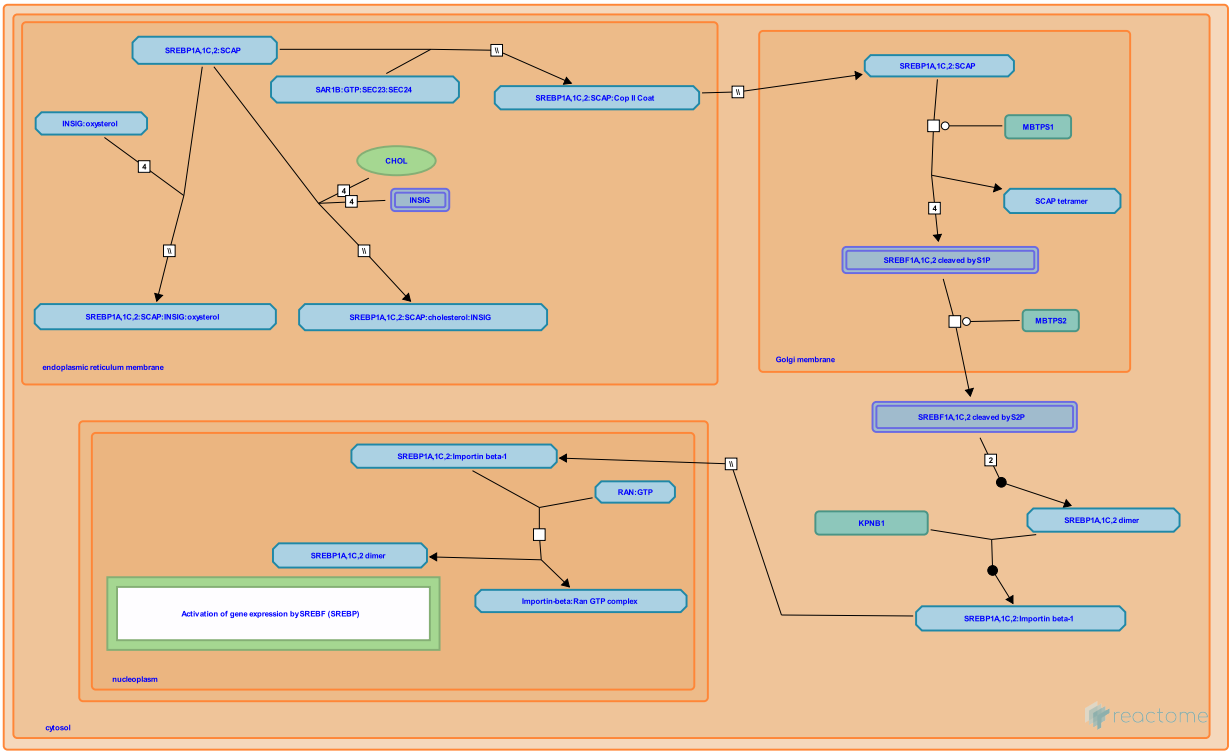
# Regulation of cholesterol biosynthesis by SREBP (SREBF)

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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).

## Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

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

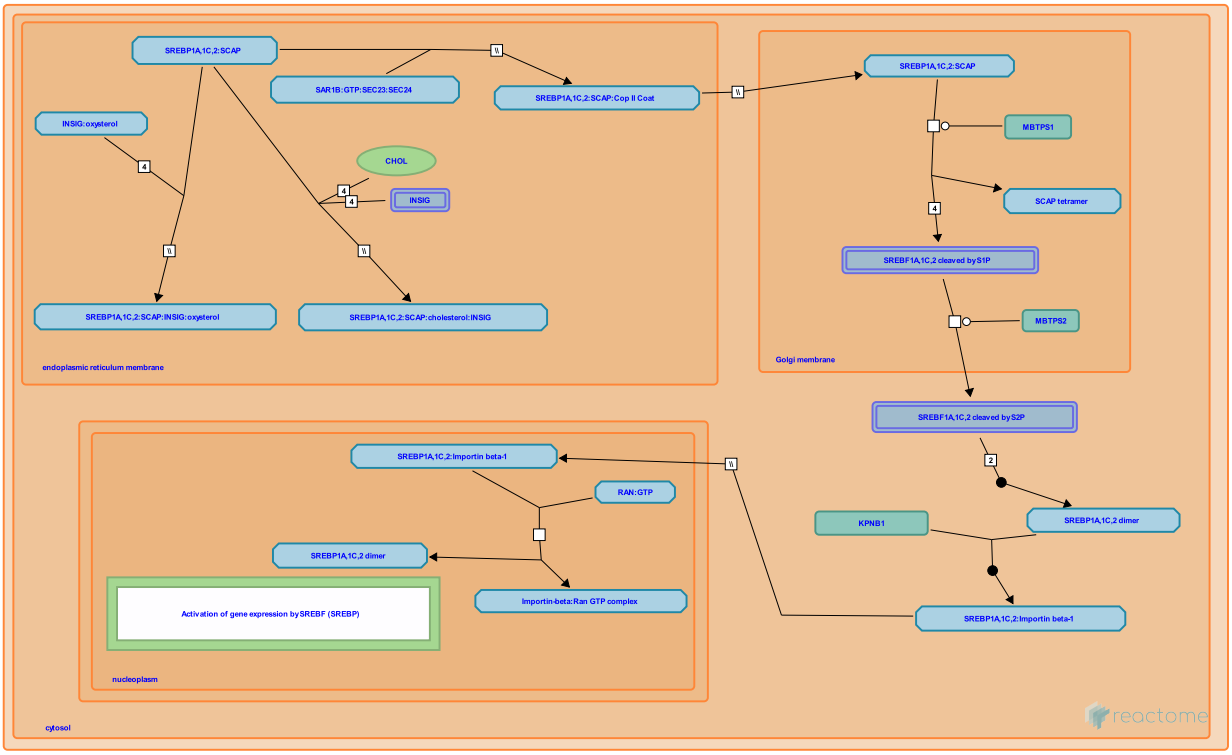
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

## Regulation of cholesterol biosynthesis by SREBP (SREBF) ↗

**Stable identifier:** R-HSA-1655829

**Compartments:** endoplasmic reticulum membrane, ER to Golgi transport vesicle membrane, Golgi membrane, nucleoplasm




Sterol regulatory element binding proteins (SREBPs, SREBFs) respond to low cholesterol concentrations by transiting to the nucleus and activating genes involved in cholesterol and lipid biosynthesis (reviewed in Brown and Goldstein 2009, Osborne and Espenshade 2009, Weber et al. 2004).
Newly synthesized SREBPs are transmembrane proteins that bind SCAP in the endoplasmic reticulum (ER) membrane. SCAP binds cholesterol which causes a conformational change that allows SCAP to interact with INSIG, retaining the SCAP:SREBP complex in the ER. INSIG binds oxysterols, which cause INSIG to bind SCAP and retain SCAP:SREBP in the endoplasmic reticulum.
In low cholesterol (below about 5 mol%) SCAP no longer interacts with cholesterol or INSIG and binds Sec24 of the CopII coat complex instead. Thus SCAP:SREBP transits with the CopII complex from the ER to the Golgi. In the Golgi SREBP is cleaved by S1P and then by S2P, releasing the N-terminal fragment of SREBP into the cytosol. The N-terminal fragment is imported to the nucleus by importin-beta and then acts with other factors, such as SP1 and NF-Y, to activate transcription of target genes. Targets of SREBP include the genes encoding all enzymes of cholesterol biosynthesis and several genes involved in lipogenesis. SREBP2 most strongly activates cholesterol biosynthesis while SREBP1C most strongly activates lipogenesis.

## Literature references


Brown, MS., Goldstein, JL. (2009). Cholesterol feedback: from Schoenheimer's bottle to Scap's MELADL. *J Lipid Res, 50*, S15-27. ↗

Osborne, TF., Espenshade, PJ. (2009). Evolutionary conservation and adaptation in the mechanism that regulates SREBP action: what a long, strange tRIP it's been. *Genes Dev, 23*, 2578-91. ↗

Stampfl, A., Boll, M., Weber, LW. (2004). Maintaining cholesterol homeostasis: sterol regulatory element-binding proteins. *World J Gastroenterol, 10*, 3081-7. ↗


## Editions

| | | |
|---|---|---|
| 2011-09-28 | Authored | May, B. |
| 2011-10-13 | Edited | May, B. |
| 2012-08-26 | Reviewed | Liang, G. |

## SREBP1A,1C,2 binds SCAP:cholesterol:INSIG and is retained in the endoplasmic reticulum ↗

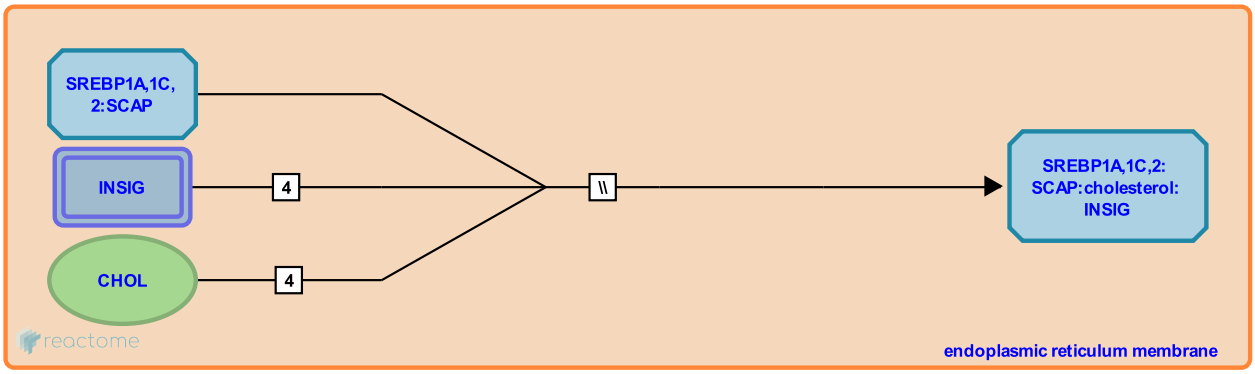
**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-2317530

**Type:** omitted

**Compartments:** endoplasmic reticulum membrane

**Inferred from:** SREBP1A/1C/2 is retained in the endoplasmic reticulum by SCAP:cholesterol:INSIG (Cricetulus griseus)




SREBPs (SREBP1A/1C/2, SREBFs) bind SCAP in the endoplasmic reticulum membrane. Luminal loop 1 of SCAP binds cholesterol which prevents SCAP from interacting with Sec24 in the CopII coat complex and allows SCAP to interact with INSIG instead. These interactions retain SCAP:SREBP1A/1C/2 in the endoplasmic reticulum. The order of assembly of the SREBP1A/1C/2:SCAP:cholesterol:INSIG complex is unknown.

### Editions

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## SREBP1A,1C,2 binds SCAP:INSIG:oxysterol and is retained in the endoplasmic reticulum ↗

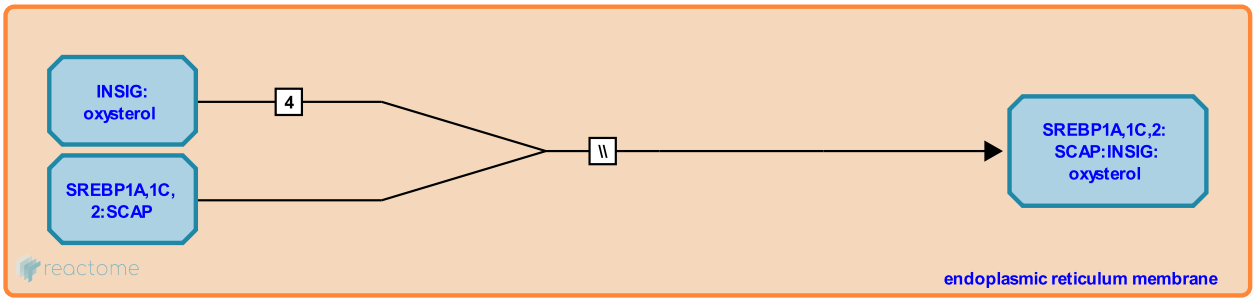
**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-2317531

**Type:** omitted

**Compartments:** endoplasmic reticulum membrane

**Inferred from:** SREBP2 (SREBF2) is retained in the endoplasmic reticulum by SCAP:INSIG2:oxysterol (Cricetulus griseus)




INSIG binds oxysterols and the INSIG:oxysterol complex interacts with SCAP subunits of the SREBP1A/1C/2:SCAP (SREBF1A/1C/2:SCAP) complex. This interaction retains the SREBP1A/1C/2:SCAP:INSIG:oxysterol complex in the endoplasmic reticulum. The order of assembly of the SREBP1A/1C/2:SCAP:INSIG:oxysterol complex is unknown.

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## SREBP1A,1C,2:SCAP binds CopII Coat Complex ↗

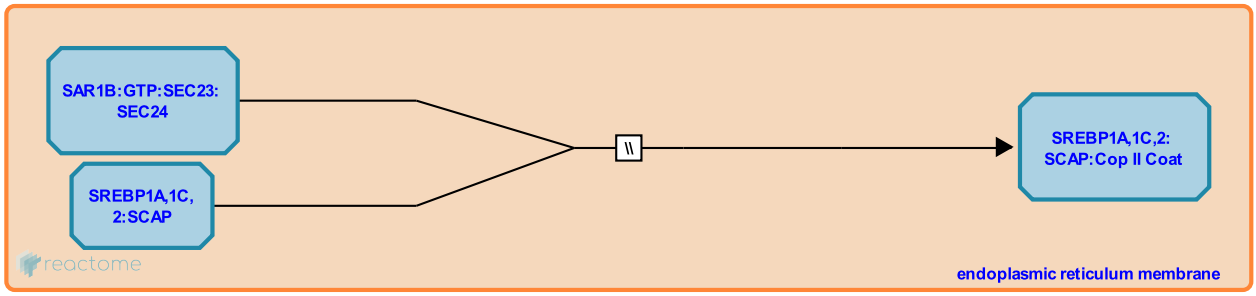
**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-1655825

**Type:** omitted

**Compartments:** endoplasmic reticulum membrane

**Inferred from:** SREBP2:SCAP Binds CopII Coat Complex (Cricetulus griseus)




SREBPs (SREBP1A, SREBP1C, SREBP2, also known as SREBFs) are transmembrane proteins that bind SCAP in the endoplasmic reticulum membrane. In the presence of cholesterol or oxysterols SCAP:SREBP1A/1C/2 binds INSIG and is retained in the endoplasmic reticulum. At cholesterol concentrations below 5 mol% SCAP changes conformation, SCAP:SREBP1A/1C/2 loses interaction with INSIG, binds the CopII coat complex, and is translocated to the Golgi.

**Followed by:** SREBP1A,1C,2:SCAP translocates to the Golgi

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| | | |
|---|---|---|
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| 2012-08-26 | Reviewed | Liang, G. |

## SREBP1A,1C,2:SCAP translocates to the Golgi ↗

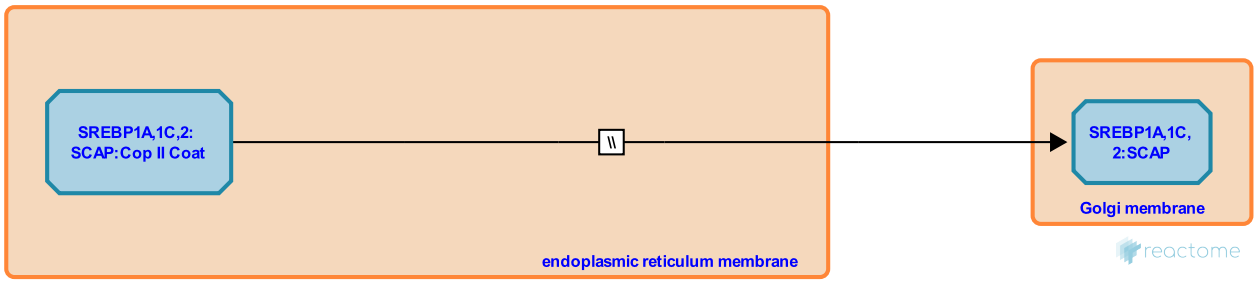
**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-1655834

**Type:** omitted

**Compartments:** endoplasmic reticulum membrane, Golgi membrane, ER to Golgi transport vesicle membrane

**Inferred from:** SREBP2:SCAP Transits to the Golgi (Cricetulus griseus)




In low concentrations of cholesterol SCAP interacts with Sec24 of the CopII coat complex causing SCAP:SREBP1A/1C/2 to be transported with the CopII complex from the endoplasmic reticulum to the Golgi.

**Preceded by:** SREBP1A,1C,2:SCAP binds CopII Coat Complex

**Followed by:** S1P hydrolyzes SREBP1A,1C,2

## Editions

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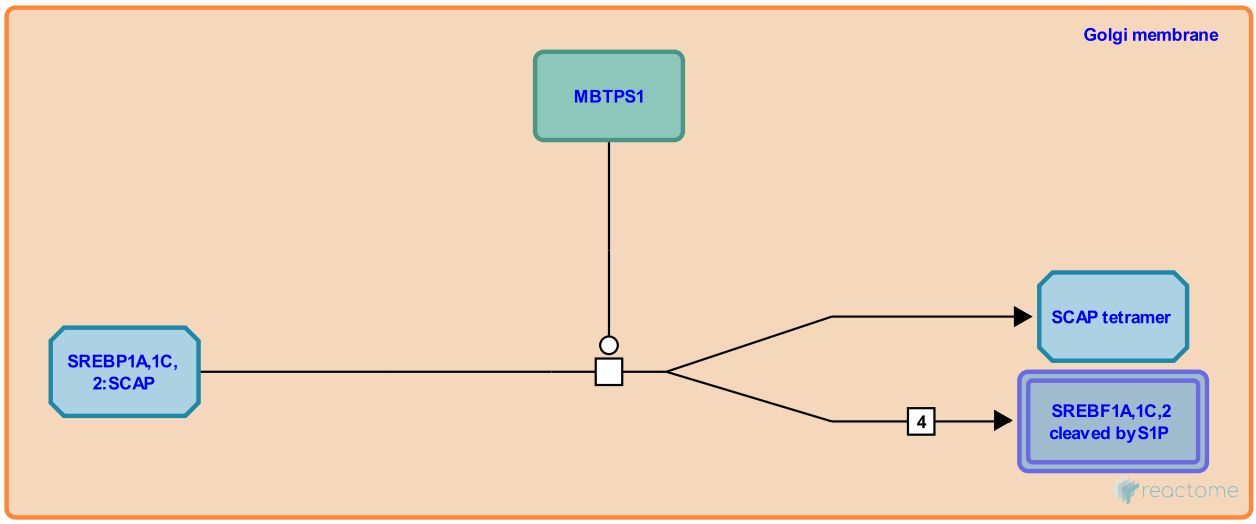
## S1P hydrolyzes SREBP1A,1C,2 ↗

**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-1655842

**Type:** transition

**Compartments:** Golgi membrane




S1P (MBTPS1, SKI-1), a membrane-bound protease in the Golgi, cleaves the intralumenal loop of SREBP1A/1C/2 (SREBF1A/1C/2), releasing the N-terminal domain of SREBP1A/1C/2, which remains bound to the membrane.

**Preceded by:** SREBP1A,1C,2:SCAP translocates to the Golgi

**Followed by:** S2P hydrolyzes SREBP1A,1C,2

## Literature references


Brown, MS., Rawson, RB., Hua, X., Duncan, EA., Sakai, J., Goldstein, JL. (1996). Sterol-regulated release of SREBP-2 from cell membranes requires two sequential cleavages, one within a transmembrane segment. *Cell, 85*, 1037-46. ↗

Brown, MS., Nohturfft, A., Sakai, J., Goldstein, JL. (1998). Cleavage of sterol regulatory element-binding proteins (SREBPs) at site-1 requires interaction with SREBP cleavage-activating protein. Evidence from in vivo competition studies. *J Biol Chem, 273*, 5785-93. ↗

Brown, MS., Wang, X., Goldstein, JL., Hua, X., Sato, R. (1994). SREBP-1, a membrane-bound transcription factor released by sterol-regulated proteolysis. *Cell, 77*, 53-62. ↗

Lazure, C., Seidah, NG., Rochemont, J., Chretien, M., Touré, BB., Benjannet, S. et al. (2000). Biosynthesis and enzymatic characterization of human SKI-1/S1P and the processing of its inhibitory prosegment. *J Biol Chem, 275*, 2349-58. ↗

Brown, MS., Cheng, D., Espenshade, PJ., Goldstein, JL. (1999). Autocatalytic processing of site-1 protease removes propeptide and permits cleavage of sterol regulatory element-binding proteins. *J Biol Chem, 274*, 22795-804. ↗


## Editions

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|---|---|---|
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| 2012-08-26 | Reviewed | Liang, G. |

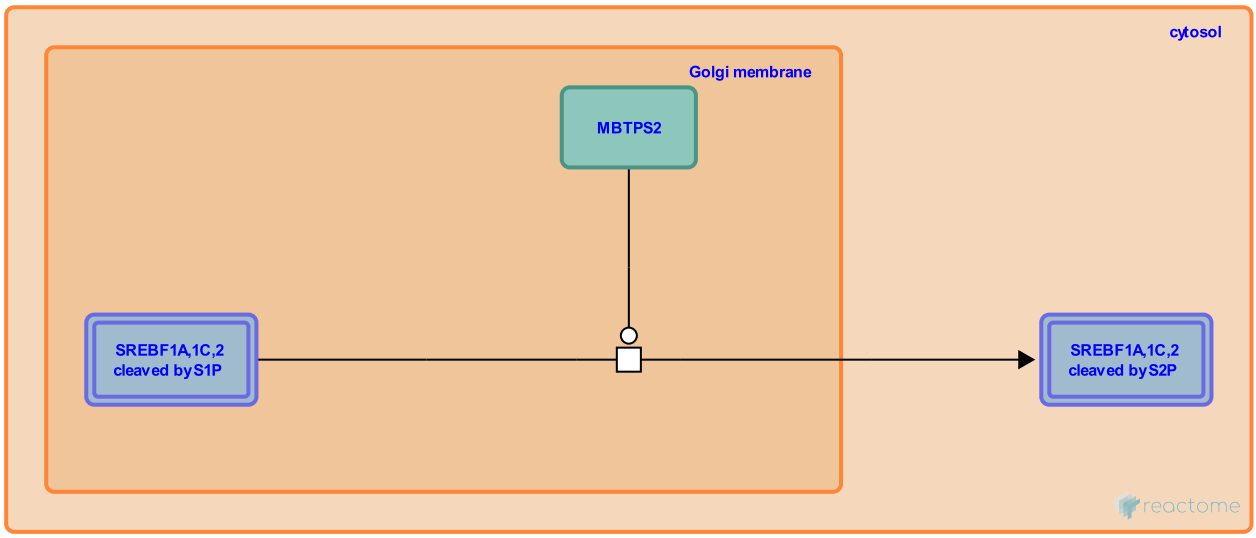
## S2P hydrolyzes SREBP1A,1C,2 ↗

**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-1655851

**Type:** transition

**Compartments:** Golgi membrane, cytosol




S2P(MBTPS2), a membrane-bound protease in the Golgi, cleaves within the transmembrane region of SREBP1A/1C/2 (SREBF1A/1C/2), releasing the N-terminal domain of SREBP1A/1C/2 into the cytosol.

**Preceded by:** S1P hydrolyzes SREBP1A,1C,2

**Followed by:** SREBP1A,1C,2 binds SREBP1A,1C,2 forming dimers

## Literature references


Brown, MS., Rawson, RB., Hua, X., Duncan, EA., Sakai, J., Goldstein, JL. (1996). Sterol-regulated release of SREBP-2 from cell membranes requires two sequential cleavages, one within a transmembrane segment. *Cell, 85*, 1037-46. ↗

Brown, MS., Wang, X., Goldstein, JL., Hua, X., Sato, R. (1994). SREBP-1, a membrane-bound transcription factor released by sterol-regulated proteolysis. *Cell, 77*, 53-62. ↗

Brown, MS., Hasan, MT., Rawson, RB., Zelenski, NG., Ye, J., Nijhawan, D. et al. (1997). Complementation cloning of S2P, a gene encoding a putative metalloprotease required for intramembrane cleavage of SREBPs. *Mol Cell, 1*, 47-57. ↗

Brown, MS., Davé, UP., Ye, J., Grishin, NV., Goldstein, JL. (2000). Asparagine-proline sequence within membrane-spanning segment of SREBP triggers intramembrane cleavage by site-2 protease. *Proc Natl Acad Sci U S A, 97*, 5123-8. ↗


## Editions

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|---|---|---|
| 2011-09-28 | Authored, Edited | May, B. |
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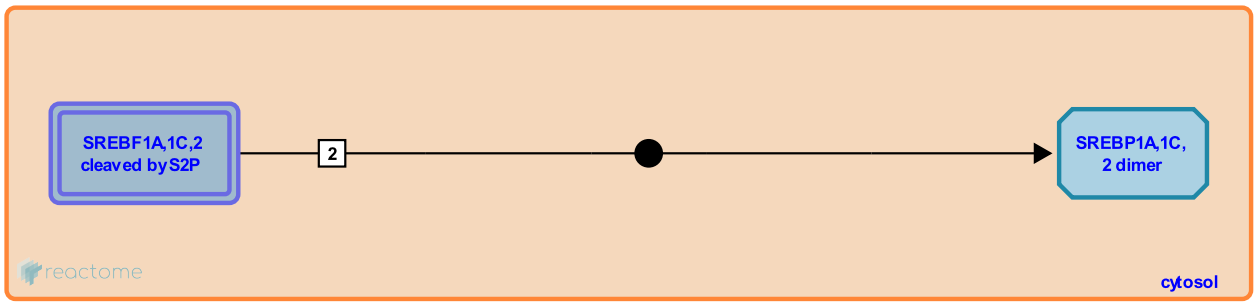
## SREBP1A,1C,2 binds SREBP1A,1C,2 forming dimers ↗

**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-2065549

**Type:** binding

**Compartments:** cytosol




The N-terminal domains of SREBPs (SREBP1A/1C/2, SREBFs) dimerize via interaction of their helix-loop-helix leucine zipper domains (Nagoshi and Yoneda 2001).

**Preceded by:** S2P hydrolyzes SREBP1A,1C,2

**Followed by:** SREBP1A,1C,2 binds Importin beta-1

## Literature references

Yoneda, Y., Nagoshi, E. (2001). Dimerization of sterol regulatory element-binding protein 2 via the helix-loop-helix-leucine zipper domain is a prerequisite for its nuclear localization mediated by importin beta. *Mol Cell Biol, 21*, 2779-89. ↗

## Editions

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| 2012-01-23 | Authored, Edited | May, B. |
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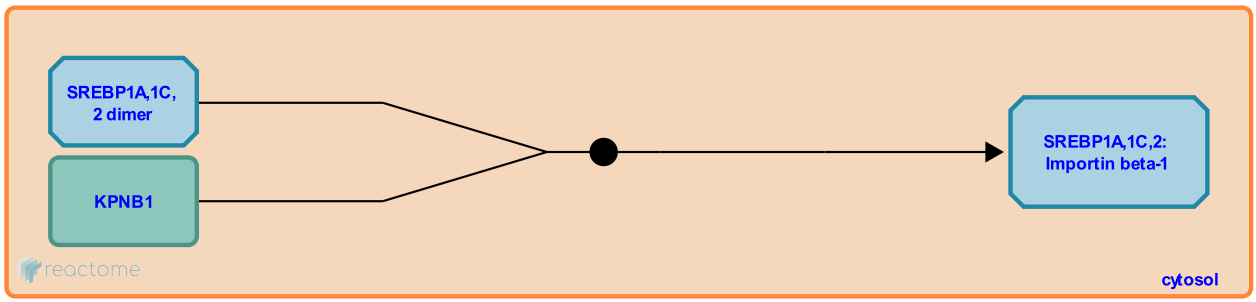
## SREBP1A,1C,2 binds Importin beta-1 ↗

**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-2065550

**Type:** binding

**Compartments:** cytosol




SREBP2 dimer (also called SREBF2 dimer) and, by inference SREBP1A,1C dimer, binds Importin beta-1 via the helix-loop-helix leucine zipper domain of SREBP1A,1C,2 (Nagoshi et al. 1999, Di Pardo et al. 2020).

**Preceded by:** SREBP1A,1C,2 binds SREBP1A,1C,2 forming dimers

**Followed by:** SREBP1A,1C,2 translocates to the nucleus

## Literature references

Morales, LC., Kadam, V., Sipione, S., Wozniak, RW., Monyror, J., Maglione, V. et al. (2020). Mutant huntingtin interacts with the sterol regulatory element-binding proteins and impairs their nuclear import. *Hum Mol Genet, 29*, 418-431. ↗

Imamoto, N., Yoneda, Y., Nagoshi, E., Sato, R. (1999). Nuclear import of sterol regulatory element-binding protein-2, a basic helix-loop-helix-leucine zipper (bHLH-Zip)-containing transcription factor, occurs through the direct interaction of importin beta with HLH-Zip. *Mol Biol Cell, 10*, 2221-33. ↗

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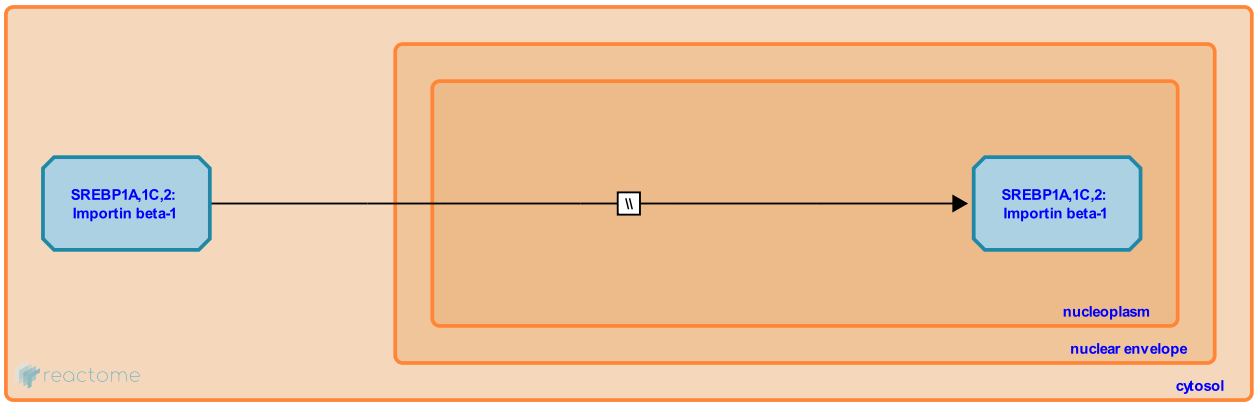
## SREBP1A,1C,2 translocates to the nucleus ↗

**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-1655831

**Type:** omitted

**Compartments:** nucleoplasm, cytosol




The N-terminal domain of SREBP1A,1C,2 (SREBF1A,1C,2) dimerizes and is imported from the cytosol into the nucleus by importin-beta (Nagoshi et al. 1999, Nagoshi and Yoned 2001, Lee et al. 2003, Di Pardo et al. 2020). In the nucleus the dimers bind DNA (Parraga et al. 1998) and activate transcription (Datta and Osborne 2005).

**Preceded by:** SREBP1A,1C,2 binds Importin beta-1

**Followed by:** SREBP1A,1C,2:Importin beta-1 dissociates

## Literature references

Yoneda, Y., Nagoshi, E. (2001). Dimerization of sterol regulatory element-binding protein 2 via the helix-loop-helix-leucine zipper domain is a prerequisite for its nuclear localization mediated by importin beta. *Mol Cell Biol, 21*, 2779-89. ↗

Brown, MS., Rawson, RB., Hua, X., Duncan, EA., Sakai, J., Goldstein, JL. (1996). Sterol-regulated release of SREBP-2 from cell membranes requires two sequential cleavages, one within a transmembrane segment. *Cell, 85*, 1037-46. ↗

Osborne, TF., Datta, S. (2005). Activation domains from both monomers contribute to transcriptional stimulation by sterol regulatory element-binding protein dimers. *J Biol Chem, 280*, 3338-45. ↗

Brown, MS., Wang, X., Goldstein, JL., Hua, X., Sato, R. (1994). SREBP-1, a membrane-bound transcription factor released by sterol-regulated proteolysis. *Cell, 77*, 53-62. ↗

Ferré-D'Amaré, AR., Párraga, A., Burley, SK., Bellsolell, L. (1998). Co-crystal structure of sterol regulatory element binding protein 1a at 2.3 A resolution. *Structure, 6*, 661-72. ↗

## Editions

| | | |
|---|---|---|
| 2011-09-28 | Authored, Edited | May, B. |
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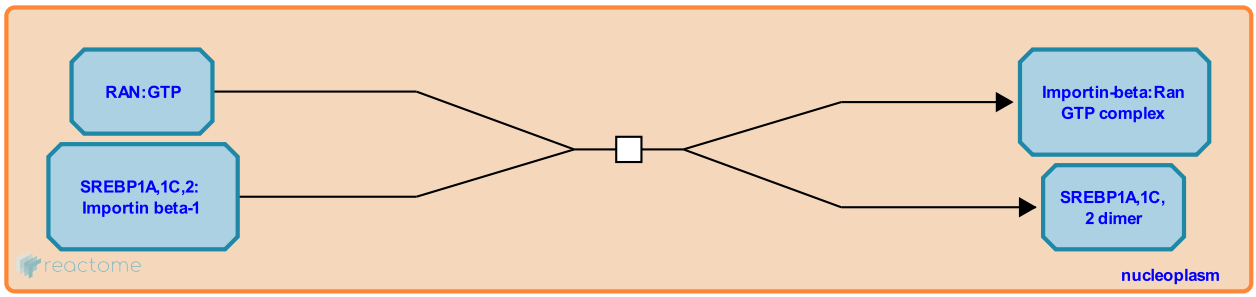
## SREBP1A,1C,2:Importin beta-1 dissociates ↗

**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-2065539

**Type:** transition

**Compartments:** nucleoplasm




SREBP1A/1C/2 (SREBF1A/1C/2) dimer dissociates from Importin beta-1 in response to Ran-GTP in the nucleoplasm (Nagoshi et al. 1999).

**Preceded by:** SREBP1A,1C,2 translocates to the nucleus

## Literature references


Imamoto, N., Yoneda, Y., Nagoshi, E., Sato, R. (1999). Nuclear import of sterol regulatory element-binding protein-2, a basic helix-loop-helix-leucine zipper (bHLH-Zip)-containing transcription factor, occurs through the direct interaction of importin beta with HLH-Zip. *Mol Biol Cell, 10*, 2221-33. ↗


## Editions

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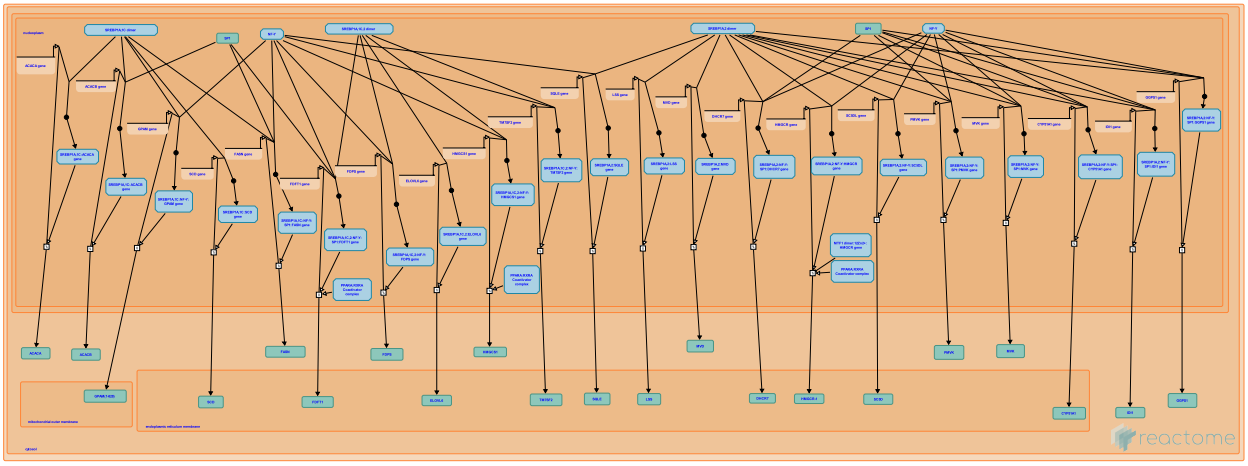
|---|---|---|
| 2012-01-23 | Authored, Edited | May, B. |
| 2012-08-26 | Reviewed | Liang, G. |

## Activation of gene expression by SREBF (SREBP) ↗

**Location:** Regulation of cholesterol biosynthesis by SREBP (SREBF)

**Stable identifier:** R-HSA-2426168

**Compartments:** nucleoplasm



After transiting to the nucleus SREBPs (SREBP1A/1C/2, SREBFs) bind short sequences, sterol regulatory elements (SREs), in the promoters of target genes (reviewed in Eberle et al. 2004, Weber et al. 2004). SREBPs alone are relatively weak activators of transcription, with SREBP1C being significantly weaker than SREBP1A or SREBP2. In combination with other transcription factors such as SP1 and NF-Y the SREBPs are much stronger activators. SREBP1C seems to more specifically target genes involved in fatty acid synthesis while SREBP2 seems to target genes involved in cholesterol synthesis (Pai et al. 1998).

## Literature references


Brown, MS., Pai, JT., Guryev, O., Goldstein, JL. (1998). Differential stimulation of cholesterol and unsaturated fatty acid biosynthesis in cells expressing individual nuclear sterol regulatory element-binding proteins. *J Biol Chem, 273*, 26138-48. ↗

Stampfl, A., Boll, M., Weber, LW. (2004). Maintaining cholesterol homeostasis: sterol regulatory element-binding proteins. *World J Gastroenterol, 10*, 3081-7. ↗

Hegarty, B., Ferré, P., Foufelle, F., Bossard, P., Eberlé, D. (2004). SREBP transcription factors: master regulators of lipid homeostasis. *Biochimie, 86*, 839-48. ↗


## Editions

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# Table of Contents