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NUTS AND BOLTS

SARS-CoV-2 signaling pathway map: A functional landscape of molecular mechanisms in COVID-19

D. A. B. Rex[1] · Shobha Dagamajalu[1] · Richard K. Kandasamy[2] · Rajesh Raju[1] · T. S. Keshava Prasad[1]

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Abstract

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). COVID-19 has been declared a pandemic by WHO. The clinical manifestation and disease progression in COVID-19 patients varies from minimal symptoms to severe respiratory issues with multiple organ failure. Understanding the mechanism of SARS-CoV-2 interaction with host cells will provide key insights into the effective molecular targets for the development of novel therapeutics. Recent studies have identified virus-mediated phosphorylation or activation of some major signaling pathways, such as ERK1/2, JNK, p38, PI3K/AKT and NF-κB signaling, that potentially elicit the cytokine storm that serves as a major cause of tissue injuries. Several studies highlight the aggressive inflammatory response particularly 'cytokine storm' in SARS-CoV-2 patients. A depiction of host molecular dynamics triggered by SARS-CoV-2 in the form of a network of signaling molecules will be helpful for COVID-19 research. Therefore, we developed the signaling pathway map of SARS-CoV-2 infection using data mined from the recently published literature. This integrated signaling pathway map of SARS-CoV-2 consists of 326 proteins and 73 reactions. These include information pertaining to 1,629 molecular association events, 30 enzyme catalysis events, 43 activation/inhibition events, and 8,531 gene regulation events. The pathway map is publicly available through WikiPathways: https://www.wikipathways.org/index.php/Pathway:WP5115.

Keywords Acute respiratory distress syndrome · RASS pathway · Protein–protein interactions · Inflammation · Interleukins · Cytokine storm

Abbreviations

ARDS	Acute Respiratory Distress Syndrome
CRS	Cytokine Release Syndrome
PTM	Post-Translational Modifications
ACE2	Angiotensin-Converting Enzyme 2
TMPRSS2	Transmembrane Serine Protease 2
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
RAAS	Renin–Angiotensin–Aldosterone System
Ang-II	Angiotensin II
ORF	Open Reading Frame
IFN	Interferon
IL	Interleukin

✉ Shobha Dagamajalu
shobha_d@yenepoya.edu.in

✉ Rajesh Raju
rajrrnbt@gmail.com

✉ T. S. Keshava Prasad
keshav@yenepoya.edu.in

D. A. B. Rex
rexprem@yenepoya.edu.in

Richard K. Kandasamy
richard.k.kandasamy@ntnu.no

[1] Center for Systems Biology and Molecular Medicine, Yenepoya Research Centre, Yenepoya (Deemed To Be University), Mangalore 575018, India

[2] Centre of Molecular Inflammation Research (CEMIR), Department of Clinical and Molecular Medicine (IKOM), Norwegian University of Science and Technology, 7491 Trondheim, Norway

Introduction

The current outbreak of coronavirus disease (COVID-19), a pandemic caused by a novel severe acute respiratory syndrome (SARS)-like coronavirus (SARS-CoV-2), was first reported from Wuhan, China (Zheng 2020). In a limited time, this epidemic has now spread to 216 countries around the world and 2 international conveyances, infected nearly 35,399,043 people and causing 1,041,824 deaths as

of October 5, 2020 (source: https://www.worldometers.info/coronavirus/). SARS-CoV-2, a single-stranded RNA virus with a genome size ranges from 26 to 32 kilobases in length, has brought the entire world to a standstill causing unimaginable mortality, morbidity and massive economic damage (Lu et al. 2020). The genome of SARS-CoV-2 expresses both structural and non-structural proteins. The Spike (S) glycoprotein, small envelope (E) protein, membrane (M) glycoprotein and nucleoprotein (N) genes encode structural proteins, whereas non-structural proteins, such as 3-chymotrypsin-like protease, papain-like protease, and RNA-dependent RNA polymerase, are encoded by the open reading frame (ORF) region. ORF region contains 28 SARS-CoV-2 polypeptides: (i) ORF1a/b, two polyproteins encoding 16 non-structural proteins NSP1 to 16; (ii) four structural proteins: S, E, M, and N; (iii) seven accessory proteins: ORF3a, ORF3b, ORF6, ORF7a, ORF7b, ORF8, ORF9b; and (iv), two hypothetical proteins ORF14 and ORF10 (Chan et al. 2020; Y. Huang et al. 2020a, b; Sicari et al. 2020).

A host cell transmembrane enzyme called transmembrane protease serine 2 (TMPRSS2) activates Spike protein/S protein of SARS-CoV-2, which facilitates the attachment of the virus to the host cell receptor called angiotensin-converting enzyme 2 (ACE2) (Bilinska et al. ICU 2020; Djomkam et al. 2020; Hoffmann et al. 2020). The spike protein of SARS-CoV-2 is composed of two subunits, S1 (bulb) for receptor binding and S2 (stalk) for membrane attachment and fusion (Yi et al. 2020). The specific fusion between S1 and the cognate receptor triggers a drastic conformational change in the S2 subunit, leading to the fusion between the SARS-CoV-2 virus envelope and the host cell membrane, which releases the nucleocapsid of the virus into the cytoplasm of the host cell (Tung and Limtung 2020). This binding of the virus to the ACE2 receptor downregulates the cellular expression of ACE2 and initiates the invasion of the virus for rapid replication (H. Zhang et al. 2020a, b). ACE2 downregulation leads to an imbalance between the renin-angiotensin system (RAS) and ACE2/angiotensin-(1–7)/MAS after infection may also contribute to multiple organ injury in SARS-CoV-2 patients (Ni et al. 2020). Studying the signaling pathways of SARS-CoV-2 infected cells is one of the fundamental ways to understand the molecular mechanism of cell entry, life cycle, host-cell response and recovery. Also, the characterization of signal transduction pathways induced by SARS-CoV-2 infection may provide key insights into significant molecular targets to develop more efficient diagnosis, tests and antiviral therapeutics and vaccines. We developed a resource of signaling events by SARS-CoV-2 infection similar to the previously published pathways including IL-18 (Rex et al. 2020), RANKL/RANK (Raju et al. 2011a), AXL (Dagamajalu et al. 2021b), prolactin (Radhakrishnan et al. 2012), endothelin (Dagamajalu et al. 2021a) and IL-33 (Pinto et al. 2018). To this end, we curated a collection of several relevant research articles, which were recently published, and built a detailed signaling map of SARS-CoV-2 infection. This pathway map comprises of 10,559 molecules undergoing five different categories of molecular reactions. These reactions are assembled through a manual annotation of the scientific literature and depicted as a single pathway map.

The SARS-CoV-2 signaling pathway map is made available through the WikiPathways Database (https://www.wikipathways.org/index.php/Pathway:WP5115).

Methodology

Literature mining and data curation of SARS-CoV-2 mediated signaling events

Research articles related to SARS-CoV-2 signaling were fetched from the literature to gather information to build a new pathway map of SARS-CoV-2. Search for articles was carried out in PubMed using the search terms such as (“SARS-CoV-2” OR "COVID-19" OR "Covid-19") AND ("pathway" OR "signaling" OR "signalling"). The abstracts of research articles thus fetched were manually read for screening them. Only those articles, which describe experimentally verified molecular reactions induced by SARS-CoV-2 were taken up for in-depth curation. We gathered SARS-CoV-2 pathway information on molecular reactions from both cell line-based in vitro studies and patient-derived clinical sample-based investigations. The signaling reactions were curated and documented based on the previously published NetPath annotation criteria (Kandasamy et al. 2009, 2010). The information on each signaling reaction was annotated and further categorized into the molecular association, catalysis (including post-translational modifications; PTMs), activation/inhibition, translocation and gene regulation events. Each signaling event described in the SARS-CoV-2 pathway are hyperlinked to PubMed identifiers of corresponding articles, from where it was fetched. The signaling reactions activated or modulated by SARS-CoV-2 were arranged topologically from protein–protein interaction to transcriptionally regulated genes following the NetSlim criteria (Raju et al. 2011b).

The curated information from each article was reviewed by an internal reviewer followed by an external reviewer assigned as a Pathway Authority, who is an experienced scientist working in the same field. All corrections and recommendations by Pathway Authority were incorporated into the signaling pathway. Manual curation of signaling events was carried out using a manual curation software called PathVisio (Kutmon et al. 2015).

Results and discussion

Development of SARS-CoV-2 signaling pathway network map

The initial PubMed search fetched 104 articles. Articles published related to the SARS-CoV-2 signaling pathway until September 2020 were thus gathered. These articles were carefully reviewed based on our annotation criteria, which finally selected 28 articles for further curation. The annotated articles yielded a total of 1629 molecular associations, 30 catalysis, 43 activation/inhibition reactions, 8,531 gene regulations and 326 protein expression events, which were induced by the SARS-CoV-2 virus (Supplementary Data 1). These events were incorporated into a representative map of the signaling network (Fig. 1). This SARS-CoV-2 signaling pathway map was submitted to WikiPathways with the ID URL: https://www.wikipathways.org/index.php/Pathway:WP5115. The WikiPathways version of the signaling pathway map can be downloaded in various compatible file formats such as png, pdf and gpml formats.

Summary of SARS-CoV-2 signaling pathway

SARS-CoV-2 enters the lungs, where the spike glycoprotein of the virus activated by a cellular TMPRSS2, which facilitates the attachment of the virus to ACE2 on cells and allowing the virus to enter the cells (Al-Horani et al. 2020; Faheem et al. 2020; Hoffmann et al. 2020; Vaduganathan et al. 2020; Walls et al. 2020; Yan et al. 2020; H. Zhang et al. 2020a, b). The proteomics study by Stukalov and the team identified the ubiquitination of ACE2 at K702 and K625 in A549-ACE2 cells (Stukalov et al., 2020). In common, NEDD4 modulates the levels of ACE2 ubiquitination, whereas PYR-41 prevented the effects of Ang-II on ACE2, indicating this ubiquitination reaction can present as a novel target for the treatment of cardiovascular complications and pulmonary arterial hypertension (Shen et al. 2020). An increase in ACE2 expression at mRNA and protein levels observed in the early phase of several cardiovascular diseases (Gheblawi et al. 2020; Michaud et al. 2020). A recent report shows that smokers have a higher risk of SARS-CoV-2 infection based on their *ACE2* expression profiles, which could contribute to variations in infection susceptibility, disease severity, and treatment outcome (Cai et al. 2020).

Several reports have described the interaction of SARS-CoV-2 proteins with cell-type-specific protein complexes contributing to various biological functions (Astuti and Ysrafil 2020). The viral proteins interact with vesicular sorting and fusion machinery and could impact a plethora of membrane proteins, such as receptors involved in thrombosis, type I/III interferons (IFNs), NF-kB and Interleukin 6 (IL-6) signaling (Blanco-Melo et al. 2020). open reading frame 3a (ORF3a) is a SARS-CoV-2 viral protein showing a pro-apoptotic activity and interacts with the The conserved vacuolar/lysosomal homotypic fusion and vacuole protein sorting (HOPS) complex, which is essential for autophagosome-lysosome fusion and its key components. Similarly, NSP6, a viral protein, is known to be involved in the regulation of lipid metabolism and autophagy. ORF3 and NSP6 interact with host autophagy receptors: (Sequestosome 1 (SQSTM1), Gamma-aminobutyric acid receptor-associated protein-like 2 (GABARAPL2), Next to BRCA1 gene 1 protein (NBR1), CALCOCO2, MAP1LC3B and TAX1BP1) leads to autophagosome / late endosome, however, the mechanism remains unknown. Open reading frame 8 (ORF8) and open reading frame 3 (ORF3) bind to transforming growth factor beta (TGFβ)-associated factors and involved in the activation of SMAD1/5. This results in the upregulation of fibrinogens, fibronectin, plasminogen activator inhibitor 1 (SERPINE1) and integrin(s), which modulates cell survival, motility and innate immune responses (Stukalov et al., 2020). Besides, ORF3a interaction induces apoptosis either by the direct activation of caspase-9 or through the activation of caspase-8, which cleaves BH3-interacting domain death agonist (Bid) to the truncated Bid (tBid) and stimulates activation of caspase-9 (Ren et al. 2020). The SARS-CoV-2 pathway describes the induction and modulation of the many downstream signaling pathways including A mitogen-activated protein kinase (MAPK), Protein kinase B (Akt), interferon I/III (IFN I/III) and transforming growth factor beta receptor (TGFBR), which forms the core innate immune and pro-inflammatory response. Previous reports have shown that SARS-CoV infection induces the activation of interferon signaling (Frieman and Baric 2008; Totura and Baric 2012). In contrast, SARS-CoV-2 is a weak inducer of IFN-I response in vitro as well as in animal models as compared to other respiratory RNA viruses (Chu et al. 2020; Hadjadj et al. 2020). In the early infection, ORF6 suppresses the interferon-mediated signaling pathway by inhibiting retinoic acid-inducible gene I (RIG-I), interferon induced with helicase C domain 1 (IFIH1), IFN-stimulated response element (ISRE), IFN-stimulated gene 56 (ISG56) and translocation of IFN regulatory factor 3 (IRF3) and signal transducer and activator of transcription 1 (STAT1), suggesting that SARS-CoV-2 antagonizes IFN production. Whereas in late time points, NSP2 and S proteins exert opposite effects in IFN production. Lei et al., have postulated that the lack of inadequate antiviral response in early-stage may be vital to the SARS-CoV-2 pathogenesis (Lei et al. 2020).

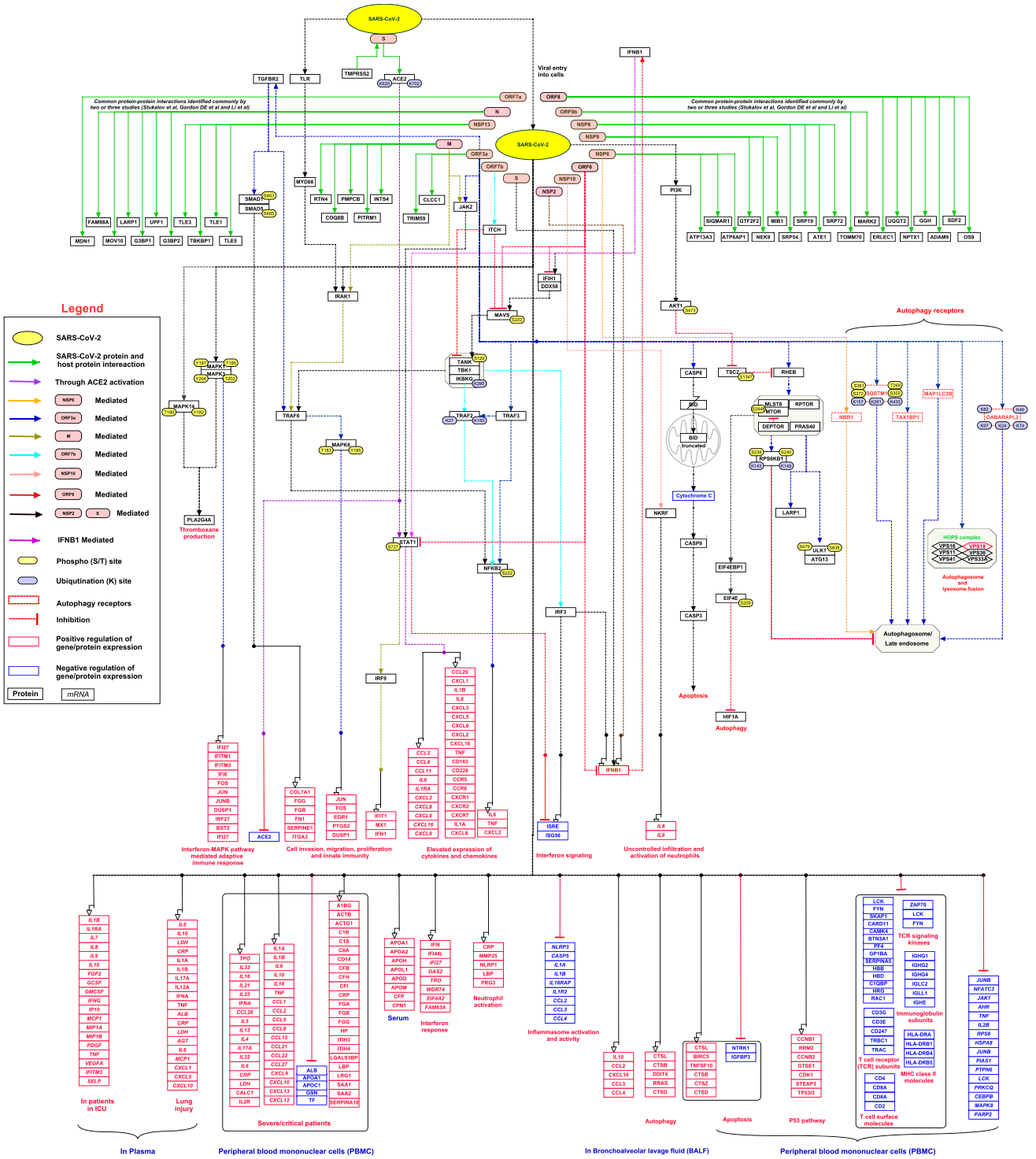

Fig. 1 A schematic representation of the SARS-CoV-2 signaling pathway. The pathway map represents protein–protein interactions and the downstream molecular events regulated by SARS-CoV-2 including molecular association, catalysis, and gene regulation events. Each event is color-coded as described in the pathway legend. Information on site and residue of post-translational modification is also included in the pathway map

SARS-CoV-2 mediates the activation of MAPK signaling pathways that trigger alterations in the platelet transcriptome and proteome, and platelet hyperreactivity, which may contribute to COVID-19 pathophysiology (Manne et al. 2020). The SARS-CoV-2 can directly activate NF-κB in A549cells (Gordon et al. 2020). SARS-CoV-2 infection induces the alteration of Akt/mTOR/HIF-1 signaling in virus-infected Vero-E6 cells, suggesting that targeting of them could be a potential therapy for the management of the disease (Appelberg et al. 2020).

Most of the SARS-CoV-2 infected patients develop mild to moderate symptoms of common viral infections such as fever, cough, and fatigue. In severe cases, they may lead to acute respiratory distress syndrome (ARDS), acute cardiac injury, acute hepatic injury, and acute kidney injury (Ni et al. 2020). We collated a list of proteins and genes elevated in COVID-19 patients from the literature, from early to late-stage based on sample type from different experimental data. Elevated levels of cytokines such as IL-1b, IL-2, IL-6, IL-8, IL-10, monocyte chemoattractant protein-1 (MCP1) and tumor necrosis factor α (TNF-α) were observed in SARS-CoV-2 infected plasma samples (Chen et al. 2020; C. Huang et al. 2020a, b; Mick et al. 2020; Qiu et al. 2020; J.J. Zhang et al. 2020a, b). Patients admitted in intensive care had significantly higher serum levels of many cytokines and chemokines such as IL-2, IL-7, IL-10, G-CSF, TNF-α, and IL-1Ra compared to those who were not in an intensive care unit (ICU). In comparison to healthy controls, they have also showed higher serum levels of IL-6, IL-9, IL-13, GM-CSF, IFN-γ, IL-1β, IL-8, and IL-17 (C. Huang et al. 2020a, b). The analysis of peripheral blood mononuclear cells (PBMCs) has revealed that interaction of NSP9 and NSP10 with NKRF (NF-KB repressor), which regulates IL-8/IL-6 mediated chemotaxis of neutrophils and over-exuberant host inflammatory response (Li et al. 2020).

SARS-CoV-2 infection induces the release of cytokines and monocyte-associated chemokines in those individuals with a diminished innate immunity causing a more severe presentation of the disease especially in elderly individuals (Costela-Ruiz et al. 2020; Song et al. 2020). This cytokine release syndrome (CRS), also called 'cytokine storm', has been found to be a major cause of tissue damage in the pathophysiology of SARS-CoV-2 (Ye et al. 2020). The pro-inflammatory cytokines in the plasma have been found to be significantly elevated in patients with severe COVID19 disease (Costela-Ruiz et al. 2020). Several cytokines such as IL-6, IL-1β, TNF-α and IFN-γ have been frequently reported to be elevated in COVID 19 disease (Del Valle et al. 2020; C. Huang et al. 2020a, b; McGonagle et al. 2020; Tang et al. 2020). IL-6, the most important cytokine in CRS, has been found to be increased in the serum of SARS-CoV-2 patients presenting ARDS (Ronco and Reis 2020; Wu et al. 2020).

Conclusions

Arrangement of molecular reactions associated with host–pathogen response from the published literature may provide vital clues for the identification of novel therapeutic intervention strategies. We believe that this SARS-CoV-2 signaling pathway map will provide a platform for the biomedical research community to accelerate the research into the complex mechanism of host–pathogen response and disease progression. It will assist in the ongoing SARS-CoV-2 research and roadmap for the prevention, control and treatment of disease.

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Declaration

Conflict of interest The authors report no conflicts of interest.

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