Abstract
Severe acute respiratory syndrome coronaviruses (SARS-CoVs) caused worldwide epidemics over the past few decades. Extensive studies on various strains of coronaviruses provided a basic understanding of the pathogenesis of the disease. Presently, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is leading a global pandemic with unprecedented challenges. This is the third coronavirus outbreak of this century. A signaling pathway map of signaling events induced by SARS-CoV infection is not yet available. In this study, we present a literature-annotated signaling pathway map of reactions induced by SARS-CoV infected cells. Multiple signaling modules were found to be orchestrated including PI3K-AKT, Ras-MAPK, JAK-STAT, Type 1 IFN and NFκB. The signaling pathway map of SARS-CoV consists of 110 molecules and 101 reactions mediated by SARS-CoV proteins. The pathway reaction data are available in various community standard data exchange formats including Systems Biology Graphical Notation (SBGN). The pathway map is publicly available through the GitHub repository and data in various formats can be freely downloadable.

Keywords COVID-19 · Post-translational modifications · Protein–protein interaction · Translocation · Differential expression

Introduction
Coronaviruses (CoVs) are enveloped, single stranded, positive sense RNA viruses that are phenotypically and genotypically diverse. CoVs can infect bats, birds, cats, dogs, pigs, mice, horses, whales, and humans (Zaki et al. 2012). The first detected human coronavirus can be traced back to studies carried out in 1965 (Kahn and McIntosh 2005). However, the field of coronavirology advanced significantly in recent years (Kahn and McIntosh 2005). Though the exact mechanism of species-to-species transmission of the virus has not been clear. From the turn of the twenty-first century three deadly CoVs: the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV; 2002), the Middle East Respiratory Syndrome coronavirus (MERS-CoV; 2012), and the ongoing 2019 novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) made a mark in history by causing havoc in different parts of the world (Guo et al. 2020). The diversity in these viruses can be attributed to RNA dependent RNA polymerases, as they possess high frequency of RNA recombination and large genome size as compared to other RNA viruses (Zaki et al. 2012). The shared proteins among the different CoVs may vary in
structure and function. However, the proteins seem to be multifunctional, indicating a common theme interconnecting CoVs (Wong and Saier 2021). The ability of SARS-CoVs to transfec hosts have been a major concern and eventually led from an epidemic to pandemic situation (Perlman and Netland 2009). SARS-CoV infection resulted in severe and potentially fatal lung disease. Majority of the patients infected with SARS-CoV showed febrile illness accompanied by weakness. Nevertheless, a considerable population of individuals developed severe inflammation of the lung, necessitating ventilator support and intensive care. Many patients from this group had acute respiratory distress syndrome (ARDS) with high mortality (Hui and Sung 2004). Individuals of this group also showed manifestations of infection in other organ systems. Lymphopenia (Wong et al. 2003a), gastrointestinal symptoms (Leung et al. 2003), impaired renal functions (Chu et al. 2005), and impaired liver function (Chan et al. 2004; Wong et al. 2003b) were other common conditions.

SARS-CoVs have a genome size of ~ 30 Kb with 14 open reading frames (ORFs) encoding the viral proteins during its infection cycle (Bruford et al. 2008; Gordon et al. 2020). These proteins mainly comprise of four structural proteins, spike (S), membrane (M), envelope (E), and nucleocapsid (N). Table 1 summarizes the functional receptors of various strains of CoVs. Broadly, CoVs infection cycle involves attachment/binding to the host cells, replicase protein expression, replication and transcription, assembly and release (Fehr and Perlman 2015). Of these, binding of CoVs to the host cell membrane receptors is a major determinant for the detection of infection cycle and host range of CoVs. To infect a new host species CoV must adapt to the receptor of the new host (Belouzard et al. 2012). Alternatively, host-factors such as, interferon-inducible transmembrane proteins can play essential role to restrict or facilitate the attachment and entry of CoVs (Bailey et al. 2014; Huang et al. 2011; Zhao et al. 2014; Zhao et al. 2018).

Various studies determined CoV proteins modulating host signaling pathways through the interactions with host proteins (Khan and Islam 2021; Munjal et al. 2021). Particularly, studies have shown that activation of intracellular signaling cascades induced upon SARS-CoV infection leads to the post-translational modifications (PTMs) and activation of downstream molecules (Garrington and Johnson 1999; Kyriakis and Avruch 2001; Whitmarsh and Davis 2000). Predominantly, CoVs infection caused altered expression of host kinases, chemokines and transcription factors to evade host-immune responses and to aid replication and assembly of viral particle (Garrington and Johnson 1999; Kyriakis and Avruch 2001; Whitmarsh and Davis 2000). Upon SARS-CoV infection, cell death has been observed in cultured Vero E6 cells (Mizutani et al. 2004c). Supplementary Table 1 summarizes the list of cell lines used to investigate the biological functions induced by SARS-CoV (Kaye 2006). The signaling pathways regulating cell death and survival in SARS-infected cells were highly complex. The in-depth understanding of these regulatory mechanisms will help in underlying the pathophysiology of SARS-CoVs infection cycle and host-range.

Despite the immense need to understand the pathology of SARS-CoVs, the signaling pathway map of reactions induced by SARS-CoV proteins are not available. This study presents the signal transduction pathways of SARS-CoV-infected cells in Graphical Pathway Markup Language (GPML) and SBGN format. GPML format is a custom XML format compatible with pathway visualisation and analysis tools such as, Cytoscape (Shannon et al. 2003) and PathVisio (Kutmon et al. 2015). SBGN is a set of three complementary visual languages that helps in representing networks of biological interactions in a standard, unambiguous manner. This would further result in efficient representation, visualization, storage, exchange, and reuse of various types of biological knowledge (Bergmann et al. 2020). Nodes describe entity pools (genes, proteins, etc.) and process (associations, influences, etc.). Edges describe the relationship between the nodes.

| Coronavirus | Receptor | References |
|-------------|----------|------------|
| HCoV-229E   | APN      | Yeager et al. (1992) |
| HCoV-NL63   | ACE2     | Hofmann et al. (2005) |
| HCoV-OC43   | 9-O-acetylated sialic acid | Lu et al. (2020) |
| HCoV-HKU1   | 9-O-acetylated sialic acid | Lu et al. (2020) |
| CCoV        | APN      | Benbacer et al. (1997) |
| BCoV        | N-acetyl-9-O-acetylneuraminic acid | Schultze and Herrler (1992) |
| SARS-CoV    | ACE2     | Li et al. (2003) |
| MERS-CoV    | DPP4     | Raj et al. (2013) |
The generation of SARS-CoV-host signaling pathway map

An extensive search of published literature was performed using PubMed to annotate the reactions induced by SARS-CoV proteins. Several query terms were used including, “SARS-CoV” AND “ACE2”, “SARS-CoV” AND “pathway” OR “signaling”. The articles were screened for information pertaining to protein–protein interactions (molecular association), PTMs (catalysis), transport (translocation of proteins between sub-cellular compartments), activation/inhibition events and gene regulation events (Sharma et al. 2015; Zhong et al. 2014) which were induced by SARS-CoV infection in host cells. The pathway map was generated using PathVisio (version 3.3.0), an open-source pathway drawing software and CellDesigner (version 4.4.2), a process diagram editor for drawing gene regulatory and biochemical networks.

Results and discussion

The signaling events orchestrated by SARS-CoV are shown in Fig. 1. A number of signaling cascades are triggered during the entire process of viral infection, from S protein-ACE2 binding for internalization into the host cells to apoptotic cell death (Li et al. 2003). S protein of SARS-CoV was cleaved at multiple motifs by host type II transmembrane serine protease (TMPRSS2) that in turn activated the process of cell–cell or virus-cell fusion (Glowacka et al. 2011). It was observed that overexpression of ACE2 allowed efficient SARS-CoV’s S driven cell–cell fusion (Glowacka et al. 2011). ACE2 and TMPRSS2 were co-expressed in type II pneumocytes (Glowacka et al. 2011). SARS-CoV was also found to be dependent on the activity of pH-dependent endosomal cysteine protease cathepsin L (CTSL) for virus-cell fusion (Glowacka et al. 2011). The binding of S with ACE2 activated CSNK2A1 mediated ACE2 phosphorylation. This led to severe immune response involving cytokines and chemokines in pneumocytes of infected patients. (Chen et al. 2010). On infection with SARS-CoV various proinflammatory factors such as CXCL8, CXCL10, CCL2, CCL3, CCL5 and COX2 were found to be triggered through RAS-MAPK-AP1 and NFκB pathways (Cinatl et al. 2005; Chen et al. 2010; Law et al. 2007; Hu et al. 2017). E protein, ORF3a and ORF8b were involved in the activation of NLRP3 inflammasomes (Nieto-Torres et al. 2015; Shi et al. 2019; Siu et al. 2019). Also, the activation of c-Fos, FosB, CREB1 and ATF2 by N protein showed its involvement in the AP1 pathway (He et al. 2003). The role of SARS-CoV proteins in innate immunity have been reported by various studies. M protein of SARS-CoV inhibited the activation of interferon regulatory factor 3 (IRF3) and interferon (IFN) synthesis by hampering the formation of a functional TRAF3-TANK-TBK1/IKKe complex (Siu et al. 2009). The N protein interfered in the association of TRIM25 and DDX58 that led to the suppression of Type I IFN production (Hu et al. 2017). ORF9b which was localized in the mitochondria (MT) induced ubiquitination and proteasomal

Fig. 1 A schematic depiction of reactions induced by severe acute respiratory syndrome coronavirus (SARS-CoV). The pathway reaction map depicts each type of reactions such as molecular associations, catalysis, and translocation events induced upon by SARS-CoV infection. Site and residue information of post-translational modifications are also provided whenever available in literature. Important pathways including, PI3K-AKT, Ras-MAPK, and NFκB were found to be activated. The edges representing the relationships between nodes are provided in the legend.
degradation of DNM1L (DRP1), leading to the elongation of MT. ORF9b possibly appropriates ITCH (AIP4), a ubiquitin E3 ligase to trigger the degradation of MAVS accompanied by loss of TRAF3 and TRAF6 thus significantly suppressing the IFN responses (Shi et al. 2014). Co-expression of nsp1 in Type I IFN pathway decreased the phosphorylation levels at Y701 and S727 of STAT1 and Y690 of STAT2 (Law et al. 2007). PLpro of SARS-CoV inhibited stimulator of interferon genes (STING)-mediated activation and translocation of IRF3 thereby preventing the induction of Type I IFN (Sun et al. 2012). PLpro also inhibited IFN production mediated through agonist induced TLR7 signaling pathway by removing the K63 linked polyubiquitination of TRAF3 and TRAF6 (Li et al. 2016a). It disrupted the STING mediated signaling and then negatively regulated type I IFN induction (Chen et al. 2014; Sun et al. 2012). It also physically interacted with the STING-TRAF3-TBK1 complex, reducing the ubiquitinated forms of STING, DDX58, TRAF-3, TBK1 and IRF3.

ORF6 (P6) of SARS-CoV could prevent IFN-β production upon infection and may be involved in the suppression of the IFN immune signaling. It targeted N-Myc (and STAT) interactor (NMI) to induce its degradation, which led to NMI-enhanced IFN signaling suppression and was also involved in blocking STAT1 nuclear translocation (Cheng et al. 2015). ORF3b was accumulated in the nucleus during the initial phase. During the later phases it got translocated to the MT where it was involved in the inhibition of signaling for the production of Type I IFN possibly by inhibiting the MAVS response to DDX58 (Freundt et al. 2009). SARS-unique domain (SUD) of Nsp3 could enhance cellular E3 ubiquitin ligase known as ring-finger and CHY zinc-finger domain containing 1 (RCHY1) that led to proteasomal degradation of TP53 resulting in downregulation of TP53 (Ma-Lauer et al. 2016). ORF8b directly interacted with IRF3 and affected its dimerization and phosphorylation status thereby suppressing IFN-β. In addition, the expression of ORF8b and ORF8ab also regulated the stability and function of IRF3 (Wong et al. 2018).

SARS-CoV infection has been shown to induce apoptosis through DNA fragmentation and activation of caspase (Mizutani et al. 2004c; Yan et al. 2004). ORF8a induced apoptosis by activating caspase-3 (Chen et al. 2007). The cytotoxic effects on entry of SARS-CoV into the host were partially inhibited by p38-MAPK14 specific inhibitor, which indicated that p38-MAPK14 pathway may be involved in cell death (Mizutani et al. 2004c). Also, the activation and phosphorylation of p38-MAPK14 and its downstream targets including MAPKAPK2, Hspb1, Rps6ka1, cREB1, ATF1 and Eif4e were observed (Mizutani et al. 2004a, 2004c, 2006). ORF3a inhibited the nuclear translocation of STAT3 leading to dysregulation in transcription of anti-apoptotic genes (Padhan et al. 2008). Infection of cells with SARS-CoV led to dephosphorylation of STAT3 at Y705 and increased the phosphorylation of STAT3 at S727 (Mizutani et al. 2004a). p38-MAPK14 pathway was shown to be associated with STAT3 dephosphorylation at Y705 (Mizutani et al. 2004a). SARS-CoV PLpro stimulated Egr-1 (Cuzd1) dependent activation of pro-fibrotic genes, TGFβ1 and THBS1 through ROS-MAPK-STAT3 pathway (Li et al. 2016b). TGFB1 dependent expression of Type I collagen was stimulated by SARS-CoV PLpro via STAT6 pathway (Wang et al. 2017). Additionally, JNK and PI3K-AKT pathways were essential for the persistence of SARS-CoV infection (Mizutani et al. 2005). AKT1 and its downstream targets, GSK3B1, PRKCI and PRKCG were phosphorylated. AKT1 was phosphorylated at serine residue (S473) (Mizutani et al. 2004b). Also, the overexpression of M protein led to downregulation of AKT1 phosphorylation thus inducing apoptosis (Chan et al. 2007). E protein of SARS-CoV activated apoptosis by sequestering anti-apoptotic BCL2L1 (Bcl-xl) to endoplasmic reticulum (Yang et al. 2005). Upon infection with SARS-CoV, N protein enhanced TGF-β/Smad3-induced expression of plasminogen activator inhibitor-1 (PAI-1) (Zhao et al. 2008). Thus, N protein modulated TGF-β signaling to block apoptosis of SARS-CoV-infected host cells while promoting tissue fibrosis (Zhao et al. 2008). ORF3a was involved in apoptotic pathway through indirect activation of TP53 by p38-MAPK (Padhan et al. 2008).

Conclusions

SARS-CoV-host signaling modules will accelerate the understanding of various molecules and their roles in the pathogenesis of infection caused by SARS-CoV-2. Most likely, SARS-CoV-host signal transduction pathway may be useful for the development of potential molecular targets for antiviral treatment against different strains of CoVs. The pathway map available through this study will thus provide the scientific community with a platform that will further help to understand the pathology of various strains of SARS-CoVs.

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Authors’ contributions JS and LB conceptualized and designed the study. KTSP, NSM, AP, LB and JS analyzed and interpreted the data.
A pathway map of signaling events triggered upon SARS-CoV infection

KTSP, NSM, GD, AK, AP, LB and JS contributed to the writing of the manuscript.

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**Data availability** Data generated during this study are available at GitHub via following URLs:

- https://github.com/js-iiob/SARS-CoV-Pathway/blob/master/SARS_CoV_Signaling_pathway_map.gpml
- https://github.com/js-iiob/SARS-CoV-Pathway/blob/master/SARS_CoV_Signaling_pathway_map_GPML.pdf
- https://github.com/js-iiob/SARS-CoV-Pathway/blob/master/SARS_CoV_Signaling_pathway_map.xml
- https://github.com/js-iiob/SARS-CoV-Pathway/blob/master/SARS_CoV_Signaling_pathway_map_SBGN.pdf

**Declarations**

**Conflict of interest** The authors declare that no competing financial interests exist.

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