KEAP1-NFE2L2 pathway


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

18/11/2022
Introduction

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

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 82

This document contains 3 pathways and 24 reactions (see Table of Contents)
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, neurodegenerative 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).

**Literature references**


**Editions**

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Under the basal resting conditions, cytosolic Nuclear factor erythroid 2-related NFE2L2 (NRF2) is maintained at low basal levels by constitutive proteasomal degradation. Kelch-like ECH associated protein 1 (KEAP1), which is a substrate adaptor protein for the Cullin 3 (CUL3)-dependent E3 ubiquitin ligase complex binds with and represses NFE2L2 by promoting its ubiquitination and subsequent proteasomal degradation (Itoh et al. 1999, Cullinan et al. 2004, Kobayashi et al. 2004, Zhang et al. 2004, Furukawa & Xiong 2005). Therefore, the KEAP1–CUL3–E3 ubiquitin ligase complex tightly regulates NFE2L2 protein to maintain it at a low level. NFE2L2 contains seven functional domains, known as Neh1-Neh7. Neh2 domain contains two motifs termed ETGE and DLG that are involved in interacting with KEAP1. The ETGE and the DLG motifs have overlapping binding sites on KEAP1, with the ETGE motif mediating a higher affinity interaction with KEAP1 than the DLG motif. One molecule of NFE2L2 interacts simultaneously with two KEAP1 molecules, with the DLG motif and the ETGE motif on NFE2L2 contacting similar sites on each member of the KEAP1 dimer (Tong et al, 2006; McMahon et al, 2006; Baird et al, 2013; Fukutomi et al, 2014). This complex assembly positions NFE2L2 appropriately to be ubiquitinated by the CUL3/RBX1 ubiquitin ligase, targeting it for degradation. In the presence of electrophiles or other NFE2L2 inducers, conformational changes within KEAP1 occur as inducers interact with KEAP1 'sensor cysteines'. These conformational changes disrupt the KEAP1-DLG motif interaction, repositioning NFE2L2 within the KEAP1 complex in such a way as to prevent its ubiquitination. In this 'hinge and latch model', saturation of the KEAP1:CUL3:RBX1 complex with mal-positioned and thus not degradable NFE2L2 allows newly translated NFE2L2 to accumulate and translocate into the nucleus to stimulate transcription (Tong et al, 2006; Tong et al, 2007; reviewed in Baird and Yamamoto, 2020)

KEAP1 and NFE2L2 mutations occur in several tumor types and KEAP1 and NFE2L2 mutations occur at a frequency of around 25% in lung cancer. The NFE2L2 pathway has multiple pro-tumorigenic functions, and NFE2L2 levels are increased in head and neck squamous cell carcinoma (HNSCC). KEAP1 somatic mutant C23Y is observed in tumors from approximately 15% of patients with lung cancer (Hayes & McMahon 2009).

Followed by: NFE2L2 inducers bind to KEAP1:CUL3:RBX1:NFE2L2, KEAP1:NEDD8-CUL3:RBX1 complex
ubiquitates NFE2L2

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KEAP1:NEDD8-CUL3:RBX1 complex ubiquitates NFE2L2

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-9755505

Type: transition

Compartments: cytosol

The KEAP1:CUL3:RBX1 E3-ubiquitin ligase complex is a negative regulator of Nuclear factor erythroid 2-related (NFE2L2). In the absence of oxidative alterations this E3-ubiquitin ligase complex is bound to NFE2L2 and targets it for ubiquitination (Cullinan et al, 2004; Kobayashi et al, 2004; reviewed in Baird and Yamamoto, 2020).

Preceded by: NFE2L2 binds KEAP1:NEDD8-CUL3:RBX1

Followed by: UBXN7:UBF1:NPLOC4:VCP hexamer binds NFE2L2:CRL3 complex

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https://reactome.org
Ubiquitinated NFE2L2 is extracted from CRL3 complex for degradation

**Location:** KEAP1-NFE2L2 pathway

**Stable identifier:** R-HSA-9758090

**Type:** dissociation

**Compartments:** cytosol

The complex of VCP/p97 with cofactors UFD1, NPLOC4 and UBXN7 extract ubiquitinated NFE2L2 from the KEAP1-CUL3 ubiquitin ligase complex prior to its 26S proteasome-mediated degradation (Tao et al, 2017; Di Gregorio et al, 2021; reviewed in van den Boom and Meyer, 2020).

**Preceded by:** UBXN7:UBF1:NPLOC4:VCP hexamer binds NFE2L2:CRL3 complex

**Followed by:** 26S proteasome degrades Ub-NFE2L2

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Ubiquitinated Nuclear factor erythroid 2-related (NFE2L2) undergoes proteasomal degradation and this maintains the protein level and activity at low levels. (Kobayashi et al, 2004; McMahon et al, 2003)

**Preceded by:** Ubiquitinated NFE2L2 is extracted from CRL3 complex for degradation

**Literature references**


UBXN7 binds VCP hexamer:UBF1:NPLOC4

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-9758088

Type: binding

Compartments: cytosol

UBXN7 interacts with a complex of VCP, UBF1 and NPLOC4 to promote the CRL3- and 26 S proteasome-mediated degradation of factors such as NFE2L2 (Alexandru et al, 2008; Tao et al, 2017).

Followed by: UBXN7:UBF1:NPLOC4:VCP hexamer binds NFE2L2:CRL3 complex

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UBXN7:UBF1:NPLOC4:VCP hexamer binds NFE2L2:CRL3 complex

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-9755507

Type: binding

Compartments: cytosol

VCP (also known as p97) is a hexameric ATPase with known roles in extracting ubiquinated substrates from multimeric E3 ligase complexes to promote their degradation by the 26S proteasome (Richly et al, 2005; Meyer et al, 2000; Rape et al, 2001; Tao et al, 2017; reviewed in van den Boom and Meyer, 2018). VCP has been shown to promote the extraction of ubiquitinated NFE2L2 from the KEAP1:CUL3:RBX1 complex in association with co-factors UBF1 and NPLOC4. UBXN7 also plays a role in the regulation of NFE2L2 protein levels, and interacts with VCP, UBF1 and NPLOC4 (Tao et al, 2017; Di Gregario et al, 2021).

Preceded by: UBXN7 binds VCP hexamer:UBF1:NPLOC4, KEAP1:NEDD8-CUL3:RBX1 complex ubiquitinates NFE2L2

Followed by: Ubiquitinated NFE2L2 is extracted from CRL3 complex for degradation

Literature references


MUL1 ubiquitinates UBXN7

**Location:** KEAP1-NFE2L2 pathway

**Stable identifier:** R-HSA-9755304

**Type:** transition

**Compartments:** cytosol, mitochondrial outer membrane

MUL1 is an E3 ligase located in the outer mitochondrial membrane with its RING domain facing the cytosol. MUL1 ubiquitinates the cullin scaffold/adaptor protein UBXN7 at lysine residues K14 and K412, promoting its 26S proteasome-dependent degradation (Cilenti et al, 2020, DiGregorio et al, 2021).

Protein levels of UBXN7, in turn, govern the stability and activity of various cullin E3 ligase complexes, including the VHL:CUL2 ligase complex and the KEAP1:CUL3 ligase complex. Ubiquitination by these CRL cullin ligase complexes promote the degradation of transcription factors such as HIF1alpha and NFE2L2, which play roles in the response to hypoxia and oxidative stress (Iwai et al. 1999, Kamura et al. 2000, Ohh et al. 2000, Groulx and Lee 2002, Maynard et al. 2003; Tao et al, 2017; Itoh et al. 1999, Cullinan et al. 2004, Kobayashi et al. 2004, Zhang et al. 2004, Furukawa & Xiong 2005). High levels of UBXN7 lead to HIF1alpha accumulation, whereas low levels of UBXN7 correlate with an increase in NFE2L2 protein.

By regulating UBXN7 levels in response to reactive oxygen species and hypoxic stress, MUL1 affects the protein levels of HIF1alpha and NFE2L2 and ultimately their targets and may contribute to a switch between glycolysis and oxidative phosphorylation. The role of MUL1 in regulating these factors through UBXN7 protein levels may contribute to the Warburg effect, common in many cancers, where cells switch to glycolysis even in the presence of adequate oxygen. Consistent with this, downregulation of UBXN7 is associated with increased oxidative phosphorylation while high levels of UBXN7 promote glycolysis (Cilenti et al, 2020; Di Gregorio et al, 2021).

**Followed by:** ub UBXN7 is degraded by the 26S proteasome

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ub UBXN7 is degraded by the 26S proteasome

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-9755306

Type: omitted

Compartments: cytosol

After MUL1-dependent ubiquitination, UBXN7 is degraded by the 26S proteasome. This results in increased levels of NFE2L2 and corresponding decreased levels in HIF1alpha (Cilenti et al, 2020; Di Gregorio et al, 2021).

Preceded by: MUL1 ubiquitinates UBXN7

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KEAP1:CUL3:RBX1-mediated degradation of NFE2L2 is relieved in the presence of oxidative or electro-philic stress, allowing NFE2L2 to translocate to the nucleus to support expression of target genes. NFE2L2 'inducers' are a varied group of endogenous and extracellular chemicals, including a number of pharmaceutical compounds approved for clinical use (reviewed in Cuadrado, 2019; Baird and Yamamoto, 2020).

The mechanism by which NFE2L2:KEAP1 complex senses the oxidative stress and triggers NFE2L2 nuclear localization is unclear. It has been proposed that KEAP1, which is rich in reactive cysteines, may directly sense the oxidative stress via thiol modification and undergo conformational changes that stabilize NFE2L2 (Itoh et al. 1999). The reactive cysteine residues within KEAP1 undergo oxidation and form an intramolecular disulfide bond. Human KEAP1 has 27 cysteine residues and among those C257, C273, C288 and C297 are most reactive and can be oxidized. C273 of one KEAP1 molecule probably forms an intermolecular disulfide bridge with C288 of a second KEAP1 molecule (Zhang & Hannink 2003, Wakabayashi et al. 2004; reviewed in Baird and Yamamoto, 2020). Different NFE2L2 inducers can be grouped on the basis of which KEAP1 cysteine residues are involved in mediating their response (reviewed in Baird and Yamamoto, 2020).

NFE2L2 inducers (e.g. sulforaphane, fumarates, and their derivatives) block ubiquitination of NFE2L2 by binding more or less irreversibly to L-cysteine 151 and other cysteine residues of KEAP1 (Brennan et al, 2015; Hu et al, 2011; Unni et al, 2020; Zhu et al, 2019). This strongly enhances induction of expression of all genes with antioxidant response elements (ARE), including HMOX1 and NQO1, among many others (Hong et al, 2005; reviewed in Baird and Yamamoto, 2020).

Sulforaphane has proved to be an effective chemoprotective agent in cell culture, carcinogen-induced and genetic animal cancer models, as well as in xenograft models of cancer (Clarke et al, 2008). These preclinical studies demonstrate chemopreventive mode of actions of isothiocyanates, mainly related to a) detoxification (induction of phase II enzymes), b) anti-inflammatory properties by down-regulation of NFkappaB activity, c) cyclin-mediated cell cycle arrest and d) epigenetic modulation by inhibition of histone deacetylase activity. First prospective clinical trials were promising in patients with risk of prostate cancer recurrence (Gründemann and Huber, 2018; Kamal et al, 2020)

In cancer treatment, sulforaphane exhibited promising inhibitory effects on breast cancer, lung cancer, liver cancer, and other malignant tumors (Wu et al, 2020)

Five clinical trials showed a significant positive correlation between sulforaphane use and autism spectrum disorder (ASD) behavior and cognitive function. The current evidence shows with minimal side ef-
effects observed that sulforaphane appears to be a safe and effective treatment option for ASD (McGuinness and Kim, 2020).

Dimethyl fumarate (DMF) was effective in reducing the proportion of patients with MS relapse at 2 years (primary endpoint of DEFINE) and the annualized relapse rate (primary endpoint of CONFIRM) compared with placebo, with reduced disability progression also observed with the drug versus placebo in DEFINE. Dimethyl fumarate also reduced disease activity measures relative to placebo in these trials (Burness and Deeks, 2014; Xu et al, 2015). DMF is completely metabolized to monomethyl fumarate (MMF), and by giving it directly the usually mild side effects are alleviated further (Wynn et al, 2020).


**Preceded by:** NFE2L2 binds KEAP1:NEDD8-CUL3:RBX1

**Literature references**


Krishnappa, G., Unni, S., Padmanabhan, B., Kommu, P., Deshmukh, P. (2020). Structural insights into the multiple binding modes of Dimethyl Fumarate (DMF) and its analogs to the Kelch domain of Keap1. *FEBS J.*


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Upon stimulation by oxidative/electrophilic stress, Nuclear factor erythroid 2-related NFE2L2 (NRF2) is phosphorylated at the transcription activation domain (TA) by Casein kinase 2 (CK2). Deletional analysis revealed the transcription activation domains Neh4 (Nrf2-ECH homology 4) and Neh5 (Nrf2-ECH homology 5) as major regions necessary for the phosphorylation. The phosphorylation of these sites correlates with NFE2L2 translocation into the nucleus and this translocation is reduced in the presence of a CK2 inhibitor (Apopa et al. 2008, Pi et al. 2007).

**Followed by:** NFE2L2 translocates from cytosol to nucleoplasm

**Literature references**

He, X., Apopa, PL., Ma, Q. (2008). Phosphorylation of Nrf2 in the transcription activation domain by casein kinase 2 (CK2) is critical for the nuclear translocation and transcription activation function of Nrf2 in IMR-32 neuroblastoma cells. *J. Biochem. Mol. Toxicol.*, 22, 63-76.


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PKC phosphorylates NFE2L2

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-8932284

Type: transition

Compartments: cytosol

Inferred from: PKC phosphorylates Nrf2 (Rattus norvegicus)

In response to oxidative stress, protein kinase C (PKC) phosphorylates NFE2L2 (NRF2) at residue serine 40 (Ser-40). It has been demonstrated that NRF2 phosphorylation at Ser-40 facilitates its nuclear translocation (Huang et al. 2002).

Followed by: NFE2L2 translocates from cytosol to nucleoplasm

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NFE2L2 translocates from cytosol to nucleoplasm

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-8932309

Type: omitted

Compartments: cytosol, nucleoplasm

Upon activation by electrophiles or reactive oxygen species Nuclear factor erythroid 2-related (NFE2L2, NRF2) accumulates in the nucleus. The mechanism by which this translocation occurs is not entirely elucidated. NFE2L2 possess two functional nuclear localization signals (NLS) one near the N-terminal region (murine NFE2L2 42-53 aa) and the other (residues 587-593) in the C-terminal region which may function in the nuclear import. It has also been demonstrated that importins might be involved in the nuclear translocation of NFE2L2. NFE2L2 associates especially with importin alpha 5 and beta 1 (Theodore et al. 2008). Nuclear import of NFE2L2 has been shown to be stimulated downstream of active PI3K signaling (Joung et al, 2007; Li et al, 2006; Martin et al, 2004). Similarly, activation of the NFE2L2 pathway has been observed downstream of some oncogenes (Best et al, 2021; Tang et al, 2021; Mitsuishi et al, 2012; De Nicola et al, 2011; Wakabayashi et al, 2014; reviewed in He et al, 2020; Kitamura and Motohashi, 2018). NFE2L2 contributes to oncogenesis through metabolic reprogramming to support proliferation and through enhanced detoxification and antioxidation capabilities (reviewed in He et al, 2020; Kitamura and Motohashi, 2018). Activation of the PI3K pathway through inactivation of PTEN and KEAP1 increases the levels of T308 phosphorylated AKT, and promotes the nuclear accumulation of NFE2L2, stimulating expression of target genes (Mitsuishi et al, 2012; Best et al, 2021).

Preceded by: PKC phosphorylates NFE2L2, CK2 phosphorylates NFE2L2

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SQSTM1 oligomerizes by virtue of its PB1 domain. Oligomerization is required for formation of inclusion bodies with ubiquitinated proteins destined for autophagic degradation, and may contribute to phagophore membrane development (Bjorkoy et al, 2005; Ciuffa et al, 2015; Itakura and Mizushima, 2011; reviewed in Lamark et al, 2017).

Followed by: HBV X protein binds SQSTM1 oligomer, SQSTM1 oligomer is phosphorylated

Literature references


SQSTM1 is phosphorylated at serine 349 by an unknown kinase (Ichimura et al, 2013; reviewed in Jiang et al, 2015; Lamark et al, 2017; Baird and Yamamoto, 2020). This serine residues lies in the STGE motif of SQSTM1 that mediates the interaction with the KELCH1 domain of KEAP1, and phosphorylation increases the strength of the binding. Binding of phosphorylated SQSTM1 to KEAP1 competes with NFE2L2 for the site and consequently stabilizes NFE2L2 (Ichimura et al, 2013; reviewed in Jiang et al, 2015; Lamark et al, 2017; Baird and Yamamoto, 2020).

**Preceded by:** SQSTM1 oligomerizes

**Followed by:** p-S349 SQSTM1 oligomer binds KEAP1:CUL3:RBX1

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https://reactome.org
p-S349 SQSTM1 oligomer binds KEAP1:CUL3:RBX1

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-9759169

Type: binding

Compartments: cytosol

SQSTM1 binds to the KEAP1 subunit of the CRL3 ubiquitin ligase complex through the KEAP1 interacting region (KIR) located at residues 339-358 (Jain et al, 2010). Like NFE2L2, SQSTM1 has a KELCH1-domain binding STGE motif that is thought to interact with the KEAP1 complex in the 'open' conformation. Binding is enhanced by phosphorylation of the SQSTM1 STGE motif (Ichimura et al, 2013; reviewed in Baird and Yamamoto, 2020).

SQSTM1 is a transcriptional target of NFE2L2 and is upregulated in the presence of cellular stressors like reactive oxygen species (ROS) and electrophiles (reviewed in Baird and Yamamoto, 2020). Upregulation of SQSTM1 under stress conditions leads to competition between NFE2L2 and SQSTM1 for KEAP1 binding and results in stabilization of NFE2L2 protein levels. This establishes a positive feedback loop as NFE2L2 is able to translocate into the nucleus to promote expression of its target genes (Jain et al, 2010).

SQSTM1 has also been shown to be a substrate for KEAP1:CUL3:RBX1-mediated ubiquitination. Ubiquitination at lysine 420 increases the ability of SQSTM1 to sequester and degrade target ubiquitinated proteins through selective autophagy (Lee et al, 2017). Some evidence shows that in addition to competing with NFE2L2 for KEAP1-binding, SQSTM1 also targets KEAP1 for sequestration and degradation through the autophagy pathway (Copple et al, 2010; reviewed in Jiang et al, 2015). Sestrin proteins may also play a role in targeting KEAP1 for SQSTM1-dependent autophagy (Bae et al, 2013; Ro et al, 2014).

Preceded by: SQSTM1 oligomer is phosphorylated

Followed by: KEAP1:CUL3:RBX1 ubiquitinates p-S349 SQSTM1 oligomer

Literature references


Lim, JM., Park, YN., Lee, HE., Sung, SH., Bae, SH., Kang, D. et al. (2013). Sestrins activate Nrf2 by promoting p62-dependent autophagic degradation of Keap1 and prevent oxidative liver damage. Cell Metab, 17, 73-84.

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KEAP1:CUL3:RBX1 ubiquitinates p-S349 SQSTM1 oligomer

**Location:** KEAP1-NFE2L2 pathway

**Stable identifier:** R-HSA-9759172

**Type:** transition

**Compartments:** cytosol

SQSTM1 is an adaptor protein that mediates aggregation of target proteins for selective autophagy (reviewed in Lamark et al, 2017). SQSTM1 also intersects with the KEAP1:NFE2L2 pathway, as it is both a transcriptional target of NFE2L2 and a regulator of KEAP1. SQSTM1 has also been shown to be a substrate for KEAP1:CUL3:RBX1-mediated ubiquitination: ubiquitination at lysine 420 increases the ability of SQSTM1 to sequester and degrade target ubiquitinated proteins through selective autophagy (Lee et al, 2017; reviewed in Baird and Yamamoto, 2020; Lamark et al, 2017). Some evidence shows that in addition to competing with NFE2L2 for KEAP1-binding, SQSTM1 also targets KEAP1 for sequestration and degradation through the autophagy pathway (Copple et al, 2010; reviewed in Jiang et al, 2015).

Although in this pathway, ubiquitination at K420 is shown after phosphorylation of SQSTM1 at S349, the order and mutual dependence of these two post-translational modifications has not been determined.

**Preceded by:** p-S349 SQSTM1 oligomer binds KEAP1:CUL3:RBX1

**Followed by:** SESN1, SESN1 bind SQSTM1 and KEAP1

**Literature references**


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https://reactome.org
SESN1 and SESN2 are proteins with roles in oxidative stress response. Both SESN1 and SESN2 interact with SQSTM1 in the context of a KEAP1:CUL3:RBX1 complex to promote the degradation of KEAP1 by selective autophagy (Bae et al, 2013; Ro et al, 2014). SESN1 and SESN2 may increase the binding affinity of SQSTM1 for its KEAP1 substrate (Bae et al, 2013).

**Preceded by:** KEAP1:CUL3:RBX1 ubiquitinates p-S349 SQSTM1 oligomer

**Followed by:** CUL3:RBX1 ubiquitinates KEAP1

**Literature references**


Lim, JM., Park, YN., Lee, HE., Sung, SH., Bae, SH., Kang, D. et al. (2013). Sestrins activate Nrf2 by promoting p62-dependent autophagic degradation of Keap1 and prevent oxidative liver damage. *Cell Metab*, 17, 73-84.

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CUL3:RBX1 ubiquitinates KEAP1

**Location:** KEAP1-NFE2L2 pathway

**Stable identifier:** R-HSA-9766645

**Type:** transition

**Compartments:** cytosol

KEAP1 is ubiquitinated by the CUL3:RBX1 complex in an SQSTM1-dependent manner (Zhang et al, 2005). Ubiquitination of KEAP1 renders it a substrate for SQSTM1-dependent degradation through the selective autophagy pathway (Zhang et al, 2005; Taguchi et al, 2012).

**Preceded by:** SESN1, SESN1 bind SQSTM1 and KEAP1

**Followed by:** MAP1LC3B binds KEAP1 and SQSTM1

**Literature references**


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https://reactome.org
MAP1LC3B binds KEAP1 and SQSTM1

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-9766677

Type: binding

Compartments: cytosol

SQSTM1 targets ubiquitinated cargo such as KEAP1 for degradation through the selective autophagy pathway. In addition to binding to the KEAP1, SQSTM1 also interacts with LC3 proteins that coat the forming autophagosome (Bjorkoy et al, 2005; Lee et al, 2017; Jain et al, 2010; reviewed in Jiang et al, 2015). Interaction between SQSTM1, ubiquitinated KEAP1 and LC3 proteins is enhanced through the binding of SESN1 and SESN2 proteins (Bae et al, 2013; Ro et al, 2014).

Preceded by: CUL3:RBX1 ubiquitinates KEAP1

Followed by: RBX1:CUL3 dissociates from forming autophagosome

Literature references


Lim, JM., Park, YN., Lee, HE., Sung, SH., Bae, SH., Kang, D. et al. (2013). Sestrins activate Nrf2 by promoting p62-dependent autophagic degradation of Keap1 and prevent oxidative liver damage. Cell Metab, 17, 73-84.


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RBX1:CUL3 dissociates from forming autophagosome

**Location:** KEAP1-NFE2L2 pathway

**Stable identifier:** R-HSA-9766656

**Compartments:** cytosol

KEAP1 is a substrate for SQSTM1-mediated autophagy (Zhang et al, 2005; Jain et al, 2010; Fan et al, 2010; Taguchi et al, 2012). Although this has not been described in molecular detail, SQSTM1-dependent targeting of KEAP1 to the autophagosome presumably involves dissociation of KEAP1 and SQSTM1 from RBX1 and CUL3.

**Preceded by:** MAP1LC3B binds KEAP1 and SQSTM1

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https://reactome.org
HBV X protein binds SQSTM1 oligomer

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-9761900

Type: binding

Compartments: cytosol

Diseases: hepatitis B

Chronic hepatitis B virus (HBV) infection stimulates expression of glucose-6-phosphate dehydrogenase (G6PD), the enzyme that catalyzes the first step of the pentose phosphate pathway (PPP). HBV-stimulated G6PD expression depends upon activation of the NFE2L2 pathway through sequestration of the KEAP1 negative regulator of NFE2L2. HBV X protein interacts with SQSTM1, also known as p62, and stimulates formation of an X:SQSTM1:KEAP1 complex. This complex disrupts the KEAP1-dependent ubiquitination of NFE2L2, stabilizing the transcription factor and allowing it to translocate to the nucleus to stimulate expression of target genes including G6PD (Liu et al, 2017; reviewed in Baird and Yamamoto, 2020; Bend-er and Hildt, 2019).

Preceded by: SQSTM1 oligomerizes

Literature references


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E3 ubiquitin ligase TRIM21 ubiquitinates SQSTM1 at lysine 7, inhibiting SQSTM1 oligomerization and therefore its ability to sequester and degrade ubiquitinated proteins (Pan et al, 2016). Among the proteins targeted by SQSTM1 is KEAP1, a negative regulator of redox response through KEAP1-mediated degradation of NFE2L2 (reviewed in Baird and Yamamoto, 2020).

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Nuclear events mediated by NFE2L2

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-9759194

Compartments: nucleoplasm

In response to chemical and other stressors, the constitutive degradation of NFE2L2 by the KEAP1:CUL3:26S proteasome system is disrupted, allowing NFE2L2 to accumulate. Stabilized NFE2L2 translocates to the nucleus where it binds to antioxidant response elements (AREs) in the promoters and enhancers of target genes to upregulate their expression (reviewed in Baird and Yamamoto, 2020).

Literature references


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The transcription factor BTB and CNC homology 1 (BACH1) is widely expressed in most mammalian tissues and functions primarily as a transcriptional suppressor by heterodimerizing with small Maf proteins and binding to Maf recognition elements in the promoters of targeted genes. It has a key regulatory role in the production of reactive oxygen species (ROS), cell cycle, heme homeostasis, hematopoiesis, and immunity and has been shown to suppress ischemic angiogenesis and promote breast cancer metastasis (Zhang et al, 2018; Okada et al, 2010).

**Literature references**


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https://reactome.org
**PRDX1 overoxidizes**

**Location:** KEAP1-NFE2L2 pathway

**Stable identifier:** R-HSA-5631885

**Type:** transition

**Compartments:** cytosol

The activity of eukaryotic PRDX1 gradually decreases with time, which is due to the overoxidation of the catalytic cysteine C52. Normally, oxidized cysteine C52-SOH is generated as a catalytic intermediate, which is subsequently reduced by thioredoxin. Occasionally, further oxidation happens, generating C52-SOOH, where the catalytic cysteine is converted to cysteine-sulfinic acid. This over-oxidation cannot be reversed by thioredoxin (Yang et al. 2002, Budanov et al. 2004). Bacterial peroxiredoxin AhpC does not undergo over-oxidation due to structural difference (Wood et al. 2003).

**Literature references**

Woo, HA., Kim, K., Yang, KS., Kang, SW., Chae, HZ., Hwang, SC. et al. (2002). Inactivation of human peroxiredoxin I during catalysis as the result of the oxidation of the catalytic site cysteine to cysteine-sulfenic acid. *J. Biol. Chem.*, 277, 38029-36.


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SRXN1 reduces hyperoxidized PRDX1 dimer

Location: KEAP1-NFE2L2 pathway

Stable identifier: R-HSA-9760094

Type: transition

Compartments: cytosol

SRXN1 is a sulfiredoxin protein that reduces hyperoxidized members of the PRDX family in response to H2O2. PRDX dimers respond to the oxidative challenge of intracellular H2O2 through the two-step formation of an internal disulphide bond during the process of H2O2 reduction. This disulphide bond can be reduced by thioredoxin (TRX), regenerating the catalytically active PRDX dimer.

In some instances, the second step in this pathway is replaced by the hyperoxidation of the PRDX dimer to sulfinic acid, which is not reduceable by TRX. While this was previously thought to be irreversible, SRXN1 has been shown to reduce sulfinic acid in some PRDX family members, restoring the enzymatic activity (Chang et al, 2004; Woo et al, 2005).

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