Dance Round COVID-19

WE DANCE ROUND IN A RING AND SUPPOSE,
BUT THE SECRET SITS IN THE MIDDLE AND KNOWS.
ROBERT FROST

FROM PATHOGENESIS TO THERAPY OF COVID-19

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The world is facing the pandemic of a new coronavirus (SARS-CoV-2) leading to the development of coronavirus disease (COVID-19). In effect, the scientific potential in the field becoming the cutting-edge of biomedical research. It is in a big race to test the available pharmacologic resource of registered antiviral drugs and to discover of novel pharmaceuticals, nutraceuticals and biologicals (such as vaccines, gene and stem cell therapy, and recombinant proteins produced biotechnologically). We argue that the knowledge of (i) angiotensin converting enzyme 2 (ACE2) receptor, (ii) viral S-glycoprotein ligand, and (iii) cellular proteases, required for the entry of Cov-2 into the target cell, may provide novel therapeutic approaches for COVID-19. Finally, we reason the described approaches could lead to the identification of better drugs for COVID-19 and post-COVID-19 syndrome.

Biomed Rev 2020; 31: 125-133

Keywords: SARS-CoV-2, COVID-19, S-glycoproteins, ACE, ACE2, antiviral drugs, cytokine storm

Received 14 December 2020, revised 22 December 2020, accepted 22 December 2020.

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INTRODUCTION

Indeed, the Earth is facing the pandemic of severe acute respiratory syndrome induced by coronavirus-2 (SARS-CoV-2, hereinafter CoV-2) leading to the development of coronavirus disease (COVID-19), the event of the year MMXX picturizing below.

Credit for Nikifor N. Chaldakov.

Since the end of 2019 many clinical trials have been performing aimed at the evaluation of effectiveness of various therapies for COVID-19. Most of them being with antiviral drugs (antivirals) that have been applied for the therapy of other infections (1, 2). Herein, we *Dance Round* the pathogenesis and therapy of COVID-19.

I. FIGHTING VIRAL INFECTION BY THE BLOCKAGE OF COV-2 ENTRY INTO THE CELL

Viruses enter cells by two main ways: (i) receptor-mediated endocytosis (RME), and (ii) receptor-mediated virus-cell fusion (receptor-mediated fusion, RMF) (3, 4). In 1990 one of us (GNC) published his hypothesis of inhibition RME of viruses as an opportunity for antiviral therapy, including for acquired immunodeficiency syndrome (AIDS) (5). A schematic portrait of CoV-2 is presented in Figure 1.

Highly innovative methods of molecular biology and virology allowed scientists to very quickly identify the molecular architecture of CoV-2 (Fig. 2).

The CoV-2 is enveloped, single-stranded RNA beta-coronavirus. Like Middle East Respiratory Syndrome coronavirus (MERS-CoV), the genome of CoV-2 encodes (i) several nonstructural proteins (e.g., chymotrypsin-

Figure 1. Scheme illustrating the new coronavirus (SARS-CoV-2), a spherical particle sized 80-100 nm in diameter. Located in the viral membrane are transmembrane spikes (S) (one of them, red arrow) composed of glycoproteins; they play a pivotal role in CoV-2 entry into the target cell. S-glycoproteins must be processed (cleaved) by the cellular protease furin (S-glycoproteins have a furin cleavage site) aimed at virus fusion with the cell surface membrane leading to the internalization of virus into the cell. Therefore, inhibitors of furin and/or others CoV-2 related proteases may have antiviral effects (6; for other viruses including human immunodeficiency virus - HIV, see 7).

like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), and (ii) structural proteins (e.g., S-glycoproteins). The four non-structural proteins are key enzymes for viral life cycle, and S-glycoproteins are indispensable for interaction with cell receptors over the time of viral entry. Therefore, these five proteins (i, ii) are suitable as targets for the development of antivirals against the invader CoV-2. They are involved in all steps of viral life in the host cell: entrance into the cell, release of viral envelope, replication of viral RNA, exit of the new-born viruses from the infected cell, followed by dissemination to other cells.

I.1. Receptor-mediated CoV-2 entrance into the target cell

The virus-cell interaction is a receptor-mediated process, leading to the viral fusion with the cell surface membrane (plasmalemma) followed by the entrance of virus into the cell. Through receptor binding domain (RBD) of S-glycoprotein, CoV-2 binds to selective domains of receptors localized within the cellular plasmalemma (4). The presence and degree of

Figure 2. Genomic organization of SARS-CoV-2. From: (8).

expression of receptors largely predetermined the specificity of pathological changes after viral attack in certain cells, tissues and organs.

Target cells for respiratory viruses are different epithelial cells of the oral cavity, bronchi and alveoli. One of the CoV-2 receptors is angiotensin converting enzyme 2 (ACE2), a single-pass transmembrane protein of pneumocytes (alveolocytes) type II secreting the pulmonary surfactant (Fig. 3). Another receptor for CoV-2 is CD147 (basigin) – Meplazumab, an anti-CD147 monoclonal antibody, has recently been applied to COVID-19 patients (see *Dance Round* by Yanév and by Chaldakov *et al* in this volume of *Biomedical Reviews*).

I.2. Physiology and pathology of ACE2

Analysis of the *Human Protein Atlas Database* shows that pulmonary cells expressing ACE2 are exceptional few, but at

the same time contain many other genes positively regulating viral reproduction and transmission. ACE 2 also presents in arterial and venous endothelial cells and arterial smooth muscle cells, in brain cells and epithelial cells of kidneys, testicles, gall bladder and brain neurons, thus the viral invasion can be happened not only in the lung (9). In the human cells, ACE2 is regulated by different genes which can increase or decrease virus replication, suggesting that ACE2 regulatory genes might be promising therapeutic targets in COVID-19.

The enzyme ACE2 functions at the final stages regulating the peptides with important roles for cardiovascular, renal and respiratory systems. It is critically involved in the homeostasis of (i) angiotensin II (Ang II) (involved in vascular contraction, cell proliferation, and profibrotic and prothrombotic activity mediated by AT1 and AT2 receptors), and (ii) Ang-(1-7) (involved in vasodilatation and antiproliferative, antifibrotic and antithrombotic activity realized *via* interaction with MAS receptor, a member of the family of G protein-coupled receptors). In effect, MAS receptor ligation by Ang-(1-7) opposes many of Ang II effects. Thus, MAS1 receptor agonists express similar therapeutic effects as Ang II receptor antagonists. The renin-angiotensin system (RAS) with possible impact sites to compensate for the effect of coronavirus is shown schematically in Figure 4.

Briefly, ACE2 is a transplasmalemmal protein whose ectodomain functions as an enzyme involved in Ang metabolism as well as a receptor for CoV-2 cellular entry. That is, ACE2 has a catalytic domain for Ang I and Ang II and a binding domain for coronavirus S-glycoproteins. Occupation of ACE2 by CoV-2 may disturb the balance of ACE-ACE2 functions that can be modified by different therapeutic approaches (see Fig. 4, also Yanév and Stoyanova in this volume of *Biomedical Reviews*).

Figure 3. Scheme of pulmonary alveolus and its cells.

of CoV-2 may indeed provide new approaches to the treatment of COVID-19, four of them listed below:

1. Receptor-binding domain (RBD) of S-glycoprotein of CoV-2 to be isolated and administered separately, thereby ligating ACE2 and saturating its available connection loci.
2. An anti-ACE2 antibody may be used or fragment of single chain antibodies (scFv) to achieve the same saturation.
3. CoV-2 to be attacked directly by using the extracellular domain of ACE2, such as a bait aimed at binding to S-glycoprotein. Fc-domain associated with ACE2 would facilitate long-term circulation in a biological environment (ACE2-Fc).

The data obtained from the RBD-docking experiments were used to map RBD-ACE-2 interactions that could be used to design small molecular inhibitors of binding site. After virtual screening of over 3000 compounds was found and already confirmed in experiments that two compounds of the anthracycline drug group (zorubicin and aclarubicin) as well as the food dye E 155 are potent RBD inhibitors of viral S-glycoproteins for ACE2 receptors (24, 25).

CoV-2 life-span is illustrated in Figure 5.

The Bulgarian contribution

In the same direction are the attempts to use antibodies in the sera of infected people or administration of monoclonal antibodies to neutralize CoV-2. Such a therapeutic approach is currently being intensively developed in Center of Antibody Therapeutics, University of Pittsburgh Medical School, Pittsburgh, PA, USA, in which leading participant is one of the most prominent Bulgarian molecular biologists Dimitar S. Dimitrov (26).

III. OTHER POTENTIAL THERAPEUTIC APPROACHES

III.1. ACE inhibitors as antiviral agents

Widely used ACE inhibitors (captopril, enalaprilat, lisinopril), drugs regulating Ang II levels, and, respectively, vascular tone, were associated with the ACE2's catalytic center. It would be important to show whether these enzyme inhibitors can indirectly change the conformation of the site of viral RBD and thus affect the interaction of ACE2 with CoV-2. It is certainly useful to test these drugs for their ability to block RBD-ACE2 interaction (27). Useful information on this issue would be the monitoring of the level of antiviral protection of the thousands of heart patients taking ACE inhibitors as main therapy.

In the initial stages of research are substances with potential to reduce the expression of ACE2 found after analysis of

Figure 5. Schematic representation of the life cycle of CoV-2 and the corresponding pharmacotherapeutic capabilities to respond to COVID-19. Source: the journal Science.

databases: (i) Connectivity Map (CMap) – Azathioprine, and (ii) JeaMoon Map (JMap) (traditional Chinese medicine): Andrographis, Urtica, Sambucus, Astragalus, also valproic acid, butyrate, and epoxomycin (28).

III.2. Repurposed and new drugs for COVID-19

Several of novel and repurposed therapeutics are: (i)

Aricitinib, an approved drug for rheumatic arthritis, whose effectiveness against CoV-2 was detected by the methods of artificial intelligence (29), (ii) **Biologicals**, human monoclonal antibodies against different pro-inflammatory cytokines; examples: **Anakirna**, a recombinant form of human interleukin-1 receptor antagonist (IL-1RA) repurposed for COVID-19 treatment, because IL-1 is one of the key pro-inflammatory cytokines involved in the development of cytokine release syndrome, **Tocilizumab** (trade name **Actemra**), humanized monoclonal antibody against interleukin-6 receptor (IL-6R), an immunosuppressive drug for the treatment of rheumatoid arthritis (30), **Meplazumab**, an anti-CD147 monoclonal antibody, because CD147 is one of the CoV-2 receptors (as mentioned above, at the section I.1.), (iii) **Lycorine**, an alkaloid present in high concentrations together with galantamine in the native endemic “swamp” snowdrop *Leucojum aestivum* (*Amaryllidaceae*), was reported to express highly antiviral activity ($EC_{50} = 1.63 \mu M$) against MERS-CoV, while protecting BALB/c mice against mortality from HCoV-OC43 by reducing viral load in the central nervous system (31); it also expresses anti-inflammatory and bronchorelaxing effect, and (iv) **Colchicine**, an old drug with new therapeutic applications (32); its anti-inflammatory properties against COVID-19-induced cytokine storm were appreciated recently (33 and their Refs numbered 124, 125); for **Omaliuzumab**, a recombinant DNA-derived humanized IgG1 monoclonal antibody that specifically binds to free human immunoglobulin E, see (34, 35).

In the same “storm”, **Pentoxifylline** (Trental) could be another anti-cytokine drug (of low price and safety) in COVID-19. It is a methyl-xanthine derivative that inhibits phosphodiesterase IV. Pentoxifylline is known as a blood rheology improving drug prescribed in patients with peripheral artery disease. Such a rheological activity may also be beneficial in COVID-19 viewed as an oxygen-deprivation disease (see Yanev in this volume of *Biomedical Reviews*). Pentoxifylline also exerts other therapeutic effects, including (i) inhibition of HIV replication, and (ii) anti-inflammatory action *via* decreasing TNF- α level. Hence, it was prescribed in patients with AIDS, especially as an adjuvant therapy in combination with other drugs (36, 37).

Mast cell stabilizers

A key source of pro-inflammatory cytokines and chemokines in pulmonary COVID-19 is the lung mast cells. The natural flavonoid **Luteolin** is a potent inhibitor of these inflammatory

factors released from mast cells (38). This can be a very effective approach to coup with mast cell-driven lung interstitial edema (39). Likewise, the mast cell stabilizers such as the anti-allergic drugs ketotifen and corticosteroids, also colchicine and pentoxifylline, may also be considered (40).

Indeed, mast cells are “master cells” as have been named by Stephen J. Galli, great in the field of mast cell research. These cells are renown for their secretion of multiple pro- and anti-inflammatory cytokines (for mast cells secreted adipokines, see 40). For instance, **adiponectin and irisin** (41) could exert their potential therapeutic effects in COVID-19 especially in obesity patients which are more susceptible to develop COVID-19 severe outcome (42, 43) - that should also be kept in curious minds.

Aptamers are single-stranded RNA or single-stranded DNA (ssDNA), which can bind and detect various nucleic and non-nucleic acids with high affinity and specificity (44). Some of newly developed DNA/RNA aptamers are used also with success as therapeutic resource, for example, blocking SARS-Cov helicase, which is absolutely necessary for viral replication (45).

III.3. Diet, nutrition, selenium and zinc and coronavirus

It is not surprising that traces of zinc in patients with COVID-19 were not found (1). The state of zinc homeostasis in the body is reflected at least of two mechanisms of the development of viral infection: (i) ACE2 is a metalloenzyme with one zinc atom to one of protein chains. The intake of **zinc** through food or synthetic agents (20 mg daily) during and after treatment would have an incentive effect for faster recovery of the organism (27), and (ii) there is evidence that facilitating cell penetration of extracellular zinc from certain substances (ionophores), such as pyrithione and chloroquine, in low concentrations inhibit viral RNA-dependent SARS-CoV RNA polymerase (46, 47), and (ii) a recent study shows that in the protein envelope of virus itself there is a labile bound zinc to cysteine, involved in maintaining the structure of the viral envelope. This implies the testing of Zn-binding preparations as a means of the destruction of CoV-2 power. Accordingly, the combined administration of **Disulfiram and Interferon** leads to encouraging results in CoV-2-infected patients (48).

Omega-3 fatty acids, especially eicosapentaenoic acid and docosahexaenoic acid, exert anti-inflammatory effects that may benefit COVI-19 patients (43) These latter data open a discussion on the therapeutic potentials of specialized pro-

resolving lipid mediators, such as resolvins, protectins, etc.

Selenium is also recommended as an important factor in the antioxidant protection (100 mcg daily) in COVID-19 (49).

Vitamin C in daily doses of 3000 mg, taken separately, also exerts a positive effect (50).

Vitamin D (51) and **polyphenols** (52) supplementation may, by stimulating expression of the neurotrophin nerve growth factor (NGF), bring preventive and curable benefits, also for brain disorders in COVID-19 as well as post-COVID syndrome (see Kostov's *Dance Round* in this volume of *Biomedical Reviews*).

FINAL MESSAGE

We reason the described novel and repurposed therapeutic approaches could lead to the identification of better drugs for COVID-19. And hope that the present *Dance Round COVID-19* provides information and knowledge of the opportunity of modern pharmacology and biotechnology to cope with CoV-2 infection. This may provoke the world scientific community to share (not commercialize) all the available scientific data to achieve overall success. Because we believe that the dissemination-of-knowledge (DOK) is an essential component of basic, clinical and translational biomedical research also in COVID-19 and post-COVID syndrome.

CONFLICT OF INTEREST

The authors declare no conflicts of interest exist.

ACKNOWLEDGEMENTS

We thank your brain-and-heart friends (BHF) for the valuable discussions.

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