SARS-CoV-1 targets host intracellular signalling and regulatory pathways

D'Eustachio, P., Messina, F., Shamovsky, V., Stephan, R.

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

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This is just an excerpt of a full-length report for this pathway. To access the complete report, please download it at the Reactome Textbook.

25/12/2022

https://reactome.org
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: 83

This document contains 1 pathway and 7 reactions (see Table of Contents)
SARS-CoV-1 targets host intracellular signalling and regulatory pathways

**Stable identifier:** R-HSA-9735871

**Diseases:** severe acute respiratory syndrome

Severe acute respiratory syndrome coronavirus type 1 (SARS-CoV1) encodes several proteins that modulate host intracellular signaling and regulatory pathways. Among them are nucleocapsid N, membrane M and 3a proteins that directly bind to host targets associated with SARS-CoV1 infection and cytokine production. This Reactome module describes several such binding events and their consequences. First, SARS-CoV1 M binds to phosphoinositidedependent protein kinase 1 (PDPK1) to inhibit PKB/Akt activation (Chan et al. 2007; Tsoi et al. 2014). Second, SARS-CoV1 N binds to SMAD3 to alter transforming growth factor β (TGFβ) signaling (Zhao et al. 2008). This interaction prevents SMAD3 from complexing with SMAD4, thereby blocking TGF-β-sensitized apoptosis. The association of N with SMAD3 also enhances the TGF-β-induced expression of PAI-1 (SERPINE1) promoting tissue fibrosis (Zhao et al. 2008). Third, N protein binding to proteasome subunit p42 (PSMC6) modulates proteasome-regulated degradation of proteins (Wang et al. 2010). Fourth, SARS-CoV1 N binds SUMO-conjugating enzyme UBC9 (UBE2I) to regulate the activity of UBE2I, affecting downstream signaling factors involved in the cell cycle, in addition to its function in the process of sumoylation (Fan et al. 2006). Finally, binding of viral 3a to the regulator and scaffolding protein caveolin81 (CAV1) may regulate virus uptake as well as the trafficking of viral structural proteins (Padhan et al. 2007).

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SARS-CoV-1 M binds to PDPK1

**Location:** SARS-CoV-1 targets host intracellular signalling and regulatory pathways

**Stable identifier:** R-HSA-9731018

**Type:** binding

**Compartments:** plasma membrane

**Diseases:** severe acute respiratory syndrome

SARS-CoV-1 M-protein induces apoptosis through caspase 8 and caspase 9 activation by down-regulating the PKB/Akt survival signalling cascade. Mechanistically M, probably located in the plasma membrane (Tseng et al, 2010), binds to 3-phosphoinositide-dependent protein kinase 1 (PDPK1), inhibiting its phosphorylation activity on the PH domain, preferentially perturbing the activity of any PDK1 downstream substrate whose phosphorylation is mediated through this domain. This mainly affects PKB/Akt activation, which is down-regulated (Chan et al, 2007; Tsoi et al, 2014).

**Literature references**


**Editions**

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Transforming growth factor-β (TGF-beta) is a well characterized cytokine and controls a variety of biological processes, it plays a pivotal role in pulmonary fibrosis. SARS-CoV-1 nucleocapsid protein (N) associates with SMAD3 and promotes SMAD3-EP300 complex formation while it interferes with the complex formation between SMAD3 and SMAD4. By this mechanism N modulates TGF-beta signaling to block apoptosis of SARS-CoV-infected host cells and meanwhile promote tissue fibrosis (Zhao et al, 2008). Elevated PAI-1 levels, pulmonary fibrosis, and key components of the TGF-beta signaling pathway are also implicated in COVID-19 (Whyte et al, 2020; Wei et al, 2020).

**Literature references**


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SARS-CoV-1 N binds SMAD3 and EP300 at the SERPINE1 gene promoter

Location: SARS-CoV-1 targets host intracellular signalling and regulatory pathways

Stable identifier: R-HSA-9737710

Type: binding

Compartments: nucleoplasm

Diseases: severe acute respiratory syndrome

Severe acute respiratory syndrome associated coronavirus type 1 (SARS-CoV-1) nucleocapsid protein (N) is mostly cytoplasmic but can localize to the nucleus (Timani KA et al. 2005; You J et al. 2005). In the nucleus, SARS-CoV-1 N protein potentiates transforming growth factor-beta (TGF-β)-induced SMAD-mediated expression of plasminogen activator inhibitor-1 (PAI-1, encoded by the SERPINE1 gene) (Zhao X et al. 2008). Under normal conditions, the plasma level of SERPINE1 is relatively low. The expression of SERPINE1 is regulated by the activated SMAD complex (SMAD3:SMAD4) (Dennler S et al. 1998; Stroschein SL et al. 1999) that binds to the promoter of the SERPINE1 gene together with the transcription factor SP1 (shown in mouse cells, Yuan H et al. 2013) and the histone acetyltransferase EP300 (p300) (Zhao X et al. 2008).

Upon SARS-CoV-1 infection, viral N associates with SMAD3 in human peripheral lung epithelial (HPL1) cells (Zhao X et al. 2008). The N binding to SMAD3 enhanced SMAD3:EP300 complex formation in human HEK293T cells. Chromatin immunoprecipitation (ChIP) assay showed the association of N and the SERPINE1 promoter in HPL1 cells that stably expressed N protein (Zhao X et al. 2008). The interaction between SARS-CoV-1 N and SMAD3 also prevented SMAD3 from complexing with SMAD4 (Zhao X et al. 2008).

Increased levels of active SERPINE1 may lead to coagulation dysfunctions which have been associated with an increased risk of ischemic cardiovascular events and tissue fibrosis (Ha H et al. 2009).

Literature references

## Editions

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SARS-CoV-1 nucleocapsid protein interacts with proteasome subunit p42 (PSMC6). Proteasomes play a central role in the degradation of short-lived and regulatory host proteins. They are also capable of degrading exogenous proteins like viral peptides (Wang et al, 2010).

**Literature references**

SARS-CoV-1 SUMO1-K62-p-S177-N dimer binds to UBE2I

**Location:** SARS-CoV-1 targets host intracellular signalling and regulatory pathways

**Stable identifier:** R-HSA-9727860

**Type:** binding

**Compartments:** cytosol

**Diseases:** severe acute respiratory syndrome

As well as getting SUMOylated by SUMO-conjugating enzyme UBC9 (UBE2I), SARS-CoV-1 nucleocapsid protein (N) binds the catalytic domain of UBE2I. Through the abundance of N in infected cells, this binding may directly regulate the activity of UBE2I, affecting downstream signaling factors involved in the cell cycle, in addition to its function in the process of sumoylation (Fan et al, 2006).

**Literature references**


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SARS-CoV-1 SUMO1-K62-p-S177-N dimer binds to 14-3-3 proteins

**Location:** SARS-CoV-1 targets host intracellular signalling and regulatory pathways

**Stable identifier:** R-HSA-9727919

**Type:** binding

**Compartments:** cytosol

**Diseases:** severe acute respiratory syndrome

SARS-CoV-1 nucleoprotein (N) was found to coimmunoprecipitate with proteins binding to a 14-3-3 antibody that recognized all the 14-3-3 isoforms. The binding was significantly reduced in the presence of kinase inhibitors, indicating that phosphorylation of N is necessary. Binding to 14-3-3 retains N in the cytosol (Surjit et al, 2005).

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SARS-CoV-1 3a tetramer binds to CAV1

**Location:** SARS-CoV-1 targets host intracellular signalling and regulatory pathways

**Stable identifier:** R-HSA-9731034

**Type:** binding

**Compartments:** Golgi membrane, endoplasmic reticulum-Golgi intermediate compartment

**Diseases:** severe acute respiratory syndrome

SARS-CoV-1 viroporin 3a is a membrane protein that translocates to the plasma membrane and, via shedding, to other cells. It forms a homotetrameric inward-rectifying potassium ion channel. While located in the ERGIC or Golgi apparatus it binds to the regulator and scaffolding protein caveolin-1 (CAV1). Through its interaction with CAV1, the 3a protein may regulate virus uptake, as well as the trafficking of structural proteins (Padhan et al. 2007).

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