CREB3 factors activate genes

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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.

30/10/2022
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 1 pathway and 21 reactions (see Table of Contents)

https://reactome.org
Members of the CREB3 family (also known as the OASIS family) are tissue-specific proteins that each contain a transcription activation domain, a basic leucine zipper (bZIP) domain that promotes dimerization and DNA binding, and a transmembrane domain that anchors the protein to the membrane of the endoplasmic reticulum (ER) (reviewed in Asada et al. 2011, Chan et al. 2011, Kondo et al. 2011, Fox and Andrew 2015). The family includes CREB3 (LUMAN), CREB3L1 (OASIS), CREB3L2 (BBF2H7, Tisp40), CREB3L3 (CREB-H), and CREB3L4 (CREB4). Activation of the proteins occurs when they transit from the ER to the Golgi and are cleaved sequentially by the Golgi resident proteases MBTPS1 (S1P) and MBTPS2 (S2P), a process known as regulated intramembrane proteolysis that releases the cytoplasmic region of the protein containing the transcription activation domain and the bZIP domain. This protein fragment then transits from the cytosol to the nucleus where it activates transcription of target genes. CREB3L1, CREB3L2, and CREB3L3 are activated by ER stress, although the mechanisms that cause the transit of the CREB3 proteins are not fully characterized. Unlike the ATF6 factors, CREB3 proteins do not appear to interact with HSPA5 (BiP) and therefore do not appear to sense unfolded proteins by dissociation of HSPA5 when HSPA5 binds the unfolded proteins.

**Literature references**


Jin, DY., Chan, CP., Kok, KH. (2011). CREB3 subfamily transcription factors are not created equal: Recent insights from global analyses and animal models. *Cell Biosci*, 1, 6.

**Editions**

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https://reactome.org
CREB3 translocates from the endoplasmic reticulum membrane to the Golgi membrane

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874200

**Type:** omitted

**Compartments:** endoplasmic reticulum membrane, Golgi membrane

**Inferred from:** ATF6 (ATF6-alpha) translocates from the endoplasmic reticulum to the Golgi (Homo sapiens)

CREB3 is expressed ubiquitously (Lu et al. 1997) and associates in the endoplasmic reticulum (ER) membrane (Stirling and O’Hare 2006) with DCSTAMP (Eleveld-Trancikova et al. 2010). Through an unclear mechanism, that may involve association of OS9 with unfolded proteins, CREB3 and DCSTAMP, which may remain in a complex, transit from the ER membrane to the Golgi membrane where CREB3 is activated by cleavage (Eleveld-Trancikova et al. 2010). CREB3 becomes activated during maturation of dendritic cells induced by lipopolysaccharide and cytokines (Eleveld-Trancikova et al. 2010).

**Followed by:** MBTPS1 (S1P) cleaves CREB3

**Literature references**


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MBTPS1 (S1P) cleaves CREB3

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874204

**Type:** transition

**Compartments:** Golgi membrane

In the Golgi membrane, CREB3 (LUMAN) is cleaved by regulated intramembrane proteolysis (Raggo et al. 2002, Liang et al. 2006, Stirling and O’Hare 2006, Eleveld-Trancikova et al. 2010). As inferred from other cleaved proteins, the reaction is probably catalyzed by MBTPS1 (S1P) at an RQLR motif (Stirling and O’Hare 2006).

**Preceded by:** CREB3 translocates from the endoplasmic reticulum membrane to the Golgi membrane

**Followed by:** MBTPS2 (S2P) cleaves CREB3

**Literature references**


**Editions**

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CREB3 is cleaved by regulated intramembrane proteolysis (RIP) (Raggo et al. 2002, Liang et al. 2006, Eleveld-Trancikova et al. 2010). As inferred from other RIP substrates, MBTPS2 (S2P) is believed to cleave CREB3 after MBTPS1 (S1P) cleaves (Raggo et al. 2002). Based on homology with cleavage sites in SREBP (SREBF) homologues, the cleavage site in CREB3 is estimated to be at about amino acid 254 at the cytoplasmic face of the transmembrane domain (Raggo et al. 2002).

**Preceded by:** MBTPS1 (S1P) cleaves CREB3

**Followed by:** CREB3 translocates from the cytosol to the nucleus

**Literature references**


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CREB3 translocates from the cytosol to the nucleus

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874197

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** ATF6 (ATF6-alpha) translocates from the cytosol to the nucleus (Homo sapiens)

Based on homology with other substrates of regulated intramembrane cleavage, cleavage by regulate intramembrane proteolysis is believed to release the N-terminal cytoplasmic domain of CREB3 into the cytosol (Raggo et al. 2002, Eleveld-Trancikova et al. 2010). The fragment is then translocated into the nucleus (Raggo et al. 2002, Eleveld-Trancikova et al. 2010) where, in combination with HCF-1, it activates target genes that contain UPRE and ERSE-II elements in their promoters (Liang et al. 2006).

**Preceded by:** MBTPS2 (S2P) cleaves CREB3

**Followed by:** CREBRF binds CREB3

**Literature references**


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CREBRF (Luman recruitment factor, LRF) binds CREB3 in the nucleus and recruits CREB3 into nuclear foci (Audas et al. 2008). CREBRF destabilizes CREB3 and reduces the transcription activation activity of CREB3 during endoplasmic reticulum stress.

**Preceded by:** CREB3 translocates from the cytosol to the nucleus

**Literature references**


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CREB3L1 translocates from the endoplasmic reticulum membrane to the Golgi membrane

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874184

**Type:** omitted

**Compartments:** endoplasmic reticulum membrane, Golgi membrane

**Inferred from:** Creb3l1 translocates from the endoplasmic reticulum to the Golgi membrane (Mus musculus)

CREB3L1 (OASIS) is normally a short-lived protein located in the endoplasmic reticulum (ER) membrane (Kondo et al. 2012) of osteoblasts, astrocytes, intestine, salivary gland, and prostate. It is targeted for proteolytic degradation by HRD1 (inferred from mouse homologs). During ER stress CREB3L1 becomes stabilized and traffics by an uncharacterized mechanism to the Golgi membrane where it is cleaved by Golgi-resident proteases MBTPS1 (S1P) and MBTPS2 (S2P) (inferred from mouse homologs).

**Followed by:** MBTPS1 (S1P) cleaves CREB3L1

**Literature references**


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In the Golgi membrane, CREB3L1 (OASIS) is cleaved in its lumenal domain (Denard et al. 2011, Denard et al. 2012, Mellor et al. 2013, Rose et al. 2014, Ward et al. 2016) by MBTPS1 (S1P) (Denard et al. 2012, inferred from mouse homologs). By inference from SREBFs (SREBPs) and other CREB3 family proteins, CREB3L1 is cleaved at an RSLL motif around amino acid residue 426.

**Preceded by:** CREB3L1 translocates from the endoplasmic reticulum membrane to the Golgi membrane

**Followed by:** MBTPS2 (S2P) cleaves CREB3L1

**Literature references**


Sarker, S., Anderson, DH., Smith, SE., Kendall, S., Just, NA., Carlsen, SA. et al. (2016). Epigenetic silencing of CREB3L1 by DNA methylation is associated with high-grade metastatic breast cancers with poor prognosis and is prevalent in triple negative breast cancers. *Breast Cancer Res.*, 18, 12.

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**MBTPS2 (S2P) cleaves CREB3L1**

**Location:** CREB3 factors activate genes  
**Stable identifier:** R-HSA-8874194  
**Type:** transition  
**Compartments:** Golgi membrane, cytosol  
**Inferred from:** Mbtps2 (S2P) cleaves Creb3l1 (Oasis) (Mus musculus)

After cleavage by MBTPS1 (S1P), CREB3L1 (OASIS) is cleaved by MBTPS2, yielding a 60 kDal cytosolic product (S2P) (Denard et al. 2011, Denard et al. 2012, Mellor et al. 2013, Rose et al. 2014, Ward et al. 2016, inferred from mouse homologs). By inference from SREBFs (SREBPs) the cleavage is believed to occur near the cytoplasmic face of the transmembrane domain about amino acid residue 375. The cleavage releases the N-terminal cytoplasmic domain into the cytosol.

**Preceded by:** MBTPS1 (S1P) cleaves CREB3L1  
**Followed by:** CREB3L1 translocates from the cytosol to the nucleus

**Literature references**


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**CREB3L1 translocates from the cytosol to the nucleus**

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874193

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** Creb3l1 (Oasis) translocates from the cytosol to the nucleus (Mus musculus)

Cleavage by MBTPS2 releases the N-terminal domain of CREB3L1 into the cytosol and it then traffics to the nucleus (Denard et al. 2011, Rose et al. 2014, Ward et al. 2016, and inferred from mouse homologs).

**Preceded by:** MBTPS2 (S2P) cleaves CREB3L1

**Literature references**


Sarker, S., Anderson, DH., Smith, SE., Kendall, S., Just, NA., Carlsen, SA. et al. (2016). Epigenetic silencing of CREB3L1 by DNA methylation is associated with high-grade metastatic breast cancers with poor prognosis and is prevalent in triple negative breast cancers. *Breast Cancer Res.*, 18, 12.


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CREB3L2 translocates from the endoplasmic reticulum membrane to the Golgi membrane

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874198

**Type:** omitted

**Compartment:** endoplasmic reticulum membrane, Golgi membrane

**Inferred from:** Creb3l2 (BBF2H7) translocates from the endoplasmic reticulum membrane to the Golgi membrane (Mus musculus)

CREB3L2 (BBF2H7) localizes to the endoplasmic reticulum (Panagopoulos et al. 2007, Kondo et al. 2012) of cells in cartilage, lungs, spleen, gonads, and nervous system where it is normally targeted for proteolytic degradation by HRD1 (inferred from mouse homologs). During ER stress, CREB3L2 becomes stabilized and traffics by an uncharacterized mechanism to the Golgi membrane where it is activated by cleavage (inferred from mouse homologs).

**Followed by:** MBTPS1 (S1P) cleaves CREB3L2

**Literature references**


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**MBTPS1 (S1P) cleaves CREB3L2**

**Location:** CREB factors activate genes

**Stable identifier:** R-HSA-8874205

**Type:** transition

**Compartments:** Golgi membrane

**Inferred from:** Mtps1 (S1P) cleaves Creb3l2 (BBF2H7) (Mus musculus)

MBTPS1 (S1P) cleaves CREB3L2 in the luminal domain. By inference from SREBFs (SREBPs) the cleavage is believed to occur at a RNLL motif at amino acid residue 430. The N-terminal product remains attached to the Golgi membrane by its transmembrane domain. The C-terminal luminal domain is eventually secreted and promotes Hedgehog signaling (Iwamoto et al. 2015).

**Preceded by:** CREB3L2 translocates from the endoplasmic reticulum membrane to the Golgi membrane

**Followed by:** MBTPS2 (S2P) cleaves CREB3L2, CREB3L2 translocates from the cytosol to the nucleus

**Literature references**


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MBTPS2 (S2P) cleaves CREB3L2

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874187

**Type:** transition

**Compartments:** Golgi membrane, cytosol

**Inferred from:** Mbtps2 (S2P) cleaves Creb3l2 (BBF2H7) (Mus musculus)

MBTPS2 (S2P) cleaves CREB3L2 near the cytoplasmic face of the transmembrane domain, releasing the cytoplasmic N-terminal domain into the cytosol (inferred from human ATF6-alpha and mouse homologs).

**Preceded by:** MBTPS1 (S1P) cleaves CREB3L2

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CREB3L2 translocates from the cytosol to the nucleus

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874191

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

**Inferred from:** Creb3l2 translocates from the cytosol to the nucleus (Mus musculus)

After cleavage by MBTPS2 the N-terminal cytoplasmic domain of CREB3L2 is released into the cytosol and traffics to the nucleus where it binds CRE-like elements in promoters of genes such as Sec23a (inferred from mouse).

**Preceded by:** MBTPS1 (S1P) cleaves CREB3L2

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CREB3L3 translocates from the endoplasmic reticulum membrane to the Golgi membrane

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874208

**Type:** omitted

**Compartments:** endoplasmic reticulum membrane, Golgi membrane

Unlike ATF6, CREB3L3 (and probably other CREB3 family members) does not interact with HSPA5 (BiP) (Llarena 2010). Instead, retention in the endoplasmic reticulum (ER) is mediated by a membrane-proximal cytoplasmic motif (Bailey et al. 2007). When the motif is deleted CREB3L3 is constitutively trafficked to the Golgi where it is cleaved (Bailey et al. 2007). In cells not experiencing ER stress, CREB3L3 is located in the ER membrane (Stirling and O’Hare 2006, Bailey et al. 2007, Llarena et al. 2010) and is rapidly turned over by the endoplasmic reticulum associated degradation (ERAD) pathway (Bailey et al. 2007). During ER stress CREB3L3 is translocated by an uncharacterized mechanism to the Golgi (Bailey et al. 2007, Llarena et al. 2010, also inferred from the mouse homolog in Zhang et al. 2006). CREB3L3 is expressed strongly in the liver and more weakly in the stomach and small intestine.

**Followed by:** MBTPS1 (S1P) cleaves CREB3L3

**Literature references**


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https://reactome.org
**MBTPS1 (S1P) cleaves CREB3L3**

**Location:** CREB factors activate genes

**Stable identifier:** R-HSA-8874206

**Type:** transition

**Compartments:** Golgi membrane

CREB3L3 at the Golgi membrane is cleaved in the luminal domain (LLarena et al. 2010) by MBTPS1 (S1P) (Bailey et al. 2007, inferred from mouse homologs in Zhang et al. 2006). By inference from cleavage of SREBFs (SREBPs), CREB3L3 is believed to be cleaved at a RTLH motif at amino acid residue 364.

**Preceded by:** CREB3L3 translocates from the endoplasmic reticulum membrane to the Golgi membrane

**Followed by:** MBTPS2 (S2P) cleaves CREB3L3

**Literature references**


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MBTPS2 (S2P) cleaves CREB3L3

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874201

**Type:** transition

**Compartments:** Golgi membrane, cytosol

After cleavage by MBTPS1, CREB3L3 in the Golgi membrane is cleaved by MBTPS2 (S2P) near the cytoplasmic face of the transmembrane domain (Bailey et al. 2007, inferred from mouse homologs in Zhang et al. 2006). By inference from cleavage of SREBFs (SREBPs), CREB3L3 is believed to be cleaved at approximately amino acid residue 323. The cleavage releases the N-terminal cytoplasmic domain into the cytosol.

**Preceded by:** MBTPS1 (S1P) cleaves CREB3L3

**Followed by:** CREB3L3 translocates from the cytosol to the nucleus

**Literature references**


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**CREB3L3 translocates from the cytosol to the nucleus**

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874202

**Type:** omitted

**Compartments:** nucleoplasm, cytosol

The N-terminal, cleavage product of CREB3L3 traffics to the nucleus (Omori et al. 2001, Bailey et al. 2007, Llarena et al. 2010) where it can interact with ATF6 and where it is observed to bind the CRE, box B, and ATF6-binding element, ERSE-I, and ERSE-II in promoters of target genes such as PEPCK.

**Preceded by:** MBTPS2 (S2P) cleaves CREB3L3

**Literature references**


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CREB3L4 translocates from the endoplasmic reticulum membrane to the Golgi membrane

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874209

**Type:** omitted

**Compartments:** endoplasmic reticulum membrane, Golgi membrane

**Inferred from:** ATF6 (ATF6-alpha) translocates from the endoplasmic reticulum to the Golgi (Homo sapiens)

CREB3L4 (CREB4) is observed in the endoplasmic reticulum (ER) and the Golgi (Stirling and O’Hare 2006). Based on homologous transcription factors possessing transmembrane domains, CREB3L4 is inferred to traffic from the ER to the Golgi where it is activated by cleavage. Stress caused by dithiothreitol causes trafficking of CREB3L4 to the Golgi but cleavage by MBTPS1 (S1P) is not observed (Stirling and O’Hare 2006).

**Followed by:** MBTPS1 (S1P) cleaves CREB3L4

**Literature references**


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MBTPS1 (S1P) cleaves CREB3L4

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874186

**Type:** transition

**Compartments:** Golgi membrane

**Inferred from:** Mbtps1 (S1P) cleaves Creb3l4 (Mus musculus)

MBTPS1 (S1P) cleaves the luminal domain of CREB3L4 (Stirling and O'Hare 2006, Ben-Aicha et al. 2007). Based on homology with SREBFs (SREBPs), other CREB3 proteins, and the mouse homolog Creb3l4 (Tisp40) the cleavage site is inferred to be at a RNIL motif at amino acid 338. The C-terminal domain of CREB3L4 interferes with cleavage and therefore may regulate the process (Stirling and O'Hare 2006). Dithiothreitol (DTT) causes trafficking but not cleavage of CREB3L4.

**Preceded by:** CREB3L4 translocates from the endoplasmic reticulum membrane to the Golgi membrane

**Followed by:** MBTPS2 (S2P) cleaves CREB3L4

**Literature references**


**Editions**

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<td>Schröder, M.</td>
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**MBTPS2 (S2P) cleaves CREB3L4**

**Location:** CREB3 factors activate genes

**Stable identifier:** R-HSA-8874195

**Type:** transition

**Compartments:** Golgi membrane, cytosol

**Inferred from:** Mtps2 (S2P) cleaves Creb3l4 (Mus musculus)

CREB3L4 (CREB4) is cleaved near the cytoplasmic face of the transmembrane domain (Stirling and O’Hare 2006, Ben-Aicha et al. 2007). Based on homology with the mouse homolog and other CREB3 proteins, MBTPS2 (S2P) cleaves CREB3L4 and the cleavage is inferred to occur at approximately amino acid 297. The cleavage releases the N-terminal domain to the cytosol.

**Preceded by:** MBTPS1 (S1P) cleaves CREB3L4

**Followed by:** CREB3L4 translocates from the cytosol to the nucleus

**Literature references**


**Editions**

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CREB3L4 translocates from the cytosol to the nucleus

Location: CREB3 factors activate genes

Stable identifier: R-HSA-8874218

Type: omitted

Compartments: nucleoplasm, cytosol

Inferred from: Creb3l4 translocates from the cytosol to the nucleus (Mus musculus)

The N-terminal domain of CREB3L4 (CREB4, AlbZIP) containing the bZIP and transcription activation domains trafficks from the cytosol to the nucleus (Stirling and O'Hare 2006, inferred from mouse Creb3l4 (Tisp40)) where it activates transcription of target genes such as HSPA5 (BiP), BAG3, DNAJC12, and KDELR3 (Qi et al. 2002, Ben Aicha et al. 2007). Expression of CREB3L4 is itself induced by androgens in prostate tissue (Qi et al. 2002).

Preceded by: MBTPS2 (S2P) cleaves CREB3L4

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