SARS-CoV-1-host interactions

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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.

18/11/2022

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.

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Literature references


Reactome database release: 82

This document contains 6 pathways and 3 reactions (see Table of Contents)
Coronaviruses are a group of enveloped viruses with single-stranded, positive-sense RNA genomes. Each of the steps of viral replication - attachment and entry, translation of viral replicase, genome transcription and replication, translation of structural proteins, and virion assembly and release - involves host factors. These interactions can cause alterations in cellular structure and physiology, and activate host stress responses, autophagy, cell death, and processes of innate immunity (Fung TS & Liu DX 2019). This Reactome module describes molecular mechanisms by which severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1) modulates host cell death pathways, innate immune responses, translation, intracellular signaling and regulatory pathways, and PDZ-mediated cell-cell junctions.

**Literature references**


SARS-CoV-1-mediated effects on programmed cell death

Location: SARS-CoV-1-host interactions

Stable identifier: R-HSA-9692913

Diseases: severe acute respiratory syndrome

Programmed cell death (PCD) pathways, including pyroptosis, apoptosis, and necroptosis, are induced in infected host cells as an integral part of host defense to restrict microbial infections and regulate inflammatory responses (reviewed in Jorgensen I et al. 2017; Galluzzi L et al. 2018). Apoptosis is a noninflammatory form of cell death driven by the initiator caspase-mediated cleavage of executioner caspase3 and 7. It facilitates degradation of the cellular contents but these are not released to the extracellular space. Necroptosis and pyroptosis are highly inflammatory forms of cell death that lead to cell lysis and release of proinflammatory cytokines such as interleukin (IL)1β, tumour necrosis factor alpha (TNFα), IL6, IL18 and cellular contents, which can cause severe inflammation (reviewed in Jorgensen I et al. 2017; Galluzzi L et al. 2018; Pasparakis M & Vandenabeele P 2015). Gasdermins (GSDMs) exert pore-forming activity in inflammasome-dependent pyroptosis, while the mixed lineage kinase domain-like (MLKL) protein functions as the executioner during necroptosis (Shi J et al. 2015; Upton JW et al. 2017). Inflammation is a fundamental protective mechanism in elimination of microorganisms, and is normally tightly regulated by certain mediators, in particular IL10, to promote resolution of inflammation (reviewed in Sugimoto MA et al. 2016). Microbial pathogens are able to trigger and/or modulate host PCD and inflammatory response through multiple mechanisms.

This Reactome module describes the roles of severe acute respiratory syndrome-associated coronavirus type 1 (SARSCoVβ1) 3a, E, and 7a proteins in the induction of host cell death pathways. SARSCoVβ1 open reading frameβ3a (3a) binds host receptor interacting serine/threonine protein kinase 3 (RIPK3), facilitating RIPK3 oligomerization and the ion channel functionality of viral 3a, inducing inflammatory cell death and release of cellular contents (Yue Y et al. 2018). Enhanced production and release of proin-
Inflammatory cytokines leads to the cytokine storm that is considered to play a major role in SARS-CoV type 1 and 2 infections (reviewed in Channappanavar R & Perlman S 2017; Yang L et al. 2020). The module also describes induction of apoptosis by SARS-CoV-1 E and 7a proteins through their interaction with anti-apoptotic BCL2L1 (Yang Y et al. 2005; Tan YX et al. 2007). Low levels of BCL2L1 may lead to enhanced function of pro-apoptotic molecules, contributing to the depletion of T lymphocytes by apoptosis (Yang Y et al. 2005). This may lead to the lymphopenia observed in SARS patients, particularly in severe cases (Diao B et al. 2020; Chen Z & Wherry EJ 2020).

Literature references


PDZ domains are protein–protein recognition sequences, consisting of 80–90 amino acids that bind to a PDZ-binding motif (PBM), usually located at the carboxy-terminus of a target protein (Hung AY & Sheng M 2002; Gerek ZN et al. 2009; Munz M et al. 2012). Proteins containing PDZ domains are typically found in the cell cytoplasm or in association with the plasma membrane and play a role in cell–cell junction formation, establishment of cellular polarity, and signal transduction pathways. The multidomain structure of PDZ-containing proteins enables them to interact with multiple binding partners simultaneously, thereby assembling larger protein complexes (Harris BZ & Lim WA 2001). Viruses also encode PBM-containing proteins that bind to cellular PDZ proteins. Viral PBMs target cellular PDZ-containing proteins involved in tight junction formation, cell polarity establishment, and apoptosis (Javier RT & Rice AP 2011).

**Literature references**


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Coronaviruses (CoVs) are positive-sense RNA viruses that replicate in the interior of double membrane vesicles (DMV) in the cytoplasm of infected cells (Stertz S et al. 2007; Knoops K et al. 2008). The viral replication and transcription are facilitated by virus-encoded non-structural proteins (SARS-CoV-1 nsp1–nsp16) that assemble to form a DMV-bound replication-transcription complex (RTC). The replication strategy of CoVs can generate both single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA) species, that may act as pathogen-associated molecular patterns (PAMPs) recognized by pattern recognition receptor (PRR) such as toll-like receptor 7 (TLR7) and TLR8, antiviral innate immune response receptor RIG-I (also known as DEAD box protein 58, DDX58) and interferon-induced helicase C domain-containing protein 1 (IFIH1, also known as MDA5) (Cervantes-Barragan L et al. 2007; Chen Y et al. 2009, 2011; Daffis S et al. 2010; Li Y et al. 2013). The activated PRRs trigger signaling pathways to produce type I and type III interferons IFNs and proinflammatory mediators that perform antiviral functions. This Reactome module describes the mechanisms underlying PRR-mediated sensing of the severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1) infection. First, endosomal recognition of viral ssRNA occurs by means of TLR7 and TLR8 which detect GU-rich ssRNA sequences. Specifically, GU-rich ssRNA oligonucleotides derived from SARS-CoV-1 stimulated mononuclear phagocytes to release considerable levels of proinflammatory cytokines TNFα, IL86 and IL812 via TLR7 and TLR8 (Li Y et al. 2013). Second, SARS-CoV-1 dsRNA replication intermediates can be recognized by cytoplasmic receptors DDX58 and IFIH1 which bind to mitochondrial antiviral-signaling protein (MAVS, IPS-1) to induce the IFN-mediated antiviral response. In addition, the module shows an antiviral function of interferon-induced protein with tetratricopeptide repeats 1 (IFIT1) that directly binds and sequesters viral single-stranded uncapped 5’-ppp RNA and cap-0 RNA (Daffis S et al. 2010). This module also describes several strategies de-
veloped by SARS-CoV-1 to evade or alter host immunity, including escaping innate immune sensors, inhibiting IFN production and signaling, and evading antiviral function of IFN stimulated gene (ISG) products. For example, viral dsRNA replication intermediates derived from SARS-CoV-1 were shown to associate with RTC bound to double membrane vesicles, which protected viral RNA from sensing by DDX58 or IFIH1 (Stertz S et al. 2007; Knoops K et al. 2008). Further, SARS-CoV-1 encodes nsp14 and nsp16 which possess guanine-N7-methyltransferase activity and 2'-O-methyl-transferase activity respectively (Chen Y et al. 2009, 2011). SARS-CoV-1 nsp14 generates 5' cap-0 viral RNA (m7GpppN, guanine N7-methylated) and nsp16 further methylates cap-0 viral RNA. These viral RNA modifications mimic the 5'-cap structure of host mRNAs allowing the virus to efficiently evade recognition by cytosolic DDX58 and IFIH1 (Chen Y et al. 2009, 2011; Daffis S et al. 2010). The nsp16-mediated ribose 2'-O-methylation of viral RNA also blocks the antiviral function of IFIT1 complexes (Menachery VD et al. 2014). Further, the uridylate-specific endoribonuclease (EndoU) activity of viral nsp15 degrades viral RNA to hide it from innate immune sensors (Bhardwaj K et al. 2006; Ricagno S et al. 2006). Moreover, SARS-CoV-1 encodes several proteins that directly bind to host targets associated with SARS-CoV-1 infection and cytokine production (Frieman M et al. 2009; Hu Y et al. 2017; Kopecky-Bromberg SA et al. 2007; Lindner H et al. 2005; Siu KL et al. 2009). This Reactome module describes several such binding events and their consequences. For example, as a de-ubiquitinating enzyme, viral nsp3 binds to and removes polyubiquitin chains of signaling proteins such as TRAF3, TRAF6, STING, IkBA, and IRF3 thereby modulating the formation of signaling complexes and the activation of IRF3/7 and NFKappaB (Sun L et al. 2012; Chen X et al. 2014; Li SW et al. 2016). This inhibits IFN production downstream of TLR7/8, DDX58, IFIH1, MAVS and STING signaling pathways. Binding of SARS-CoV-1 nucleocapsid (N) protein to E3 ubiquitin ligase TRIM25 inhibits TRIM25-mediated DDX58 ubiquitination and DDX58-mediated signaling pathway (Hu Y et al. 2017). Next, SARS-CoV-1 membrane (M) protein targets IBK1/IKBKE and TRAF3 to prevent the formation of the TRAF3:TANK:TBK1/IKBKE complex and thereby inhibits TBK1/IKBKE-dependent activation of IRF3/IRF7 transcription factors downstream of DDX58, IFIH1 and adaptor MAVS (Siu KL et al. 2009; 2014). The ion channel activities of open reading frame 3a (orf3a or 3a) and E contribute to activation of the NLRP3 inflammasome leading to highly inflammatory pyroptotic cell death (Nieto Torres JL et al. 2015; Chen IY et al. 2019; Yue Y et al. 2018). Viral 3a promoted the NLRP3-mediated formation of PYCARD (ASC) speck by interaction with both TRAF3 and PYCARD (ASC) (Siu KL et al. 2019). Binding of 3a to caspase-1 (CASP1) enhanced CASP1-mediated cleavage of interleukin 1 beta (IL1B) downstream of the NLRP3 inflammasome pathway (Yue Y et al. 2018). Like 3a, SARS-CoV-1 8b was found to bind to NLRP3 activating the NLRP3 inflammasome and triggering IL1B release (Shi CS et al. 2019). 8b was also shown to bind IRF3, inhibiting subsequent IRF3 dimerization (Wong et al. 2018). At the plasma membrane, binding of SARS-CoV-1 7a to host BST2 disrupts the antiviral tethering function of BST2 which restricts the release of diverse mammalian enveloped viruses (Taylor JK et al. 2015). SARS-CoV-1 9b (orf9b) inhibits the MAVS-mediated production of type I IFNs by targeting TOMM70 on the mitochondria (Jiang HW et al. 2020). SARS-CoV-1 6 (orf6) inhibits the IFN signaling pathway by tethering karyopherins KPNA2 and KPNB1 to the endoplasmic reticulum (ER)/Golgi intermediate compartment (ERGIC) and thus blocking the KPNA1:KPNB1-dependent nuclear import of STAT1 (Frieman M et al. 2007). Binding of SARS-CoV-1 nsp1 to peptidyl-prolyl isomerases (PPIases) and calcipressin-3 (RCAN3) significantly activates the cyclophilin A/NFAT pathway, ultimately enhancing the induction of the IL-2 promoter (Pfefferle et al, 2011; Law et al, 2007). At last, SARS-CoV-1 3b, after translocating to the nucleus, binds to transcription factor RUNX1 and increases its promoting activity (Varshney et al, 2012).

**Literature references**


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Severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1) nonstructural protein 1 (nsp1) and nucleocapsid protein (N) disrupt mRNA translation upon SARS-CoV-1 infection in human cells.

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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 3-phosphoinositide-dependent 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 (TGF-β) 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 caveolin1 (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 SUMO-p-N binds to NPM1

**Location:** SARS-CoV-1-host interactions

**Stable identifier:** R-HSA-9727886

**Type:** binding

**Compartments:** nucleolus, granular component

**Diseases:** severe acute respiratory syndrome

Nucleophosmin (NPM1) is a mainly nucleolar phosphoprotein that shuttles between the nucleolus and cytoplasm. NPM1 is involved in a variety of biological processes such as centrosome duplication, ribosome biogenesis, intracellular transport, apoptosis and mRNA splicing (Lindström MS 2011). NPM1 is also implicated in various viral infections including human immunodeficiency virus type 1 (HIV-1) (Gadad SS et al. 2011), adenovirus (Samad MA et al. 2007), herpes simplex virus 1 (HSV-1) (Lymberepoulos MH et al. 2011) and severe acute respiratory syndrome coronavirus type 1 (SARS-CoV-1) (Zeng Y et al. 2008).

The glutathione S-transferase (GST)-tagged N protein of SARS-CoV-1 binds to endogenous NPM1 in HeLa cell lysates (Zeng Y et al. 2008). Co-immunoprecipitation assay further confirmed the interaction of NPM1 and the viral N protein in N-expressing HeLa cells. An in vitro phosphorylation assay using HeLa cell lysates showed that the binding of N protein inhibited the phosphorylation of NPM1 at Thr199 by CDK2 which can lead to cell cycle arrest (Zeng Y et al. 2008). SARS-CoV-1 N protein co-localized with the NPM1 protein in the perinuclear region of HeLa cells. NPM1 usually plays a role in nuclear import of the viral proteins to which it binds. It is unclear if the binding of SARS-CoV-1 N with NPM1 is involved with sub-cellular localization of N (Zeng Y et al, 2008). Similar findings were reported for the N protein of porcine epidemic diarrhea virus (PEDV), which belongs to the Alphacoronavirus genus in the Coronaviridae family (Shi D et al. 2017). Binding of the PEDV N protein to NPM1 prevented proteolytic cleavage of NPM1 by caspase-3 leading to increased cell survival (Shi D et al. 2017).

This Reactome event shows the interaction between SARS-CoV-1 N and host NPM1.

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[https://reactome.org](https://reactome.org)
SARS-CoV-1 SUMO1-K62-p-S177-N dimer binds to HNRNPA1

**Location:** SARS-CoV-1-host interactions

**Stable identifier:** R-HSA-9727869

**Type:** binding

**Compartments:** cytosol

**Diseases:** severe acute respiratory syndrome

Heterogeneous nuclear ribonucleoprotein A1 (HNRNPA1) is involved in the packaging of pre-mRNA into hnRNP particles and the transport of poly(A) mRNA from the nucleus to the cytoplasm. SARS-CoV-1 nucleocapsid protein (N), the most abundant protein in SARS infection, binds to HNRNPA1. It is unknown whether this affects host mRNA transport or viral transcription (Luo et al, 2005).

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

**Location:** SARS-CoV-1-host interactions

**Stable identifier:** R-HSA-9727857

**Type:** binding

**Compartments:** cytosol

**Diseases:** severe acute respiratory syndrome

SARS coronavirus nucleoprotein binds and inhibits the liver isoform of pyruvate kinase (PKL), an enzyme of the glycolysis pathway. It is reasonable to assume that this inhibition is likely to cause the death of the hepatocytes, which results in the elevation of serum alanine aminotransferase and liver dysfunction noted in most SARS patients (Wei et al, 2012).

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