Antigen activates B Cell Receptor (BCR)

leading to generation of second messengers


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.

12/09/2019
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: 70

This document contains 1 pathway and 25 reactions (see Table of Contents)
Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-983695

**Compartments:** extracellular region, plasma membrane, cytosol

Mature B cells express IgM and IgD immunoglobulins which are complexed with Ig-alpha (CD79A, MB-1) and Ig-beta (CD79B, B29) to form the B cell receptor (BCR) (Fu et al. 1974, Fu et al. 1975, Kunkel et al. 1975, Van Noesal et al. 1992, Sanchez et al. 1993, reviewed in Brezski and Monroe 2008). Binding of antigen to the immunoglobulin activates phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) in the cytoplasmic tails of Ig-alpha and Ig-beta by Src family tyrosine kinases, including LYN, FYN, and BLK (Nel et al. 1984, Yamanashi et al. 1991, Flaswinkel and Reth 1994, Saouaf et al. 1994, Hata et al. 1994, Saouaf et al. 1995, reviewed in Gauld and Cambier 2004, reviewed in Harwood and Batista 2010). The protein kinase SYK may also be involved in phosphorylating the ITAMs.


Activated SYK and other kinases phosphorylate BLNK (SLP-65, BASH) and BCAP. LYN and FYN phosphorylate CD19. Phosphorylated BLNK, BCAP, and CD19 serve as scaffolds which recruit effectors to the plasma membrane and assemble large complexes, the signalosomes. BCAP and CD19 recruit phosphoinositol 3-kinase (PI3K). BLNK recruits phospholipase C gamma (predominantly PLC-gamma2 in B cells, Coggeshall et al. 1992), NCK, BAM32, BTK, VAV1, and SHC. The effectors are phosphorylated by SYK and other kinases.

Phosphorylated BCAP recruits PI3K, which is phosphorylated by a SYK-dependent mechanism (Kuwah-

PLC-gamma hydrolyzes phosphatidylinositol-4,5-bisphosphate to yield inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (Carter et al. 1991, Kim et al. 2004). IP3 binds receptors on the endoplasmic reticulum and causes release of Ca2+ ions from the ER into the cytosol. The depletion of calcium from the ER in turn activates STIM1 to interact with ORAI and TRPC1 channels (and possibly other TRP channels) in the plasma membrane, resulting in an influx of extracellular calcium ions (Mori et al. 2002, Muik et al. 2008, Luik et al. 2008, Park et al. 2009).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author(s)</th>
<th>Reviewed By</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-09-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
The Immunoglobulin of the BCR binds antigen

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-983696

**Type:** binding

**Compartments:** plasma membrane


**Followed by:** CD19 is phosphorylated, LYN, FYN, BLK phosphorylate ITAMs of Ig-alpha (CD79A) and Ig-beta (CD79B)

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-09-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>

https://www.reactome.org
LYN, FYN, BLK phosphorylate ITAMs of Ig-alpha (CD79A) and Ig-beta (CD79B)

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-983709

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** Phosphorylation of ITAMs of Ig-alpha (Cd79a) and Ig-beta (Cd79b) (Mus musculus)

The B cell receptor (BCR) comprises an immunoglobulin complexed with a heterodimer of Ig-alpha (CD79A, MB-1) and Ig-beta (CD79B, B29). After immunoglobulin IgM or IgD binds antigen the associated Ig-alpha and Ig-beta are each observed to be phosphorylated at two tyrosine residues in the cytoplasmic immunoreceptor tyrosine-activated motif (ITAM) (Sanchez et al. 1993, Hata et al. 1994, Saouaf et al. 1994, Saouaf et al. 1995). Saouaf et al. (1995) showed that the kinase Blk could phosphorylate both tyrosines of each ITAM and that the kinase SYK specifically bind phosphorylated but not unphosphorylated ITAMs. In mouse the kinase Lyn and other kinases phosphorylate one tyrosine and Syk is believed to phosphorylate the other (Yamanashi et al. 1991, Flaswinkel and Reth 1994, Rolli et al. 2002).

**Preceded by:** The Immunoglobulin of the BCR binds antigen

**Followed by:** SYK binds the activated BCR

**Literature references**


### Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-09-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
**SYK binds the activated BCR**

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-983700

**Type:** binding

**Compartments:** plasma membrane


**Preceded by:** LYN, FYN, BLK phosphorylate ITAMs of Ig-alpha (CD79A) and Ig-beta (CD79B)

**Followed by:** SYK autophosphorylates at the activated BCR

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-10-31</td>
<td>Author, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
SYK autophosphorylates at the activated BCR

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers  
**Stable identifier:** R-HSA-983707  
**Type:** transition  
**Compartments:** plasma membrane


**Preceded by:** SYK binds the activated BCR  
**Followed by:** p-6Y-SYK phosphorylates BLNK (SLP65)

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-09-28</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
p-6Y-SYK phosphorylates BLNK (SLP65)

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-983703

**Type:** transition

**Compartments:** plasma membrane

BLNK (SLP-65, BASH) forms a stable complex with GRB2, SOS1, and CIN85 in the cytosol. The complex is recruited to the plasma membrane where activated (phosphorylated) SYK phosphorylates BLNK at tyrosines 72, 84, 96, 178, and 189 (Fu et al. 1998, Chiu et al. 2002, inferred from mouse in Wienands et al. 1998, from chicken in Oellerich et al. 2009). Phosphorylated BLNK serves as a scaffold that binds effector molecules such as Phospholipase C. As inferred from mouse, BLNK interacts with phosphorylated tyrosines on CD79A (Ig-alpha) (Engels et al. 2001, Kabak et al. 2002).

**Preceded by:** SYK autophosphorylates at the activated BCR

**Followed by:** p-PIK3AP1 (p-BCAP) binds PIK3CD:PIK3R1 (PI3K delta), Phosphorylated BLNK (SLP65, in Antigen:p-BCR:p-SYK:p-BLNK:CIN85:GRB2:SOS1) binds BTK, PLCG2, VAV1, NCK1

**Literature references**


## Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010-10-31</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>

https://www.reactome.org
Phosphorylated BLNK (SLP65, in Antigen:p-BCR:p-SYK:p-BLNK:CIN85:GRB2:SOS1) binds BTK, PLCG2, VAV1, NCK1

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-9606151

**Type:** binding

**Compartments:** plasma membrane

Phosphorylated BLNK (also called BASH or SLP-65) at the plasma membrane recruits BTK, PLC gamma, VAV, GRB2, and NCK (Fu and Chan 1997, Fu et al. 1998, Wienands et al. 1998, Su et al. 1999, Baba et al. 2001, Chiu et al. 2002). The SH2 domain of BTK binds phosphorylated BLNK (Hashimoto et al. 1999, Su et al. 1999, Baba et al. 2001). BLNK is constitutively bound to CIN85 and phosphorylated BLNK is bound to a large complex containing CIN85, SOS1, GRB2, phosphorylated SYK, and the B cell receptor.

**Preceded by:** p-6Y-SYK phosphorylates BLNK (SLP65)

**Followed by:** p-SYK and LYN phosphorylate BTK

**Literature references**


p-SYK and LYN phosphorylate BTK

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-9606163

**Type:** uncertain

**Compartments:** plasma membrane

**Inferred from:** LYN, SYK phosphorylate BTK (Gallus gallus), Lyn, p-Syk phosphorylate Btk (Mus musculus)

LYN and activated (phosphorylated) SYK phosphorylate BTK (Baba et al. 2001, Lin et al. 2009, also inferred from chicken homologs and mouse homologs) after BTK is recruited to the plasma membrane by phosphorylated BLNK (Baba et al. 2001) and phosphoinositol 3,4,5-trisphosphate (PIP3) (Salim et al. 1996). Phosphorylation of tyrosine-551 occurs within 30 seconds of B cell receptor activation and returns to low phosphorylation after 30 minutes (Nisitani et al. 1999).

**Preceded by:** Phosphorylated BLNK (SLP65, in Antigen:p-BCR:p-SYK:p-BLNK:CIN85:GRB2:SOS1) binds BTK, PLCG2, VAV1, NCK1

**Followed by:** BTK autophosphorylates

**Literature references**


<table>
<thead>
<tr>
<th>Date</th>
<th>Role</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-14</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2018-07-18</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
**BTK autophosphorylates**

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-9606159

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** Btk autophosphorylates (Mus musculus)

After phosphorylation on tyrosine-551 by LYN or SYK, BTK autophosphorylates tyrosine-223 (Wahl et al. 1997, Nore et al. 2003, and inferred from mouse homologs). Maximum autophosphorylation occurs 5 minutes after activation of the B cell receptor and returns to low phosphorylation after 30 minutes (Nisitani et al. 1999).

**Preceded by:** p-SYK and LYN phosphorylate BTK

**Followed by:** Phosphorylated BTK phosphorylates PLCG2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author(s)</th>
<th>Reviewer(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-14</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2018-07-18</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
Phosphorylated BTK phosphorylates PLCG2

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-9606162

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** Phosphorylation of PLC-gamma (Rattus norvegicus)

Activated BTK (BTK phosphorylated on tyrosine-551 and tyrosine-223) bound to phosphorylated BLNK phosphorylates phospholipase gamma-2 (PKCG2) on tyrosines 753, 759, and 1217 (Rodriguez et al. 2001 and inferred from the rat homolog) thereby activating PLCG2 to hydrolyze phosphatidylinositol 4,5-bisphosphate, yielding the second messengers diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) (Carter et al. 1991, Roifman and Wang 1992, Kim et al. 2004, Sekiya et al. 2004). PLCG2 also binds phosphoinositol 3,4,5-trisphosphate (PIP3) produced by PI3K at the plasma membrane.

**Preceded by:** BTK autophosphorylates

**Followed by:** BLNK (SLP-65) Signalosome hydrolyzes phosphatidyinositol bisphosphate forming diacylglycerol and inositol-1,4,5-trisphosphate

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-14</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2018-07-18</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>

https://www.reactome.org
CD19 is phosphorylated

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-9606883

**Type:** uncertain

**Compartments:** plasma membrane

**Inferred from:** Cd19 is phosphorylated (Mus musculus)

In response to BCR activation, CD19 in a stable complex with VAV1 is phosphorylated by Src kinases (Chalupny et al. 1993, inferred from mouse homologs in Xu et al. 2002), one of which may be LYN (inferred from mouse homologs).

**Preceded by:** The Immunoglobulin of the BCR binds antigen

**Followed by:** p-CD19:VAV binds PI3K and GRB2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-22</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2018-07-18</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>

Preceded by: CD19 is phosphorylated

Followed by: CD19 Signalosome phosphorylates PI(4,5)P2 forming PI(3,4,5)P3

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-22</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2018-07-18</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
p-PIK3AP1 (p-BCAP) binds PIK3CD:PIK3R1 (PI3K delta) 

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-9606160

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** PIK3AP1 (BCAP) binds PIK3CD:PIK3R1 (Gallus gallus)

Phosphorylated PIK3AP1 (BCAP) binds the p85 subunit of phosphoinositide 3-kinase (PI3K) (inferred from chicken homologs). PIK3AP1 is phosphorylated by LYN in response to activation of CD19.

**Preceded by:** p-6Y-SYK phosphorylates BLNK (SLP65)

**Followed by:** BCAP Signalosome phosphorylates PI(4,5)P2 forming PI(3,4,5)P3

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-14</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2018-07-18</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
PI(3,4,5)P3 (PIP3) binds DAPP1 (BAM32) and DAPP1 is phosphorylated

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-9606884

**Type:** uncertain

**Compartments:** plasma membrane

DAPP1 (BAM32) is recruited to the plasma membrane by the binding of its PH domain to phosphoinositol 3,4,5-trisphosphate (PIP3) (Dowler et al. 1999, Marshall et al. 2000, Ferguson et al. 2000). DAPP1 also binds phosphatidylinositol 3,4-bisphosphate (Dowler et al. 1999, Ferguson et al. 2000) and therefore remains bound at the plasma membrane after PIP3 has been dephosphorylated by phosphatases. At the plasma membrane DAPP1 is phosphorylated by a Src family kinase, likely LYN in B cells (Dowler et al. 2000).

**Preceded by:** BCAP Signalosome phosphorylates PI(4,5)P2 forming PI(3,4,5)P3, CD19 Signalosome phosphorylates PI(4,5)P2 forming PI(3,4,5)P3

**Followed by:** p-DAPP1 (p-BAM32) binds PLCG2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-22</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2018-07-18</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>

[https://www.reactome.org](https://www.reactome.org)
p-DAPP1 (p-BAM32) binds PLCG2

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-9606894

**Type:** binding

**Compartments:** plasma membrane

Phosphorylated DAPP1 (BAM32) bound to phosphoinositol 3,4,5-trisphosphate (PIP3) at the plasma membrane binds phospholipase gamma-2 (PLCG2) (Marshall et al. 2000).

**Preceded by:** PI(3,4,5)P3 (PIP3) binds DAPP1 (BAM32) and DAPP1 is phosphorylated

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2018-04-23</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2018-07-18</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
BCAP Signalosome phosphorylates PI(4,5)P2 forming PI(3,4,5)P3

Location: Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

Stable identifier: R-HSA-2045911

Type: transition

Compartments: plasma membrane

PI3K generates phosphoinositol-3,4,5-trisphosphate (PIP3) from PIP2 after activation of the BCR (Gold et al. 1992, Chantry et al. 1997). Experiments in mice indicate that PI3K associated with BCAP is partly responsible for the activity (Aiba et al. 2008). (PI3K associated with CD19 is also partly responsible (Aiba et al. 2008).)

Preceded by: p-PIK3AP1 (p-BCAP) binds PIK3CD:PIK3R1 (PI3K delta)

Followed by: PI(3,4,5)P3 (PIP3) binds DAPP1 (BAM32) and DAPP1 is phosphorylated

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-01-10</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>

https://www.reactome.org
CD19 Signalosome phosphorylates PI(4,5)P2 forming PI(3,4,5)P3

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-2076220

**Type:** transition

**Compartments:** plasma membrane

PI3K generates phosphoinositol-3,4,5-trisphosphate (PIP3) from PIP2 after activation of the BCR (Gold et al. 1992). Experiments in mice indicate that PI3K associated with CD19 is partly responsible for the activity (Buhl et al. 1997, Otero et al. 2001, Aiba et al. 2008). (PI3K associated with BCAP is also partly responsible (Aiba et al. 2008).)

**Preceded by:** p-CD19:VAV binds PI3K and GRB2

**Followed by:** PI(3,4,5)P3 (PIP3) binds DAPP1 (BAM32) and DAPP1 is phosphorylated

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Edition</th>
<th>Authored, Edited</th>
<th>Reviewed</th>
<th>Revised</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-01-10</td>
<td>Authored, Edited</td>
<td>May, B.</td>
<td></td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
<td></td>
</tr>
</tbody>
</table>

https://www.reactome.org
BLNK (SLP-65) Signalosome hydrolyzes phosphatidylinositol bisphosphate forming diacylglycerol and inositol-1,4,5-trisphosphate

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-1112666

**Type:** transition

**Compartments:** plasma membrane, cytosol


**Preceded by:** Phosphorylated BTK phosphorylates PLCG2

**Followed by:** IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel

**Literature references**


<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-01-19</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-169680

**Type:** binding

**Compartments:** cytosol, endoplasmic reticulum membrane

**Inferred from:** IP3 binds to the IP3 receptor, opening the Ca2+ channel (Rattus norvegicus)

The IP3 receptor (IP3R) is an IP3-gated calcium channel. It is a large, homotetrameric protein, similar to other calcium channel proteins such as ryanodine. The four subunits form a 'four-leafed clover' structure arranged around the central calcium channel. Binding of ligands such as IP3 results in conformational changes in the receptor's structure that leads to channel opening.

**Preceded by:** BLNK (SLP-65) Signalosome hydrolyzes phosphatidyinositol bisphosphate forming diacylglycerol and inositol-1,4,5-trisphosphate

**Followed by:** IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004-03-31</td>
<td>Authored</td>
<td>Jassal, B., Le Novere, N.</td>
</tr>
<tr>
<td>2006-10-10</td>
<td>Edited</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2009-06-02</td>
<td>Reviewed</td>
<td>Gillespie, ME.</td>
</tr>
</tbody>
</table>
IP3R: I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol

Location: Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

Stable identifier: R-HSA-169683

Type: transition

Compartments: endoplasmic reticulum membrane

Inferred from: Calcium release from intracellular stores by IP3 receptor activation (Rattus norvegicus)

IP3 promotes the release of intracellular calcium.

Preceded by: IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel

Followed by: STIM1 oligomerizes, Calcium binds calmodulin

Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004-03-31</td>
<td>Authored</td>
<td>Jassal, B., Le Novere, N.</td>
</tr>
<tr>
<td>2006-10-10</td>
<td>Edited</td>
<td>Jassal, B.</td>
</tr>
<tr>
<td>2009-06-02</td>
<td>Reviewed</td>
<td>Gillespie, ME.</td>
</tr>
</tbody>
</table>
**STIM1 oligomerizes**

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-1168376

**Type:** transition

**Compartments:** endoplasmic reticulum membrane, endoplasmic reticulum lumen, cytosol

In the resting state the luminal domain of STIM1 binds Ca2+ ions within the endoplasmic reticulum and this binding prevents dimerization of STIM1 (Luik et al. 2008). Upon depletion of Ca2+ ions from the endoplasmic reticulum, STIM1 is no longer bound to Ca2+ and forms homodimers (Muik et al. 2008, Luik et al. 2008, Park et al. 2009).

**Preceded by:** IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol

**Followed by:** STIM1 binds TRPC1 forming STIM1:TRPC1 complex, STIM1 activation of CRAC

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011-01-19</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
**STIM1 activation of CRAC**

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-434700

**Type:** binding

**Compartments:** plasma membrane

**Inferred from:** Stim activation of CRAC (Drosophila melanogaster)

Sustained calcium signalling in lymphocytes and platelets requires the uptake of extracellular calcium when intracellular stores are depleted. The process whereby intracellular calcium depletion stimulates calcium uptake is often referred to as Store-operated calcium entry (SOCE). Store depletion is sensed by stromal interaction molecule 1 (STIM1), which then translocates to the plasma membrane and associates with 2 dimers of Orai to form a calcium-release activated calcium (CRAC) channel.

**Preceded by:** STIM1 oligomerizes

**Followed by:** CRAC translocates calcium from the extracellular region to the cytosol

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author/Reviewer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-09-04</td>
<td>Authored</td>
<td>Akkerman, JW.</td>
</tr>
<tr>
<td>2010-06-07</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-06-07</td>
<td>Reviewed</td>
<td>Kunapuli, SP.</td>
</tr>
</tbody>
</table>
STIM1 binds TRPC1 forming STIM1:TRPC1 complex

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-2089927

**Type:** binding

**Compartments:** endoplasmic reticulum membrane, plasma membrane

The polybasic region of STIM1 interacts with 2 aspartate residues in the C-terminal region of TRPC1 (Zeng et al. 2008, Huang et al. 2006). The STIM1:TRPC1 complex can form a ternary complex with ORAI1 (Ong et al. 2007, Jardin et al. 2008) and ORAI participates in function of STIM1:TRPC1 channels (Cheng et al. 2008, Cheng et al. 2011). As inferred from chicken DT40 cells, TRPC1 (and possibly other TRP channels) participates in store-operated calcium influx during signaling by the B cell receptor (Mori et al. 2002).

**Preceded by:** STIM1 oligomerizes

**Followed by:** TRPC1 translocates calcium from the extracellular region to the cytosol

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-01-31</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td>Wienands, J.</td>
</tr>
</tbody>
</table>
CRAC translocates calcium from the extracellular region to the cytosol

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-434798

**Type:** transition

**Compartments:** plasma membrane

**Inferred from:** Calcium influx via CRAC (Drosophila melanogaster)

Activation of Calcium-release-activated (CRAC) channels allows influx of calcium. The Orai component of CRAC is responsible for the selectivity of the channel, while the Stim component is responsible for activation.

**Preceded by:** STIM1 activation of CRAC

**Followed by:** Calcium binds calmodulin

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009-09-04</td>
<td>Authored</td>
<td>Akkerman, JW.</td>
</tr>
<tr>
<td>2010-06-07</td>
<td>Edited</td>
<td>Jupe, S.</td>
</tr>
<tr>
<td>2010-06-07</td>
<td>Reviewed</td>
<td>Kunapuli, SP.</td>
</tr>
</tbody>
</table>
TRPC1 translocates calcium from the extracellular region to the cytosol

Location: Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

Stable identifier: R-HSA-2089943

Type: transition

Compartment(s): cytosol, extracellular region, plasma membrane

TRPC1 forms a channel that transports Ca$^{2+}$ across the plasma membrane. TRPC1 is gated by STIM1 (Ong et al. 2007).

Preceded by: STIM1 binds TRPC1 forming STIM1:TRPC1 complex

Followed by: Calcium binds calmodulin

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Reviewed By</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012-01-31</td>
<td>Authored, Edited</td>
<td>Wienands, J.</td>
</tr>
<tr>
<td>2012-02-11</td>
<td>Reviewed</td>
<td></td>
</tr>
</tbody>
</table>
**Calcium binds calmodulin**

**Location:** Antigen activates B Cell Receptor (BCR) leading to generation of second messengers

**Stable identifier:** R-HSA-74448

**Type:** binding

**Compartments:** cytosol

**Inferred from:** Calcium binds calmodulin (Bos taurus)

Upon increase in calcium concentration, calmodulin (CaM) is activated by binding to four calcium ions (Crouch and Klee 1980).

**Preceded by:** IP3R:I(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol, CRAC translocates calcium from the extracellular region to the cytosol, TRPC1 translocates calcium from the extracellular region to the cytosol

**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004-03-31</td>
<td>Authored</td>
<td>Jassal, B., Le Novere, N.</td>
</tr>
<tr>
<td>2008-01-11</td>
<td>Reviewed</td>
<td>Rush, MG.</td>
</tr>
<tr>
<td>2008-11-06</td>
<td>Edited</td>
<td>Jassal, B.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction 1

Antigen activates B Cell Receptor (BCR) leading to generation of second messengers 2

- The Immunoglobulin of the BCR binds antigen 4
- LYN, FYN, BLK phosphorylate ITAMs of Ig-alpha (CD79A) and Ig-beta (CD79B) 5
- SYK binds the activated BCR 7
- SYK autophosphorylates at the activated BCR 8
- p-6Y-SYK phosphorylates BLNK (SLP65) 9
- Phosphorylated BLNK (SLP65, in Antigen:p-BCR:p-SYK:p-BLNK:CIN85:GRB2:SOS1) binds BTK, PLCG2, VAV1, NCK1 11
- p-SYK and LYN phosphorylate BTK 13
- BTK autophosphorylates 15
- Phosphorylated BTK phosphorylates PLCG2 16
- CD19 is phosphorylated 17
- p-CD19:VAV binds PI3K and GRB2 18
- p-PIK3AP1 (p-BCAP) binds PIK3CD:PIK3R1 (PI3K delta) 19
- PI(3,4,5)P3 (PIP3) binds DAPP1 (BAM32) and DAPP1 is phosphorylated 20
- p-DAPP1 (p-BAM32) binds PLCG2 21
- BCAP Signalosome phosphorylates PI(4,5)P2 forming PI(3,4,5)P3 22
- CD19 Signalosome phosphorylates PI(4,5)P2 forming PI(3,4,5)P3 23
- BLNK (SLP-65) Signalosome hydrolyzes phosphatidyinositol bisphosphate forming diacylglycerol and inositol-1,4,5-trisphosphate 24
- IP3 binds to the IP3 receptor, opening the endoplasmic reticulum Ca2+ channel 26
- IP3R:1(1,4,5)P3 tetramer transports Ca2+ from ER lumen to cytosol 27
- STIM1 oligomerizes 28
- STIM1 activation of CRAC 29
- STIM1 binds TRPC1 forming STIM1:TRPC1 complex 30
- CRAC translocates calcium from the extracellular region to the cytosol 31
- TRPC1 translocates calcium from the extracellular region to the cytosol 32
- Calcium binds calmodulin 33

Table of Contents 34