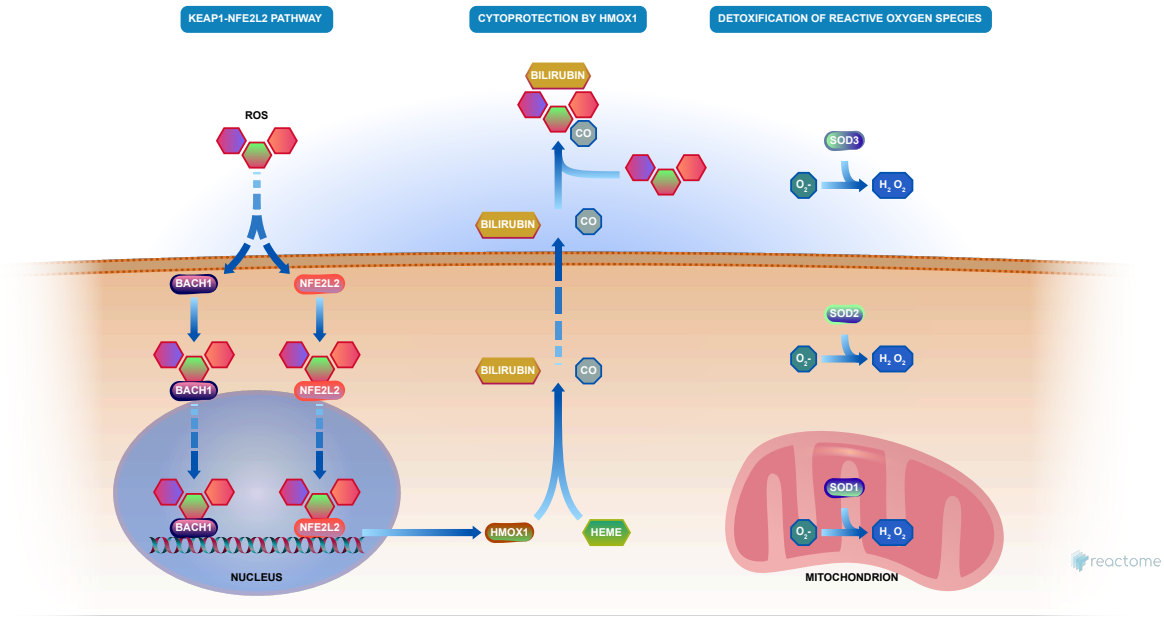
Cellular response to chemical stress



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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

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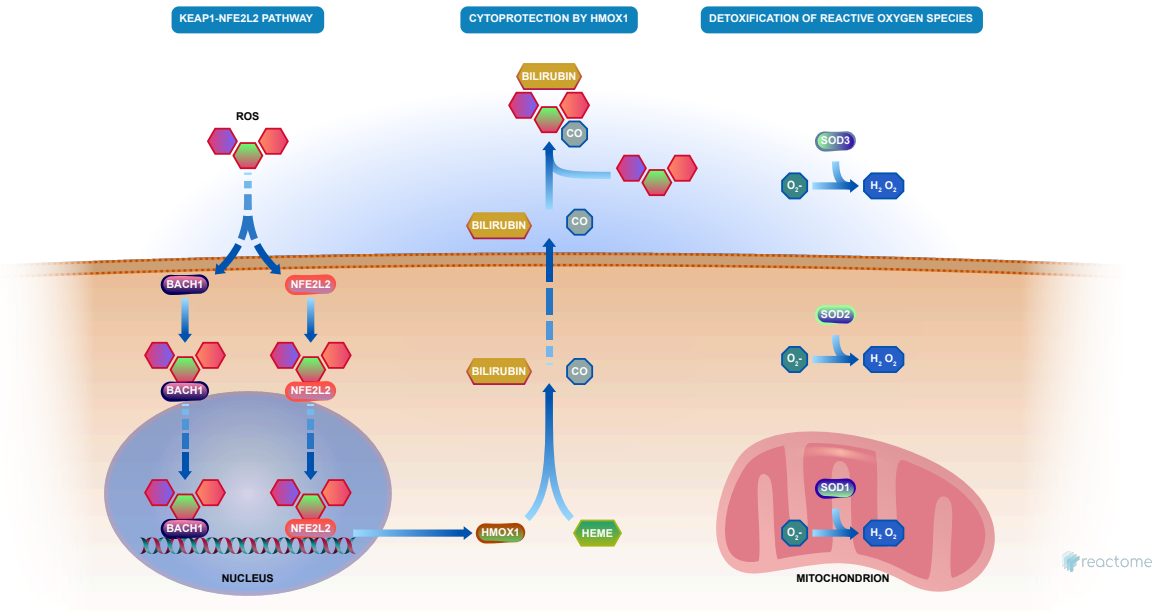
Cellular response to chemical stress ↗

Stable identifier: R-HSA-9711123



Cells are equipped with versatile physiological stress responses to prevent hazardous consequences resulting from exposure to chemical insults of endogenous and exogenous origin. Even at equitoxic doses, different stressors induce distinctive and complex signaling cascades. The responses typically follow cell perturbations at the subcellular organelle level.

Expression of heme oxygenase 1 (HMOX1) is regulated by various indicators of cell stress. Cytoprotection by HMOX1 is exerted directly by HMOX1 and by the antioxidant metabolites it produces through the degradation of heme (Origassa et al, 2013; Ryter et al, 2006).

Reactive oxygen and nitrogen species (RONS) are important mediators of chemical stress, as they are produced endogenously in mitochondria, and also result from redox activities of many toxins and heavy metal cations. The points of RONS action in the cell are plasma and ER membrane lipids, as well as DNA, both acting as sensors for the cellular response. On the other hand, chemotherapeutic agents exert their action via generation of RONS and induction of cancer cell apoptosis, while drug resistance associates with RONS-induced cancer cell survival (Sampadi et al, 2020; Moldogazieva et al, 2018).

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Editions

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KEAP1-NFE2L2 pathway ↗

Location: Cellular response to chemical stress

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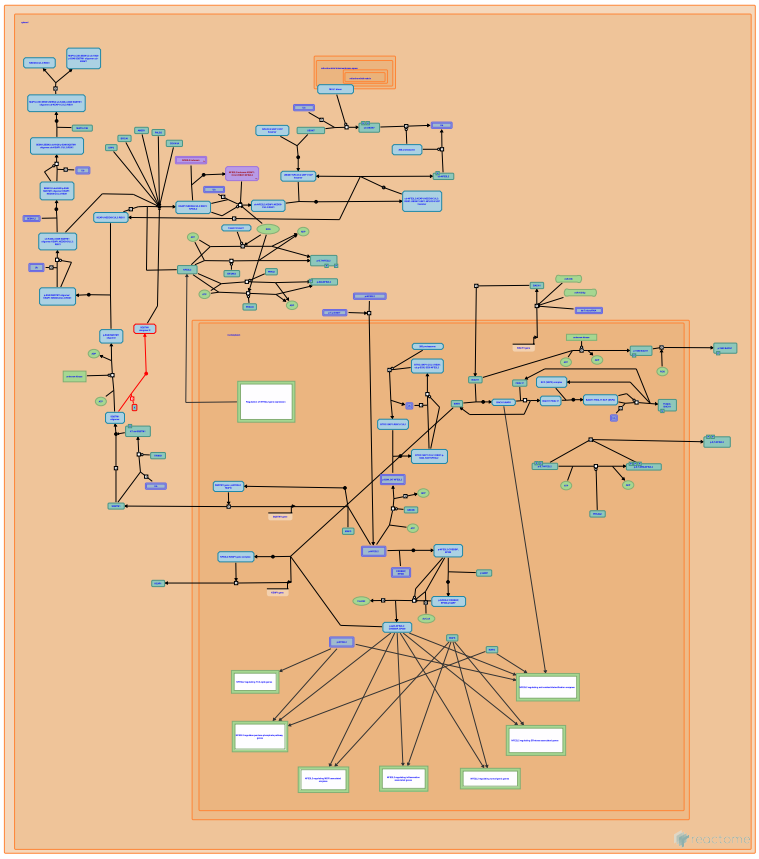

The KEAP1:NFE2L2 (KEAP1-NRF2, Kelch-like ECH-associated protein 1-Nuclear Factor (erythroid-derived 2)-like 2) regulatory pathway plays a central role in protecting cells against multiple homeostatic responses including adaptation to oxidative, inflammatory, metabolic, proteotoxic and xenobiotic stresses. The NFE2L2 transcriptome has been implicated in protection against many chronic diseases including cardiovascular, metabolic, neurodgenerative and respiratory diseases (reviewed in Cuadrado et al, 2018; Baird and Yamamoto, 2020). In cancer, NFE2L2 plays a critical role in the metabolic reprogramming, directing metabolic intermediates into the Warburg and pentose phosphate pathways to support proliferative growth and redox homeostasis (reviewed in He et al, 2020; Ge et al, 2020; Hayes et al, 2020; Kitamura and Hotomashi, 2018)

KEAP1 is a redox sensor that together with CUL3/RBX1 forms part of an E3 ubiquitin ligase, which tightly regulates the activity of the transcription factor NFE2L2 by targeting it for ubiquitination and proteasome-dependent degradation. Oxidative modifications or electrophile adduct formation with redox-sensitive cysteines within KEAP1 renders this protein unable to target bound NFE2L2 for ubiquitination and allows newly translated NFE2L2 to accumulate within the cell and translocate to the nucleus where it can promote its transcriptional program (reviewed in Cuadrado et al, 2019; Baird and Yamamoto, 2020).

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Cytoprotection by HMOX1 ↗

Location: Cellular response to chemical stress

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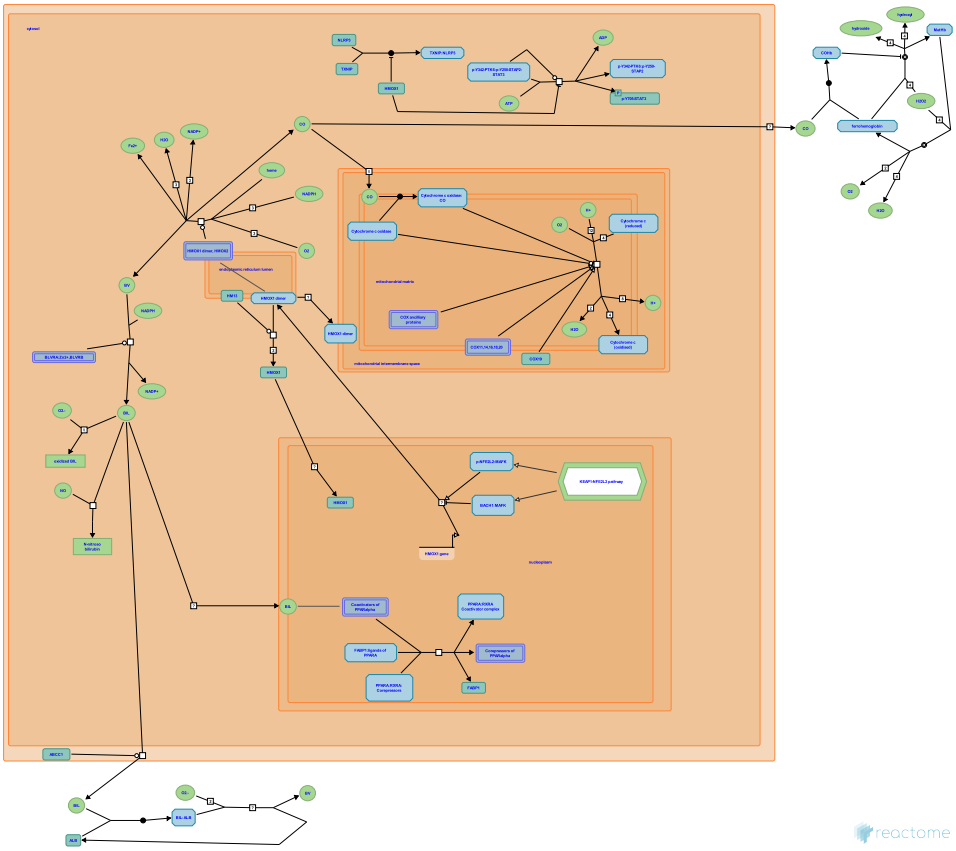

Expression of heme oxygenase 1 (HMOX1) is regulated by various indicators of cell stress, while HMOX2 is expressed constitutively. Both catalyze the breakdown of heme into biliverdin (BV), carbon monoxide (CO), and ferrous iron. Biliverdin is immediately reduced to bilirubin (BIL). Both bilirubin and carbon monoxide can localize to different compartments and outside the cell. Cytoprotection by HMOX1 is exerted directly by HMOX1 and by the antioxidant metabolites produced through the degradation of heme. Additionally, due to the reactive nature of labile heme, its degradation is intrinsically protective.

HMOX1 confers cytoprotection against cell death in various models of lung and vascular injury by inhibiting apoptosis, inflammation, and immune cell proliferation. It binds to the NACHT domain of NLRP3 inflammasome, blocking its activation. In mouse it directly binds STAT3 to control the generation of pathogenic Th17 cells during neutrophilic airway inflammation. It also blocks phosphorylation of STAT3 by PTK6 and co-inhibits Socs3, a negative feedback factor of Stat3 activation, as well as RORγt, thereby decreasing Th2 and Th17 immune responses, and alleviating airway inflammation.

The beneficial effects of the three products generated by HMOX1 differ not only in their inherent molecular mechanisms, but also in their downstream cellular targets. To date, this is the only enzymatic system known to exhibit such characteristics. Iron is a vital component of many biological systems and is capable of producing hydroxyl radicals via fenton chemistry. For this reason, iron is sequestered by the storage multimer ferritin and to prevent oxidative damage while maintaining the iron pool. On the other hand, the protective effects of bilirubin and CO are broadly recognized, which has led to their consideration as therapeutics for a range of diseases. Bilirubin has been recognized as one of the most potent antioxidants in nature, and moderate increases of its serum level have been shown in numerous large-scale population and epidemiological studies to have a protective effect against cardiovascular and metabolic disease. These effects are mediated by bilirubin scavenging of superoxide anions and reactive nitrogen species (RNS), and by activating the transcription factor PPAR-alpha.

CO and biliverdin/bilirubin, have been shown to exert protective effects in the liver against a number of stimuli, as in chronic hepatitis C and in transplanted liver grafts. CO possesses intriguing signaling properties affecting numerous critical cellular functions including but not limited to inflammation, cellular proliferation, and apoptotic cell death. Binding of CO with key ferrous hemoproteins serves as a posttranslational modification that regulates important processes as diverse as aerobic metabolism, oxidative stress, and mitochondrial bioenergetics. The most important of

these is the mitochondrial cytochrome c oxidase (Cco). By locally blocking mitochondrial respiration the main source of reactive oxygen species (ROS) in the cell is switched off. Additionally CO enables efficient reduction of methemoglobin (MetHb) by H2O2, thus preventing the generation of free heme in hemorrhagic diseases and malaria (Origassa and Câmara, 2013; Morse et al, 2009; Ryter et al, 2006; Cooper and Brown, 2008; Hinds and Stec, 2008).

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Editions

2020-11-12	Authored, Edited	Stephan, R.
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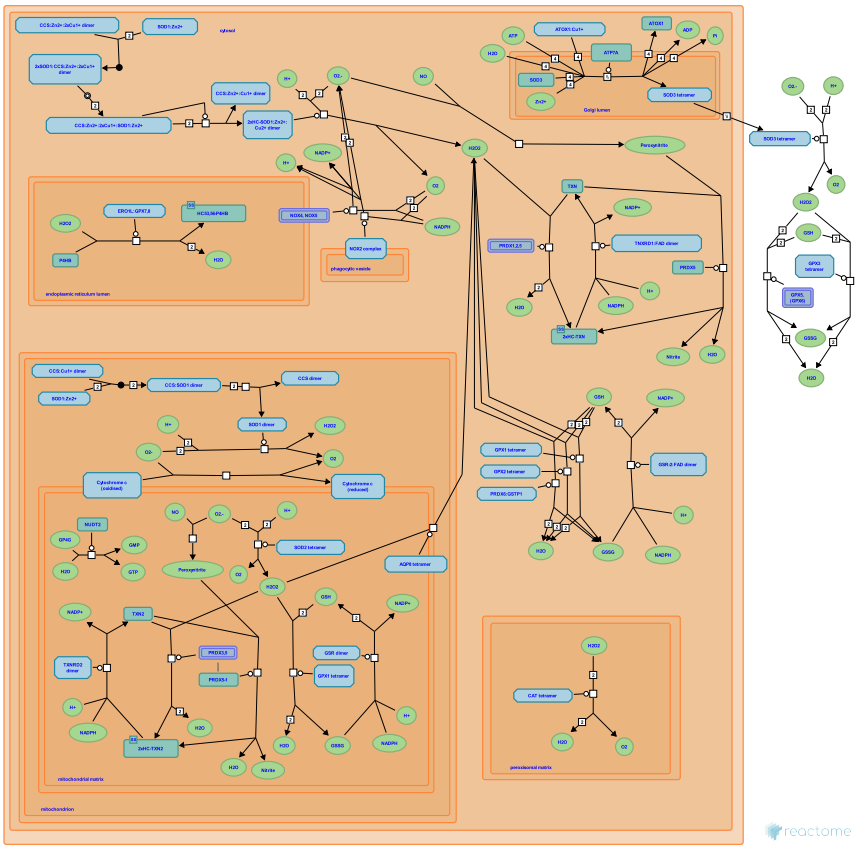
Detoxification of Reactive Oxygen Species ↗

Location: Cellular response to chemical stress

Stable identifier: R-HSA-3299685

Compartments: cytosol, mitochondrial matrix, endoplasmic reticulum lumen, mitochondrial intermembrane space, extracellular region, mitochondrial inner membrane, peroxisomal matrix



Reactive oxygen species such as superoxide (O2.-), peroxides (ROOR), singlet oxygen, peroxynitrite (ONOO-), and hydroxyl radical (OH.) are generated by cellular processes such as respiration (reviewed in Murphy 2009, Brand 2010) and redox enzymes and are required for signaling yet they are damaging due to their high reactivity (reviewed in Imlay 2008, Buettner 2011, Kavdia 2011, Birben et al. 2012, Ray et al. 2012). Aerobic cells have defenses that detoxify reactive oxygen species by converting them to less reactive products. Superoxide dismutases convert superoxide to hydrogen peroxide and oxygen (reviewed in Fukai and Ushio-Fukai 2011). Catalase and peroxidases then convert hydrogen peroxide to water.
Humans contain 3 superoxide dismutases: SOD1 is located in the cytosol and mitochondrial intermembrane space, SOD2 is located in the mitochondrial matrix, and SOD3 is located in the extracellular region. Superoxide, a negative ion, is unable to easily cross membranes and tends to remain in the compartment where it was produced. Hydrogen peroxide, one of the products of superoxide dismutase, is able to diffuse across membranes and pass through aquaporin channels. In most cells the primary source of hydrogen peroxide is mitochondria and, once in the cytosol, hydrogen peroxide serves as a signaling molecule to regulate redox-sensitive proteins such as transcription factors, kinases, phosphatases, ion channels, and others (reviewed in Veal and Day 2011, Ray et al. 2012). Hydrogen peroxide is decomposed to water by catalase, decomposed to water plus oxidized thioredoxin by peroxiredoxins, and decomposed to water plus oxidized glutathione by glutathione peroxidases (Presnell et al. 2013).

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Editions

2013-04-20	Authored, Edited	May, B.
2013-11-01	Reviewed	Kavdia, M.

Table of Contents