Cellular responses to stress

Chen, JJ., D'Eustachio, P., Echeverria, PC., Gillespie, ME., Gopinathrao, G., Guo, X., Matthews, L., May, B., Orlic-Milacic, M., Pani, B., Picard, D., Rantanen, K., Rothfels, K., Samarajiwa, S., Shamovsky, V., Somers, J., Stephan, R., Urano, F.

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Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
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Reactome database release: 88

This document contains 11 pathways (see Table of Contents)

Cellular responses to stress ↗

Stable identifier: R-HSA-2262752

Cells are subject to external molecular and physical stresses such as foreign molecules that perturb metabolic or signaling processes, and changes in temperature or pH. Cells are also subject to internal molecular stresses such as production of reactive metabolic byproducts. The ability of cells and tissues to modulate molecular processes in response to such stresses is essential to the maintenance of tissue homeostasis (Kultz 2005). Specific stress-related processes annotated here are **cellular response to hypoxia**, **cellular response to heat stress**, **cellular senescence**, **HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand**, **response of EIF2AK1 (HRI) to heme deficiency**, **heme signaling**, **cellular response to chemical stress**, **cellular response to starvation**, and **unfolded protein response**.

Literature references

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Editions

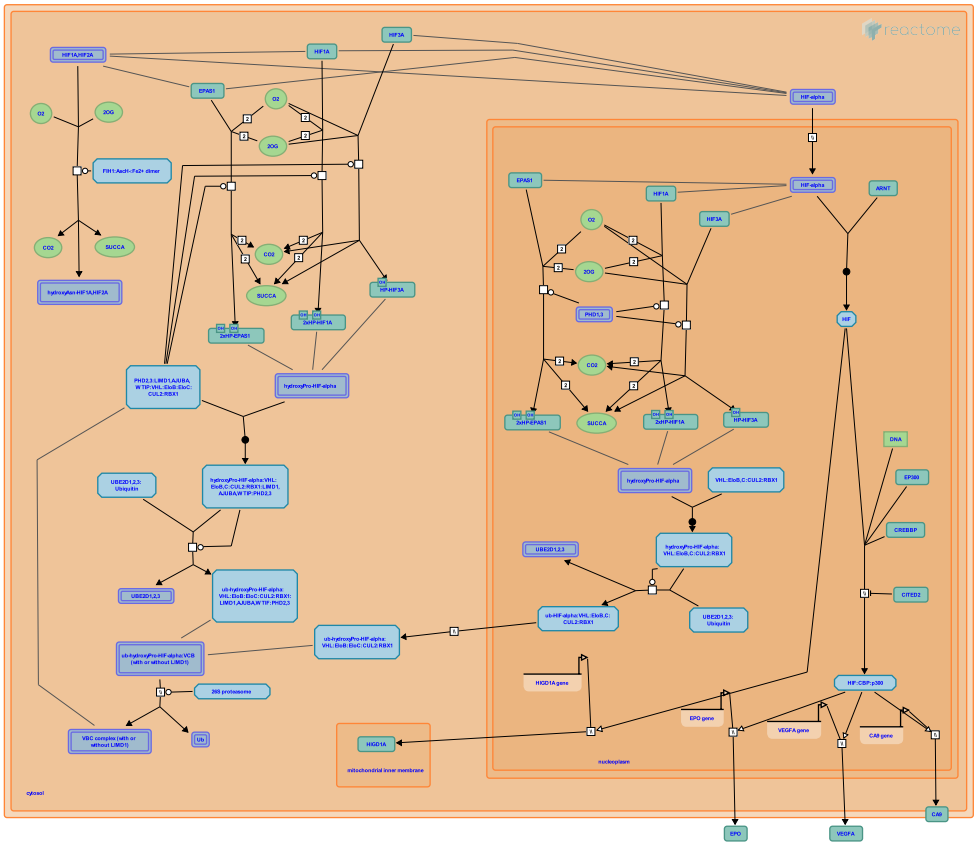
2012-05-20	Reviewed	D'Eustachio, P.
2012-05-20	Authored, Edited	Matthews, L.
2024-02-28	Reviewed	Matthews, L.

Cellular response to hypoxia ↗

Location: Cellular responses to stress

Stable identifier: R-HSA-1234174

Compartments: nucleoplasm, cytosol



Oxygen plays a central role in the functioning of human cells: it is both essential for normal metabolism and toxic. Here we have annotated one aspect of cellular responses to oxygen, the role of hypoxia-inducible factor in regulating cellular transcriptional responses to changes in oxygen availability.

In the presence of oxygen members of the transcription factor family HIF-alpha, comprising HIF1A, HIF2A (EPAS1), and HIF3A, are hydroxylated on proline residues by PHD1 (EGLN2), PHD2 (EGLN1), and PHD3 (EGLN3) and on asparagine residues by HIF1AN (FIH) (reviewed in Pouyssegur et al. 2006, Semenza 2007, Kaelin and Ratcliffe 2008, Nizet and Johnson 2009, Brahimi-Horn and Pouyssegur 2009, Majmundar et al. 2010, Loenarz and Schofield 2011). Both types of reaction require molecular oxygen as a substrate and it is probable that at least some HIF-alpha molecules carry both hydroxylated asparagine and hydroxylated proline (Tian et al. 2011).
Hydroxylated asparagine interferes with the ability of HIF-alpha to interact with p300 and CBP while hydroxylated proline facilitates the interaction of HIF-alpha with the E3 ubiquitin ligase VHL, causing ubiquitination and proteolysis of HIF-alpha. Hypoxia inhibits both types of hydroxylation, resulting in the stabilization of HIF-alpha, which then enters the nucleus, binds HIF-beta, and recruits p300 and CBP to activate target genes such as EPO and VEGF.

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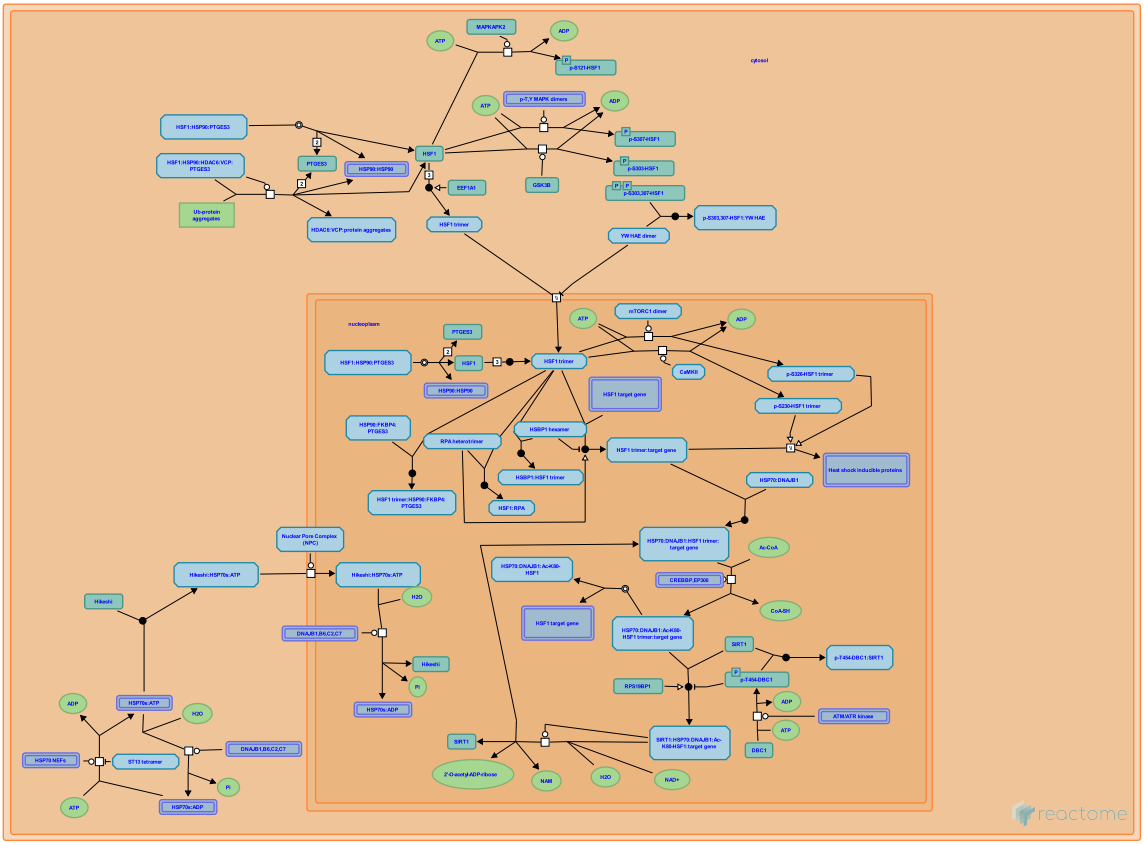
Editions

2011-03-09	Authored, Edited	May, B.
2012-05-19	Reviewed	Rantanen, K.

Cellular response to heat stress ↗

Location: Cellular responses to stress

Stable identifier: R-HSA-3371556



In response to exposure to elevated temperature and certain other proteotoxic stimuli (e.g., hypoxia, free radicals) cells activate a number of cytoprotective mechanisms known collectively as "heat shock response". Major aspects of the heat shock response (HSR) are evolutionarily conserved events that allow cells to recover from protein damage induced by stress (Liu XD et al. 1997; Voellmy R & Boellmann F 2007; Shamovsky I & Nudler E 2008; Anckar J & Sistonen L 2011). The main hallmark of HSR is the dramatic alteration of the gene expression pattern. A diverse group of protein genes is induced by the exposure to temperatures 3-5 degrees higher than physiological. Functionally, most of these genes are molecular chaperones that ensure proper protein folding and quality control to maintain cell proteostasis.

At the same time, heat shock-induced phosphorylation of translation initiation factor eIF2alpha leads to the shutdown of the nascent polypeptide synthesis reducing the burden on the chaperone system that has to deal with the increased amount of misfolded and thermally denatured proteins (Duncan RF & Hershey JWB 1989; Sarkar A et al. 2002; Spriggs KA et al. 2010).

The induction of HS gene expression primarily occurs at the level of transcription and is mediated by heat shock transcription factor HSF1(Sarge KD et al. 1993; Baler R et al. 1993). Human cells express five members of HSF protein family: HSF1, HSF2, HSF4, HSFX and HSFY. HSF1 is the master regulator of the heat inducible gene expression (Zuo J et al. 1995; Akerfelt M et al. 2010). HSF2 is activated in response to certain developmental stimuli in addition to being co-activated with HSF1 to provide promoter-specific fine-tuning of the HS response by forming heterotrimers with HSF1 (Ostling P et al. 2007; Sandqvist A et al. 2009). HSF4 lacks the transcription activation domain and acts as a repressor of certain genes during HS (Nakai A et al. 1997; Tanabe M et al. 1999; Kim SA et al. 2012). Two additional family members HSFX and HSFY, which are located on the X and Y chromosomes respectively, remain to be characterized (Bhowmick BK et al. 2006; Shinka T et al. 2004; Kichine E et al. 2012).

Under normal conditions HSF1 is present in both cytoplasm and nucleus in the form of an inactive monomer. The monomeric state of HSF1 is maintained by an intricate network of protein-protein interactions that include the association with HSP90 multichaperone complex, HSP70/HSP40 chaperone machinery, as well as intramolecular interaction of two conserved hydrophobic repeat regions. Monomeric HSF1 is constitutively phosphorylated on Ser303 and Ser 307 by (Zou J et al. 1998; Knauf U et al. 1996; Kline MP & Moromoto RI 1997; Guettouche T et al.

2005). This phosphorylation plays an essential role in ensuring cytoplasmic localization of at least a subpopulation of HSF1 molecules under normal conditions (Wang X et al. 2004).

Exposure to heat and other proteotoxic stimuli results in the release of HSF1 from the inhibitory complex with chaperones and its subsequent trimerization, which is promoted by its interaction with translation elongation factor eEF1A1 (Baler R et al. 1993; Shamovsky I et al. 2006; Herbomel G et al 2013). The trimerization is believed to involve intermolecular interaction between hydrophobic repeats 1-3 leading to the formation of a triple coil structure. Additional stabilization of the HSF1 trimer is provided by the formation of intermolecular S-S bonds between Cys residues in the DNA binding domain (Lu M et al.2008). Trimeric HSF1 is predominantly localized in the nucleus where it binds the specific sequence in the promoter of hsp genes (Sarge KD et al. 1993; Wang Y and Morgan WD 1994). The binding sequence for HSF1 (HSE, heat shock element) contains series of inverted repeats nGAAn in head-to-tail orientation, with at least three elements being required for the high affinity binding. Binding of the HSF1 trimer to the promoter is not sufficient to induce transcription of the gene (Cotto J et al. 1996). In order to do so, HSF1 needs to undergo inducible phosphorylation on specific Ser residues such as Ser230, Ser326. This phosphorylated form of HSF1 trimer is capable of increasing the promoter initiation rate. HSF1 bound to DNA promotes recruiting components of the transcription mediator complex and relieving promoter-proximal pause of RNA polymerase II through its interaction with TFIIH transcription factor (Yuan CX & Gurley WB 2000).

HSF1 activation is regulated in a precise and tight manner at multiple levels (Zuo J et al. 1995; Cotto J et al. 1996). This allows fast and robust activation of HS response to minimize proteotoxic effects of the stress. The exact set of HSF1 inducible genes is probably cell type specific. Moreover, cells in different pathophysiological states will display different but overlapping profile of HS inducible genes.

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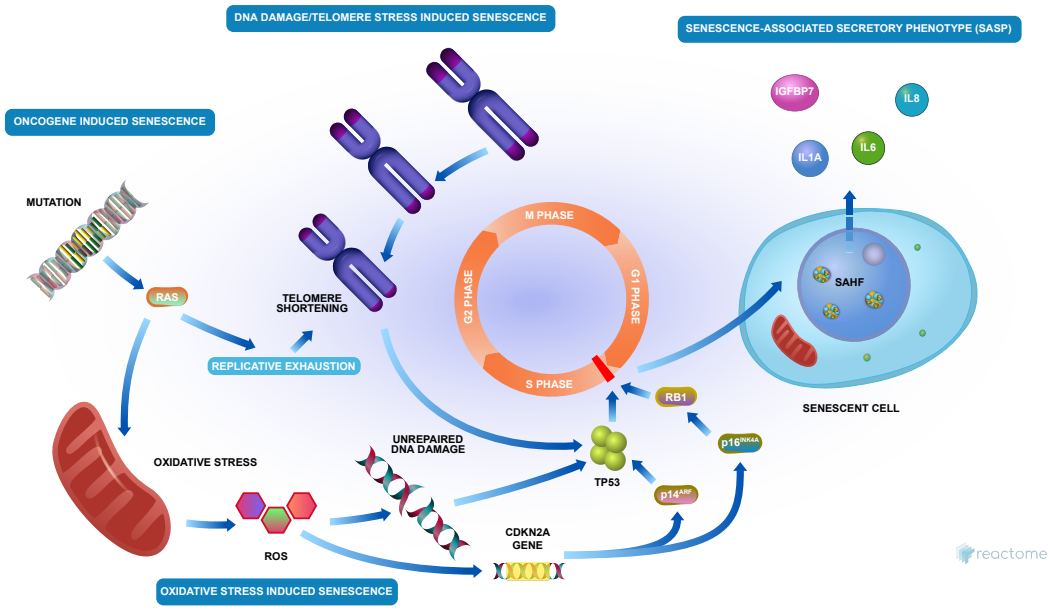
Editions

2013-10-29	Authored	Shamovsky, V.
2014-02-17	Reviewed	Pani, B.
2014-02-17	Edited	Shamovsky, V.

Cellular Senescence ↗

Location: Cellular responses to stress

Stable identifier: R-HSA-2559583



Cellular senescence involves irreversible growth arrest accompanied by phenotypic changes such as enlarged morphology, reorganization of chromatin through formation of senescence-associated heterochromatic foci (SAHF), and changes in gene expression that result in secretion of a number of proteins that alter local tissue environment, known as senescence-associated secretory phenotype (SASP).

Senescence is considered to be a cancer protective mechanism and is also involved in aging. Senescent cells accumulate in aged tissues (reviewed by Campisi 1997 and Lopez-Otin 2013), which may be due to an increased senescence rate and/or decrease in the rate of clearance of senescent cells. In a mouse model of accelerated aging, clearance of senescent cells delays the onset of age-related phenotypes (Baker et al. 2011).

Cellular senescence can be triggered by the aberrant activation of oncogenes or loss-of-function of tumor suppressor genes, and this type of senescence is known as the oncogene-induced senescence, with RAS signaling-induced senescence being the best studied. Oxidative stress, which may or may not be caused by oncogenic RAS signaling, can also trigger senescence. Finally, the cellular senescence program can be initiated by DNA damage, which may be caused by reactive oxygen species (ROS) during oxidative stress, and by telomere shortening caused by replicative exhaustion which may be due to oncogenic signaling. The senescent phenotype was first reported by Hayflick and Moorhead in 1961, when they proposed replicative senescence as a mechanism responsible for the cessation of mitotic activity and morphological changes that occur in human somatic diploid cell strains as a consequence of serial passaging, preventing the continuous culture of untransformed cells-the Hayflick limit (Hayflick and Moorhead 1961).

Secreted proteins that constitute the senescence-associated secretory phenotype (SASP), also known as the senescence messaging secretome (SMS), include inflammatory and immune-modulatory cytokines, growth factors, shed cell surface molecules and survival factors. The SASP profile is not significantly affected by the type of senescence trigger or the cell type (Coppe et al. 2008), but the persistent DNA damage may be a deciding SASP initiator (Rodier et al. 2009). SASP components function in an autocrine manner, reinforcing the senescent phenotype (Kuilman et al. 2008, Acosta et al. 2008), and in the paracrine manner, where they may promote epithelial-to-mesenchymal transition (EMT) and malignancy in the nearby premalignant or malignant cells (Coppe et al. 2008).

Senescent cells may remain viable for years, such as senescent melanocytes of moles and nevi, or they can be removed by phagocytic cells. The standard marker for immunohistochemical detection of senescent cells is senescence-associated beta-galactosidase (SA-beta-Gal), a lysosomal enzyme that is not required for senescence.

For reviews of this topic, please refer to Collado et al. 2007, Adams 2009, Kuilman et al. 2010. For a review of differential gene expression between senescent and immortalized cells, please refer to Fridman and Tainsky 2008.

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Editions

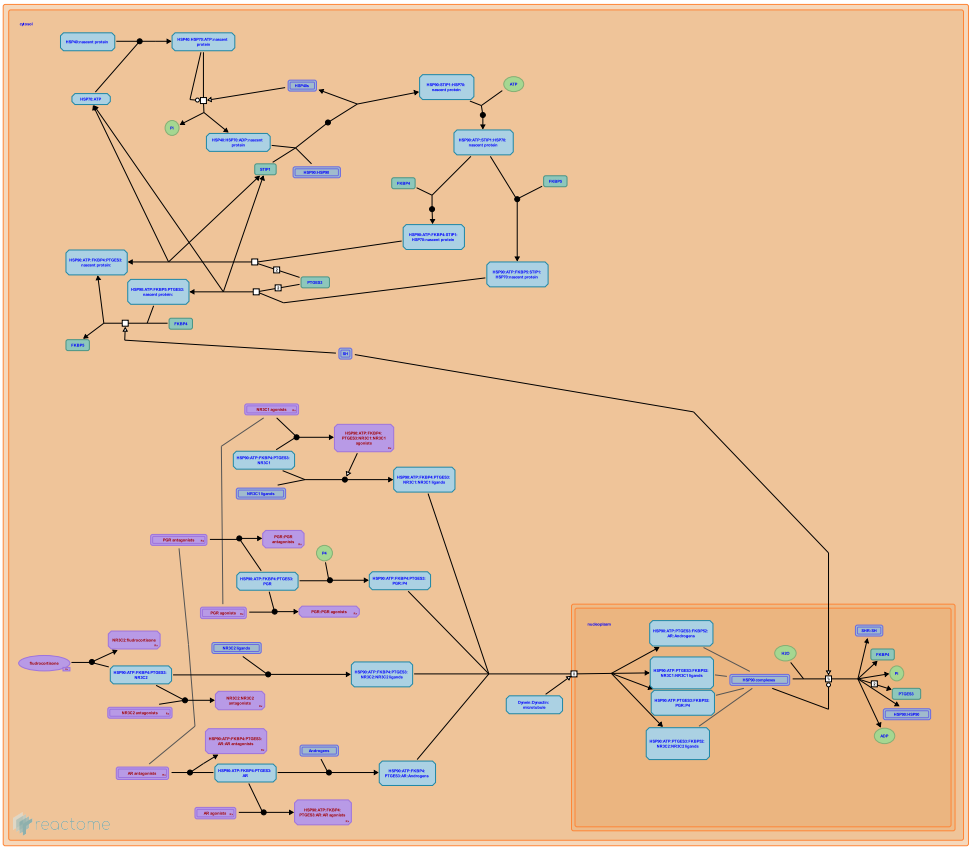
2013-07-15	Edited	D'Eustachio, P., Matthews, L.
2013-07-15	Authored	Orlic-Milacic, M.
2013-09-03	Reviewed	Samarajiwa, S.
2013-09-30	Revised	Orlic-Milacic, M.

HSP90 chaperone cycle for steroid hormone receptors (SHR) in the presence of ligand ↗

Location: Cellular responses to stress

Stable identifier: R-HSA-3371497

Compartments: cytosol



Steroid hormone receptors (SHR) are transcription factors that become activated upon sensing steroid hormones such as glucocorticoids, mineralocorticoids, progesterone, androgens, or estrogen (Escriva et al 2000; Griekspoor A et al. 2007; Eick GN & Thornton JW. 2011). Depending on SHR type and the presence of ligand, they show different subcellular localizations. Whereas both unliganded and liganded estrogen receptors (ERalpha and ERbeta) are predominantly nuclear, unliganded glucocorticoid (GR) and androgen receptors (AR) are mostly located in the cytoplasm and completely translocate to the nucleus only after binding hormone (Htun H et al. 1999; Stenoien D et al. 2000; Tyagi RK et al. 2000; Cadepond F et al. 1992; Jewell CM et al. 1995; Kumar S et al. 2006). The unliganded mineralocorticoid receptor (MR) is partially cytoplasmic but can be found in nucleus in the ligand-bound or ligand-free form (Nishi M & Kawata M 2007). The progesterone receptor (PR) exists in two forms (PRA and PRB) with different ratios of nuclear versus cytoplasmic localization of the unliganded receptor. In most cell contexts, the PRA isoform is a repressor of the shorter PRB isoform, and without hormone induction it is mostly located in the nucleus, whereas PRB distributes both in the nucleus and in the cytoplasm (Lim CS et al. 1999; Griekspoor A et al. 2007). In the absence of ligand, members of the steroid receptor family remain sequestered in the cytoplasm and/or nucleus in the complex with proteins of HSP70/HSP90 chaperone machinery (Pratt WB & Dittmar KD1998). The highly dynamic ATP-dependent interactions of SHRs with HSP90 complexes regulate SHR cellular location, protein stability, competency to bind steroid hormones and transcriptional activity (Echeverria PC & Picard D 2010). Understanding the mechanism of ATPase activity of HSP90 is mostly based on structural and functional studies of the Saccharomyces cerevisiae Hsp90 complexes (Meyer P et al. 2003, 2004; Ali MM et al. 2006; Prodromou C et al. 2000; Prodromou C 2012). The ATPase cycle of human HSP90 is less well understood, however several studies suggest that the underlying enzymatic mechanisms and a set of conformational changes that accompany the ATPase cycle are highly similar in both species (Richter K et al. 2008; Vaughan CK et al. 2009). Nascent SHR proteins are chaperoned by HSP70 and HSP40 to HSP90 cycle via STIP1 (HOP) (and its TPR domains) (Hernández MP et al. 2002a,b; EcheverriaPC & Picard D 2010; Li J et al. 2011). The ATP-bound form of HSP90 leads to the displacement of STIP1 by immunophilins FKBP5 or FKBP4 resulting in conformational changes that allow efficient hormone binding (Li J et al. 2011). PTGES3 (p23) binds to HSP90 complex finally stabilizing it in the conformation with a high hormone binding affinity. After hydrolysis of ATP the hormone bound SHR is released from HSP90 complex.

The cytosolic hormone-bound SHR can be transported to the nucleus by several import pathways such as the dynein-based nuclear transport along microtubules involving the transport of the entire HSP90 complex or nuclear localization signals (NLS)-mediated nuclear targeting by importins (Tyagi RK et al. 2000; Cadepond F et al. 1992; Jewell CM et al. 1995; Kumar S et al. 2006). It is worth noting that GR-importin interactions can be ligand-dependent or independent (Freedman & Yamamoto 2004; Picard & Yamamoto 1987). In the nucleus ligand-activated SHR dimerizes, binds specific sequences in the DNA, called Hormone Responsive Elements (HRE), and recruits a number of coregulators that facilitate gene transcription. Nuclear localization is essential for SHRs to transactivate their target genes, but the same receptors also possess non-genomic functions in the cytoplasm.

The Reactome module describes the ATPase-driven conformational cycle of HSP90 that regulates ligand-dependent activation of SHRs.

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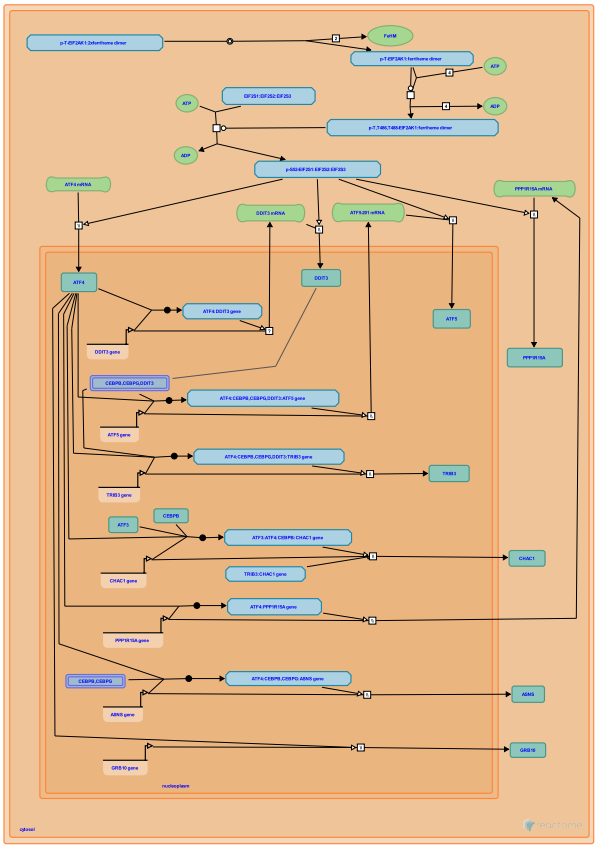
Editions

2016-09-17	Reviewed	Rothfels, K.
2016-11-19	Authored	Shamovsky, V.
2017-02-22	Reviewed	Picard, D., Echeverria, PC.
2017-02-25	Edited	Shamovsky, V.

Response of EIF2AK1 (HRI) to heme deficiency ↗

Location: Cellular responses to stress

Stable identifier: R-HSA-9648895



The kinases of the integrated stress response phosphorylate EIF2S1 (eIF2-alpha) to regulate cellular translation. The kinases comprise PERK (also called EIF2AK3), which responds to unfolded protein in the endoplasmic reticulum; EIF2AK2 (also called PKR), which responds to cytosolic double-stranded RNA; EIF2AK4 (also called GCN2), which responds to amino acid deficiency; and EIF2AK1 (also called heme-regulated inhibitor, HRI, and heme-controlled repressor, HCR), which responds to heme deficiency and cytosolic unfolded protein. Each molecule of EIF2AK1 binds two molecules of heme, one bound near the N-terminus and one bound at the kinase insert (KI) domain that inhibits the kinase activity of EIF2AK1 (inferred from the rabbit homolog in Chefalo et al. 1998, Rafie-Kolpin et al. 2000, inferred from the mouse homolog in Misanova et al. 2006, Hirai et al. 2007, Igarashi et al. 2008). Dissociation of heme from the KI domain activates the kinase activity of EIF2AK1, which autophosphorylates (inferred from the mouse homolog in Bauer et al. 2001, Rafie-Kolpin et al. 2003, Igarashi et al. 2011) and then phosphorylates EIF2S1 (Bhavnani et al. 2018, inferred from the rabbit homologs in Chefalo et al. 1998, Rafie-Kolpin et al. 2000, inferred from the mouse homologs in Lu et al. 2001, Rafie-Kolpin et al. 2003, Igarashi et al. 2011).
Phosphorylated EIFS1 causes a reduction in general cellular translation and thereby coordinates globin synthesis with heme availability during erythropoiesis (inferred from mouse knockout in Han et al. 2001, reviewed in Chen et al. 2014). Translation of mitochondrial and cytosolic ribosomal proteins is most severely reduced, causing a decrease in cellular protein synthesis (inferred from mouse homologs in Zhang et al. 2019). Lack of EIF2AK1 causes accumulation of unfolded globins devoid of heme and consequent anemia in iron-deficient mice (inferred from mouse knockout in Han et al. 2001). Activation of the cytoplasmic unfolded protein response and impaired mitochondrial respiration are also observed in HRI deficiency (inferred from mouse homologs in Zhang et al. 2019).
Phosphorylation of EIFS1 activates translation of certain mRNAs such as ATF4, ATF5, and DDIT3 (CHOP) that have upstream ORFs (inferred from mouse homologs in Harding et al. 2000). ATF4 in turn activates programs of gene expression that ameliorate effects of the stress to maintain mitochondrial function, redox homeostasis, and erythroid differentiation (inferred from mouse homologs in Zhang et al. 2019). Unresolved stress, however, can eventually lead to apoptosis regulated by DDIT3. EIF2AK1 also represses mTORC1 (mechanistic target of mechanistic target of rapamycin complex 1) signaling via ATF4-mediated induction of GRB10 as a feedback mechanism to attenuate erythropoietin-mTORC1-stimulated ineffective erythropoiesis in iron deficiency anemia (inferred from mouse homologs in Zhang et al. 2018 and Zhang et. al. 2019).
EIF2AK1 is also activated by heat shock, arsenite (oxidative stress), and osmotic stress (inferred from mouse homologs in Lu et al. 2001). The mechanisms by which these stresses act on EIF2AK1 are independent of heme but are not yet fully elucidated. Furthermore, EIF2AK1 is involved in the production of human fetal hemoglobin, and

EIF2AK1-mediated stress response has emerged as a potential therapeutic target for hemoglobinopathies (reviewed in Chen and Zhang 2019).
In addition to regulation of erythropoiesis, EIF2AK1 shows effects outside of the erythroid lineage, including requirement for the maturation and functions of macrophages (inferred from mouse homologs in Liu et al. 2007), reduction in endoplasmic reticulum stress in hepatocytes, activation of hepatic expression of fibroblast growth factor, and mediation of translation of GRIN2B (GluN2B. a subunit of the NMDA receptor) and BACE1 in the nervous system (reviewed in Burwick and Aktas 2017). HRI-integrated stress response is activated in human cancer cell lines and primary multiple myeloma cells, and has emerged as a molecular target of anticancer agents (reviewed in Burwick and Aktas 2017; reviewed in Chen and Zhang 2019).

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Editions

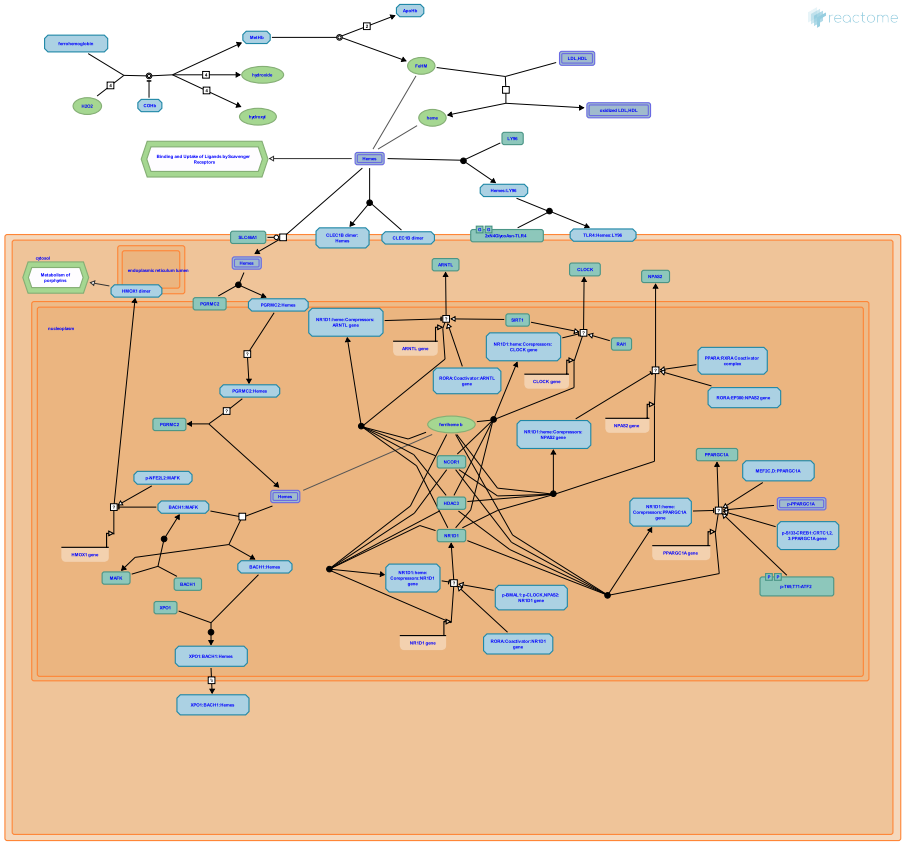
2019-06-10	Authored, Edited	May, B.
2019-10-22	Reviewed	Chen, JJ.

Heme signaling ↗

Location: Cellular responses to stress

Stable identifier: R-HSA-9707616

Compartments: cytosol, extracellular region, nucleoplasm, plasma membrane, nuclear envelope



Extracellular hemoglobin, a byproduct of hemolysis, can release its prosthetic heme groups upon oxidation. Blood plasma contains proteins that scavenge heme. It is estimated that about 2–8% of the heme released in plasma becomes ‘bioavailable’, being internalized by bystander cells. If the heme degradation capacity of a cell, represented by heme oxidase 1 and 2, cannot be ramped up sufficiently then heme signaling and reactivity puts cells under stress. Platelets are activated by heme, and macrophages switch to the inflammatory type (Donegan et al, 2019; Gouveia et al, 2019).

Free (labile) heme accumulates in the blood stream in great amounts under pathological conditions like viral infections and malaria, but also ARDS amd COPD. The locally affected cells' primary reaction is to upregulate heme oxidase 1 (HMOX1) expression. HMOX1 induction in these cells not only removes heme from circulation but also triggers a functional switch toward the anti-inflammatory phenotype (Vijayan et al, 2018). However, heme scavenging and degradation systems may get overwhelmed by the sheer amount of heme present.

Heme promotes platelet activation, complement activation, vasculitis, and thrombosis (Bourne et al, 2020; Merle et al, 2018). Heme was recognized to act as a danger signal, damage-associated molecular pattern (DAMP), or alarmin (Soares and Bozza, 2016) and was shown to activate Toll-like receptor 4 (TLR4) signaling (Figueiredo et al, 2007; Janciauskiene et al, 2020). It also has a role as corepressor in the circadian clock system (Ko and Takahashi, 2006). BACH1 is regulated by heme in a cell, thus placing heme as a signaling molecule in gene expression in higher eukaryotes. The regulation of BACH1 by heme may be important for the stress response in general (Suzuki et al, 2004).

Extracellular hemoglobin, a byproduct of hemolysis, can release its prosthetic heme groups uponoxidation. Due to the reactive nature of free heme, the blood plasma contains proteins that scavenge heme. It is estimated that about 2–8% of the heme released in plasma becomes ‘bioavailable’, being internalized by bystander cells. Failure of nearby cells to sufficientlymetabolize free heme can incite platelet activation, macrophage differentiation, and oxidative stress (Donegan et al, 2019; Gouveia et al, 2019).

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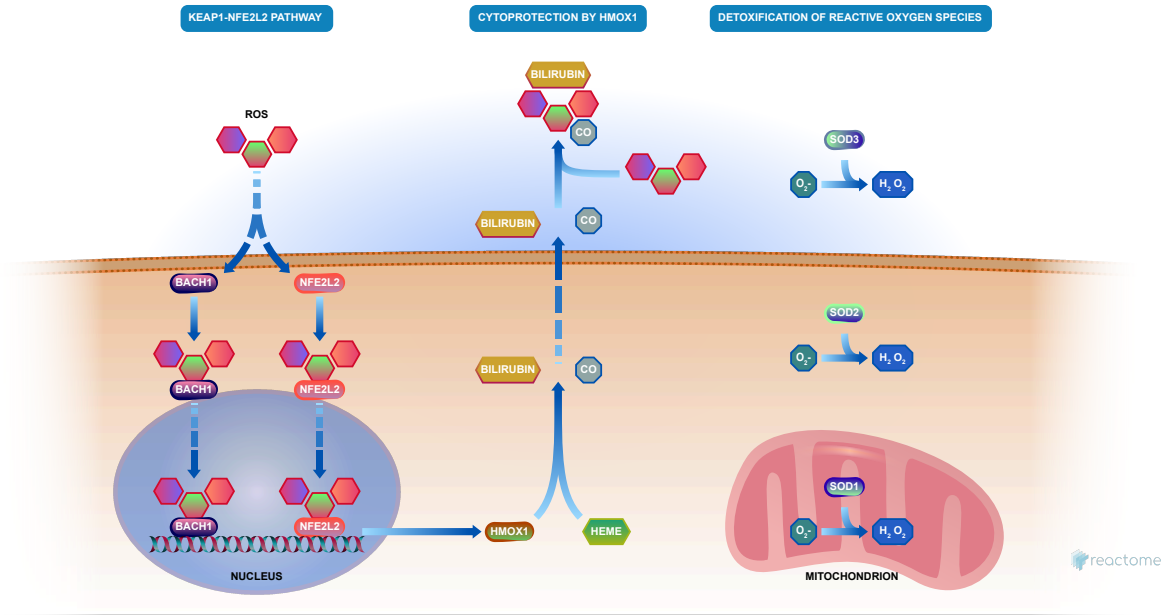
Editions

2020-11-12	Authored, Edited	Stephan, R.
2021-01-23	Reviewed	Somers, J.

Cellular response to chemical stress ↗

Location: Cellular responses to 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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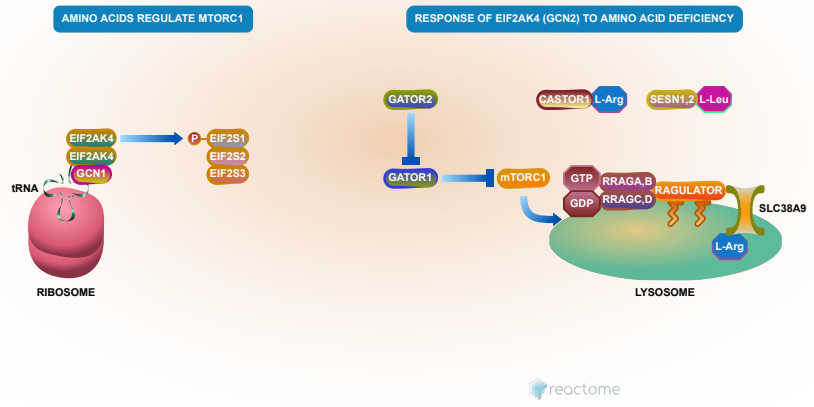
2021-02-19	Edited	D'Eustachio, P.

Cellular response to starvation ↗

Location: Cellular responses to stress

Stable identifier: R-HSA-9711097



Deprivation of nutrients triggers diverse short- and long terms adaptations in cells. Here we have annotated two aspects of cellular responses to amino acid deprivation, ones mediated by EIF2AK4 and ones mediated by mTORC.

EIF2AK4 (GCN2) senses amino acid deficiency by binding uncharged tRNAs near the ribosome, and phosphorylating EIF2S1 (reviewed in Chaveroux et al. 2010, Castilho et al. 2014, Gallinetti et al. 2013, Bröer and Bröer 2017, Wek 2018). This reduces translation of most mRNAs but increases translation of mRNAs, notably ATF4, that mediate stress responses (reviewed in Kilberg et al. 2012, Wortel et al. 2017; Dever and Hinnebusch 2005).

The mTORC1 complex acts as an integrator that regulates translation, lipid synthesis, autophagy, and cell growth in response to multiple inputs, notably glucose, oxygen, amino acids, and growth factors such as insulin (reviewed in Sabatini 2017, Meng et al. 2018, Kim and Guan 2019).

MTOR, the kinase subunit of mTORC1, is activated by interaction with RHEB:GTP at the cytosolic face of lysosomal membrane (Long et al. 2005, Tee et al. 2005, Long et al. 2007, Yang et al. 2017). This process is regulated by various individual amino acids (reviewed in Zhuang et al. 2019, Wolfson and Sabatini 2017, Yao et al. 2017) and is reversed in response to the removal of amino acids, through the action of TSC1 (Demetriades et al. 2014).

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Editions

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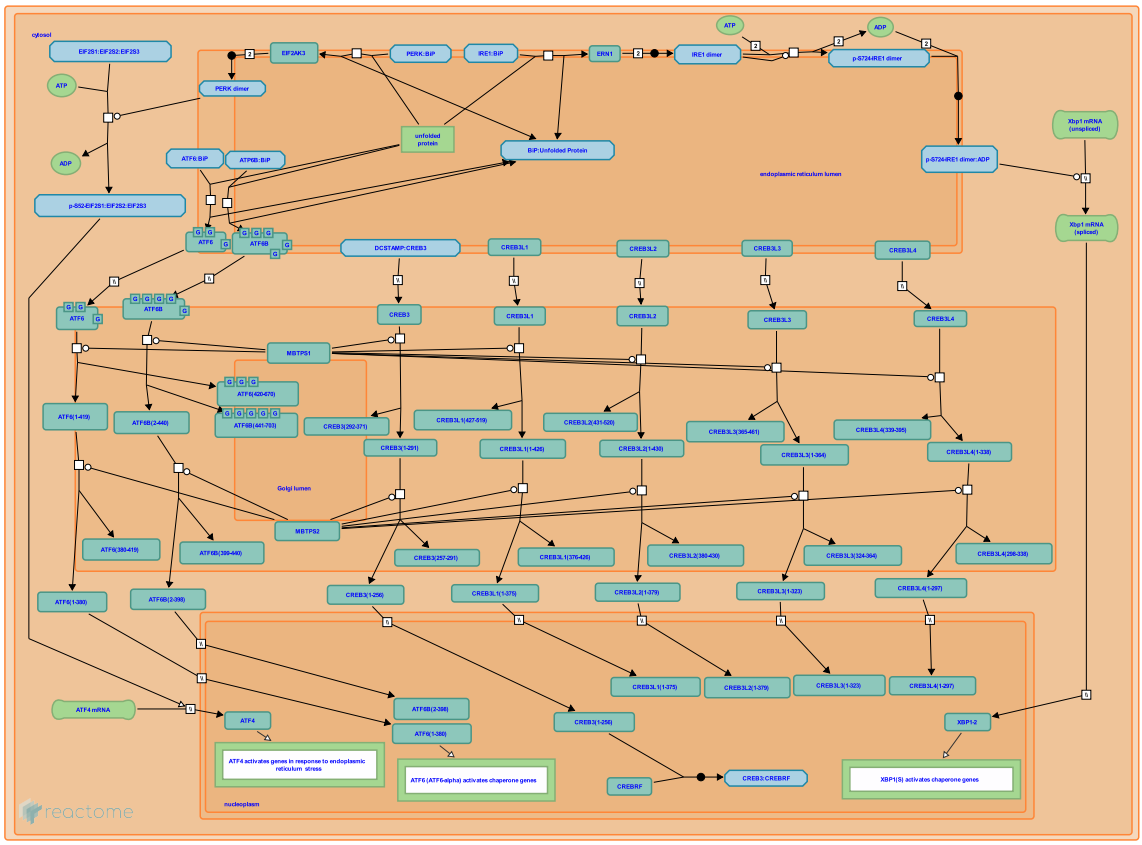
Unfolded Protein Response (UPR) ↗

Location: Cellular responses to stress

Stable identifier: R-HSA-381119

Compartments: endoplasmic reticulum membrane, nucleoplasm, Golgi membrane, endoplasmic reticulum lumen, cytosol



The Unfolded Protein Response (UPR) is a regulatory system that protects the Endoplasmic Reticulum (ER) from overload. The UPR is provoked by the accumulation of improperly folded protein in the ER during times of unusually high secretion activity. Analysis of mutants with altered UPR, however, shows that the UPR is also required for normal development and function of secretory cells.
One level at which the URP operates is transcriptional and translational regulation: mobilization of ATF6, ATF6B, CREB3 factors and IRE1 leads to increased transcription of genes encoding chaperones, while mobilization of PERK (pancreatic eIF2alpha kinase, EIF2AK3) leads to phosphorylation of the translation initiation factor eIF2alpha and global down-regulation of protein synthesis.
ATF6, ATF6B, and CREB3 factors (CREB3 (LUMAN), CREB3L1 (OASIS), CREB3L2 (BBF2H7, Tisp40), CREB3L3 (CREB-H), and CREB3L4 (CREB4)) are membrane-bound transcription activators that respond to ER stress by transiting from the ER membrane to the Golgi membrane where their transmembrane domains are cleaved, releasing their cytosolic domains to transit to the nucleus and activate transcription of target genes. IRE1, also a resident of the ER membrane, dimerizes and autophosphorylates in response to ER stress. The activated IRE1 then catalyzes unconventional splicing of XBP1 mRNA to yield an XBP1 isoform that is targeted to the nucleus and activates chaperone genes.

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Editions

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2010-04-30	Reviewed	Urano, F.

Cellular response to mitochondrial stress ↗

Location: Cellular responses to stress

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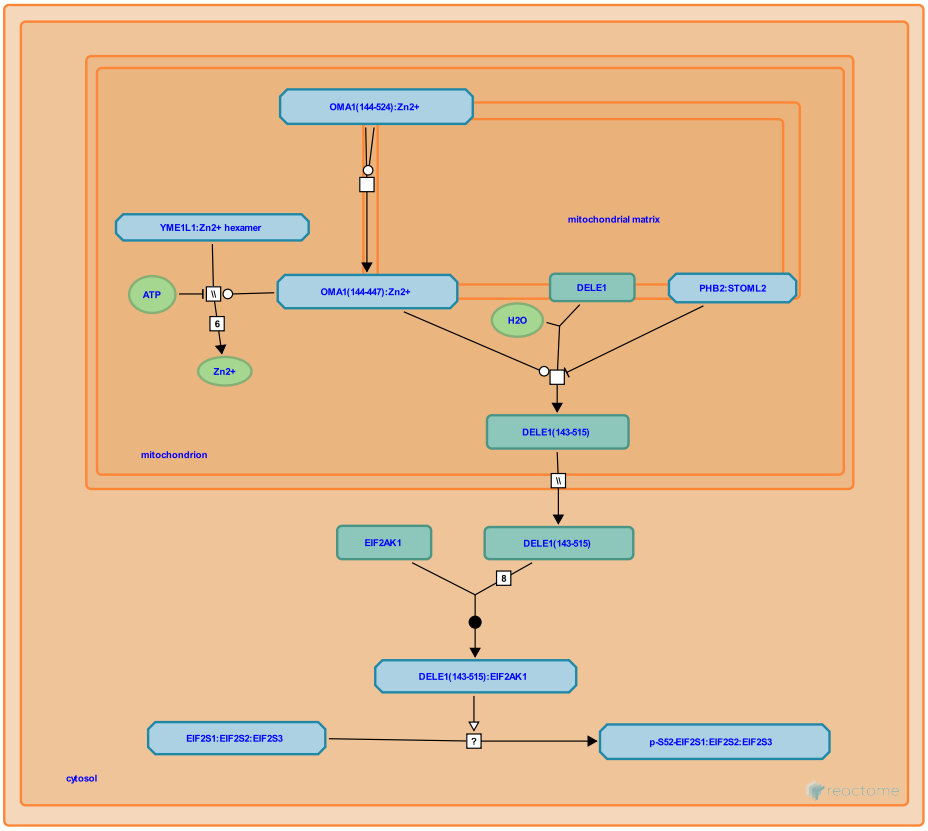

Mitochondrial stress caused by depolarization of the mitochondrial inner membrane, inhibition of proton flux across the mitochondrial inner membrane, or insufficient protein import capacity caused by inhibition of ATP synthase or iron deficiency is communicated to the cytosol and nucleus, resulting in decreased protein production and increased transcription of chaperones and metabolic genes among others. This pathway is known as the mitochondrial stress response and is a part of mitochondrial signaling and the integrated stress response (Reviewed in Eckl et al. 2021, Picard and Shirihai 2022, Lu et al. 2022, Liu and Birsoy 2023). The mitochondrial stress response participates in adapting cells to harsher environments and, hence, plays a role in tumor progression and metastasis (reviewed in Lee et al. 2022).
In unstressed mitochondria, DELE1 is constitutively imported into the mitochondrial matrix and degraded by the LONP1 ATP-dependent protease (Fessler et al. 2022, Sekine et al. 2023). Mitochondrial stress inhibits the complete transit of DELE1 into the matrix and activates the inner membrane protease OMA1 by self-cleavage (Fessler et al. 2022, Sekine et al. 2023, inferred from the mouse Oma1 homolog in Baker et al. 2014, Zhang et al. 2014). Activated OMA1 cleaves the N-terminal region of DELE1 on the outer face of the inner membrane as DELE1 is unable to fully cross the inner membrane (Fessler et al. 2020, Guo et al. 2020, Fessler et al. 2022). The resulting C-terminal fragment of DELE1 egresses from the intermembrane space to the cytosol where it oligomerizes to form an octamer (Yang et al. 2023) which binds and activates EIF2AK1, a constituent kinase of the integrated stress response that phosphorylates EIF2S1, the alpha subunit of the eukaryotic translation initiation factor 2 (eIF2) (Fessler et al. 2020, Guo et al. 2020, Cheng et al. 2022). Phosphorylation of EIF2S1 inhibits general translation but increases translation of specific mRNAs that possess upstream open reading frames (reviewed in Wek 2018). Among these mRNAs are the transcription factors DDIT3 (CHOP), ATF4, and ATF5, which activate expression of chaperone genes among others.

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Editions

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