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Therapeutic approaches to coronavirus infection according to "One Health" concept

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ABSTRACT

Coronaviridae constantly infect human and animals causing respiratory, gastroenteric or systemic diseases. Over time, these viruses have shown a marked ability to mutate, jumping over the human-animal barrier, thus becoming from enzootic to zoonotic. In the last years, numerous therapeutic protocols have been developed, mainly for severe acute respiratory syndromes in humans. The aim of this review is to summarize drugs or other approaches used in coronavirus infections focusing on different roles of these molecules or bacterial products on viral adhesion and replication or in modulating the host's immune system. Within the "*One Health*" concept, the study of viral pathogenic role and possible therapeutic approaches in both humans and animals is essential to protect public health.

1. Introduction

Over the past 17 years, three global outbreaks in humans have occurred due to viruses belonging to the genus betacoronavirus: SARS-Coronavirus-1 (SARS-CoV-1) in 2003, MERS-Coronavirus (MERS-CoV) in 2012 and SARS-Coronavirus-2 (SARS-CoV-2) in 2019 (World Health Organization, 2020; CDCP, 2019). These coronaviruses cause respiratory and gastroenteric diseases in mammals similar to alpha- and deltacoronaviruses (Masters and Perlman, 2013). Both genera belong to *Coronaviridae,* a family of positive sense, single-stranded RNA viruses with envelope, with large protrusions in the surface (van Regenmortel et al., 2000). The genome of these viruses encodes for structural proteins such as nucleocapsid protein (N), membrane protein (M), envelope protein (E), spike protein (S), and in some coronaviruses the envelope-associated hemagglutinin-esterase protein (HE) (Li, 2016; Schoeman and Fielding, 2019), and for non-structural proteins (nsp) such as proteases (nsp3 and nsp5) and RdRp (nsp12) (Elfiky et al., 2017; Kilianski and Baker, 2014). CoV entry occurs either via the plasma membrane with the help of cell surface proteases such as TMPRSS2 or via endocytosis, through the splitting of S proteins into two functional subunits: the S1 (harboring the receptor-binding domain) that binds of the surface unit, and the S2 (containing the membrane fusion domains) that allows fusion of viral and cellular membranes (Hoffmann et al., 2020; Tripet et al., 2004). Defined as enzootic, for a long time, some of these viruses have crossed the animal-human barrier becoming zoonotic (Chan et al., 2013b), due to their ability to mutate and recombine adapting that way to new host range (Li, 2016). It is widely recognized that animals were the spillover source for SARS-CoV-2 infection in men (Schmiege et al., 2020; Di Teodoro et al., 2020). To deepen the link among animal-men-SARS-COV-2, the susceptibility of many animals to the virus has been investigated and it has been shown that animals such as cats, ferrets and minks are susceptible to the infection, while chickens and pigs are not; interestingly, respiratory *ex-vivo* organ cultures of cattle and sheep further suggested that also these animal species may be susceptible to the infection (Di Teodoro et al., 2020). Much information is available in veterinary medicine on animal coronaviruses, so that such knowledge may be of help also in human medicine to better understand how the virus behaves and how to face it. For example, in birds, CoVs have been detected in a lot of different species such as domestic fowl, turkeys, penguins, pigeons, duck, etc. But also bats, some rodents, swine, ruminants, horses, dogs, cats, ferrets, wolves, red foxes and many other wild carnivores are known to host CoVs (Decaro and Lorusso, 2020), suggesting that both human and veterinary medicine may benefit from a "One health" approach.

Studies in animal models allowed to characterize the viral pathogenesis of human coronaviruses (SARS-CoV-1 and MERS-CoV) and to actuate new therapeutically approaches (Sutton and Subbarao, 2015). In general, two types of therapeutic strategies can be recognized: the first aiming directly to counteract the etiological agent, the second aiming to control the host immune-response.

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2. Therapeutical approaches against the virus entry and the RNA replication

2.1. Nucleotide and nucleoside analogue inhibitors

These molecules are chemically synthesized of pyrimidine and purines and administered as precursors (Pruijssers and Denison, 2019). Nucleotide and nucleoside inhibitors compete with nucleotide substrate to bind active site of polymerase; these analogues can induce mutations that impair the RNA structure and RNA-protein functions or can cause chain termination in replicating viral genomes incorporating foreign nucleotides (Gao et al., 2020; Pruijssers and Denison, 2019). Numerous molecules (Fig. 1), have been proposed for coronavirus infections, and their activity has been demonstrated primarily in human coronavirus such as: acyclic fleximer nucleoside analogues (Peters et al., 2015); 6-Azauridine (Pyrc et al., 2006); Gemcitabine hydrochloride (Dyall et al., 2014); BCX4430 (Warren et al., 2014); β-d-N4-hydroxycytidine (Barnard et al., 2004) and the 1-β-d-ribofuranosyl-1, 2,4-triazole-3-carboxyamide (ribavirin) (Chan et al., 2013a); Mizoribine and Ribavirin (Saijo et al., 2005). However, the evidence of efficacy is inconclusive. Recently, the GS-441524 (parent nucleoside of Remdesivir), a broad-spectrum RNA polymerase inhibitor, has been proposed. It was developed in response to the Ebola outbreak (Mulangu et al., 2019), filoviruses, paramyxoviruses, and pneumoviruses (Lo et al., 2017). Its anti-CoV activity was shown in cats with feline infectious peritonitis (Murphy et al., 2018), in a mouse model of SARS-CoV-1 (Sheahan et al., 2017) and in nonhuman primate model of MERS-CoV infection (Martinez, 2020), but its mechanism is still unclear. This adenosine nucleotide analogue can get incorporated into viral RNA and cause premature chain termination (Warren et al., 2016); by intracellular phosphorylation, the active NTP (Nucleoside Triphosphate) analog works as a competitor of the natural nucleoside triphosphates in RNA synthesis (Warren et al., 2016). Remdesivir can also interfere with the nsp12 polymerase, a non-structural protein which mediates the RNA replication (Shannon et al., 2020). Another nucleoside analog used for the treatment of feline infectious peritonitis in cats is Mutian X (Addie et al., 2020). This drug is a synthetic adenosine analogue associated with nicotinamide mononucleotide, Crocin I, S-Adenosylmethionine, Silymarin, thus stopping RNA replication (Addie et al., 2020). However, as an RNA virus, coronaviruses have an intrinsic genetic variability, which results in a high mutation rate and are therefore able to develop drug-resistance for these molecules (Agostini et al., 2018).

2.2. Viral protease inhibitors

By specific proteases, as papain-like protease and 3C-like protease (3CLpro), coronaviruses can cleave polyproteins and release non-structural proteins (nsp), as the NSP1–16, which have important functions in maturation or production of functional viral proteins (Sarma et al., 2020). These viral proteins, similar in human coronavirus and feline coronavirus, are key factors for RNA replication and transcription and, for this reason; they are target for protease inhibitors. A peptidyl

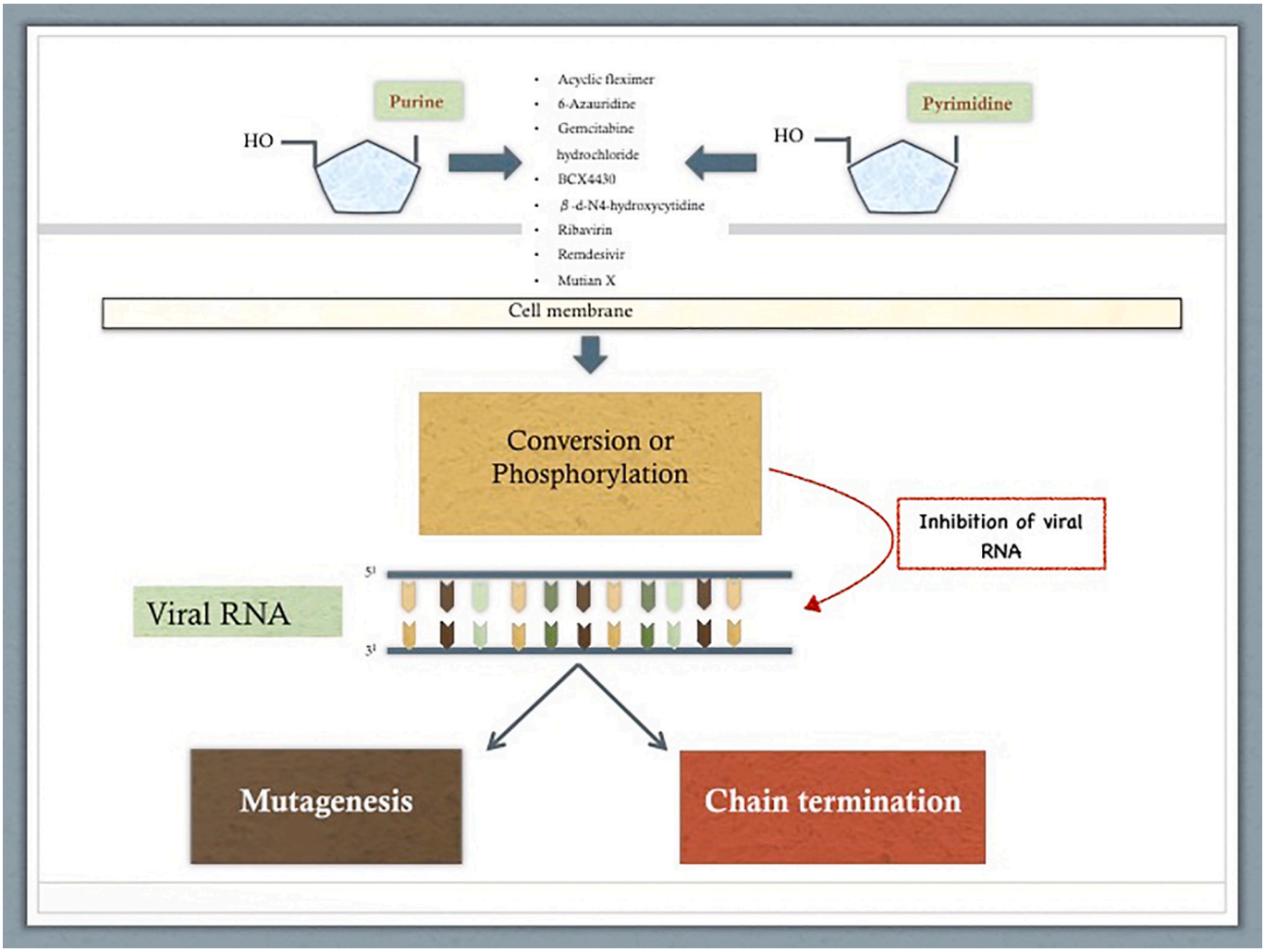

Fig. 1. Schematic representation of nucleotide and nucleoside inhibitors on viral RNA.

compounds targeting viral 3C-like protease has proven effective against feline infectious peritonitis in cat (Kim et al., 2015). This protease inhibitor, the GC376, has been tested in 20 sick cats, however the results did not demonstrate complete efficacy of the treatment (Pedersen et al., 2018). Anti-SARS-CoV-2 action has been demonstrated in protease inhibitors such as Lopinavir, Saquinavir (Dayer et al., 2017), and a formulation of two structurally related protease inhibitor for the treatment of SARS-Cov-2: Lopinavir associated with Ritonavir (Kaletra, Abbott Laboratories ® North Chicago) (Jin et al., 2020). In patients with HIV infection, it has been shown that Lopinavir can prevent subsequent infections of cells arresting maturation of HIV-1 (Cvetkovic and Goa, 2003). Lopinavir is an HIV-1 protease inhibitor, which hinders the formation of infectious virions but has poor bioavailability, therefore it comes co-formulated with ritonavir, which can inhibit the cytochrome P450 3A4 isoenzyme increasing lopinavir blood levels (Chandwani and Shuter, 2008). Finally, recent studies are demonstrating effectiveness of a triple combination composed by interferon beta-1b, Lopinavir–Ritonavir, and Ribavirin (nucleoside analogue) in patients with COVID-19, if administered within one week of symptom onset (Hung et al., 2020).

2.3. Cellular protease inhibitors

Viruses use specific proteins present in cell for entry (Böttcher et al., 2006; Glowacka et al., 2011). Through the cleavage of the surface glycoprotein spike (S) at two different sites, coronaviruses can enter in the host cell (Bestle et al., 2020). This step is mediated by host cell proteases. Among human and animal species these proteases are different and the species-specificity of coronaviruses is determined by the recognition of a functional receptor. Studies have shown that different proteases can activate the virus including trypsin, cathepsin, transmembrane serine proteases (in particular TMPRSS2), aminopeptidase N, and furin; some of which play major roles in a broad range of viruses (Heald-Sargent and Gallagher, 2012; Millet and Whittaker, 2015; Ou et al., 2020; Luan et al., 2020). In the cat, the receptor for type II feline coronavirus is the feline aminopeptidase N (fAPN) (Miguel et al., 2002). In the dog, Canine respiratory coronavirus (CRCoV) uses a caveolin-dependent endocytosis and a mechanism like that used by MERS-CoV by a transmembrane protease serine 2 (TMPRSS2) (Szczepanski et al., 2018). The gene TMPRSS2 encodes proteins that belong to the serine protease family (Böttcher et al., 2006). In SARS-CoV-1 and MERS-CoV, the TMPRSS2 and the endosomal cysteine protease cathepsin L prime the S proteins, facilitating the entry of the virus and the splitting of the protein into two functional subunits: S1 which binds of the surface unit, and S2 which allows fusion of viral and cellular membranes (Hoffmann et al., 2020; Tripet et al., 2004). In general, the respiratory and gut epithelia are targeted for many coronavirus genera where the pathogen can cause a localized or systemic infection (Siddell et al., 2005). The metallopeptidase named angiotensin-converting enzyme 2 (ACE2) is a specific receptor present in different types of cells such as lung, gut, and prostate epithelial cells (Hamming et al., 2004; Song et al., 2020). In SARS-CoV-1, TMPRSS2 can modulate viral spread in the host by co-expression of ACE2 (Mossel et al., 2008), which binds to the S1 domain of the SARS-CoV-1 spike protein (Li et al., 2003). SARS-CoV-2 evolved to possess a furin cleavage site at its S1/S2 site essential to cleave viral fusion proteins allowing entry into human lung cells (Hoffmann et al., 2020). Furin is a type transmembrane protein expressed in tissues and cells, which cleaves the precursors of cell surface receptors and adhesion molecules, but has also a key role as fusion protein of a broad range of viruses such as HIV, Ebola virus, and yellow fever virus (Rockwell et al., 2002; Bestle et al., 2020). Clinical studies showed the effectiveness of camostat mesylate and nafamostat mesylat (Kawase et al., 2012; Hoffmann et al., 2020; Breining et al., 2021). These molecules are cellular serine protease inhibitor (Kawase et al., 2012), which are able to inhibit the TMPRSS2 stopping SARS-CoV-2 infection in lung cells (Hoffmann et al., 2020). Chloroquine has been shown to be effective against the coronaviruses by different mechanisms of action (Barnard et al., 2006; Gies et al., 2020; Yao et al., 2020). It works as an entry inhibitor by impairing endosomal-mediated entry inhibiting the fusion of the virus to the cell membrane by modulation of the endosomal pH, and prevents acidification, which several viruses use for the fusion and entry process (Vigerust and Shepherd, 2007; Rolain et al., 2007).

2.4. N-linked glycosylation inhibitor

Enveloped viruses use cellular glycosylation pathway to modify their biogenesis, antigenicity and infectivity (Vigerust and Shepherd, 2007). The most used type of glycosylation is the N-glycosylation, which begins in the endoplasmic reticulum on a peptide chain. In this reaction, a standard carbohydrate chain is added at the nitrogen atom of a side chain of asparagine (Vigerust and Shepherd, 2007). Studies showed that the N-linked glycosylation on hepatitis C virus (HCV), Ebola (Eichler et al., 2006), Hendra (Bossart et al., 2005), Nipah (Aguilar et al., 2006), and SARS-CoV-1 (Oostra et al., 2006) have key roles in tropism infectivity and immune evasion (Goffard and Dubuisson, 2003). In SARS-CoV-1 and SARS-CoV-2, the surface protein involved in target cell attachment and fusion processes is the spike glycoprotein (S) (Hoffmann et al., 2020; Tripet et al., 2004), a 1255-amino acid precursor polypeptide characterized by 23 potential N-linked glycosylation sites (Xiao et al., 2003). All N-glycosylation sites occur on the amide nitrogen of an asparagine residue (Asn) with exposure of N-acetylglucosamine glycan (GlcNAc) attached to asparagine in β configuration (Stanley et al., 2017). A new therapeutic protocol involves the use of the enzyme asparaginase, which can break down asparagine and inhibits its formation, reducing the synthesis of N-acetylglucosamine molecules (Bellini et al., 2020). Studies showed the antiviral activity of L-asparaginase against HIV-1, retrovirus and herpesvirus infections (Maral and Werner, 1971; Avramis et al., 2001). In this way, the SARS-COV-2 viral coating and cellular infection are stopped. Chloroquine, or alternatively Hydroxychloroquine, has anti-inflammatory and immunomodulatory activities and can also interfere with the glycosyltransferases's activity (Al-Bari, 2017). It has been shown to be effective *in vitro* and in mouse models against the SARS-CoV-2 by different mechanisms of action (Barnard et al., 2006; Gies et al., 2020; Yao et al., 2020). Chloroquine, as mentioned above, can inhibit the fusion of the virus to the cell membrane by modulation of the endosomal pH (Vigerust and Shepherd, 2007; Rolain et al., 2007) and it can also stop the association between calnexin and calreticulin, misfolding viral proteins (Vigerust and Shepherd, 2007).

3. Host-directed therapeutical approaches and against the immune response modulation

Similar to other viruses, coronavirus has the ability to evade the cellular defense (Cheng et al., 2007). Once into the target cell, there may be an inflammatory and apoptotic response followed by a regenerative organ activity or evolves in syndrome (Cheng et al., 2007). The ability to evade the immune system is well represented by the feline coronavirus (FCov). This virus is classified in two serotypes, basing on differences of the S protein amino acid sequence and antibody neutralization (Shiba et al., 2007; Lewis et al., 2015). The two biotypes, referred to feline enteric coronavirus (FECV) and feline infectious peritonitis virus (FIPV), differ for the disease they cause. The FIPV biotype is considered highly virulent and leads to a lethal disease called feline infectious peritonitis (FIP) (Pedersen et al., 1984). The major target cells of FIPV are monocytes and macrophages in which the virus is able to replicate and trigger an activation of these cells (Dewerchin et al., 2005). The infected and activated monocytes express cytokines such as IL-1β, IL-6, IL-10, TNF-α and adhesion molecules (Malbon et al., 2019; Foley et al., 2003) triggering a cytokine storm. Moreover, antibodies enhance the uptake and replication of FIPV in target cells and contribute to a type III hypersensitivity vasculitis (Pedersen, 2009). Although in the cat, an individual

predisposition to the development of FIP has not yet been fully demonstrated, it is conceivable that a genetic risk factors may have a role in disease progression, as has recently been demonstrated in humans (The Severe Covid-19 GWAS Group, 2020). These recent studies show that genomic regions on chromosome 3 and 9 are associated with severe COVID-19 (Zeberg and Pääbo, 2020). As happens in the cat with FIP, it is known that the severity of disease caused by coronaviruses is due to the "cytokine storm". The immune-response in SARS-CoV-1, MERS-CoV, and SARS-CoV-2 is characterized by an excessive production of proinflammatory cytokines such as the interferon gamma-induced protein 10 (IP10), which activates cytotoxic T lymphocytes and monocytes in lung tissue (Wong et al., 2004). The so called "cytokine storm" can damage the lung, brain, cardiovascular system, gastrointestinal tract, liver, kidney, microcirculation, and eyes (Bhaskar et al., 2020) resulting in multiorgan dysfunction (Fig. 2). For this excessive response of the immune system, several drugs with immunomodulatory, anti-inflammatory and immuno-suppressive effect have been proposed. However, their use in diseases caused by coronaviruses in both human and veterinary medicine is still debated. Some molecules have been chosen to activate the shelter while others have observed to block the receptors managed by "harmful" cytokines. Characterized by a repairing and protective role are the following agents: type I interferon alone or in combination by its broad-spectrum antiviral effect (Cinatl et al., 2003), mesenchymal stem cells which can reduce the inflammatory infiltrate (Lee et al., 2009), intravenous immunoglobulin (Jolles et al., 2005), specific neutralizing antibodies (Zhou and Zhao, 2020) and human monoclonal antibody such as REGN3048 and eculizumab (de Wit et al., 2018; Diurno et al., 2020). Agents proposed to manage "harmful" cytokines are: anti-interleukin-6 receptor such as sarilumab (Rose-John, 2012), interleukin-1 (IL-1) receptor antagonists, such as anakinra (McCreary and Pogue, 2020), and thalidomide which decreases the synthesis of TNF-alpha (Zhu et al., 2014). Corticosteroids are known to reduce the numbers of CD4 and CD8 T cells and cytokine levels inducing immunosuppression. Studies suggested the role of corticosteroid treatment in SARS patients. These drugs can reduce proinflammatory cytokines playing a major role in lung immunopathology, however corticosteroids can induce immunosuppression leading to enhanced respiratory disease or increased CoV shedding (McCreary and Pogue, 2020; Veronese et al., 2020). Even in cats with FIP, both anti-inflammatory and immuno-suppressive drugs such as prednisolone, alkylating drugs (cy-clophosphamide), and inhibitors of specific cytokines (pentoxyfylline) have been used to reduce clinical signs, but without evidence about the disease outcome (Pedersen, 2014). In a study conducted in 2017, the Polyprenyl Immunostimulant was proposed as treatment for the reduction of clinical signs in sixty cats affetcted by FIP (Legendre et al., 2017). This drug can upregulate Th-1 type pathway *via* toll-like receptors, however, there have been no further studies demonstrating its benefit. On the basis of some preliminary case reports, showing a mild disease course in COVID-19 affected patients, maintained in a regimen of immunosuppression by calcineurin inhibitors (CNIs) (Zhu et al., 2020; Guillen et al., 2020; D'Antiga, 2020; Monti et al., 2020), such as cyclosporine (Cys) and

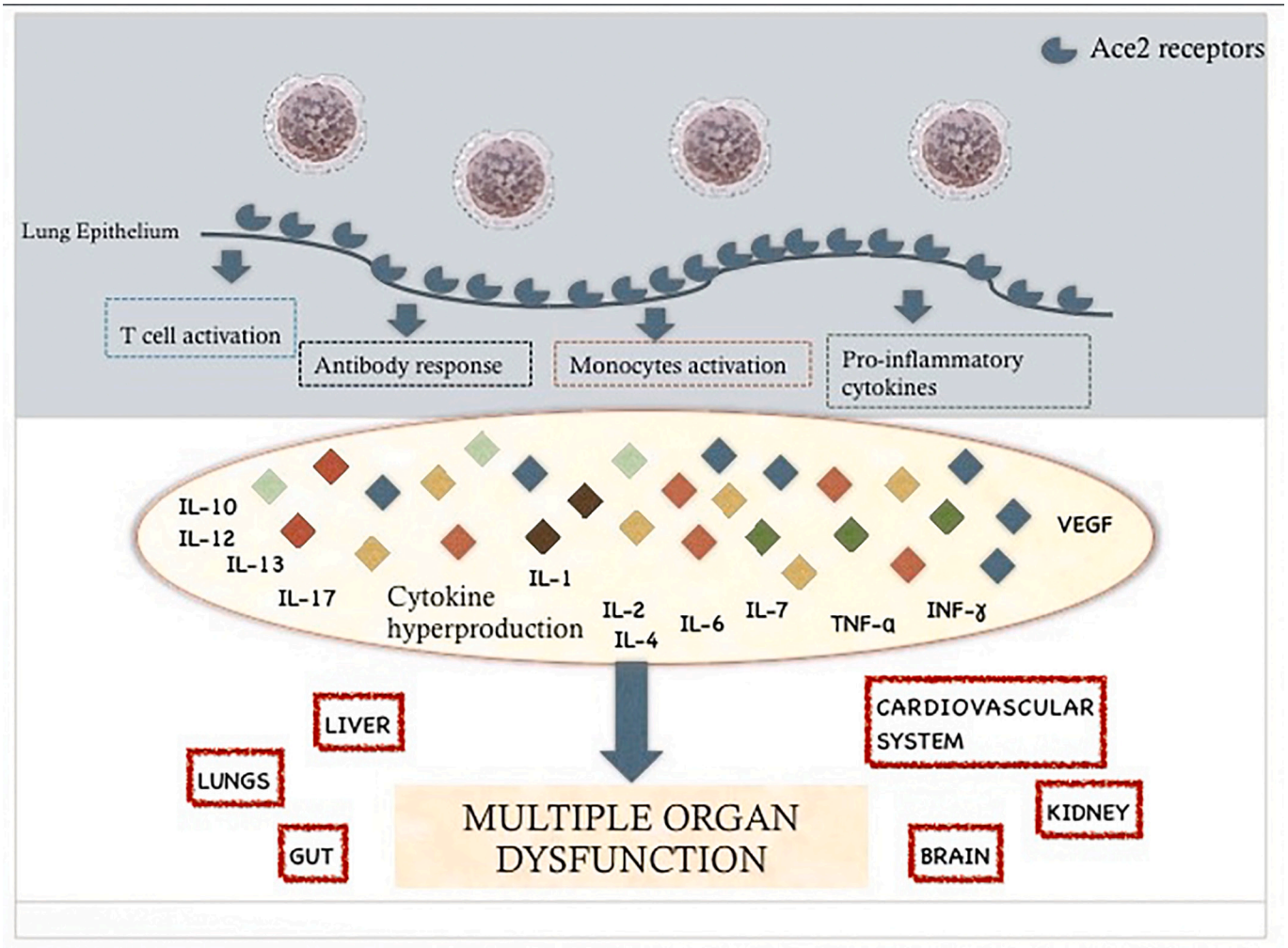

Fig. 2. Schematic representation of the "cytokines storm".

tacrolimus (TAC), which are currently used in the setting of transplantation (Kuypers, 2020) and Rheumatic Disorders (RMDs) (Cavagna et al., 2020b), different studies were performed to evaluate also a potential antiviral activity of these molecules (Cavagna et al., 2020a). On the other hand, immunosuppressive treatments are being studied as possible therapeutic options in the hyper-inflammatory phase of the COVID-19 (Mehta et al., 2020). The antiviral effect of CNIs has been evidenced in vitro against some coronavirus strains (Pfefferle et al., 2011; Ma-Lauer et al., 2020; Carbajo-Lozoya et al., 2012; de Wilde et al., 2011). Clinical evidences of COVID-19 course in patients treated with CNIs alone or in association with other immune-suppressants (ISs) appears to be generally mild, without development of superimposed infections despite immunosuppression, and that also in the case of SARS-COV-2 related lung involvement or of previously diagnosed interstitial lung disease (ILD). Substantially, CNIs based chronic immunosuppressive regimens do not increase the risk of severe course of COVID-19 or complications, decreasing the mortality rate (Cavagna et al., 2020a). The CNIs based chronic immunosuppressive regimens influences the clinical course of the disease preventing the occurrence of the huge alveolar macrophage activation, with consequent release of pro-inflammatory cytokines that has been described in the context of SARS-COV-2 (Mehta et al., 2020). In fact, although high sensitivity C-reactive protein (hs-CRP) levels were similar between confirmed COVID-19 with and without immunosuppression, IL-6 levels were much lower in the immunosuppressed group. Interestingly, both Cys and TAC inhibit viral replication in a number of CoV strains, including SARS-CoV-1, through the inhibition of peptidyl-prolyl cis-trans isomerases, such as cyclophilin A and FK506-binding proteins, that are cellular interaction partners of CoV non-structural protein 1 (Nsp1) (Pfefferle et al., 2011; Ma-Lauer et al., 2020; Carbajo-Lozoya et al., 2012). In this sense, it is conceivable that Cys and TAC exert antiviral activity also towards SARS-CoV-2. On this basis, it is reasonable to add also CNIs in the list of ISs possible therapeutic options for COVID-19 (Sarzi-Puttini et al., 2020).

4. New approaches of bacteriotheraphy

The live microbes, such as probiotics, possess health benefits on the host when administered in appropriately adequate amount. Several studies showed they role in, stimulating mucosal barrier function and modulating the immune system (Brown and Valiere, 2004) exerting beneficial effects through modulation of vitamin D (Li et al., 2015). Similarly to other *Coronaviridae*, as FECoV in the cat, ferret enteric CoV (FRECV), and CRCoV in dogs, the invasive process of SARS-COV-2 is due to enzymes which are linked to intestinal epithelial cells (IECs). Coronaviruses constantly change their binding patterns; the potential target in the lungs (as in primates or in *Mustelidae* or *Felidae*) or macrophages (mainly in *Felidae*) can change, but not in the small intestine, where it remains constant. The IECs could be a reservoir for coronaviruses (Feng et al., 2020). Different studies show that some strains of *Lactobacilli* and *Bifidobacteria* could inhibit viruses such as influenza virus, rhinovirus, respiratory syncytial virus, adenovirus, and pneumovirus (Leyer et al., 2009; Li et al., 2019). Chinese researchers have investigated changes in the microbiota in patients died by Covid-19, showing a significant decrease in *Bifidobacteria* and *Lactobacilli*, and an increase in opportunistic bacteria such as *Corynebacterium* or *Ruthenibacterium*. The severity of hypoxemia was strongly correlated with high levels of immune cells and markers of inflammation. In addition, during the acute respiratory distress syndrome (ARDS) of affected patients, a decrease in the tissue oxygenation, also in GI tract, can alter the composition of the gut microbiota decreasing proportion of oxygen-tolerant organisms and increasing anaerobic phyla, as *Clostridiales* (Albenberg et al., 2014).

The link between hyper inflammation and intestinal dysbiosis appears to be a high risk for ARDS. In the acute phase, virus cDNA was detected in blood in 10% of patients and in stool of 50% of patients, suggesting that feces could be a mode of contamination (Leung et al., 2003). The gut involvement might explain the wide variation in viral load from one test to another in the same patients (Yu et al., 2020). Recently, studies demonstrated that the use of oral bacteriotherapy could be an option to treat COVID-19. A select mixture of bacteria, previously demonstrated with antiviral activity (Li et al., 2019), was administered with anti-COVID-19 treatment (chloroquine, antibiotics, and/or tocilizumab) and compared to other COVID-19 positive treated subjects, without bacteriotherapy (Ceccarelli et al., 2020; D'Ettorre et al., 2020). Results suggested a different surviving rate (four deaths vs. zero death in probiotic treated patients), and a lower estimated risk to develop respiratory failure during COVID-19 course (D'Ettorre et al., 2020). Also for the other signs and symptoms associated with COVID-19, i.e. diarrhea, fever, cough, dyspnea, asthenia, and myalgia a significant improvement is already evident as early as after 24 hours after the start of the bacteriotherapy, and seventy-two hours after the start of the bacteriotherapy, the 100% of treated patients showed a remission of symptoms vs. about the 45% of the control group (D'Ettorre et al., 2020). These results suggest a possibility important role of the "*gut-lung axis*" in the control of the COVID-19 infection (Enaud et al., 2020; Dumas et al., 2018). Studies show that during corona- and influenza-virus infections, certain bacteria (generally opportunistic or pathogen species) can support the viral activation either by secreting proteases that cleave Spikes or influenza hemagglutinin (HA) or due to activation of cellular proteases, possibly contributing to the intracellular virus entry (Böttcherì-Friebertshäuser et al., 2013). In this sense, an oral bacteriotherapy could reduce this viral "priming" at intestinal level. There are potential anatomical communications and complex pathways involving intestine and lungs (GLA) (Enaud et al., 2020; Dumas et al., 2018). The mesenteric lymphatic system is the pathway between the lungs and the intestine, through which bacteria or fragments or metabolites, can cross the intestinal barrier to reach systemic circulation and influence the pulmonary immune response (Bingula et al., 2017; McAleer and Kolls, 2018; Trompette et al., 2014). It has been showed that mice with SCFAs receptors deficiency show increased inflammatory responses in experimental models of asthma (Trompette et al., 2014). Short chain fatty acids (SCFAs), produced primarily by bacterial fermentation of dietary fiber, act in the lungs as signaling to attenuate inflammatory and allergic responses (Cait et al., 2018; Anand and Mande, 2018). Additionally, oral bacteriotherapy enhance the cellular antioxidative defense systems protecting against reactive oxygen species (ROS) generated by viruses (Hosakote et al., 2011). By using selected bacterial strains, enhancing the production of both the nuclear factor erythroid 2p45-related factor 2 (Nrf2) and its target Heme oxygenase-1 (HO-1) (Castelli et al., 2020), an antiviral effect was induced through a reduction of oxidative stress. Nrf2 and HO-1 have significant antiviral activity against viruses, including HIV, hepatitis B virus, influenza virus, respiratory syncytial virus, dengue virus, and Ebola virus among others (Devadas and Dhawan, 2006; Protzer et al., 2007; Hashiba et al., 2001; Ma et al., 2016; Janyra et al., 2017; Tseng et al., 2016; Hill-Batorski et al., 2013). Notably, beneficial properties of HO-1 expression have been reported for viruses responsible for lung disease, as demonstrated in a Mice model in which an overexpressed HO-1 in the lungs lead to a lower inflammatory cells infiltration, decreased apoptosis of respiratory epithelial cells, preventing an exacerbated immune response in this tissue, and subsequent damage (Hashiba et al., 2001). As mentioned above, the cytokine storm is an offensive inflammatory response resulting from COVID-19 infection characterized with a hyper-production of pro-inflammatory molecules. Probiotics can exert functional roles in preserving the equilibrium between innate and adaptive immune response. However, there is still little scientific evidence on the usefulness of bacteriotherapy in coronavirus infections in human and veterinary medicine.

5. Conclusion

Coronaviruses are showing a high ability to mutate and jump the animal-human barrier, acquiring over time the zoonotic role. As shown

by coronaviruses in animals, this pathogen can often cause a fatal disease. In the cat, the virulent biotype of FCoV results in lethal inflammation, associated with systemic and neurological disorders; in the dog, the virus can infect the upper respiratory gastro-enteric tracts leading to fatal disease; in the pig, the porcine CoV causes significant morbidity and mortality of piglets due to enteric and nervous system infection; in the cattle, the infection by Bovine CoVs causes severe or fatal infection (Weiss and Navas-Martin, 2005; Amer, 2018). Within the "*One Health concept*", it is necessary to improve the knowledge and the study of their pathogenic role in both human and animals. Different therapeutic protocols have been proposed during the global outbreaks of SARS-CoV-1, MERS-CoV and SARS-CoV-2. These approaches can counteract the viral entry phase, as a target, or can act modulating the cytokines storm aggravating clinical symptoms. However, a definitive protocol has not yet been reached. However, to date, the therapeutic protocols proposed for both animal and human coronaviruses are a palliative to limit the worsening of the disease. Furthermore, even if experimental studies have shown the efficacy of antivirals against feline coronavirus (Pedersen et al., 2019; Dickinson et al., 2020), it cannot be excluded that coronaviruses are able to rapidly acquire resistance factors to specific antiviral drugs. In author's opinion the use of probiotics and postbiotics products can be an interesting option in the management of patients hospitalized for coronavirus spp. infection, both human and animals.

Declaration of Competing Interest

The authors declare no conflict of interest.

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