Identifying Potential Clues On Covid-19 Through Coronavirus-Related Literature Using A Data-Driven Approach With The Help Of A Text Mining-Based Software, PredictSearch.

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Abstract- Huge amounts of scientific publications are produced daily in particular in many fields of medicine and biological science. Managing these data and deducing valuable information to identify significant clues to understand a physiological or pathological mechanism as well as to propose therapeutic solutions are urgently needed. Here we describe the use of a dedicated text mining-based software, PredictSearch (PS) to explore, through a literature survey, significant correlations between terms related to coronavirus infection. Our search highlighted some features of antiviral compounds such as chloroquine and glycyrrhizin and their impacts on apoptotic cell death, cell cycle and endocytic pathway in the course of coronavirus infection. In addition, the reported mechanisms through which the virus can avoid the interferon-induced antiviral state should pave the way to identify efficient therapies. This study demonstrates the importance of informatics tools such as PredictSearch dedicated to scientific literature survey to adapt previous knowledge to new health issues on a particular topical subject like Covid-19 pandemia.

Index Terms- SARS-CoV2, literature search, text mining

I. Brief PredictSearch description

PS allows determining links between biological terms and/or molecules (genes, proteins, metabolites, chemical compounds) within title/abstracts of publications of the PubMED database. Title or abstracts quoting at least one gene were all collected as at the beginning, its main use was to decipher the impact of gene modulation evaluated by transcriptomic analysis (microarray). Then, these titles/abstracts were submitted to text mining through an anti-dictionary that removes terms not biologically relevant or, taken alone, too general such as "repair", "synthesis", "expression", "DNA", "protein", "cells".... However, these terms were stored in a specialized data base named "generic words" within a specific dictionary. Moreover our anti-dictionary preserves meaningful concepts defined as a series of terms, even those including "generic words" (e.g. "interferon expression", "DNA repair"). Iterative searches start by dropping within our working window either one or several genes of our gene data base (right panel in figure 1) or a particular term/concept using the "Search" tab (left panel in figure1). The "Annotate" tab allows to see all the terms/concepts (either classified by *p-value*, number of publications or alphabetical order) correlated with the term(s)/gene(s) selected in the working window. Like for genes, each of these terms found in either one or all dictionaries can be dropped into the working window and new correlation searches with these added terms can be performed. At the bottom of the screen, the "Abstracts" tab lists all the publications in which selected terms are co-cited.

II. Antiviral molecules related to coronavirus

In the present study, we choose two key words as baits: "coronavirus" and "antiviral" (Fig.1). At first, selecting only "coronavirus" led to the identification of 2704 words present in dictionaries encompassing terms of biological process, "customizable words" (issued from biological dictionaries), generic words, composed words (series of words) and key words (all terms that were not retained by the anti-dictionary and absent in the other dictionaries). Adding the term "antiviral" reduced the number of words to 185 (Fig.1). Among those exhibiting a p value <0,05, in addition to angiotensin (p value=3e-03) and interferon (p value= 1e-02), the top thirty words contained chemical or herbal compounds such as "glycyrrhizin" (p value= 3e-06), "PLPRO" (papain-like protease, p value= 8e-05), 6-azauridine (p value= 4e-04), nelfinavir (p value= 4e-03), and chloroquine (p value= 2e-02). In order to avoid missing publications that did not contain a gene name, search for title/abstracts citing a combination of the selected terms was performed on all PubMed. Noteworthy, glycyrrhizin, nelfinavir, chloroquine were all co-cited in a study of 2006 launched to evaluate several potential antivirals against SARS coronavirus infections (1).

Selecting "coronavirus", "antiviral" and "glycyrrhizin" led to 6 publications (1, 2, 3, 4, 5, 6). Glycyrrhizin is one of the constituents of glycyrrhiza glabra (liquorice) root. Animal and in vitro studies demonstrated a reduction of viral activity in herpes simplex virus encephalitis and influenza A virus pneumonia, and revealed antiviral activity against HIV-1, SARS related coronavirus, respiratory syncytial virus, arboviruses and vesicular

stomatitis virus. Of different compounds (ribavirin, 6-azauridine, pyrazofuridin or mycophenolic acid), glycyrrhizin was the most active in inhibiting replication of the SARS-associated virus (6). 6-azauridin was cited only in the title/abstract of two more publications (7, 8). While a search for “nelfinavir” with "coronavirus" and "antiviral" identified 4 publications (1, 9, 10, 11), 27 publications were found quoting in their titles/abstracts our baits and "chloroquine". Moreover, 15 were published in 2020, none in 2019, but no more than one per year was listed for the period between 2003 and 2018. The earliest report in 2003 (12) was focused on the observation that astrocytes were the major targets for mouse hepatitis virus (MHV) persistence. It showed also that expression of the pro-apototic Bnip3 gene was reduced following MHV infection and that chloroquine significantly inhibited the repression of Bnip3 promoter activity induced by the acidic-pH dependent MHV mutant OBLV60 (Fig.2). The next publication in 2004 (13) reported that chloroquine phosphate induced a significant antiviral activity in vitro in cells infected with the severe acute respiratory syndrome coronavirus (SARS-CoV).

III. Chloroquine activities

The first publication mentioning a therapeutic effect of chloroquine phosphate on COVID-19 patients appeared on March 2020 (14). The same month, two other publications evaluated the use of chloroquine against COVID-19. One can be considered as the first evidence that hydroxychloroquine was more potent than chloroquine to inhibit SARS-CoV-2 in vitro (15). The second reviewed the different activities involved in the antiviral activity of chloroquine (16). This last publication prompted us to add to our query, terms like: "quinone reductase"; "sialic acid"; "alkalinization"; "endosome"; "glycosylation" and "p38 MAPK" using the search tab.

Keeping chloroquine as the common bait, a search for terms correlated with "endosome" led to indentify 2407 terms, with "glycosylation" 665, with "syalic acid" 201 and with "alkalinization" 196. The most significant gene shared among all these terms was *NEU1* (neuraminidase 1), which codes for a lysosomal enzyme that cleaves terminal sialic acid residues from substrates such as glycoproteins and glycolipids. Interestingly, "neuraminidase" was also co-cited with "coronavirus" in 48 publications (the earliest being published in 1976). Neuraminidase inhibitors are a class of drugs that block the viral neuraminidase enzyme of the influenza virus by preventing its budding from the host cell (17).

Genes that were cited with either "coronavirus", "glycyrrhizin" and "chloroquine" led separately to 609, 503 and 2001 genes, respectively. However, only few genes were co-cited with at least two of these terms.

CASP8 (caspase 8) encodes a member of the cysteine-aspartic acid protease (caspase family). This protein is involved in programmed cell death (apoptosis) induced by various apoptotic stimuli such as stress triggered by UV irradiation, reactive oxygen species (ROS), but also by bacterial or viral infection. CASP8 was one of the caspases activated by canine coronavirus (CCoV) and this activation results in apoptosis (18). Similarly, apoptosis together with CASP8 activity was increased in cells infected with the equine coronavirus (19). However, glycyrrhizin was reported to induce apoptosis through CASP8 activation and TP53 increase (20).

CTSB (cathepsin B) encodes a member of the C1 family of peptidases. One proteic product generated by this gene is a lysosomal cystein protease with both endopeptidase and exopeptidase activity that may play a role in protein turnover. It has been shown that the ability of different strains of feline coronavirus to infect cells were highly dependent of host cell CTSB activity for entry into the host cell as well as on the low pH of endocytic compartments (21). It was suggested that host cell cathepsins may play a role in the distinct tropisms displayed by different feline coronavirus biotypes. An inhibition of *CTSB* expression and a stabilization of lysosomal membranes by the biologically active metabolite of glycyrrhizin, 18beta-glycyrrhetinic, which can prevent free fatty acid-induced lipid accumulation and cell apoptosis in vitro, were observed (22).

BCL2 (Bcl2 apoptosis regulator) encodes an integral outer mitochondrial membrane protein that blocks the apoptotic cell death. It has been shown that canine coronavirus type II decreased Bcl2 expression in cytosol (23). Moreover, expression of the SARS-CoV nucleocapsid (SARS-CoV N) protein was reported to down-regulate BCL2 levels and to induce apoptosis (24). On the other hand, Parris (25) proposed an interesting hypothesis that linked BCL2, chloroquine and coronavirus. Indeed, chloroquine facilitates apoptosis of abnormally persistent T-cell clones by suppressing NF-kappa-B, which enhances the expression of anti-apoptotic proteins such as BCL2. Based on this observation, one may hypothesize that prophylactic exposure to pro-apoptotic chloroquine drugs caused natural selection for strains of viruses and other parasites that have enhanced anti-apoptotic abilities. Hence, drugs that suppress BCL2 or restore TP53 function might be effective in restoring the parity of resistance to apoptosis between infected and uninfected cells. Similarly to chloroquine, 18beta-glycyrrhetinic acid can induce apoptotic cell death at least in part through reducing BCL2 level (26).

TP53 encodes a transcriptional factor that responds to various cellular stresses to regulate expression of target genes resulting in cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism. Although apoptosis induced by coronavirus infectious bronchitis virus was shown to be independent of TP53, infection imposed a growth-inhibitory effect on cultured cells by inducing a cell cycle arrest at S and G(2)/M phases (27). However, depending on the cellular models, an activation of TP53 pathway and a suppression of cell growth by chloroquine were reported (28).

Furthermore, chloroquine and hydroxychloroquine were also known as potent inhibitors of autophagy, a process that performs the self-digestion of damaged cells to generate ATP and other essential biosynthetic molecules to temporarily avoid cell death (29). In addition to raise the lysosomal pH (30), chloroquine may block the fusion between autophagosomes and lysosomes through its ability to disorganize golgi and endosomal systems (31). Autophagy inhibition induces an endoplasmic reticulum stress that in turn initiates apoptosis (Fig. 2). Although in the case of viral infection, autophagy can be either proviral or antiviral (32, 33), it was shown that the viral nsp6 protein of different coronaviruses including severe acute respiratory syndrome virus activates autophagy (34). Although like apoptosis, autophagy can be considered as an antiviral defense at the early step of viral

infection, viruses can subvert and exploit, later on, multiple steps of the autophagic pathway to evade immune responses and facilitate viral replication (reviewed in 35). It has been demonstrated that autophagy is required for the formation of complexes resulting from the binding of coronavirus hepatitis virus (MHV) to double membrane vesicles (DMVs) and that DMV formation significantly enhances the efficiency of the virus replication (36). However, MHV replication or release might depend neither on the autophagic factor ATG-5, by which cells deliver DMVs containing cytoplasm or cytoplasmic organelles to the lysosome, nor on an intact autophagic pathway (37). The controversial involvement of autophagy in viral replication may depend on the type of viruses used or cells tested as well as on the different techniques used in studying autophagy.

Nevertheless, autophagosomes that are produced during autophagy fuse with the endosomal pathway (Fig. 2). The endocytic pathway is used for CoVs to enter host cell towards the participation of the subunit viral protein S2 (38). The first publication co-citing "coronavirus" and "endocytic pathway" appeared in 2001 (39) and concerned the human coronavirus HcoV-229E. Since then, several studies have firmly established the role of the endocytic pathway in controlling the virus entry into the host cell.

IV. Impacts of SARS-CoV/ACE2 interaction

It has been reported that chloroquine, known to inhibit acidification of endosomes during the events of replication and infection (15), exhibited an antiviral effect either before or after exposure to SARS-CoV through interfering with terminal glycosylation of the cellular receptor, angiotensin-converting enzyme 2 (ACE2). From 325 PubMed reports containing “SARS-CoV” and “angiotensin-converting enzyme”, 155 were published up to the end of April 2020. ACE2, expressed in a variety of tissues including both the upper and lower respiratory tract, myocardium and the gastrointestinal mucosa (40), is the main receptor for coronavirus entry into cells (Fig. 3). Moreover, SARS-CoV2 may also infect endothelial cells (41), which indeed express ACE2 (42). The TNF-alpha converting enzyme (TACE) activated by the spike protein of SARS-CoV (SARS-S protein) was found to promote ACE2 ectodomain shedding (Fig. 3), and therefore the entry of SARs-CoV as well as TNF production (43). Loss of ACE2 that is translocated from the cell surface to endosomes after binding to the SARS-S protein, might lead to several deleterious events (Fig. 3). While ACE2 exhibits anti-inflammatory activity, ACE2 deficiency results in vascular inflammation and an inflammatory response that contributes to atherosclerotic plaque formation (44). These events relied on the activity of ACE2, which is involved in the conversion of angiotensin 1 into angiotensin 1-9 and production of the vasodilatator 1-7 angiotensin from angiotensin 2. Indeed, ACE2 can block its homolog ACE inhibiting the conversion of angiotensin 1 into angiotensin 2 (Fig. 3). Loss of ACE2 will therefore lead to an increase of angiotensin 2 and as a consequence to vasoconstriction, elevation of blood pressure and ROS production through NADPH oxidase activation (45). It can be speculated that at the site where vasoconstriction occurs, TNF release and/or atherosclerotic plaque inducing inflammatory cytokines will trigger endothelial barrier dysfunction. Disruption of the endothelial barrier will affect pulmonary alveoli, required for gas exchange causing ultimately acute respiratory distress syndrome (ARDS), a syndrome that is known to be the main cause of the mortality of SARS-CoV 2 infected patients. Moreover, pulmonary infection with the human SARS-CoV in mice led to an ACE2-dependent myocardial infection with a mark decrease in ACE2 expression (46), which, as described above, will result in deleterious effects due to angiotensin 2 accumulation (Fig.3).

V. Interferon pathway and coronavirus infection

The endocytic pathway may be even more important in our understanding of the CoVid-19 syndrome considering it can be associated with IFN resistance (Fig. 4). Tan et al. (47) tested several drugs in culture for their antiviral ability against SARS-CoV, including neuraminidase inhibitors and showed complete inhibition of cytopathic effects for some interferon (IFN) subtypes and human leukocyte interferon-α.

However, it was well established that SARS-CoV employs multiple passive and active mechanisms to avoid induction of type I interferons in cells. Loss of an efficient IFN response is likely to contribute to the establishment of a viremia early in infection. By contrast, high secretion of chemokines such as IP-10 and IL-8 might be responsible for massive immune cell infiltrations found in the lung of infected patients and the dysregulation of adaptive immunity (48).

Coronavirus can evade from the IFN system through several distinct mechanisms. Indeed, the antiviral effect of IFN relies in part on the expression of the 2'-5' Oligo adenylate synthetase (OASE). This enzyme, once activated by double strand (ds) RNAs, synthesizes 2'-5' oligo adenylates (2'-5'A), which as dimers or tetramers stimulate the dsRNA dependent-RNase L leading to the degradation of cytoplasmic and viral RNAs (Fig. 4). However several viruses exhibit a 2'-5' phosphodiesterase-like activity such as the viral protein ns2 of the coronavirus MHV, which confers virulence by cleaving 2'-5' A resulting in no activation of Rnase L (49, 50). In addition to the viral inhibition of the 2'-5'A/Rnase L system, it was shown that in SARS-CoV infected fibroblasts, no detectable induction of IFN-β occurs (51, 52, 53).

On the other hand, it was reported that absence of IFN-β results from the loss of activation of IRF3 (IFN regulatory factor 3), which is essential for IFN-β production (54). IRF3 synthesis is achieved through the combined activities of different factors (RING-1, MDA-5, PKR) activated in response to 5'triphosphorylated single stranded (ss) RNA or dsRNA (Fig. 4). It was suggested that loss of IRF3 might result from the impaired sensing of coronavirus by pathogen recognition receptors (PRRs) such as TLRs (Toll like receptors). One hypothesis was that dsRNA replication intermediates are located within the double membrane vesicles whose formation are induced, as we mentioned earlier, by virus infection and consequently will be protected from PRR sensing (54). Noteworthy, in contrast to coronavirus RNA, sensing with the IFN-inducer poly (I:C), polyinosinic:polycytidylic acid, a syntethic double strand RNA, resulted in IFN-β transcription and intranasal treatment with poly (I:C) was found to protect aged mice from lethal respiratory virus infections (55). It has to be noticed that whereas myeloid dentritic

cells (mDCs) and fibroblasts failed to produce IFN, plasmacytoid cells (pDCs) in the course of MHV infection are able to produce type I IFNs towards TLR7 (56). Noteworthy, elderly women had reduced number of pDCs and reduced TLR7/8 response compared to young adults (57). In contrast, seric markers involved in inflammation were increased in elderly and high levels of IL-6 correlated with increased morbidity and mortality were observed (58). Altogether these results are reminiscent of the observations that elderly with Covid-19 disease were indeed more prone in a context of a cytokine storm to respiratory illnesses resulting in higher mortality rates in such a population.

VI. Conclusive remarks

Investigating associated terms with "coronavirus" and "antiviral", PredictSearch allowed to identify within the literature several antiviral drugs or biological molecules including chloroquine and glycyrrhizin. Iterative queries highlighted different processes that might suggest how the virus can counteract at an early step the cellular defenses. Indeed, modulation of cell growth and induction of apoptosis are two common strategies used by many viruses to regulate their infection cycles. As other viruses, coronavirus infection leads at first to the induction of a cellular stress in the host cell. This stress has to be considered as a protective response of the host cell to avoid virus propagation through the induction of cell growth arrest and apoptosis. However, we report a hypothesis to explain how cellular resistance to apoptotic cell death might allow selecting some cells to survive and to constitute an important virus reservoir after cell recovery. It is suggested that the anti-viral activity of chloroquine or glycyrrhizin relies in part on their ability to induce apoptosis of the infected cells that were selected to survive. However this apoptosis will be triggered by events distinct from those induced at first by the viral stress. For instance, chloroquine can induce lysosomal stress and provoke a TP53-dependent cell death that does not require caspase-mediated apoptosis (59). Therefore, according to the inhibitory effect of chloroquine on autophagy and its ability to induce apoptosis, the benefit of the treatment should be considered in a time window when the virus alters these events for its survival and spread. The resulting impact of chloroquine on autophagy should also reduce not only the viral induced formation of cytoplasmic vesicles such as DMVs but also provoke alkalinization of these subcellular structures leading to the degradation of viral RNA replication intermediates. Moreover, localization of these intermediates within DMVs avoids viral sensing, an event crucial for an induced IFN expression in different cell types with the exception of pDCs, which are reduced in elderly. It can be speculated that to bypass the reduced expression of IFN in the course of coronavirus infection, use of poly (I/C) that in contrast to dsRNAs induces IFN expression, can be a therapeutic option in combination with an anti-IL6 treatment. Other factors downstream of IFN can also be proposed to provide an antiviral state such as 2'-5'A that can be combined with poly (I/C) together with an inhibitor of 2'-5' phosphodiesterase activity of the viral ns2 protein to avoid 2'-5'A degradation and Rnase L inactivation.

Thus, we believed that the correlations found by PredictSearch analysis based on existing knowledge might highlight important tracks to speed the identification of therapeutic approaches helping to fight new syndromes like Covid-19. More generally, this work illustrates how dedicated computational tools respond to the urgent need to deal with an exponential increase of publications.

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Conflicts of Interest

The authors declare no conflict of interest

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Legends of figures:

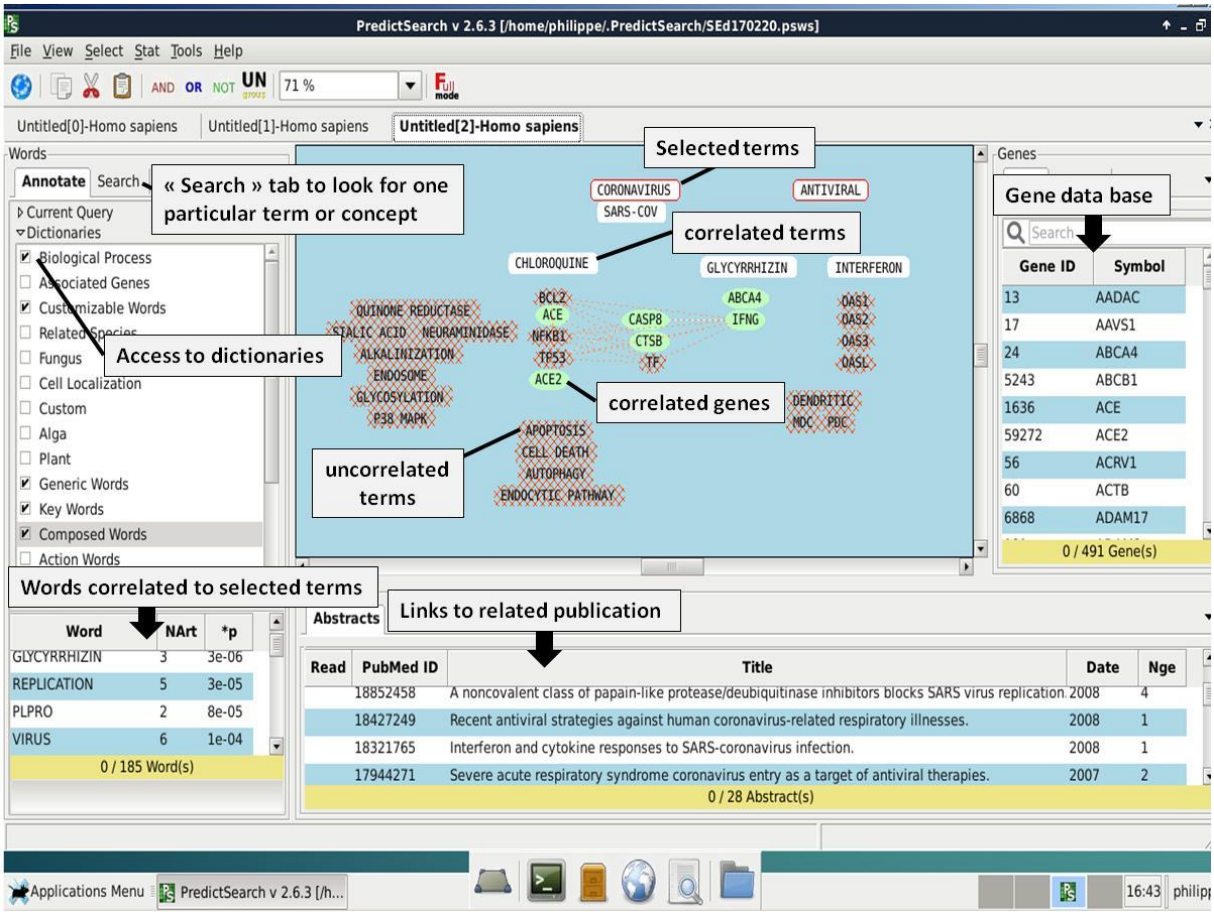
Figure 1: Screenshot capture of main PredictSearch features.

Figure 2: Schematic representation of the terms/concepts correlated to apoptosis, endocytic pathway, autophagy and coronavirus. Legends are indicated on the top right of the figure in a gray box.

Figure 3: Schematic representation of the terms/concepts correlated to ACE2 pathway and SARS-CoV infection. See figure 2 for legends.

Figure 4: Schematic representation of the terms/concepts correlated to interferon and viral infection. See figure 2 for legends.

Figure 1


PredictSearch v 2.6.3 [/home/philippe/.PredictSearch/SEd170220.psws]
File View Select Stat Tools Help
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Untitled[1]-Homo sapiens
Untitled[2]-Homo sapiens
Selected terms
« Search » tab to look for one particular term or concept
correlated terms
Gene data base
Access to dictionaries
correlated genes
uncorrelated terms
Words correlated to selected terms
Links to related publication
CORONAVIRUS
SARS-COV
ANTIVIRAL
CHLOROQUINE
GLYCYRRHIZIN
INTERFERON
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0 / 185 Word(s)
0 / 28 Abstract(s)

Figure 2

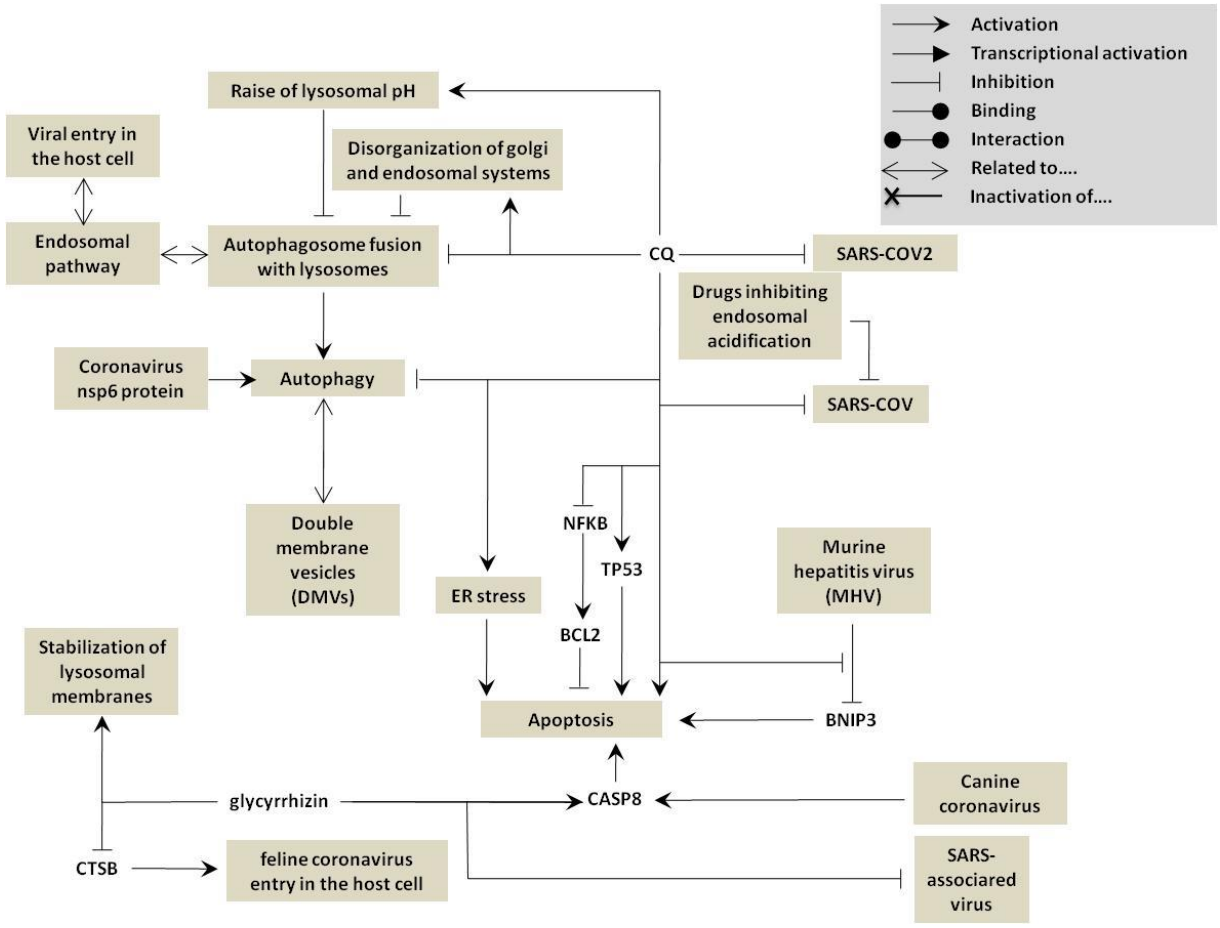

Activation
Transcriptional activation
Inhibition
Binding
Interaction
Related to....
Inactivation of....
Raise of lysosomal pH
Viral entry in the host cell
Disorganization of golgi and endosomal systems
Endosomal pathway
Autophagosome fusion with lysosomes
CQ
SARS-COV2
Drugs inhibiting endosomal acidification
Coronavirus nsp6 protein
Autophagy
SARS-COV
Double membrane vesicles (DMVs)
NFKB
TP53
ER stress
Murine hepatitis virus (MHV)
BCL2
Stabilization of lysosomal membranes
Apoptosis
BNIP3
glycyrrhizin
CASP8
Canine coronavirus
CTSB
feline coronavirus entry in the host cell
SARS-associared virus

Figure 3

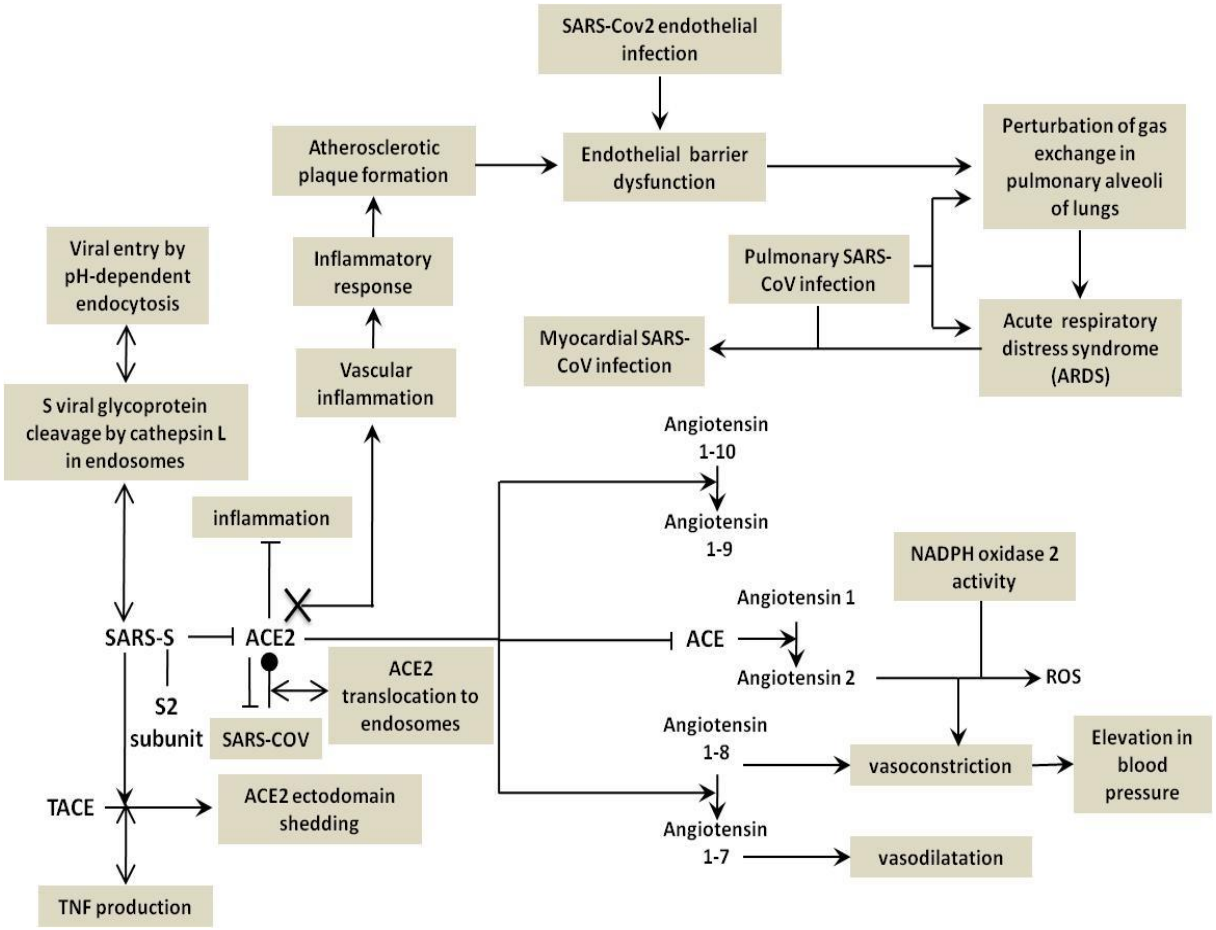
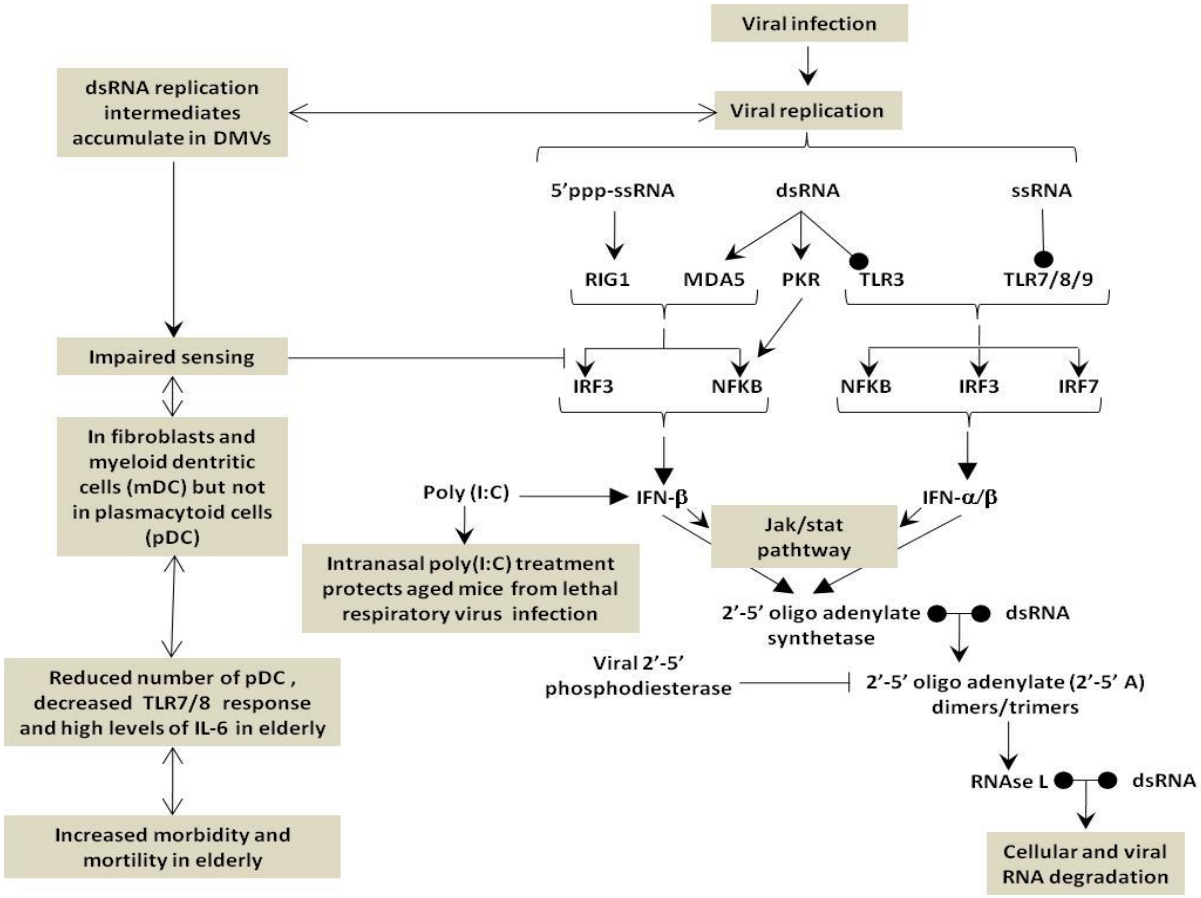

SARS-Cov2 endothelial infection
Atherosclerotic plaque formation
Endothelial barrier dysfunction
Perturbation of gas exchange in pulmonary alveoli of lungs
Viral entry by pH-dependent endocytosis
Inflammatory response
Pulmonary SARS-CoV infection
Myocardial SARS-CoV infection
Acute respiratory distress syndrome (ARDS)
Vascular inflammation
S viral glycoprotein cleavage by cathepsin L in endosomes
Angiotensin 1-10
Angiotensin 1-9
inflammation
NADPH oxidase 2 activity
Angiotensin 1
SARS-S
ACE2
ACE
Angiotensin 2
ROS
ACE2 translocation to endosomes
S2 subunit
SARS-COV
Angiotensin 1-8
vasoconstriction
Elevation in blood pressure
TACE
ACE2 ectodomain shedding
Angiotensin 1-7
vasodilatation
TNF production

Figure 4


Viral infection
dsRNA replication intermediates accumulate in DMVs
Viral replication
5'ppp-ssRNA
dsRNA
ssRNA
RIG1
MDA5
PKR
TLR3
TLR7/8/9
Impaired sensing
IRF3
NFKB
NFKB
IRF3
IRF7
In fibroblasts and myeloid dentritic cells (mDC) but not in plasmacytoid cells (pDC)
Poly (I:C)
IFN-β
IFN-α/β
Jak/stat pathtway
Intranasal poly(I:C) treatment protects aged mice from lethal respiratory virus infection
2'-5' oligo adenylate synthetase
dsRNA
Viral 2'-5' phosphodiesterase
2'-5' oligo adenylate (2'-5' A) dimers/trimers
Reduced number of pDC , decreased TLR7/8 response and high levels of IL-6 in elderly
RNAse L
dsRNA
Increased morbidity and mortility in elderly
Cellular and viral RNA degradation