Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

Orlic-Milacic, M., Rivero Crespo, F.

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.

20/02/2020
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: 71

This document contains 1 pathway and 11 reactions (see Table of Contents)
Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

Stable identifier: R-HSA-5625886

Compartments: cytosol, nucleoplasm

PKN1, activated by phosphorylation at threonine T774, binds activated AR (androgen receptor) and promotes transcription from AR-regulated promoters. On one hand, phosphorylated PKN1 promotes the formation of a functional complex of AR with the transcriptional coactivator NCOA2 (TIF2) (Metzger et al. 2003). On the other hand, binding of phosphorylated PKN1, in complex with the activated AR, to androgen-responsive promoters of KLK2 and KLK3 (PSA) genes, leads to PKN1-mediated histone phosphorylation. PKN1-phosphorylated histones recruit histone demethylases KDM4C (JMJD2C) and KDM1A (LSD1), and the ensuing demethylation of histones associated with the promoter regions of KLK2 and KLK3 genes increases their transcription (Metzger et al. 2005, Metzger et al. 2008).

Literature references


## Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
<td>Rivero Crespo, F.</td>
</tr>
<tr>
<td>2015-02-02</td>
<td>Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
</tbody>
</table>
**Phosphorylated PKN1 binds androgen receptor (AR)**

**Location:** Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

**Stable identifier:** R-HSA-5625717

**Type:** binding

**Compartments:** nucleoplasm

Activated PKN1 binds androgen-activated AR (androgen receptor) (Metzger et al. 2003).

**Followed by:** p-T774-PKN1:AR:Androgen complex translocates to the nucleus

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author</th>
<th>Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
<td>Rivero Crespo, F.</td>
</tr>
</tbody>
</table>
p-T774-PKN1:AR:Androgen complex translocates to the nucleus

**Location:** Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

**Stable identifier:** R-HSA-5625738

**Type:** transition

**Compartments:** cytosol, nucleoplasm

Binding of activated PKN1 to the androgen-activated AR (androgen receptor) promotes translocation of the p-T774-PKN1:AR:Androgen complex into the nucleus (Metzger et al. 2003).

**Preceded by:** Phosphorylated PKN1 binds androgen receptor (AR)

**Followed by:** PKN1 stimulates association of AR with NCOA2

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Edition Date</th>
<th>Authorship</th>
<th>Editors</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
<td>Rivero Crespo, F.</td>
</tr>
</tbody>
</table>
PKN1 stimulates association of AR with NCOA2

**Location:** Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

**Stable identifier:** R-HSA-5625745

**Type:** binding

**Compartments:** nucleoplasm

Binding of PKN1 to androgen-activated AR (androgen receptor) promotes the formation of a functional complex of AR with the transcriptional coactivator NCOA2 (TIF2) (Metzger et al. 2003).

**Preceded by:** p-T774-PKN:AR:Androgen complex translocates to the nucleus

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Authorship Details</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
<td>Rivero Crespo, F.</td>
</tr>
</tbody>
</table>
PKN1:AR complex binds promoters of KLK2 and KLK3 genes

**Location:** Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

**Stable identifier:** R-HSA-5625774

**Type:** binding

**Compartments:** nucleoplasm

PKN1 in complex with the activated AR (androgen receptor) binds promoters of KLK2 and KLK3 (PSA) genes (Metzger et al. 2008).

**Followed by:** PKN1 phosphorylates histone 3 of nucleosomes associate with KLK2 and KLK3 promoters

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
</tr>
</tbody>
</table>

https://www.reactome.org
PKN1 phosphorylates histone 3 of nucleosomes associate with KLK2 and KLK3 promoters

**Location:** Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

**Stable identifier:** R-HSA-5625784

**Type:** transition

**Compartments:** nucleoplasm

PKN1 (PRK1), recruited to promoters of KLK2 and KLK3 (PSA) genes through association with the activated androgen receptor (AR), phosphorylates promoter-bound nucleosomes on threonine residue T12 (also labeled as T11 in literature) of histone 3, creating the H3T11 mark (Metzger et al. 2008).

**Preceded by:** PKN1:AR complex binds promoters of KLK2 and KLK3 genes

**Followed by:** Demethylase KDM4C binds KLK2 and KLK3 promoters

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
</tr>
</tbody>
</table>

https://www.reactome.org
Demethylase KDM4C binds KLK2 and KLK3 promoters

**Location:** Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

**Stable identifier:** R-HSA-5625796

**Type:** binding

**Compartments:** nucleoplasm

Phosphorylation of histone 3 at threonine residue T12 (also labeled in literature as T11) by PKN1 enables recruitment of demethylase KDM4C (JMJD2C) to trimethylated histone 3 at KLK2 and KLK3 promoters (Metzger et al. 2008). KDM4C specifically binds to trimethylated lysine residues (Whetstine et al. 2006).

**Preceded by:** PKN1 phosphorylates histone 3 of nucleosomes associate with KLK2 and KLK3 promoters

**Followed by:** KDM4C demethylates Me3K-10-H3 associated with KLK2 and KLK3 promoters

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Authorship</th>
<th>Authored/Edited</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
<td></td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
<td>Rivero Crespo, F.</td>
<td></td>
</tr>
</tbody>
</table>
KDM4C demethylates Me3K-10-H3 associated with KLK2 and KLK3 promoters

**Location:** Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

**Stable identifier:** R-HSA-5625797

**Type:** transition

**Compartments:** nucleoplasm

KDM4C (JMJD2C) demethylates trimethylated lysine K10 of histone 3 in nucleosomes associated with promoters of KLK2 and KLK3 (PSA) genes (Metzger et al. 2008), converting it to dimethylated lysine (Whetstine et al. 2006).

**Preceded by:** Demethylase KDM4C binds KLK2 and KLK3 promoters

**Followed by:** Demethylase KDM1A binds KLK2 and KLK3 promoters

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
</tr>
</tbody>
</table>

https://www.reactome.org
Demethylase KDM1A binds KLK2 and KLK3 promoters

**Location:** Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

**Stable identifier:** R-HSA-5625849

**Type:** binding

**Compartments:** nucleoplasm

PKN1-mediated phosphorylation of histone H3 threonine residue 12 (also labeled in literature as Thr11) enables recruitment of KDM1A (LSD1) demethylase to AR-regulated promoters KLK2 and KLK3 (PSA) (Metzger et al. 2008).

**Preceded by:** KDM4C demethylates Me3K-10-H3 associated with KLK2 and KLK3 promoters

**Followed by:** KDM1A demethylates dimethylated H3K9 (Me2K-10-H3) at KLK2 and KLK3 promoters

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Authors/Editors</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
<td>Rivero Crespo, F.</td>
</tr>
</tbody>
</table>
KDM1A demethylates dimethylated H3K9 (Me2K-10-H3) at KLK2 and KLK3 promoters

**Location:** Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

**Stable identifier:** R-HSA-5625848

**Type:** transition

**Compartments:** nucleoplasm

PKN1-mediated phosphorylation of histone H3 threonine residue T12 (also labeled in literature as Thr11) enables demethylation of histone H3 lysine K10 (also labeled in literature as K9) by demethylase KDM1A (LSD1) (Metzger et al. 2008). KDM1A acts on dimethylated and monomethylated H3K9 at AR-regulated promoters (Metzger et al. 2005), so it is shown that demethylation of dimethylated H3K9 (Me2K-10-H3) by KDM1A happens after demethylation of trimethylated H3K9 (Me3K-10-H3) by KDM4C (JMJD2C).

**Preceded by:** Demethylase KDM1A binds KLK2 and KLK3 promoters

**Followed by:** KDM1A demethylates monomethylated H3K9 (MeK-10-H3) at KLK2 and KLK3 promoters

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Authorship Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
</tr>
</tbody>
</table>

https://www.reactome.org
KDM1A demethylates monomethylated H3K9 (MeK-10-H3) at KLK2 and KLK3 promoters

**Location:** Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

**Stable identifier:** R-HSA-5625870

**Type:** transition

**Compartments:** nucleoplasm

PKN1-mediated phosphorylation of histone H3 threonine residue T12 (also labeled in literature as Thr11) enables demethylation of histone H3 lysine K10 (also labeled in literature as K9) by demethylase KDM1A (LSD1) (Metzger et al. 2008). KDM1A acts on dimethylated and monomethylated H3K9 at AR-regulated promoters (Metzger et al. 2005), so it is shown that KDM1A-mediated demethylation of monomethylated H3K9 (MeK-10-H3) happens sequentially after KDM1A-mediated demethylation of dimethylated H3K9 (Me2K-10-H3).

**Preceded by:** KDM1A demethylates dimethylated H3K9 (Me2K-10-H3) at KLK2 and KLK3 promoters

**Followed by:** PKN1 in complex with AR positively regulates expression of KLK2 and KLK3

**Literature references**


**Editions**

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
</tr>
</tbody>
</table>
PKN1 in complex with AR positively regulates expression of KLK2 and KLK3

Location: Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3

Stable identifier: R-HSA-5625883

Type: omitted

Compartments: extracellular region, nucleolus

PKN1-facilitated demethylation of histones at promoters of KLK2 and KLK3 genes stimulates transcription of KLK2 and KLK3 (Metzger et al. 2005, Metzger et al. 2008).

Preceded by: KDM1A demethylates monomethylated H3K9 (MeK-10-H3) at KLK2 and KLK3 promoters

Literature references


Editions

<table>
<thead>
<tr>
<th>Date</th>
<th>Author/Editor</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014-10-24</td>
<td>Authored, Edited</td>
<td>Orlic-Milacic, M.</td>
</tr>
<tr>
<td>2014-12-26</td>
<td>Authored</td>
<td>Rivero Crespo, F.</td>
</tr>
</tbody>
</table>
# Table of Contents

- **Introduction**
- Activated PKN1 stimulates transcription of AR (androgen receptor) regulated genes KLK2 and KLK3
  - Phosphorylated PKN1 binds androgen receptor (AR)
  - p-T774-PKN1:AR:Androgen complex translocates to the nucleus
  - PKN1 stimulates association of AR with NCOA2
  - PKN1:AR complex binds promoters of KLK2 and KLK3 genes
  - PKN1 phosphorylates histone 3 of nucleosomes associate with KLK2 and KLK3 promoters
  - Demethylase KDM4C binds KLK2 and KLK3 promoters
  - KDM4C demethylates Me3K-10-H3 associated with KLK2 and KLK3 promoters
  - Demethylase KDM1A binds KLK2 and KLK3 promoters
  - KDM1A demethylates dimethylated H3K9 (Me2K-10-H3) at KLK2 and KLK3 promoters
  - KDM1A demethylates monomethylated H3K9 (MeK-10-H3) at KLK2 and KLK3 promoters
  - PKN1 in complex with AR positively regulates expression of KLK2 and KLK3