TNFR1-mediated ceramide production

Gillespie, ME., Shamovsky, V., Wajant, H.

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.
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: 75

This document contains 1 pathway and 3 reactions (see Table of Contents)
TNFR1-mediated ceramide production

Stable identifier: R-HSA-5626978

TNF-alpha activates sphingomyelinase (SMASE) proteins to catalyze hydrolysis of sphingomyeline into ceramide. Two types of SMASE can be distinguished downstream of TNFR1 signaling, acid and neutral SMASEs (Adam-Klages S et al. 1996, 1998). Neutral SMASE (such as SMPD2,3) has a pH optimum of 7.4, requires Mg2+ ions and is found at the plasma membrane (Rao BG and Spence MW 1976). Acid SMASE is active at pH 4-5, is Zn2+-dependent and is mainly localized in the lysosomes. The death domain of TNFR1 that is responsible for the initiation of the apoptotic pathway also mediates activation of an acid SMASE. The two proapoptotic adaptor proteins TRADD and FADD are also involved in the activation of acid SMASE signaling events (Schwandner R et al. 1998). TNF-alpha can also activate the pro-apoptotic acidic SMASE via caspase-8 mediated activation of caspase-7 which in turn proteolytically cleaves and activates the 72kDa pro-acid SMASE form (Edelmann B et al. 2011). Neutral SMASE(SMPD) binds to adaptor protein NSMAF (FAN), which bridges it to NSMASE-activating domain (NSD) of TNFR1 (Adam D et al. 1996; Adam-Klages S et al. 1996; Ségui B et al. 2001). Activation of SMPD2,3 leads to an accumulation of ceramide at the cell surface.

Ceramide metabolism generates a cascade of bioactive lipids, all of which carry a specific signaling capacity. Ceramide can be converted by ceramidase into sphingosine, which in turn is phosphorylated by sphingosine kinase into sphingosine-1-phosphate (S1P). These lipids exert opposite biological effects: ceramide and sphingosine are able to induce anti-proliferative and pro-apoptotic responses, whereas S1P is a cytoprotective molecule that promotes cell growth and counteracts apoptotic stimuli (Cuvillier O et al.1996).

Literature references

## Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-02-15</td>
<td>Edited</td>
<td>Shamovsky, V.</td>
</tr>
<tr>
<td>2015-03-12</td>
<td>Reviewed</td>
<td>Gillespie, ME.</td>
</tr>
<tr>
<td>2015-05-12</td>
<td>Authored</td>
<td>Shamovsky, V.</td>
</tr>
<tr>
<td>2015-08-25</td>
<td>Reviewed</td>
<td>Wajant, H.</td>
</tr>
</tbody>
</table>
TNF-alpha:TNFR1 binds NSMAF

**Location:** TNFR1-mediated ceramide production

**Stable identifier:** R-HSA-5626988

**Type:** binding

**Compartments:** cytosol, plasma membrane

TNF-alpha-induced signaling by TNFR1 promotes the activation of sphingomyelin phosphodiesterase (sphingomyelinase or SMASE) signaling pathways. SMASE is a family of agonist-activated effector enzymes that hydrolyze phospholipids on the membrane compartments to produce ceramide, a lipid-signaling molecule.

Factor associated with neutral sphingomyelinase activation (FAN or NSMAF) is an adaptor protein that constitutively binds to the neutral SMASE activation domain (NSD) of TNFR1 (Adam-Klages S et al. 1996). NSMAF (FAN) is thought to directly link TNFR1 to the activation of neutral sphingomyelinase (N-SMASE) such as sphingomyelin phosphodiesterase 2 or 3 (SMPD2, SMPD3).

**Followed by:** TNF-alpha:TNFR1:NSMAF binds GNB2L1

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-02-15</td>
<td>Edited</td>
<td>Shamovsky, V.</td>
</tr>
<tr>
<td>2015-03-12</td>
<td>Reviewed</td>
<td>Gillespie, ME.</td>
</tr>
<tr>
<td>2015-05-12</td>
<td>Authored</td>
<td>Shamovsky, V.</td>
</tr>
<tr>
<td>2015-08-25</td>
<td>Reviewed</td>
<td>Wajant, H.</td>
</tr>
</tbody>
</table>

https://reactome.org
** TNF-alpha:TNFR1:NSMAF binds GNB2L1 **

- **Location:** TNFR1-mediated ceramide production
- **Stable identifier:** R-HSA-5626982
- **Type:** binding
- **Compartments:** cytosol, plasma membrane

Guanine nucleotide-binding protein subunit beta-2-like 1 (GNB2L1), which is also known as a receptor for activated protein kinase C (RACK1), interacts with NSMAF (FAN) in vitro as shown by glutathione S-transferase-based coprecipitation assays as well as coimmunoprecipitation experiments using human embryonic kidney 293 (HEK293) cells (Tcherkasowa AE et al. 2002). Confocal laser-scanning microscopy studies suggest that overexpressed NSMAF (FAN) and GNB2L1 (RACK) colocalize at the plasma membrane together with TNFR1 (Tcherkasowa AE et al. 2002). Furthermore, isolation of TNF receptors containing vesicles from TNF-stimulated Jurkat or HeLa cells by help of biotinylated TNF and MACS Streptavidin Microbeads derived and coupled with immunoblotting assay showed that GNB2L1(RACK1) interacts with TNF1 (Philipp S et al. 2010). The data suggest that GNB2L1(RACK1) modulates activation of neutral sphingomyelinase (N-SMASE) triggered by TNF.

**Preceded by:** TNF-alpha:TNFR1 binds NSMAF  
**Followed by:** TNF-alpha:TNFR1:NSMAF:GNB2L1 associates with SMPD2,3

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-02-15</td>
<td>Edited</td>
<td>Shamovsky, V.</td>
</tr>
<tr>
<td>2015-03-12</td>
<td>Reviewed</td>
<td>Gillespie, ME.</td>
</tr>
<tr>
<td>2015-05-12</td>
<td>Authored</td>
<td>Shamovsky, V.</td>
</tr>
<tr>
<td>2015-08-25</td>
<td>Reviewed</td>
<td>Wajant, H.</td>
</tr>
</tbody>
</table>
TNF-alpha:TNFR1:NSMAF:GNB2L1 associates with SMPD2,3

**Location:** TNFR1-mediated ceramide production

**Stable identifier:** R-HSA-5626981

**Type:** binding

**Compartments:** plasma membrane

Sphingolipid signaling is initiated by neutral sphingomyelinase (neutral SMASE), a family of agonist-activated effector enzymes.

**Preceded by:** TNF-alpha:TNFR1:NSMAF binds GNB2L1

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>By</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015-02-15</td>
<td>Edited</td>
<td>Shamovsky, V.</td>
</tr>
<tr>
<td>2015-03-12</td>
<td>Reviewed</td>
<td>Gillespie, ME.</td>
</tr>
<tr>
<td>2015-05-12</td>
<td>Authored</td>
<td>Shamovsky, V.</td>
</tr>
<tr>
<td>2015-08-25</td>
<td>Reviewed</td>
<td>Wajant, H.</td>
</tr>
</tbody>
</table>
Table of Contents

Introduction

TNFR1-mediated ceramide production

 TNF-alpha:TNFR1 binds NSMAF

 TNF-alpha:TNFR1:NSMAF binds GNB2L1

 TNF-alpha:TNFR1:NSMAF:GNB2L1 associates with SMPD2,3

Table of Contents

https://reactome.org