, SP.

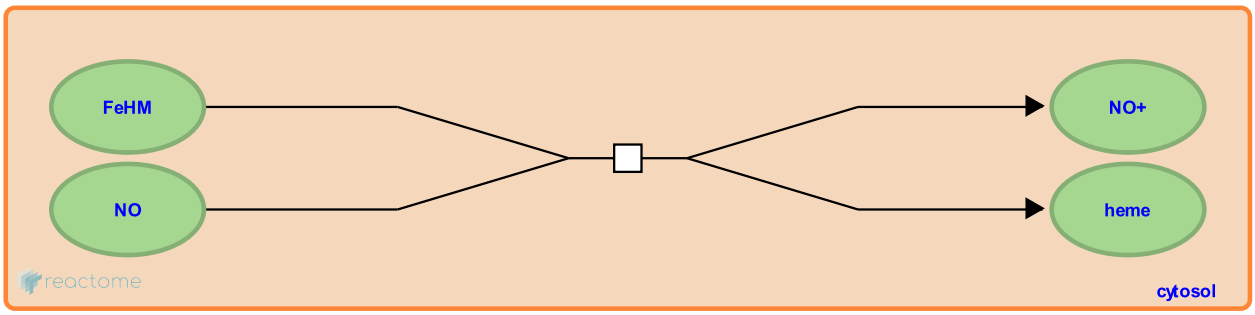
Nitric oxide oxidizes to nitrosyl ion ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-1222512

Type: transition

Compartments: cytosol



Production of nitrosyl ion from nitric oxide is much faster when catalyzed by metal ions than via NO2 or N2O3. An alternative mechanism is by reaction with superoxide which is less probable in macrophages because they downregulate pathways leading to superoxide when NO is produced (Kharitonov et al. 1995, Clancy et al. 1994).

Preceded by: Nitric Oxide Synthase (NOS) produces Nitric Oxide (NO)

Followed by: Glutathione scavenges nitrosyl

Literature references

Sundquist, AR., Kharitonov, VG., Sharma, VS. (1995). Kinetics of nitrosation of thiols by nitric oxide in the presence of oxygen. *J Biol Chem, 270*, 28158-64. ↗

Levartovsky, D., Yegudin, J., Leszczynska-Piziak, J., Clancy, RM., Abramson, SB. (1994). Nitric oxide reacts with intracellular glutathione and activates the hexose monophosphate shunt in human neutrophils: evidence for S-nitrosoglutathione as a bioactive intermediary. *Proc Natl Acad Sci U S A, 91*, 3680-4. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

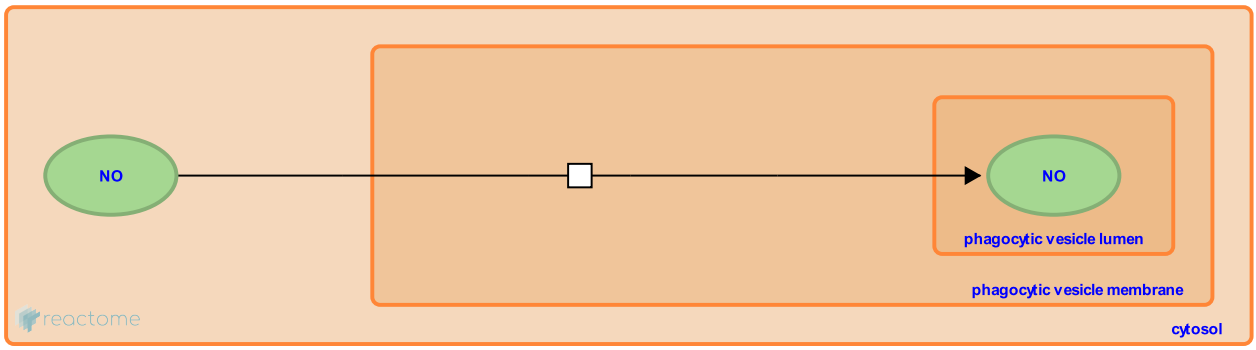
Nitric oxide diffuses into the phagosome ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-1222686

Type: transition

Compartments: phagocytic vesicle membrane, cytosol



Nitric oxide diffuses into the phagosome (Clancy et al. 1994). Although NO has been shown to be critical for control of *Mtb* infection in mice, its role in human infection is less clear. Instead, the generation of antimicrobial defence molecules including cathelicidin in a vitamin D-dependent pathway is much better established (Fabri et al. 2011, Martineau et al. 2011).

Preceded by: Nitric Oxide Synthase (NOS) produces Nitric Oxide (NO)

Followed by: Nitric oxide enters the bacterium

Literature references

Steinmeyer, A., Stenger, S., Sieling, PA., Modlin, RL., Jo, EK., Zügel, U. et al. (2011). Vitamin D is required for IFN-gamma-mediated antimicrobial activity of human macrophages. *Sci Transl Med, 3*, 104ra102. ↗

Oni, T., Bangani, N., Bashe, L., Martineau, AR., de Azevedo, V., Timms, PM. et al. (2011). Reciprocal seasonal variation in vitamin D status and tuberculosis notifications in Cape Town, South Africa. *Proc Natl Acad Sci U S A, 108*, 19013-7. ↗

Levartovsky, D., Yegudin, J., Leszczynska-Piziak, J., Clancy, RM., Abramson, SB. (1994). Nitric oxide reacts with intracellular glutathione and activates the hexose monophosphate shunt in human neutrophils: evidence for S-nitrosoglutathione as a bioactive intermediary. *Proc Natl Acad Sci U S A, 91*, 3680-4. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

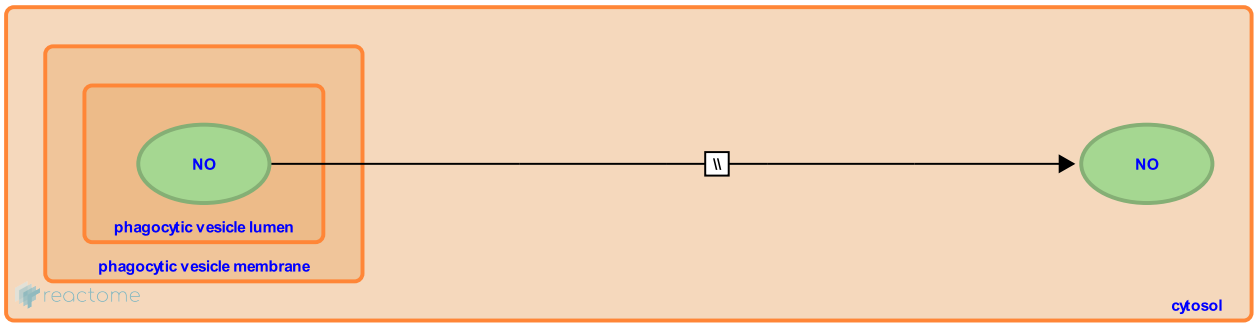
Nitric oxide enters the bacterium ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-1222662

Type: omitted

Compartments: cytosol



NO enters the bacterium (Clancy et al. 1994).

Preceded by: Nitric oxide diffuses into the phagosome

Literature references

Levartovsky, D., Yegudin, J., Leszczynska-Piziak, J., Clancy, RM., Abramson, SB. (1994). Nitric oxide reacts with intracellular glutathione and activates the hexose monophosphate shunt in human neutrophils: evidence for S-nitrosoglutathione as a bioactive intermediary. *Proc Natl Acad Sci U S A, 91*, 3680-4. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

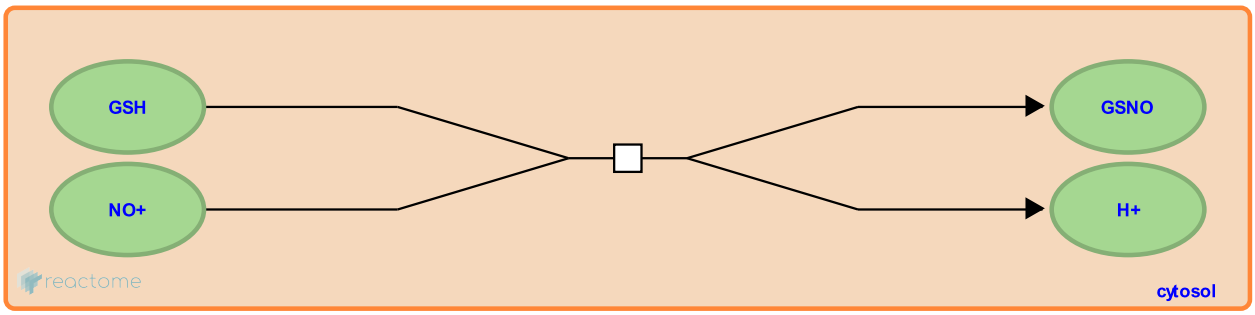
Glutathione scavenges nitrosyl ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-1222384

Type: transition

Compartments: cytosol



In the host cell cytosol, glutathione (GSH) scavenges nitrosyl, yielding S-nitrosoglutathione (GSNO). Both GSH and GSNO are effective against *Mtb* (Venketaraman et al. 2005).

Preceded by: Nitric oxide oxidizes to nitrosyl ion

Literature references

Connell, ND., Venketaraman, V., Talaue, MT., Dayaram, YK. (2005). Glutathione and nitrosoglutathione in macrophage defense against Mycobacterium tuberculosis. *Infect Immun, 73*, 1886-9. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

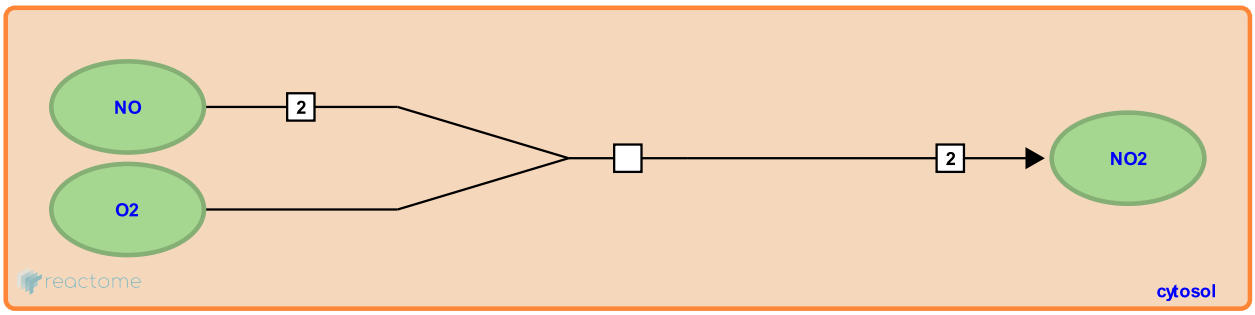
Nitric oxide and O2 react to NO2 ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6803989

Type: transition

Compartments: cytosol



Nitric oxide reacts with O2 to produce NO2 at neutral pH.

Under normal physiological conditions, when the rates of nitric oxide (NO) production are low, NO can interact directly with biological molecules. Generally, these types of reactions may serve protective regulatory and/or anti-inflammatory functions (Hummel SG et al. 2006; Wink DA et al. 2001). High NO fluxes under pathological conditions enable formation of NO-derived reactive intermediates. The most prevalent NO-derived reactive species produced in vivo are dinitrogen trioxide (N2O3) and peroxynitrite (ONOO-), both of which can mediate additional nitrosative and/or oxidative reactions (Grisham MB et al. 1999; Wink DA & Mitchell JB 1998; Ali AA et al. 2013). N2O3 production requires oxidation of NO first to NO2 which will then combine with NO to form N2O3. Although this reaction is very slow at physiological levels of nitric oxide, it has been suggested that hydrophobic environments, such as those found in the cellular membrane, can accelerate this reaction (Liu X et al. 1997; Moller MN et al. 2007). N2O3 formation regulates the function of many target proteins through the coupling of a nitroso moiety (NO+) to a reactive sulfhydryl group on cysteine, ultimately leading to the formation of RSNO, a process commonly known as S-nitrosylation (Broniowska KA & Hogg N 2012).

Followed by: NO and NO2 react to N2O3

Literature references

Grisham, MB., Jourd'Heuil, D., Wink, DA. (1999). Nitric oxide. I. Physiological chemistry of nitric oxide and its metabolites:implications in inflammation. *Am. J. Physiol., 276,* G315-21. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

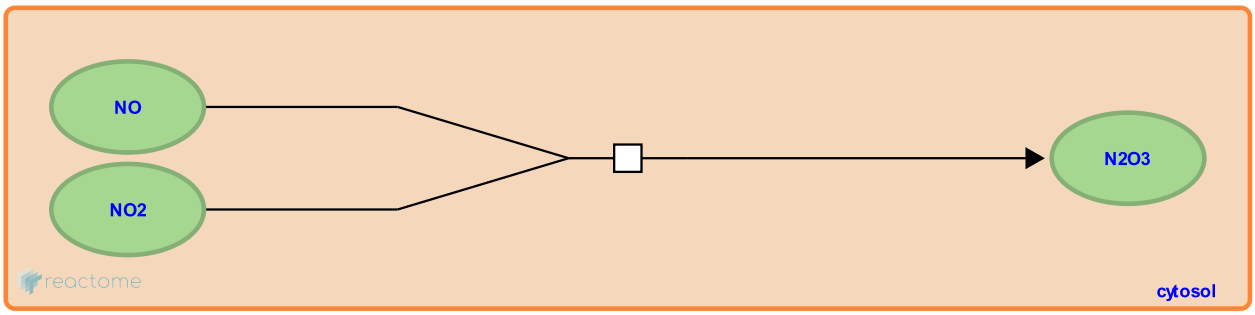
NO and NO2 react to N2O3 ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6804006

Type: transition

Compartments: cytosol



NO2 reacts with NO to produce N2O3 .

Under normal physiological conditions, when the rates of nitric oxide (NO) production are low, NO can interact directly with biological molecules. Generally, these types of reactions may serve protective regulatory and/or anti-inflammatory functions (Hummel SG et al. 2006; Wink DA et al. 2001). High NO fluxes under pathological conditions enable formation of NO-derived reactive intermediates. The most prevalent NO-derived reactive species produced in vivo are dinitrogen trioxide (N2O3) and peroxynitrite (ONOO-), both of which can mediate additional nitrosative and/or oxidative reactions (Grisham MB et al. 1999; Wink DA & Mitchell JB 1998; Ali AA et al. 2013). N2O3 production requires oxidation of NO first to NO2 which will then combine with NO to form N2O3. Although this reaction is very slow at physiological levels of nitric oxide, it has been suggested that hydrophobic environments, such as those found in the cellular membrane, can accelerate this reaction (Liu X et al. 1997; Moller MN et al. 2007). N2O3 formation regulates the function of many target proteins through the coupling of a nitroso moiety (NO+) to a reactive cysteine, ultimately leading to the formation of RSNO, a process commonly known as S-nitrosylation (Broniowska KA & Hogg N 2012).

Preceded by: Nitric oxide and O2 react to NO2

Literature references

Grisham, MB., Jourd'Heuil, D., Wink, DA. (1999). Nitric oxide. I. Physiological chemistry of nitric oxide and its metabolites:implications in inflammation. *Am. J. Physiol., 276,* G315-21. ↗

Joshi, MS., Thomas, DD., Miller, MJ., Lancaster, JR., Liu, X. (1998). Accelerated reaction of nitric oxide with O2 within the hydrophobic interior of biological membranes. *Proc. Natl. Acad. Sci. U.S.A., 95,* 2175-9. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

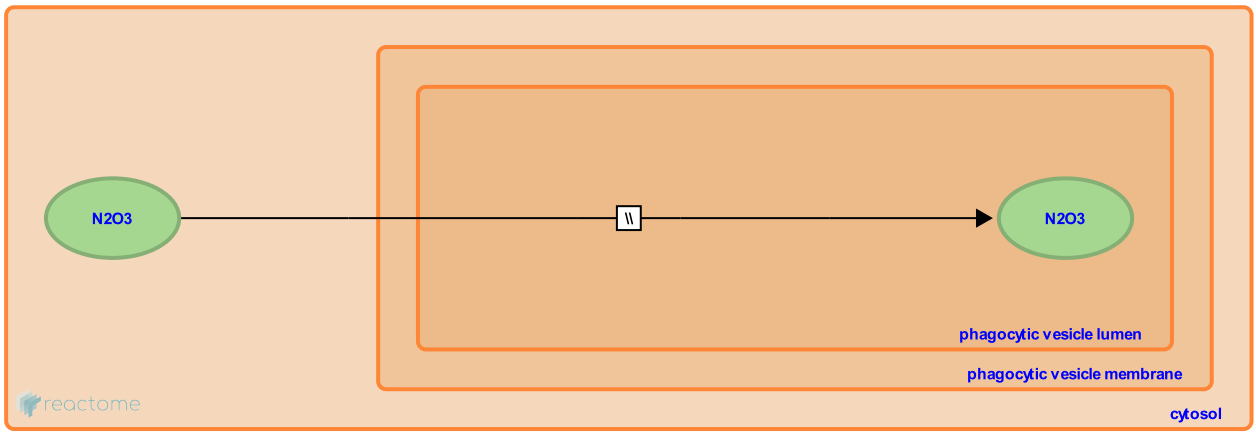
N2O3 diffuses to phagosome ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6804035

Type: omitted

Compartments: phagocytic vesicle lumen, phagocytic vesicle membrane, cytosol



The uncharged N2O3 molecule is thought to be able to diffuse through the cell membrane (Grisham MB et al. 1999; Basu S et al. 2007)

Literature references

Grisham, MB., Jourd'Heuil, D., Wink, DA. (1999). Nitric oxide. I. Physiological chemistry of nitric oxide and its metabolites:implications in inflammation. *Am. J. Physiol., 276*, G315-21. ↗

Mitchell, JB., Wink, DA. (1998). Chemical biology of nitric oxide: Insights into regulatory, cytotoxic, and cytoprotective mechanisms of nitric oxide. *Free Radic. Biol. Med., 25*, 434-56. ↗

Gladwin, MT., Patel, R., Kim-Shapiro, DB., King, SB., Huang, J., Hogg, N. et al. (2007). Catalytic generation of N2O3 by the concerted nitrite reductase and anhydrase activity of hemoglobin. *Nat. Chem. Biol., 3*, 785-94. ↗

Rice-Evans, C., Oldreive, C. (2001). The mechanisms for nitration and nitrotyrosine formation in vitro and in vivo: impact of diet. *Free Radic. Res., 35*, 215-31. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

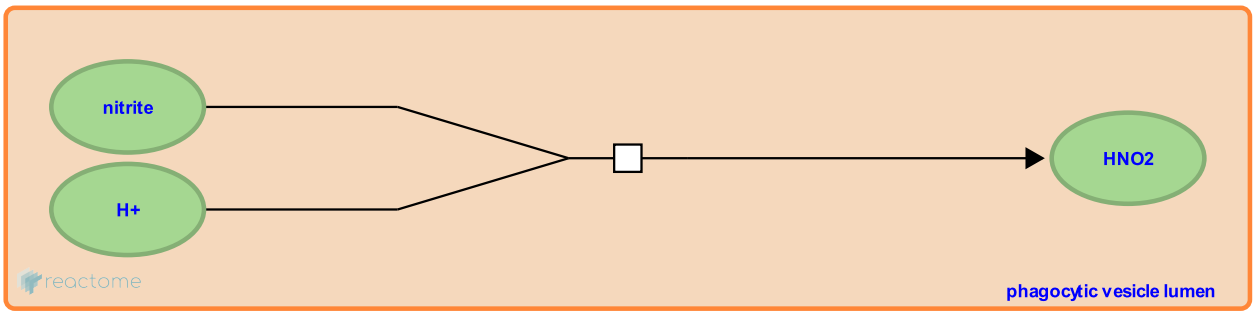
Nitrite ion and HNO2 form a conjugated acid-base pair ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6803998

Type: transition

Compartments: phagocytic vesicle lumen



In the acidic conditions nitrite (NO2-) and nitrous acid (HNO2) present as a conjugated acid-base pair. HNO2 can further react with an additional HNO2 to produce N2O3 (Oldreive C & Rice-Evans C. 2001). N2O3 formation regulates the function of many target proteins through the coupling of a nitroso moiety (NO+) to a reactive cysteine, ultimately leading to the formation of RSNO, a process commonly known as S-nitrosylation (Broniowska KA & Hogg N 2012).

Followed by: HNO2 produces N2O3

Literature references

Grisham, MB., Jourd'Heuil, D., Wink, DA. (1999). Nitric oxide. I. Physiological chemistry of nitric oxide and its metabolites:implications in inflammation. *Am. J. Physiol., 276*, G315-21. ↗

Rice-Evans, C., Oldreive, C. (2001). The mechanisms for nitration and nitrotyrosine formation in vitro and in vivo: impact of diet. *Free Radic. Res., 35*, 215-31. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

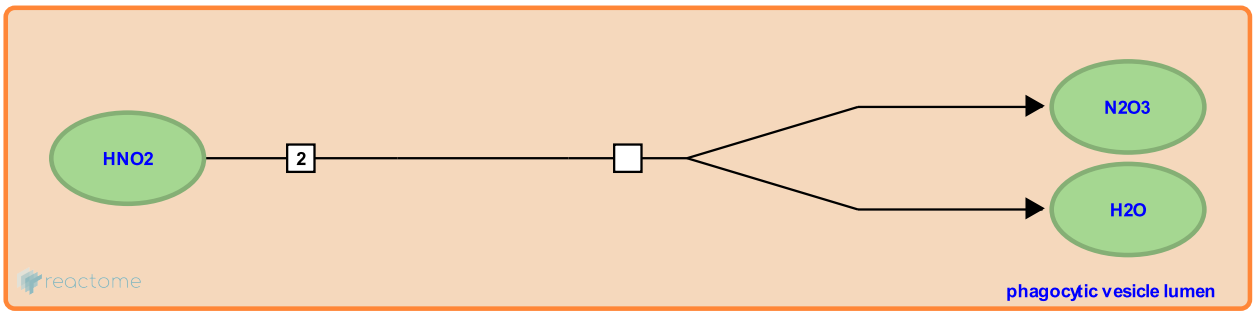
HNO2 produces N2O3 ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6803999

Type: transition

Compartments: phagocytic vesicle lumen



In the acidic conditions nitrite (NO2-) and nitrous acid (HNO2) present as a conjugated acid-base pair. HNO2 can further react with an additional HNO2 to produce N2O3 (Oldreive C & Rice-Evans C. 2001). N2O3 formation regulates the function of many target proteins through the coupling of a nitroso moiety (NO+) to a reactive cysteine, ultimately leading to the formation of RSNO, a process commonly known as S-nitrosylation (Broniowska KA & Hogg N 2012).

Preceded by: Nitrite ion and HNO2 form a conjugated acid-base pair

Literature references

Grisham, MB., Jourd'Heuil, D., Wink, DA. (1999). Nitric oxide. I. Physiological chemistry of nitric oxide and its metabolites:implications in inflammation. *Am. J. Physiol., 276*, G315-21. ↗

Rice-Evans, C., Oldreive, C. (2001). The mechanisms for nitration and nitrotyrosine formation in vitro and in vivo: impact of diet. *Free Radic. Res., 35*, 215-31. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

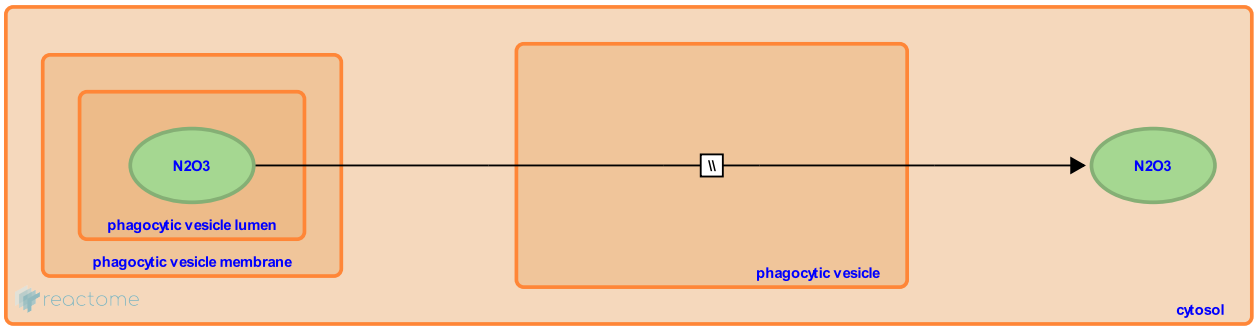
N2O3 enters bacteria ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6803988

Type: omitted

Compartments: phagocytic vesicle



The uncharged N2O3 molecule is thought to be able to diffuse through the cell membrane (Grisham MB et al. 1999; Basu S et al. 2007)

Followed by: S-nitrosylation of cysteine residues in proteins by N2O3

Literature references

Grisham, MB., Jourd'Heuil, D., Wink, DA. (1999). Nitric oxide. I. Physiological chemistry of nitric oxide and its metabolites:implications in inflammation. *Am. J. Physiol., 276*, G315-21. ↗

Mitchell, JB., Wink, DA. (1998). Chemical biology of nitric oxide: Insights into regulatory, cytotoxic, and cytoprotective mechanisms of nitric oxide. *Free Radic. Biol. Med., 25*, 434-56. ↗

Gladwin, MT., Patel, R., Kim-Shapiro, DB., King, SB., Huang, J., Hogg, N. et al. (2007). Catalytic generation of N2O3 by the concerted nitrite reductase and anhydrase activity of hemoglobin. *Nat. Chem. Biol., 3*, 785-94. ↗

Rice-Evans, C., Oldreive, C. (2001). The mechanisms for nitration and nitrotyrosine formation in vitro and in vivo: impact of diet. *Free Radic. Res., 35*, 215-31. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

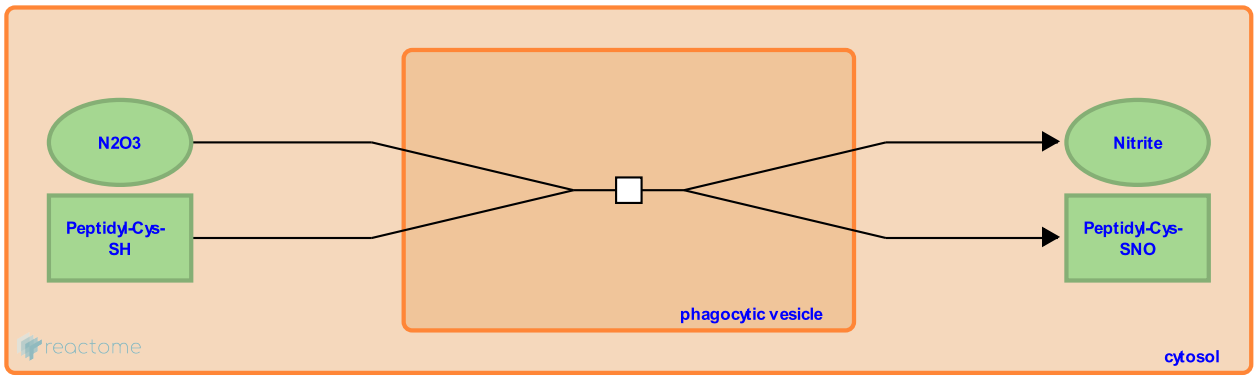
S-nitrosylation of cysteine residues in proteins by N2O3 ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6803978

Type: transition

Compartments: phagocytic vesicle



S-nitrosylation (SNO) is a selective post-translational protein modification that is mediated by nitric oxide radicals. SNO involves the covalent attachment of nitric oxide (NO) to the sulfur atom of cysteine to produce an S-N=O adduct. SNO critically regulates protein activity, localization and stability (Broniowska KA & Hogg N 2012; Ali AA et al. 2013)

Preceded by: N2O3 enters bacteria

Literature references

Broniowska, KA., Hogg, N. (2012). The chemical biology of S-nitrosothiols. *Antioxid. Redox Signal., 17*, 969-80. ↗

Robson, T., Coulter, JA., Ali, AA., Migaud, MM., Ogle, CH., Hirst, DG. et al. (2013). The contribution of N2O3 to the cytotoxicity of the nitric oxide donor DETA/NO: an emerging role for S-nitrosylation. *Biosci. Rep., 33*. ↗

Bryan, NS., Grisham, MB. (2007). Methods to detect nitric oxide and its metabolites in biological samples. *Free Radic. Biol. Med., 43*, 645-57. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

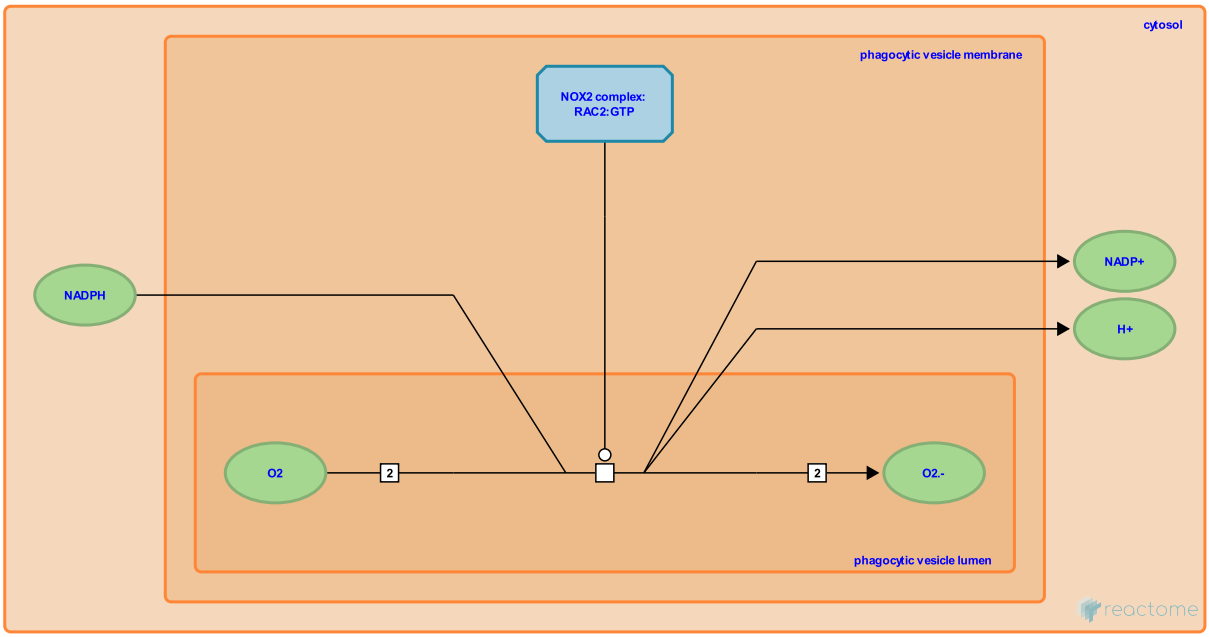
NOX2 generates superoxide anion from oxygen ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6789092

Type: transition

Compartments: phagocytic vesicle lumen, phagocytic vesicle membrane, cytosol



Phagocytic cells kill microorganisms by ingesting them into phagocytic vacuoles (phagosomes). Phagocytosis is accompanied by the activation of the NADPH oxidase (NOX2 complex), a multiprotein enzyme complex, that assembles in the phagosomal membrane (Winterbourn C et al. 2006). The NOX2 complex shuttles electrons from NADPH in the cytoplasm across the membrane to oxygen in the phagosomal lumen converting oxygen into the superoxide radical anion (O2.-). As this electron transfer creates a charge imbalance that would otherwise depolarize the membrane, NADPH oxidase activity is accompanied by activation of the V-ATPase and voltage-gated proton channel (Demaurex N & El Chemaly A 2010; El Chemaly A et al. 2010; Nunes P et al. 2013).

Defects in NADPH oxidase components are associated with chronic granulomatous disease (CGD) (de Oliveira-Junior EB et al. 2011). Phagocytic cells of CGD patients are unable to produce superoxide ion, and their efficiency in bacterial killing is significantly impaired (Johnston RB Jr et al. 1975; de Oliveira-Junior EB et al. 2011). In addition, macrophages from CGD patients exhibit abnormal function because these cells release higher levels of anti-inflammatory cytokines and lower levels of proinflammatory cytokines in response to bacterial stimuli (Rahman FZ et al. 2009).

Followed by: Superoxide and nitric oxide react to peroxynitrite in the phagosome, Superoxide anion dismutates to H2O2

Literature references

Dahlgren, C., Karlsson, A. (2002). Assembly and activation of the neutrophil NADPH oxidase in granule membranes. *Antioxid. Redox Signal., 4*, 49-60. ↗

Babior, BM. (1999). NADPH oxidase: an update. *Blood, 93*, 1464-76. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

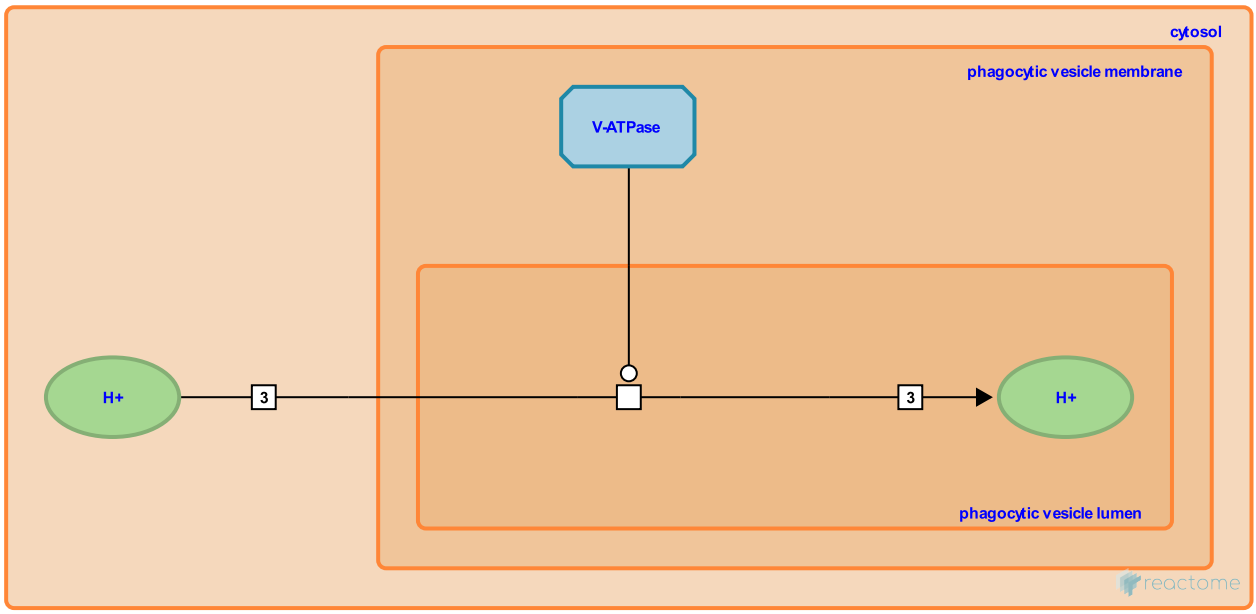
Intraphagosomal pH is lowered to 5 by V-ATPase ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-1222516

Type: transition

Compartments: phagocytic vesicle lumen, phagocytic vesicle membrane, cytosol



The function of V-type proton pumping ATPases is basically the same as that of F-type ATPases, except that V-ATPases cannot synthesize ATP from the proton motive force, the reverse reaction of pumping. When pumping, ATP hydrolysis drives a 120 degree rotation of the rotor which leads to movement of three protons into the phagosome (Adachi et al. 2007).

Followed by: Protonation of superoxide

Literature references

Yoshida, M., Furuike, S., Oiwa, K., Itoh, H., Nishizaka, T., Adachi, K. et al. (2007). Coupling of rotation and catalysis in F(1)-ATPase revealed by single-molecule imaging and manipulation. *Cell, 130*, 309-21. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

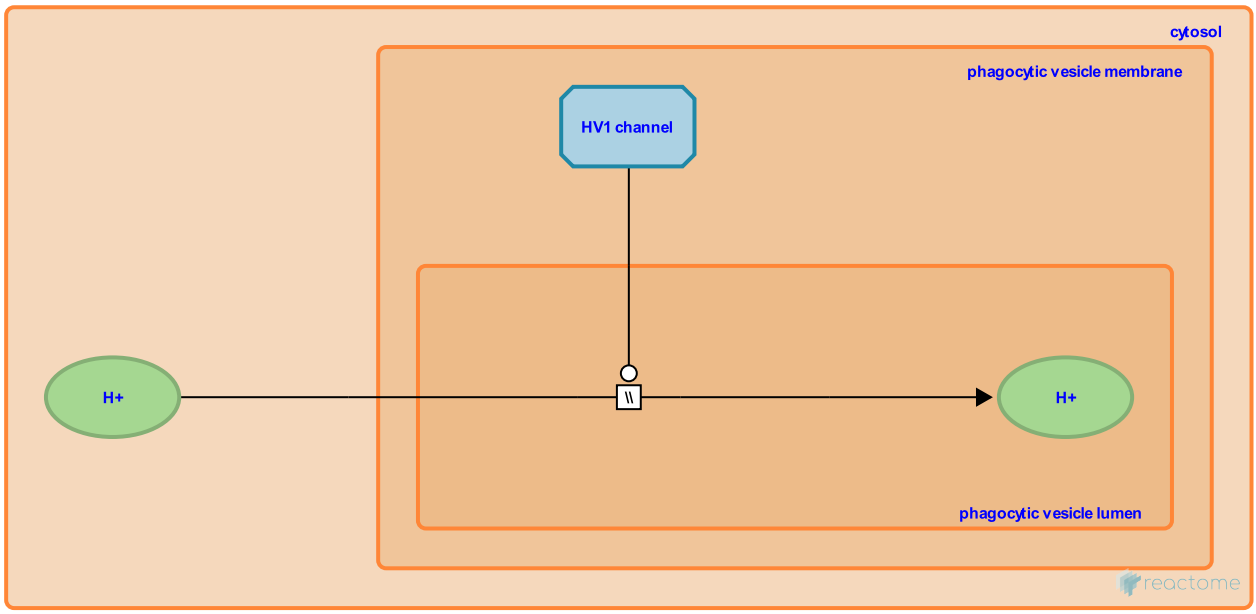
HV1-mediated H+ transfer ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6788999

Type: omitted

Compartments: phagocytic vesicle lumen, phagocytic vesicle membrane, cytosol



The NADPH oxidase complex (NOX2) assembles in the phagosomal membrane upon activation to shuttles electrons from NADPH in the cytoplasm across the membrane to oxygen in the phagosomal lumen converting oxygen into the superoxide radical anion (O2.-) (Winterbourn CC et al. 2006). The large flux of electrons across the membrane-bound NOX2 complex together with H+ release during the oxidation and regeneration of NADPH in cytosol create a charge imbalance that depolarizes the membrane. To compensate the membrane depolarization NADPH oxidase activity is accompanied by activation of a voltage-gated proton (HV1) channel (Demaurex N & El Chemaly A 2010; El Chemaly A et al. 2010; Petheo GL et al. 2010; Kovacs I et al. 2014; Henderson LM et al. 1987, 1988; Nunes P et al. 2013). Proton channels extrude the cytosolic acid, repolarize the phagosomal membrane, and deliver cytosolic protons to the phagocytic vesicle lumen (Henderson LM et al. 1987, 1988; Morgan D et al. 2009; El Chemaly A et al. 2010).

The crucial function of voltage gated proton channels in compensating the electrogenic activity of NADPH oxidase during phagocytosis was demonstrated in human phagocytes (DeCoursey TE et al. 2000; Morgan D et al. 2009; Petheo GL et al. 2010; Kovacs I et al. 2014; Henderson LM et al. 1987, 1988). Hv1 knockout (KO) mice have been shown to lack detectable proton current in bone marrow or peripheral blood phagocytic cells (Morgan D et al. 2009; Ramsey IS et al. 2009; El Chemaly A et al. 2010; Capasso M et al. 2010). Furthermore, VSOP/Hv1-/- mouse cells had a more acidic cytosol, were more depolarized, and produced less superoxide and hydrogen peroxide than neutrophils from wild-type mice (Morgan D et al. 2009; El Chemaly A et al. 2010).

HV1 channels differentially regulate the phagosomal pH in neutrophils and macrophages. In macrophages, HV1 channels contributed to rapid phagosomal acidification together with V-ATPases, proton transporters, that are delivered to nascent phagosomes to generate a transmembrane pH gradient of >4 (El Chemaly A et al, 2014). In contrast, HV1 channels maintained a higher pH by sustaining high-level ROS production that is thought to inhibit V-ATPase accumulation on phagosomes in neutrophils (Jankowski A et al. 2002). In a 2015 study using a probe that is more sensitive at higher pH, an average pH closer to 9 was measured in individual phagosomes in neutrophils (Levine AP et al. 2015). The early alkalization of neutrophil phagosomes was also linked to proton consumption during the generation of hydrogen peroxide (Segal AW et al. 1981; Levine AP et al. 2015). Neutrophil phagosomes also exhibited a high proton leak, which was initiated upon activation of the NADPH oxidase, and this activation counteracted phagosomal acidification (Jankowski A et al. 2002).

Literature references

Henderson, LM., Chappell, JB., Jones, OT. (1987). The superoxide-generating NADPH oxidase of human neutrophils is electrogenic and associated with an H+ channel. *Biochem. J., 246*, 325-9. ↗

Henderson, LM., Chappell, JB., Jones, OT. (1988). Superoxide generation by the electrogenic NADPH oxidase of human neutrophils is limited by the movement of a compensating charge. *Biochem. J., 255*, 285-90. ↗

Orient, A., Réthi, B., Kovács, I., Geiszt, M., Rajki, A., Lányi, A. et al. (2010). Molecular and functional characterization of Hv1 proton channel in human granulocytes. *PLoS ONE, 5*, e14081. ↗

DeCoursey, TE. (2010). Voltage-gated proton channels find their dream job managing the respiratory burst in phagocytes. *Physiology (Bethesda), 25*, 27-40. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

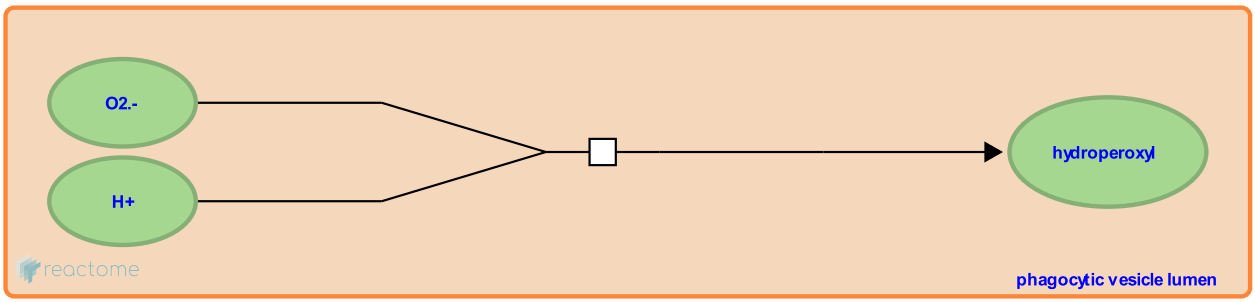
Protonation of superoxide ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-1222353

Type: transition

Compartments: phagocytic vesicle lumen



Superoxide gets protonated (Korshunov & Imlay 2002).

Preceded by: Intraphagosomal pH is lowered to 5 by V-ATPase

Followed by: Hydroperoxyl enters the bacterium

Literature references

Imlay, JA., Korshunov, SS. (2002). A potential role for periplasmic superoxide dismutase in blocking the penetration of external superoxide into the cytosol of Gram-negative bacteria. *Mol Microbiol, 43*, 95-106. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

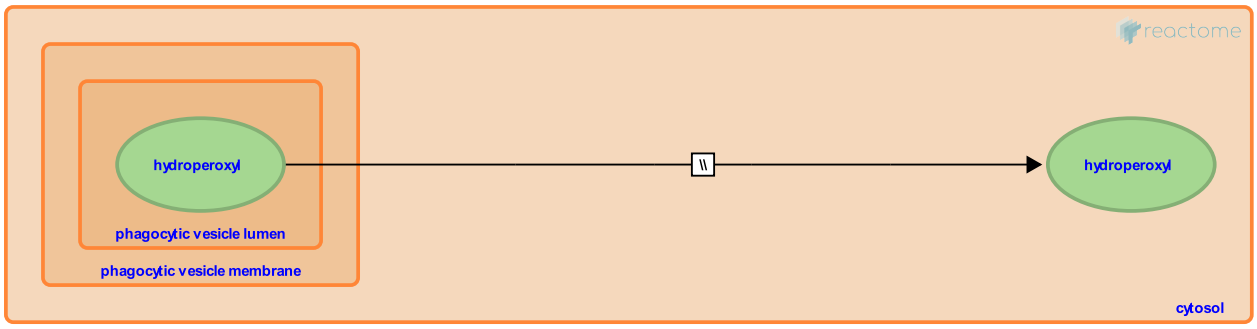
Hydroperoxyl enters the bacterium ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-1222342

Type: omitted

Compartments: cytosol



Superoxide can enter the bacterium when acidic conditions apply. Together with a proton it forms the uncharged hydroperoxyl radical (OOH·) which is membrane permeable (Nathan & Shiloh 2000, Zahrt & Deretic 2002, Warner & Mizrahi 2006, Spagnolo et al, 2004).

Preceded by: Protonation of superoxide

Literature references

Zahrt, TC., Deretic, V. (2002). Reactive nitrogen and oxygen intermediates and bacterial defenses: unusual adaptations in Mycobacterium tuberculosis. *Antioxid Redox Signal, 4*, 141-59. ↗

Warner, DF., Mizrahi, V. (2006). Tuberculosis chemotherapy: the influence of bacillary stress and damage response pathways on drug efficacy. *Clin Microbiol Rev, 19*, 558-70. ↗

D'Orazio, M., Törö, I., Spagnolo, L., Pedersen, JZ., Carugo, O., Rotilio, G. et al. (2004). Unique features of the sodC-encoded superoxide dismutase from Mycobacterium tuberculosis, a fully functional copper-containing enzyme lacking zinc in the active site. *J Biol Chem, 279*, 33447-55. ↗

Shiloh, MU., Nathan, C. (2000). Reactive oxygen and nitrogen intermediates in the relationship between mammalian hosts and microbial pathogens. *Proc Natl Acad Sci U S A, 97*, 8841-8. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

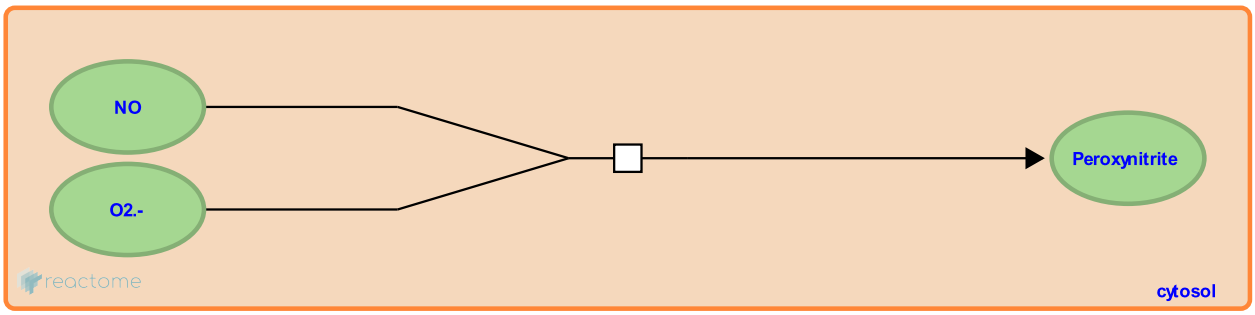
Superoxide and nitric oxide react to peroxynitrite ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-1222407

Type: transition

Compartments: cytosol



Nitric oxide and superoxide rapidly combine to form peroxynitrite (Pryor & Squadrito 1995).

Preceded by: Nitric Oxide Synthase (NOS) produces Nitric Oxide (NO)

Followed by: Peroxynitrite enters the bacterium

Literature references

Squadrito, GL., Pryor, WA. (1995). The chemistry of peroxynitrite: a product from the reaction of nitric oxide with superoxide. *Am J Physiol, 268*, L699-722. ↗

Huie, RE., Padmaja, S. (1993). The reaction of no with superoxide. *Free Radic. Res. Commun., 18*, 195-9. ↗

Kalyanaraman, B., Zielonka, J., Sikora, A., Joseph, J. (2010). Peroxynitrite is the major species formed from different flux ratios of co-generated nitric oxide and superoxide: direct reaction with boronate-based fluorescent probe. *J. Biol. Chem., 285*, 14210-6. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

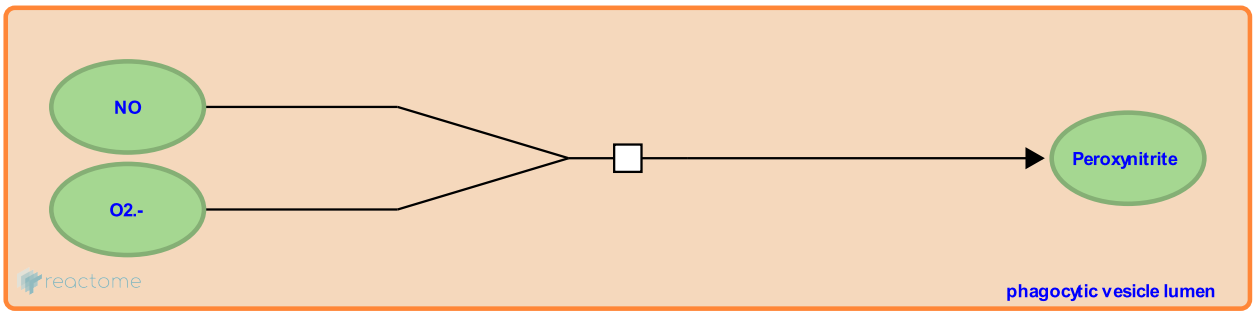
Superoxide and nitric oxide react to peroxynitrite in the phagosome ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-8942052

Type: transition

Compartments: phagocytic vesicle lumen



Inside the phagosome, nitric oxide and superoxide react at diffusion controlled rates with each other to yield peroxynitrite (Prolo C et al. 2014; Ferrer-Sueta G & Radi R 2009).

Preceded by: NOX2 generates superoxide anion from oxygen, Nitric Oxide Synthase (NOS) produces Nitric Oxide (NO)

Literature references

Alvarez, MN., Radi, R., Prolo, C. (2014). Peroxynitrite, a potent macrophage-derived oxidizing cytotoxin to combat invading pathogens. *Biofactors, 40*, 215-25. ↗

Squadrito, GL., Pryor, WA. (1995). The chemistry of peroxynitrite: a product from the reaction of nitric oxide with superoxide. *Am J Physiol, 268*, L699-722. ↗

Huie, RE., Padmaja, S. (1993). The reaction of no with superoxide. *Free Radic. Res. Commun., 18*, 195-9. ↗

Kalyanaraman, B., Zielonka, J., Sikora, A., Joseph, J. (2010). Peroxynitrite is the major species formed from different flux ratios of co-generated nitric oxide and superoxide: direct reaction with boronate-based fluorescent probe. *J. Biol. Chem., 285*, 14210-6. ↗

Editions

2012-04-30	Reviewed	Warner, D.
2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

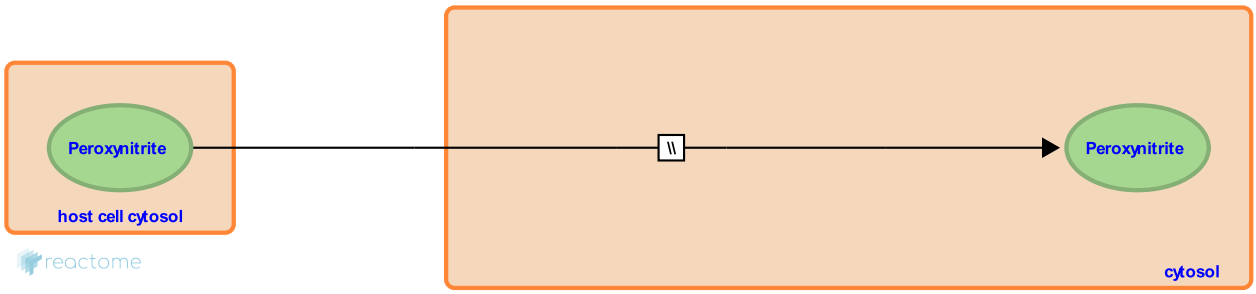
Peroxynitrite enters the bacterium ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-1470073

Type: omitted

Compartments: cytosol



Peroxynitrite can rapidly permeate biological membranes (Marla et al. 1997, Venugopal et al. 2011).

Preceded by: Superoxide and nitric oxide react to peroxynitrite

Followed by: Peroxynitrite oxidizes Cys residues, Peroxynitrite oxidizes Peptide-Methionine residues

Literature references

Bryk, R., Ehrt, S., Rath, P., Venugopal, A., Rhee, K., Shi, S. et al. (2011). Virulence of Mycobacterium tuberculosis depends on lipoamide dehydrogenase, a member of three multienzyme complexes. *Cell Host Microbe, 9*, 21-31. ↗

Groves, JT., Marla, SS., Lee, J. (1997). Peroxynitrite rapidly permeates phospholipid membranes. *Proc Natl Acad Sci U S A, 94*, 14243-8. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

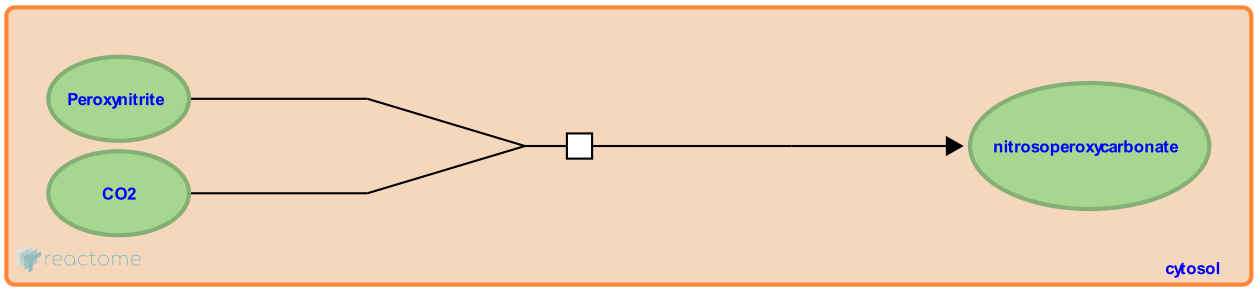
Peroxynitrite and carbon dioxide react to nitrosoperoxycarbonate ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-8942075

Type: transition

Compartments: cytosol



Peroxynitrite anion rapidly reacts with carbon dioxide to yield a reactive adduct, nitrosoperoxycarbonate anion (ONOOCOO-), which can participate in oxidation and nitration processes, thus redirecting the primary reactivity of peroxynitrite (Denicola A et al. 1996).

Literature references

Radi, R., Freeman, BA., Denicola, A., Trujillo, M. (1996). Peroxynitrite reaction with carbon dioxide/bicarbonate: kinetics and influence on peroxynitrite-mediated oxidations. *Arch. Biochem. Biophys., 333*, 49-58. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

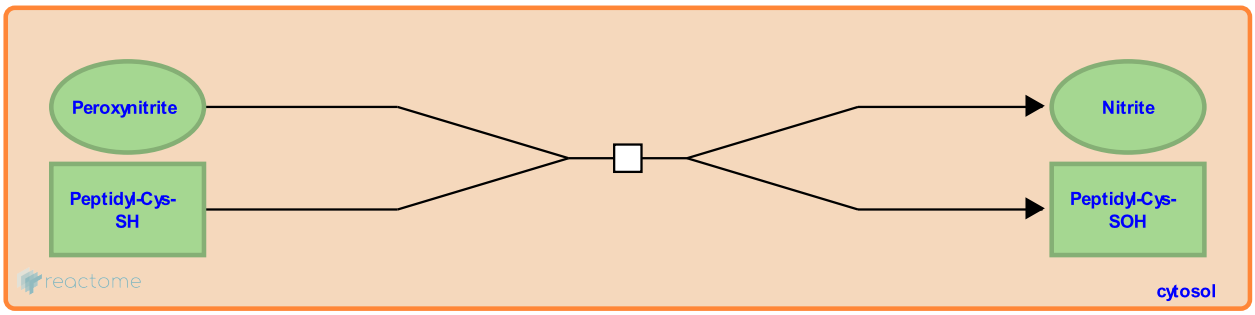
Peroxynitrite oxidizes Cys residues ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-8948180

Type: transition

Compartments: cytosol



Peroxynitrite anion (ONOO-) is a potent oxidant that mediates oxidation of protein sulfhydryls.

Preceded by: Peroxynitrite enters the bacterium

Literature references

Poole, LB. (2015). The basics of thiols and cysteines in redox biology and chemistry. *Free Radic. Biol. Med., 80*, 148-57. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

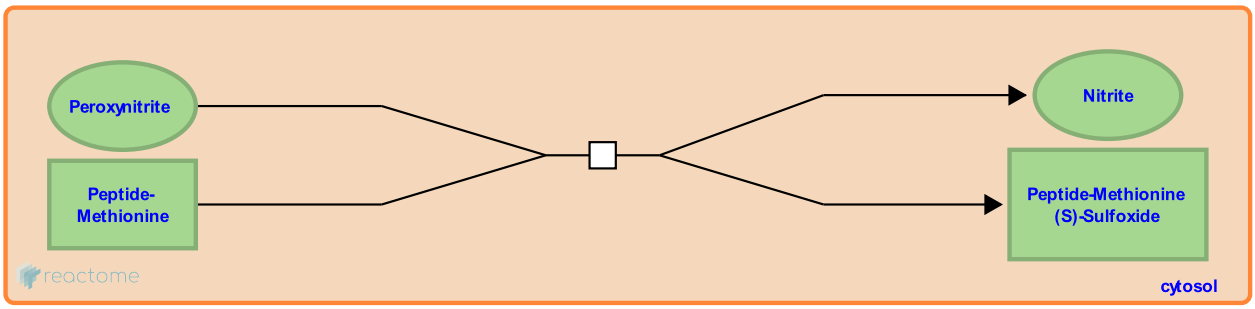
Peroxynitrite oxidizes Peptide-Methionine residues ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-1222411

Type: transition

Compartments: cytosol



Within the bacterial cell, peroxynitrite (ONOO-) is able to oxidize methionine residues on peptides, forming methionine sulfoxide residues with itself being reduced to nitrite (NOO-) (Pryor et al. 1994).

Preceded by: Peroxynitrite enters the bacterium

Literature references

Jin, X., Squadrito, GL., Pryor, WA. (1994). One- and two-electron oxidations of methionine by peroxynitrite. *Proc Natl Acad Sci U S A, 91*, 11173-7. ↗

Editions

2011-01-10	Authored	Stephan, R.
2011-02-28	Edited	Jassal, B.
2012-04-30	Reviewed	Warner, D.

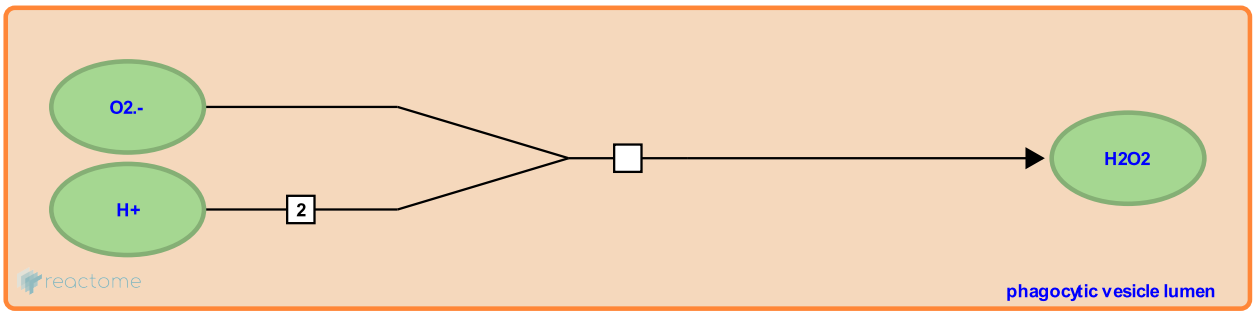
Superoxide anion dismutates to H2O2 ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6788975

Type: transition

Compartments: phagocytic vesicle lumen



Within the phagosome, two superoxide anions (O2.-) can react with each other and two H+ molecules to form oxygen and hydrogen peroxide (H2O2)(Root RK & Metcalf JA 1977; Fridovich I 1978; Johnston RB Jr et al. 1975; Rada B & Leto TL 2008; Winterbourn CC & Kettle AJ 2013). This dismutation of superoxide can occur spontaneously and is faster at lower pH. Unlike superoxide anion, which is short-lived and local in its effect, hydrogen peroxide is longer-lasting and membrane-permeable, so it can diffuse away from the site of production. H2O2 can react with a limited range of biocompounds, but the derivatives of H2O2 such as hydroxyl radical are far more reactive.

Preceded by: NOX2 generates superoxide anion from oxygen

Followed by: H2O2 oxidizes Cys residues to form Cys-sulfenic acid, Hydrogen peroxide enters the bacterium

Literature references

Fridovich, I. (1978). The biology of oxygen radicals. *Science, 201*, 875-80. ↗

Hampton, MB., Livesey, JH., Kettle, AJ., Winterbourn, CC. (2006). Modeling the reactions of superoxide and myeloperoxidase in the neutrophil phagosome: implications for microbial killing. *J. Biol. Chem., 281*, 39860-9. ↗

Metcalf, JA., Root, RK. (1977). H2O2 release from human granulocytes during phagocytosis. Relationship to superoxide anion formation and cellular catabolism of H2O2: studies with normal and cytochalasin B-treated cells. *J. Clin. Invest., 60*, 1266-79. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

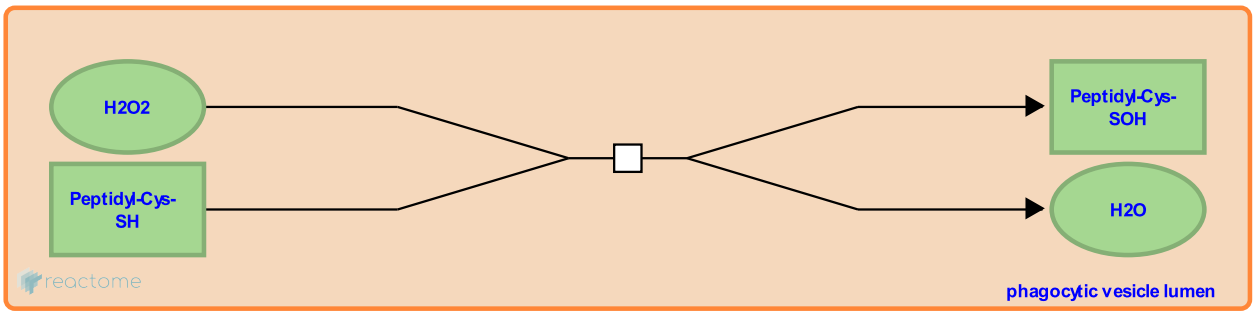
H2O2 oxidizes Cys residues to form Cys-sulfenic acid ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-9626753

Type: transition

Compartments: phagocytic vesicle lumen



In the phagosome, hydrogen peroxide (H2O2) is formed from the dismutation of superoxide that occurs either spontaneously or via reactions catalyzed by myeloperoxidase (MPO). Even though H2O2 is generated from superoxide at a high rate, it stabilizes in the low micromolar range (Winterbourn CC 2008; Winterbourn CC & Kettle AJ 2013). H2O2 is efficiently consumed by MPO to generate HOCl. If chloride is limited, MPO functions more as a catalyst for removal of superoxide and H2O2. Although H2O2 can permeate bacteria, it is unlikely to be directly bactericidal at the concentrations achieved in the phagosome (Winterbourn CC & Kettle AJ 2013). H2O2 reacts rapidly with heme proteins, thus MPO is likely to be its main target within phagosomes (Paumann-Page M et al. 2013; Winterbourn CC 2013). H2O2 can oxidize thiol proteins (Paulsen CE & Carroll KS 2013; Winterbourn CC 2013). The initial oxidation product of the cysteine (Cys) residue is sulfenic acid (Cys-SOH) (Wall SB et al. 2012; Paulsen CE & Carroll KS 2013; Trujillo M et al 2016). The Cys-SOH is highly reactive, its stability is influenced by neighboring cysteine residues (Cys-SH), which can generate a more stable disulfide bond. The formation of disulfide bridges, either between the same or different polypeptide chains, is important for protein structure and folding, and is often involved in the regulation of protein function. Alternatively, sulfenic acids can be overoxidized to form irreversible sulfinic acid (Cys-SO2H) or sulfonic acid (Cys-SO3H) (Wall SB et al. 2012; Paulsen CE & Carroll KS 2013; Trujillo M et al 2016).

Preceded by: Superoxide anion dismutates to H2O2

Literature references

Kettle, AJ., Winterbourn, CC. (2013). Redox reactions and microbial killing in the neutrophil phagosome. *Antioxid. Redox Signal., 18*, 642-60. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

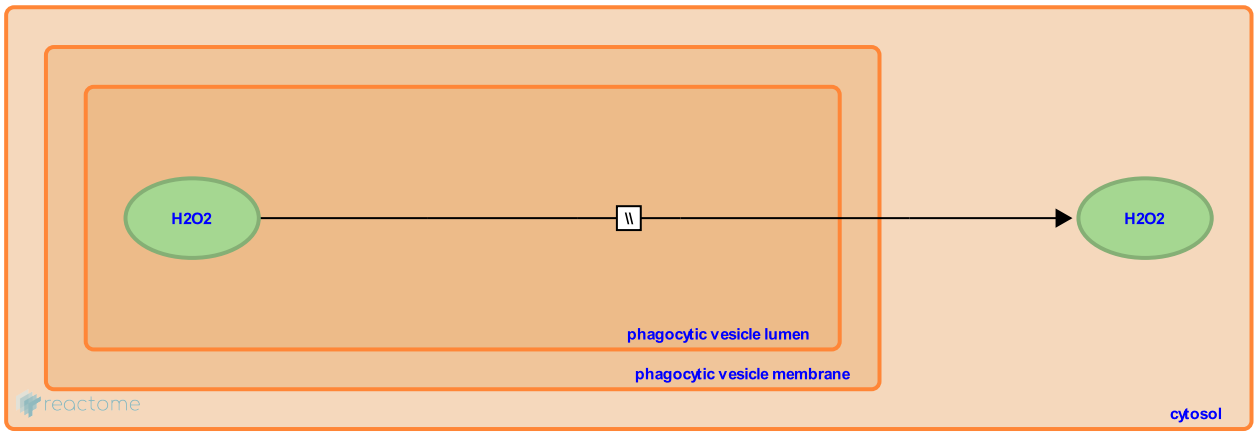
Hydrogen peroxide enters the bacterium ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6789077

Type: omitted

Compartments: phagocytic vesicle lumen, cytosol



Unlike superoxide anion, which is short-lived and local in its effect, hydrogen peroxide is longer-lasting and membrane-permeable, so it can diffuse away from the site of production (Winterbourn CC et al. 2006). Though H2O2 can permeate bacteria, it is unlikely to be directly bactericidal at the concentrations achieved in the phagosome. Its relatively benign nature is explicable in terms of its chemistry. Although it has a high two-electron reduction potential (H2O2/H2O;1.77V) and is therefore a strong oxidant, a high activation energy makes it a kinetically sluggish oxidant of most biomolecules (Winterbourn CC et al. 2006). However, the derivatives of H2O2 such as hydroxyl radical (OH.) are far more reactive (Root RK & Metcalf JA 1977; Winterbourn CC et al. 2006). Hydroxyl radical is produced by interaction of Fe2+ with hydrogen peroxide (Fenton reaction). Rates of reaction with iron-sulfur clusters are sufficiently fast for H2O2 to damage dehydratases and kill bacteria by mechanisms in which site-directed Fenton chemistry targets vulnerable molecules in the bacterial cytosol and the bacterial DNA (Keyer K & Imlay JA 1996; Jang S & Imlay JA 2007).

Preceded by: Superoxide anion dismutates to H2O2

Followed by: Hydrogen peroxide and Fe2+ react to hydroxyl, hydroxide and Fe3+

Literature references

Hampton, MB., Livesey, JH., Kettle, AJ., Winterbourn, CC. (2006). Modeling the reactions of superoxide and myeloperoxidase in the neutrophil phagosome: implications for microbial killing. *J. Biol. Chem., 281*, 39860-9. ↗

Shiloh, MU., Nathan, C. (2000). Reactive oxygen and nitrogen intermediates in the relationship between mammalian hosts and microbial pathogens. *Proc Natl Acad Sci U S A, 97*, 8841-8. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

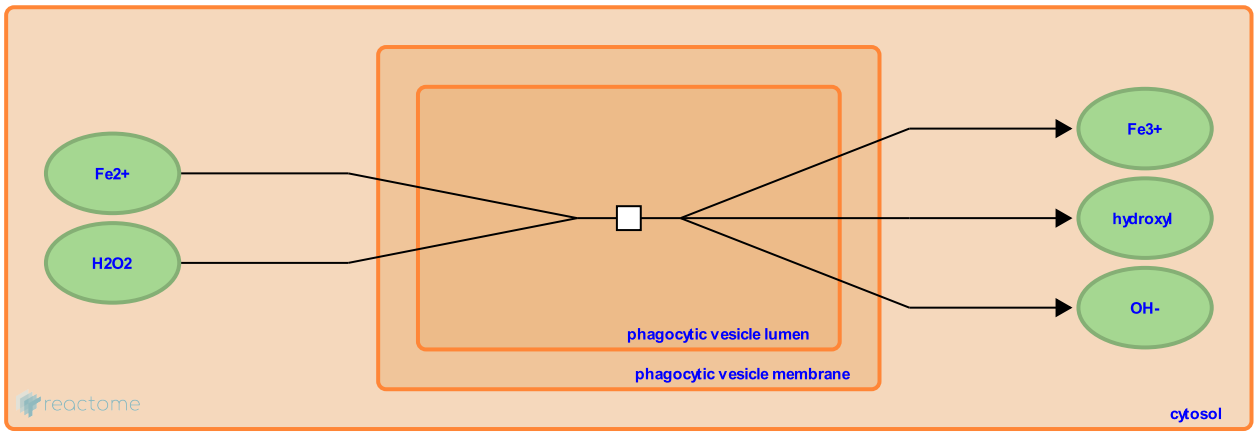
Hydrogen peroxide and Fe2+ react to hydroxyl, hydroxide and Fe3+ ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6789160

Type: transition

Compartments: phagocytic vesicle lumen



Hydrogen peroxide (H2O2) is membrane-permeable and relatively stable, so it can diffuse away from the site of production (Winterbourn CC et al. 2006). Though H2O2 can permeate bacteria, it is unlikely to be directly bactericidal at the concentrations achieved in the phagosome. The derivatives of H2O2 such as hydroxyl radical (OH.) are far more reactive (Root RK & Metcalf JA 1977; Winterbourn CC et al. 2006). Hydroxyl radical is produced by interaction of free ferrous iron (Fe2+) with hydrogen peroxide (Fenton-like reaction). The increase of free Fe2+ concentration within the bacterial cell is associated with superoxide (O2.-) that oxidatively attacks iron-sulfur [4Fe-4S] clusters of dehydratases such that they release ferrous iron, which can then rapidly react with H2O2 (Liochev SI & Fridovich I 1994). Thus, H2O2 may damage dehydratases and kill bacteria by mechanisms in which site-directed Fenton chemistry targets vulnerable molecules in the bacterial cytosol and the bacterial DNA (Keyer K & Imlay JA 1996; Jang S & Imlay JA 2007).

Preceded by: Superoxide anion reacts with Fe-S cluster, Hydrogen peroxide enters the bacterium

Followed by: Hydroxyl radical reacts with the base and sugar moiety of DNA

Literature references

Hampton, MB., Livesey, JH., Kettle, AJ., Winterbourn, CC. (2006). Modeling the reactions of superoxide and myeloperoxidase in the neutrophil phagosome: implications for microbial killing. *J. Biol. Chem., 281*, 39860-9. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

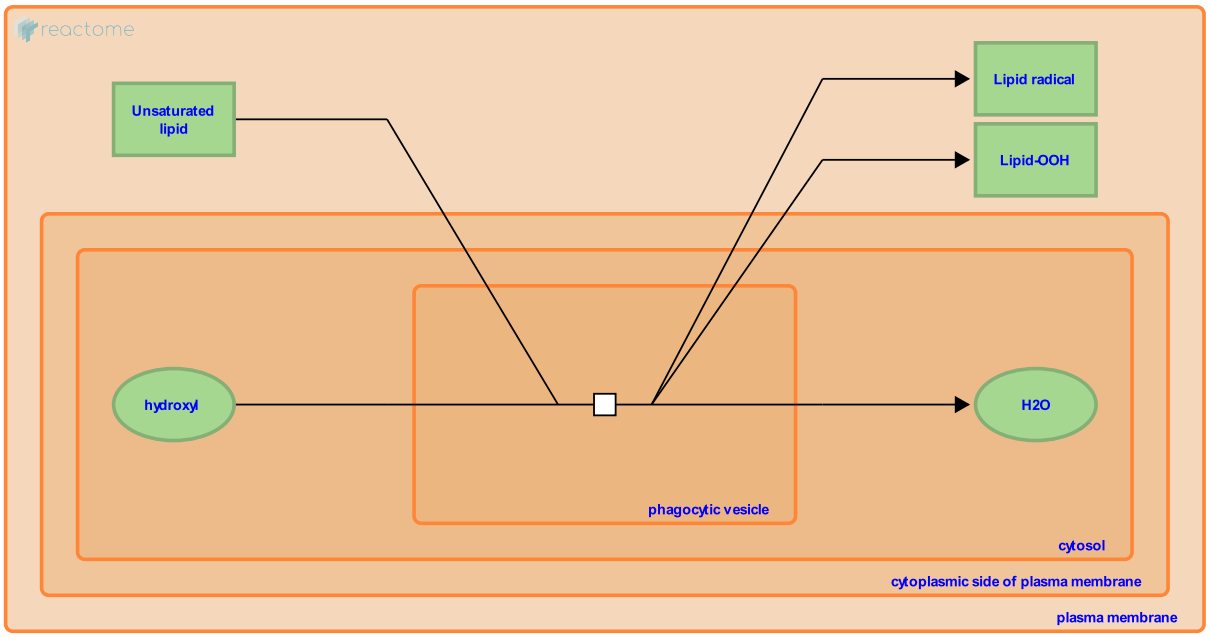
Hydroxyl-initiated lipid peroxidation ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6789042

Type: transition

Compartments: phagocytic vesicle



The hydroxyl radical reacts instantaneously with any biological molecule (RH) from which it can abstract a hydrogen atom. The resulting free radical is more stable and hence longer-lived than the hydroxyl radical.

Membranes are formed by amphiphilic lipids which in most cases studied are glycerophospholipids, composed of two fatty acids, a glycerol moiety, a phosphate group and a variable head group. Bacterial membranes present a large diversity of amphiphilic lipids, including phosphatidylglycerol, phosphatidylethanolamine, cardiolipin and the less frequent phospholipids such as phosphatidylcholine and phosphatidylinositol. Bacteria can also form phosphorus-free membrane lipids such as ornithine lipids, sulfolipids, diacylglyceryl-N,N,N-trimethylhomoserine, glycolipids, diacylglycerol, hopanoids and others. Commonly, the hydrophobic moieties of amphiphilic membrane lipids are formed by linear fatty acids that can be saturated or unsaturated (containing often one and rarely two or more double bonds). (OH.)-dependent abstraction of a hydrogen atom from an unsaturated fatty acid initiates the process of lipid peroxidation by generating a lipid radical, which rapidly adds oxygen to form a lipid peroxyl radical LOO. (not shown here). The peroxyl radicals in turn can further react with lipid molecules to continue the chain reaction, producing lipid hydroperoxides (LOOH), that can break down to more radical species

Literature references

Girotti, AW. (1998). Lipid hydroperoxide generation, turnover, and effector action in biological systems. *J. Lipid Res., 39*, 1529-42. ↗

Parizotto, NA., Gupta, A., Vecchio, D., Vatansever, F., Yin, R., Sadasivam, M. et al. (2013). Antimicrobial strategies centered around reactive oxygen species--bactericidal antibiotics, photodynamic therapy, and beyond. *FEMS Microbiol. Rev., 37*, 955-89. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

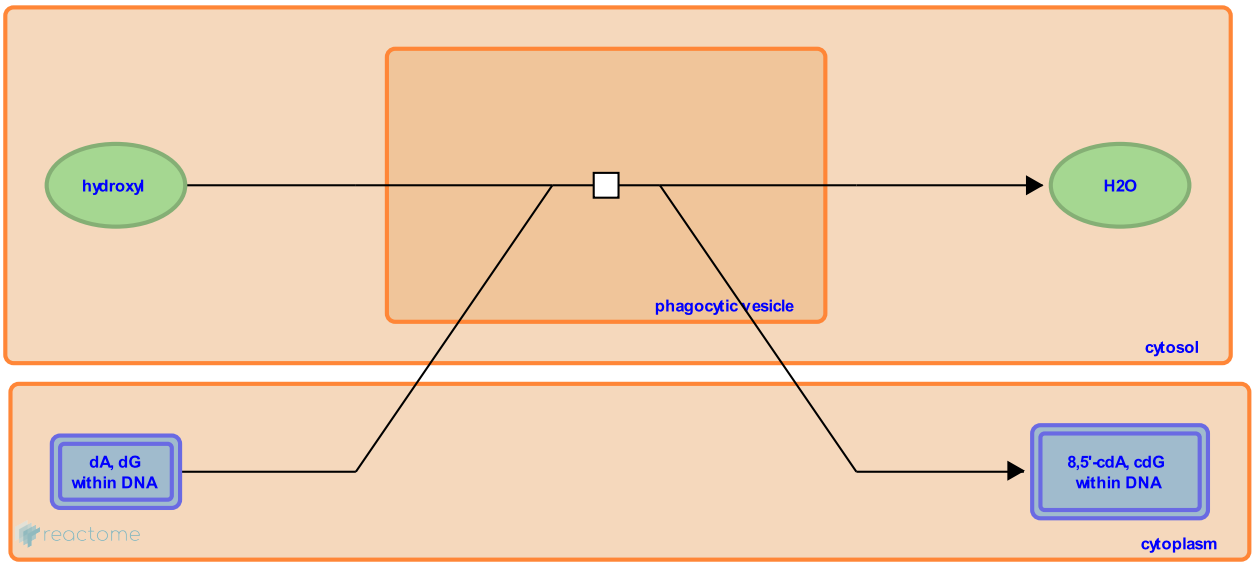
Hydroxyl radical reacts with the base and sugar moiety of DNA ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6789114

Type: transition

Compartments: phagocytic vesicle



The hydroxyl radical (•OH) is a highly reactive oxygen species (ROS) that efficiently reacts with nearby biomolecules at diffusion-controlled rates of reaction. The generation of •OH by Fenton type-driven reactions is believed to take place in a site-specific manner, for example, involving metal ions in close proximity or bound to DNA (Cadet J & Wagner JR 2013).

Hydroxyl radical reacts with both the basepairs of DNA and the sugar moiety in the oligonucleotides (Dedon PC 2008; Cadet J & Wagner JR 2014). •OH reacts with 2'-deoxyribose in DNA by H abstraction from all its carbons leading to five C-centered radicals (Dedon PC 2008; Cadet J & Wagner JR 2013). The abstraction at C1' gives 2-deoxyribonolactone, the abstraction at C5′ gives 3′-phosphoglycoaldehyde, and abstraction at C4′ gives an intermediate unsaturated dialdehyde that can couple with cytosine to form a DNA inter- or intrastrand cross-link (Dedon PC 2008; Sczepanski JT et al. 2011; Cadet J & Wagner JR 2013). In addition, the C5′-centered radicals of 2-deoxyribose can react with the purine ring in the same nucleoside to produce 8,5'-cyclo-2′-deoxyguanosine (8,5'-cyclo-dGuo) or 8,5'-cyclo-2′-deoxyadenosine (8,5'-cyclo-dAdo), which are among the major lesions in DNA that are formed by attack of hydroxyl radical (Jaruga P et al. 2002; Chatgilialoglu C et al. 2011).

Preceded by: Hydrogen peroxide and Fe2+ react to hydroxyl, hydroxide and Fe3+

Literature references

Balasubramanian, B., Tullius, TD., Pogozelski, WK. (1998). DNA strand breaking by the hydroxyl radical is governed by the accessible surface areas of the hydrogen atoms of the DNA backbone. *Proc. Natl. Acad. Sci. U.S.A., 95*, 9738-43. ↗

Dizdaroglu, M., Jaruga, P. (2012). Mechanisms of free radical-induced damage to DNA. *Free Radic. Res., 46*, 382-419. ↗

Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

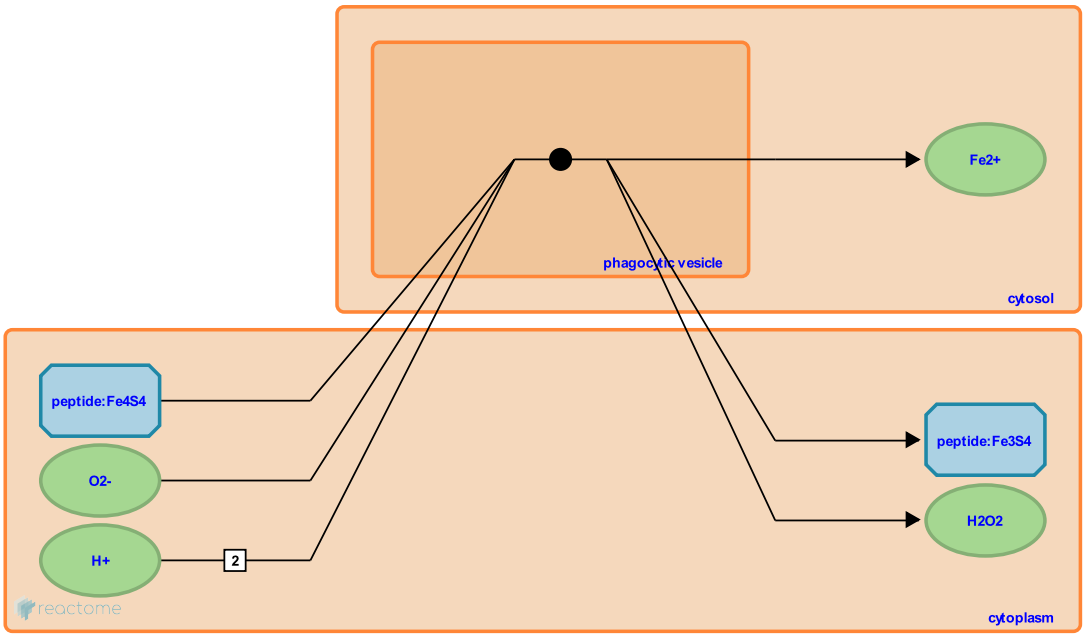
Superoxide anion reacts with Fe-S cluster ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-6789109

Type: binding

Compartments: phagocytic vesicle



Iron-sulfur (Fe-S) clusters are ubiquitous, evolutionary ancient and functionally versatile prosthetic groups found in a variety of metalloproteins. In most Fe-S proteins, the clusters function as electron-transfer groups in mediating one-electron redox processes. Fe-S clusters may also participate in iron/sulfur storage or regulate enzyme activity and substrate binding. As stress sensors, Fe-S clusters may regulate gene expression. Fe-S clusters have variable compositions such as 2Fe-2S, 3Fe-4S, 4Fe-4S centers. Solvent-exposed [4Fe-4S](2+) clusters are sensitive to oxidation and can be damaged (or disassembled) by reactive oxygen species. Superoxide (O2.-) and hydrogen peroxide (H2O2) oxidize [4Fe-4S](2+) into unstable [4Fe-4S](3+) intermediate, which is degraded to a [3Fe-4S](+) cluster. This process releases free iron (Fe(2+)) and inactivates the enzyme. High concentration of Fe(2+) under oxidative stress elevates ROS toxicity by catalyzing Fenton reaction that generates hydroxyl radical (OH.) from H2O2. Hydroxyl radical reacts with all macromolecules, including proteins, peptidoglycans, lipids or DNA.

Followed by: Hydrogen peroxide and Fe2+ react to hydroxyl, hydroxide and Fe3+

Literature references

Rouault, TA. (2014). Iron-sulfur clusters and molecular oxygen: function, adaptation, degradation, and repair, Iron-Sulfur Clusters in Chemistry and Biology.

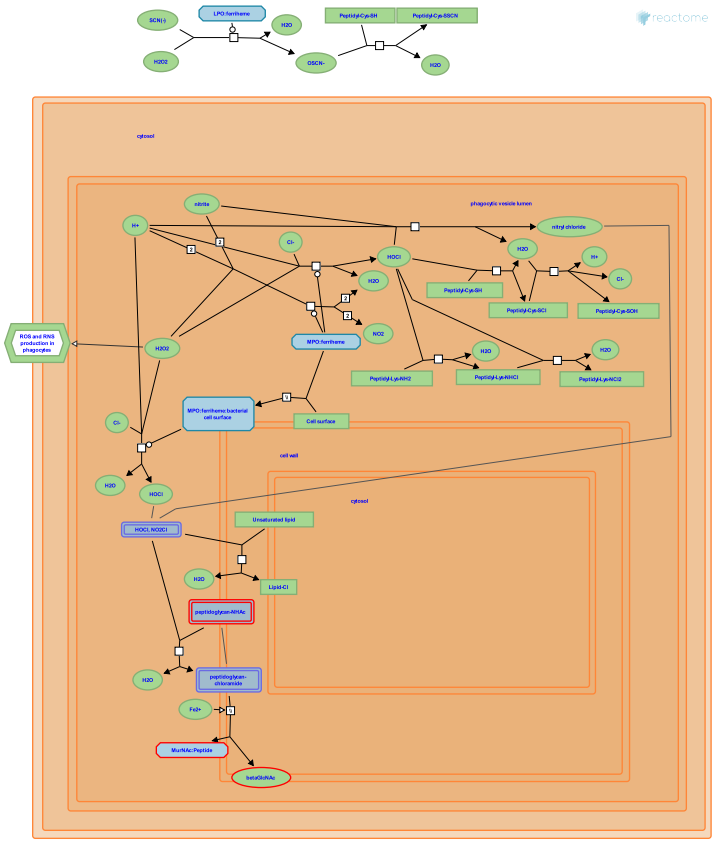
Editions

2018-10-23	Authored, Edited	Shamovsky, V.
2018-11-07	Reviewed	Nüsse, O.

Events associated with phagocytolytic activity of PMN cells ↗

Location: ROS and RNS production in phagocytes

Stable identifier: R-HSA-8941413



When neutrophils engulf bacteria they enclose them in small vacuoles (phagosomes) into which superoxide is released by activated NADPH oxidase (NOX2) on the internalized neutrophil membrane. The directional nature of NOX2 activity creates a charge imbalance that must be counteracted to prevent depolarization of the membrane and the shutdown of activity (Winterbourn CC et al. 2016). Also, protons are produced in the cytosol and consumed in the external compartment (for example, the phagosome) through the dismutation of superoxide. Both situations are largely overcome by a balancing flow of protons transported by voltage-gated proton channels, primarily VSOP/HV1, which are activated in parallel with the oxidase (Demaurex N & El Chemaly A 2010; El Chemaly A et al. 2010; Petheo GL et al. 2010; Kovacs I et al. 2014; Henderson LM et al. 1987, 1988). The pH of the phagosome is regulated by these activities. In contrast to the phagosomes of macrophages, in which pH drops following particle ingestion, neutrophil phagosomes remain alkaline during the period that the oxidase is active. Until recently, their pH has been accepted to lie between 7.5 and 8. However, in a 2015 study using a probe that is more sensitive at higher pH, an average pH closer to 9 was measured in individual phagosomes (Levine AP et al. 2015).

The superoxide dismutates to hydrogen peroxide, which is used by myeloperoxidase (MPO) to generate other oxidants, including the highly microbicidal species such as hypochlorous acid (Winterbourn CC et al. 2013, 2016).

Literature references

Kettle, AJ., Winterbourn, CC. (2013). Redox reactions and microbial killing in the neutrophil phagosome. *Antioxid. Redox Signal., 18*, 642-60. ↗

Hampton, MB., Kettle, AJ., Winterbourn, CC. (2016). Reactive Oxygen Species and Neutrophil Function. *Annu. Rev. Biochem., 85*, 765-92. ↗

Editions

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2018-11-07	Reviewed	Nüsse, O.

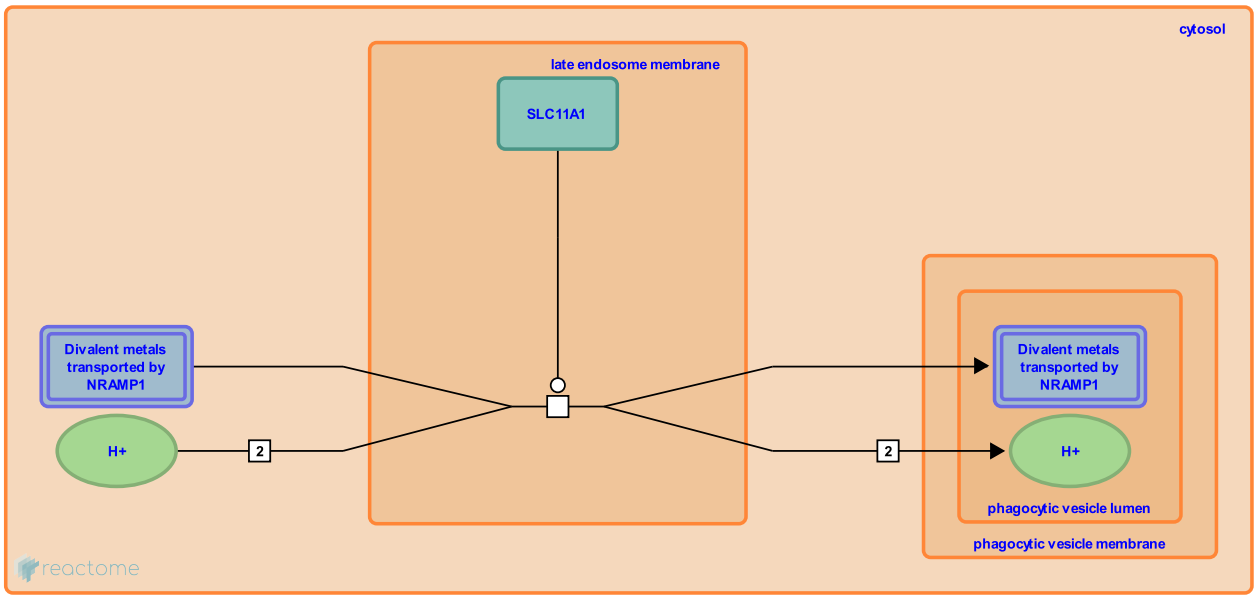
NRAMP1 transports divalent metal ions across phagosomal membranes of macrophages ↗

Location: ROS and RNS production in phagocytes

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 bivalent 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 (Fe2+), zinc (Zn2+) and manganese (Mn2+) 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.

Table of Contents