Regulation of cholesterol biosynthesis by SREBP (SREBF)

Liang, G., May, B.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

The contents of this document may be freely copied and distributed in any media, provided the authors, plus the institutions, are credited, as stated under the terms of Creative Commons Attribution 4.0 International (CC BY 4.0) License. For more information see our license.

06/02/2019
**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: 67

This document contains 2 pathways and 10 reactions (see Table of Contents)
Regulation of cholesterol biosynthesis by SREBP (SREBF)

Stable identifier: R-HSA-1655829

Compartment: endoplasmic reticulum membrane, ER to Golgi transport vesicle membrane, Golgi membrane, nucleoplasm

Sterol regulatory element binding proteins (SREBs, 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


<table>
<thead>
<tr>
<th>Editions</th>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-09-28</td>
<td>Authored</td>
<td></td>
<td>May, B.</td>
</tr>
<tr>
<td>2011-10-13</td>
<td>Edited</td>
<td></td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
<td></td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-06-10</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
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.

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-06-10</td>
<td>Authored, Edited</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
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

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Reviewer</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-09-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
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, ER to Golgi transport vesicle membrane, Golgi 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**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-09-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
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**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-09-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
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**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-09-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
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**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-01-23</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
**SREBP1A,1C,2 binds Importin beta-1**

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

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

**Type:** binding

**Compartments:** cytosol

SREBP1A/1C/2 (SREBF1A/1C/2) dimer binds Importin beta-1 via the helix-loop-helix leucine zipper domain of SREBP1A/1C/2 (Nagoshi et al. 1999).

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

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

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-01-23</td>
<td>Authored, Edited</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
</tr>
</tbody>
</table>

https://www.reactome.org
SREBP1A,1C,2 translocates to the nucleus

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

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

**Type:** omitted

**Compartments:** cytosol, nucleoplasm

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). 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**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-09-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
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


Editions

<table>
<thead>
<tr>
<th>Edition Date</th>
<th>Author/Editor</th>
<th>Reviewed By</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-01-23</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
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


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-07-26</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-08-26</td>
<td>Reviewed</td>
<td>Liang, G.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

- Regulation of cholesterol biosynthesis by SREBP (SREBF) 2
  - SREBP1A,1C,2 binds SCAP:cholesterol:INSIG and is retained in the endoplasmic reticulum 4
  - SREBP1A,1C,2 binds SCAP:INSIG:oxysterol and is retained in the endoplasmic reticulum 5
  - SREBP1A,1C,2:SCAP binds CopII Coat Complex 6
  - SREBP1A,1C,2:SCAP translocates to the Golgi 7
  - S1P hydrolyzes SREBP1A,1C,2 8
  - S2P hydrolyzes SREBP1A,1C,2 9
  - SREBP1A,1C,2 binds SREBP1A,1C,2 forming dimers 10
  - SREBP1A,1C,2 binds Importin beta-1 11
  - SREBP1A,1C,2 translocates to the nucleus 12
  - SREBP1A,1C,2:Importin beta-1 dissociates 13
  - Activation of gene expression by SREBF (SREBP) 14

Table of Contents 15