Negative regulation of activity of TFAP2 (AP-2) family transcription factors

Bogachek, MV., Dawid, IB., May, B., Orlic-Milacic, M., Weigel, RJ., Zarelli, VE.

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.

22/11/2021
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: 78

This document contains 1 pathway and 6 reactions (see Table of Contents)
Negative regulation of activity of TFAP2 (AP-2) family transcription factors

Stable identifier: R-HSA-8866904

Transcriptional activity of TFAP2 (AP-2) transcription factor family homo- and heterodimers is inhibited by binding of KCTD1 or KCTD15 to the AP-2 transactivation domain (Ding et al. 2009, Zarelli and Dawid 2013). Transcriptional activity of TFAP2A, TFAP2B and TFAP2C is also negatively regulated by SUMOylation mediated by UBE2I (UBC9) (Eloranta and Hurst 2002, Berlato et al. 2011, Impens et al. 2014, Bogachek et al. 2014). Binding of the tumor suppressor WWOX to TFAP2C inhibits TFAP2C translocation to the nucleus (Aqeilan et al. 2004). Transcription of the TFAP2A gene may be inhibited by CREB and E2F1 (Melnikova et al. 2010).

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Activity</th>
<th>Users</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-03-14</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2016-05-04</td>
<td>Reviewed</td>
<td>Dawid, IB., Zarelli, VE.</td>
</tr>
<tr>
<td>2016-05-17</td>
<td>Reviewed</td>
<td>Weigel, RJ., Bogachek, MV.</td>
</tr>
</tbody>
</table>
**WWOX binds TFAP2C**

**Location:** Negative regulation of activity of TFAP2 (AP-2) family transcription factors

**Stable identifier:** R-HSA-8864569

**Type:** binding

**Compartments:** cytosol

The tumor suppressor WWOX associates with TFAP2C (AP-2 gamma) in the cytosol and prevents TFAP2C nuclear translocation and TFAP2C-mediated transcription. WWOX is also able to bind to TFAP2A, but the biological role of this interaction has not been examined (Aqeilan et al. 2004). Low levels of WWOX and high levels of TFAP2C are associated with tamoxifen resistance in breast cancer (Guler et al. 2007).

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-03-14</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2016-05-04</td>
<td>Reviewed</td>
<td>Dawid, IB., Zarelli, VE.</td>
</tr>
<tr>
<td>2016-05-17</td>
<td>Reviewed</td>
<td>Weigel, RJ., Bogachek, MV.</td>
</tr>
</tbody>
</table>
**KCTD1 binds TFAP2 homo- and heterodimers**

**Location:** Negative regulation of activity of TFAP2 (AP-2) family transcription factors

**Stable identifier:** R-HSA-8864343

**Type:** binding

**Compartments:** nucleoplasm

The BTB domain at the N-terminus of KCTD1 binds to the N-terminal transactivation domain of TFAP2 (AP-2) family transcription factors. Binding of KCTD1 to TFAP2A, TFAP2B and TFAP2C inhibits their transcriptional activity, thus acting as a negative regulator (Ding et al. 2009). Based on sequence similarity, KCTD1 is assumed to interact with TFAP2D and TFAP2E.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Editor(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-03-14</td>
<td>Authored,Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2016-05-04</td>
<td>Reviewed</td>
<td>Dawid, IB., Zarelli, VE.</td>
</tr>
<tr>
<td>2016-05-17</td>
<td>Reviewed</td>
<td>Weigel, RJ., Bogachek, MV.</td>
</tr>
</tbody>
</table>
KCTD15 binds TFAP2 homo- and heterodimers

**Location:** Negative regulation of activity of TFAP2 (AP-2) family transcription factors

**Stable identifier:** R-HSA-8864361

**Type:** binding

**Compartments:** nucleoplasm

**Inferred from:** kctd15 binds tfap2b,tfap2c dimers (Danio rerio)

KCTD15 binds to the transactivation domain of the TFAP2 (AP-2) family transcription factors and inhibits their transcriptional activity without affecting their protein levels, dimerization or nuclear localization. KCTD15-mediated inhibition of TFAP2 inhibits neural crest formation. KCTD15 interaction with TFAP2A was demonstrated using human and zebrafish proteins, while KCTD15 interaction with TFAP2B and TFAP2C is inferred from their ability to inhibit AP-2 reporter activity (Zarelli and Dawid 2013). Based on sequence similarity, it is assumed that TFAP2D and TFAP2E are candidate interaction partners of KCTD15.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016-03-14</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2016-05-04</td>
<td>Reviewed</td>
<td>Dawid, IB., Zarelli, VE.</td>
</tr>
<tr>
<td>2016-05-17</td>
<td>Reviewed</td>
<td>Weigel, RJ., Bogachek, MV.</td>
</tr>
</tbody>
</table>
SUMOylation of TFAP2A with SUMO1

Location: Negative regulation of activity of TFAP2 (AP-2) family transcription factors

Stable identifier: R-HSA-3234081

Type: transition

Compartments: nucleoplasm

Inferred from: SUMOylation of TFAP2C with SUMO1 (Homo sapiens)

UBE2I (UBC9) interacts with TFAP2A, TFAP2B and TFAP2C, and the interaction site has been mapped to the C terminal region of TFAP2C; SUMOylation occurs on lysine-10 (Eloranta and Hurst 2002). As lysine-10 is conserved in TFAP2A and TFAP2B, SUMOylation of these factors is assumed to be on lysine-10 (Eloranta and Hurst 2002; Impens et al. 2014). SUMOylation causes a reduction in AP-2 transcriptional activation function but is required for its repressive function. A dominant negative mutant of UBC9 led to increased activation and reduced repressor function of TFAP2A and C, supporting the role of UBC9 in SUMOylation (Eloranta and Hurst 2002; Berlato et al. 2011). Isoform 1a of TFAP2A is SUMOylated, isoforms 1b and 1c lack lysine 10 and are not SUMOylated (Berlato et al. 2011). TFAP2D and TFAP2E lack lysine-10 and are assumed not to be SUMOylated. SUMOylation of TFAP2A blocked its ability to induce the expression of luminal genes and repression of basal genes (Bogachek et al. 2014). Disruption of the sumoylation pathway by knockdown of sumoylation enzymes, mutation of the SUMO-target lysine of TFAP2A, or treatment with sumoylation inhibitors induced MET in basal breast cancers, which was dependent on TFAP2A (Bogachek et al. 2014).

Literature references


Editions

<table>
<thead>
<tr>
<th>Editions</th>
<th>Author, Edited</th>
<th>Reviewed, Edited</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-03-27</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2016-03-14</td>
<td>Edited</td>
<td>Dawid, IB., Zarelli, VE.</td>
</tr>
<tr>
<td>2016-05-04</td>
<td>Reviewed</td>
<td>Weigel, RJ., Bogachek, MV.</td>
</tr>
<tr>
<td>2016-05-17</td>
<td>Reviewed</td>
<td></td>
</tr>
</tbody>
</table>
SUMOylation of TFAP2B with SUMO1

**Location:** Negative regulation of activity of TFAP2 (AP-2) family transcription factors

**Stable identifier:** R-HSA-3234084

**Type:** transition

**Compartments:** nucleoplasm

**Inferred from:** SUMOylation of TFAP2C with SUMO1 (Homo sapiens)

UBE2I (UBC9) interacts with the C terminal region of TFAP2B (Eloranta and Hurst 2002). As inferred from TFAP2C, SUMOylation of TFAP2B occurs at lysine in the VKYE motif and, therefore UBC9 is assumed to catalyze the ligation of SUMO1 to TFAP2B.

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-03-27</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2016-03-14</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2016-05-04</td>
<td>Reviewed</td>
<td>Dawid, IB., Zarelli, VE.</td>
</tr>
<tr>
<td>2016-05-17</td>
<td>Reviewed</td>
<td>Weigel, RJ., Bogachek, MV.</td>
</tr>
</tbody>
</table>
SUMOylation of TFAP2C with SUMO1

Location: Negative regulation of activity of TFAP2 (AP-2) family transcription factors

Stable identifier: R-HSA-3234094

Type: transition

Compartments: nucleoplasm

UBE2I (UBC9) interacts with the C-terminal region of TFAP2C (Eloranta and Hurst 2002). SUMOylation of TFAP2C occurs at lysine-10 and causes a reduction in its transcriptional activation activity. A dominant negative mutant of UBC9 led to increased activity of TFAP2C therefore UBC9 is assumed to catalyze the ligation of SUMO1 to TFAP2C.

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013-03-27</td>
<td>Authored, Edited</td>
<td>May, B.</td>
</tr>
<tr>
<td>2016-03-14</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2016-05-04</td>
<td>Reviewed</td>
<td>Dawid, IB., Zarelli, VE.</td>
</tr>
<tr>
<td>2016-05-17</td>
<td>Reviewed</td>
<td>Weigel, RJ., Bogachek, MV.</td>
</tr>
</tbody>
</table>
# Table of Contents

Introduction

- Negative regulation of activity of TFAP2 (AP-2) family transcription factors
  - WWOX binds TFAP2C
  - KCTD1 binds TFAP2 homo- and heterodimers
  - KCTD15 binds TFAP2 homo- and heterodimers
  - SUMOylation of TFAP2A with SUMO1
  - SUMOylation of TFAP2B with SUMO1
  - SUMOylation of TFAP2C with SUMO1