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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

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7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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ავტორთა საყურადღებოდ!

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2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

THE PECULIARITY OF COVID- 19 GENOME AND THE CORONAVIRUS RNA TRANSLATION PROCESS AS APOTENTIAL TARGET FOR ETIOTROPIC MEDICATIONSWITH ADENINE AND OTHER NUCLEOTIDE ANALOGUES (REVIEW)

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Coronaviruses (CoVs) belong to the family Coronaviridae. They are further subdivided into four genera: alphacoronavirus (α-CoV), betacoronavirus (β-CoV), gammacoronavirus (γ-CoV) and deltacoronavirus (δ-CoV)[6,48]. Both α- and β-CoVs infect mammals, while δ- and γ-CoVs infect birds. In early December 2019, the cases of pneumonia of unknown etiology were reported in Wuhan. After identifying the genome sequence of infected patients, it was revealed that the causative agent was a new type of coronavirus, namely SARS-CoV-2. Like SARS-CoV and MERS-CoV, the newly formed SARS-CoV-2 virus belongs to the group of β-CoVs.

The incubation period for SARS-CoV-2 is on average 3-7 days, although it can be up to 2-14 days [28, 43], which coincides with other known CoV incubation periods (e.g., SARS-CoV incubation period is on average 5 days, although it may increase to 2–14 days [4], the incubation period for MERS-CoV is approximately 5-7 days, although it can be up to 2-14 das [5, 34]. Asymptomatic patients can effectively transmit SARS-CoV-2 during the incubation period, [24].

The goal of the present article is to summarize and analysis the literature data,concerning specific features of COVID -19 virus and to consider the potential targets for etiotropic therapy.

Genetic sequence. The genetic sequence of SARS-CoV-2 is 70% similar to the SARS-CoV sequence. Like the latter, SARS-CoV-2 uses the ACE2 (Angiotensin-Converting Enzyme/Enzyme 2) receptor to enter the cell and infect humans [46,54]. However, with the main antigen component, i.e. the S protein, it differs significantly from its predecessor. The S protein of SARS-CoV-2 binds to the human ACE2 receptor at 10- to 20-fold higher affinity, facilitating the spread of the virus among humans [44]. It should also be noted that the respiratory tracts are not the only route of transmission of the SARS-CoV-2 virus, and it is also transmitted even during close contact. Recent studies have shown that some patients with confirmed COVID 19 experience dyspeptic symptoms such as diarrhea, vomiting, nausea [22,32]. The enteric symptoms of COVID 19 are associated with the presence of the ACE2 receptors in the digestive tract [37].

SARS-CoV-2 uses the genomic RNA as a template to translate pp1a (polyprotein 1a) and pp1ab (polyprotein 1ab). These proteins (pp1a, pp1ab) produce nonstructural proteins (MSPs) in double-membrane vesicles (DMVs) to form the replication/transcription complex (RTC) [25].

Negative-stranded RNA (Coronavirus Genomic RNA (-)) is produced by replication of the complex. As a result of the transient transcription of its RNA-dependent RNA polymerase (RdRp), subgenomic RNAs of different lengths (sgRNAs) are produced [9]. Translation of each sgRNAs results in the production of viral proteins, and replication of negative-stranded RNA (Coronavirus Genomic RNA (-)) yields positive-stranded RNA (+).

The SARS-CoV-2 genome and subgenome contain at least 6 open reading frames (ORFs). The first ORF (ORF1a/b) is 2/3 of the total genome length of SARS-CoV-2; it produces two polypeptides pp1a and pp1ab. Proteolytic cleavage of ORF1a/b results in producing 15/16 NSPs (nonstructural proteins), 4 structural proteins, and 5 complimentary proteins (ORF3a, ORF6, ORF7a, ORF8, and ORF9) [23,47].

ORF1a encodes the production of pp1a, a molecular weight of which is 486 kDa. The pp1a protein contains Plpro (the papain-like protease), 3CLpro, and two membrane proteins MP1 (nsp4 - nonstructural protein 4) and MP2 (nsp6 - nonstructural protein 6).

NSP1 inhibits the synthesis of the cellular proteins in an infected cell. The cell is forced to regulate mainly viral protein synthesis. Moreover, the protein NSP1 does not allow the cellular antiviral proteins to aggregate that is necessary to stop the virus [17,40]. The function of the protein NSP2 has not been determined, only its ability to participate in the placement of endosomes along the cell has been identified [16,29]. The protein NSP3 performs two important functions: 1 -it provides the release of other viral proteins after which they begin to perform their own function; 2 - it changes the function of the proteins of the infected cell.

NSP3 is released by pp1a/1ab via a papain-like protease domain that is part of NSP3 itself [7].NSP4, along with other proteins, is involved in the formation of fluid-containing blisters in an infected cell[38]. NSP5 is specialized in breaking down proteins, causing other NSPs to be activated and start to act [3,55,56].NSP6 is involved in the formation of viral blisters along with the NSP3 and the NSP4 proteins [12,27]. NSP7 and NSP8 help NSP12 generate a copy of the virus RNA genome that gives rise to offspring viruses [14]. NSP9 penetrates into the nucleus with the help of small channels in the cell nucleus and influences the movement of molecules from the nucleus [13,51].The protein NSP10, along with NSP16, disguises a viral gene and prevents the attack of antiviral proteins in human cells that have the ability to detect and destroy viral RNA [8,15]. The function of the NSP11 protein is unknown [2]. The Protein NSP11, together with NSP12,concentrates nucleotides in the coronavirus genome. The ability of the antiviral drug remdesivir to interact with the coronavirus NSP12protein has been identified; studies are being carried out regarding the widespread use of this drug in treatment [1,41].

In a normal state, the viral RNA is twisted. It is assumed that the NSP13 protein destroys viral RNA and thus makes it available for action on proteins involved in the production of new viral copies [11]. The NSP14 protein correctsthe errors (incorrectly added nucleotides) made by the NSP12 protein during duplication of the coronavirus [15,52]. The protein NSP15 [53] supposedlyprotects the virus from the antiviral activities of the cell [19].

The underlying ORF1b is expressed as a pp1a fusion protein through a mechanism that involves the movement of the ribosomal backbone during translation [20,26].The result is the protein pp1ab (≈790 kDa) that already contains ORF 1b containing the helicase domain (nsp13) [39], exonuclease(nsp14), endoribonuclease (nsp15), and nsp16.

The remaining ORFs make up about one-third of the genome length, are located near the 3'-end, and encode at least four types of structural proteins:

- The E protein - a structural protein of the coronavirus membrane that forms the lipid vesicles of the virus. Inside the cell, these vesicles fix proteins that are involved in the human gene regulation process.

- The M protein - a membrane protein of coronavirus. It participates in the formation of the outer membrane of the virus;

- The S-S protein - forms the protective outer layer of the coronavirus RNA genome on the surface of the virus. In micrographs, the club-shaped spikes that stud the surface of coronaviruses are glycoproteins that give the appearance of a radiate crown. Their parts expand and attach to the ACE2 protein in human airway cells. Then it enters the cell.

- The N protein - protects viral RNA, promotes the internal stability of the virus. Most of the N proteins coalesce into a long helix and lead to the formation of the helical nucleocapsid.

So, the SARS-CoV (COVID-19) genome encodes the so-called "auxiliary proteins" that create a favorable environment inside the cell of the host organism, which promotes its multiplication. The ORF3a protein damages the host cell membrane, thus allowing new viruses to come out of the cell. This is what causes pneumonia – a symptom typical for COVID-19.

ORF6 inhibits the signals sent by the infected cell to the immune system, in addition, it inhibits the activity of some proteins in the cell.

When the virus starts coming out of an infected cell, the cell can bind it with the help of the tetherin protein. ORF7 is thought to reduce the supply of the tetherin protein in an infected cell, making it easier for viruses to leave the cell. It also provokes "cell suicide" (apoptosis) that significantly damages the lungs. The function of the ORF8protein is unknown. ORF9b and ORF9c are coronavirus "auxiliary proteins"; ORF9b inhibits the action of the key proteininterferon in the fight against cellular viruses; the function of the ORF9c protein is unknown.

Treatment. The general treatment strategy for COVID-19 involves bed rest and controlled intake of adjuvant medications. It is also recommended to maintain water and electrolyte balance while monitoring other vital parameters (heart rate, blood pressure, pulse, respiration rate, etc.). Some scientists are counting on the possible antiviral effects of IFNα.

Interferon-alpha (IFNα) belongs to the type I IFN family. It plays an important role in resistance to viral infections, inhibits viral infections by interfering with virus replication, and activates the host's immune response. In vitro experiments have shown that IFNα effectively inhibits SARS-CoV replication[46,47].As revealed, IFNα protects cynomolgus macaques from SARS CoV [18,31,57]. Moreover, pilot clinical trials have shown positive therapeutic effects when using IFNα in patients with SARS [46].

Table lists the medications used to treat COVID-19 and shows the targets for their action.

As shown in Table, all of the antiviral drugs listed above have some antiviral (anti-SARS-CoV2) effects, and may have a certainresult on the process of treating SARS-CoV2. The main targets of current medications are:

- Viral RNA-dependent RNA polymerase RdRp (Remdisivir inhibits RNA-dependent RNA polymerase (RdRp), thus blocking the production of viral proteins; However, in contrast, 3-5 exoribonucleases of the virus inhibit the action of remdesivir and reduce the antiviral effect of this drug);

- Viral 3Clpro or PLpro (the papain-like proteins lopinavir/ritonavir block already formed proteins, thus preventing further production of viral proteins);

- The Virus transmembrane S protein and transmembrane protease serine-2 [TMPRSS2] inhibitors(arbidol and Camostat mesylate] can prevent the interaction of the S protein and the cellular receptor ACE2);

- The ACE 2 receptor on the host cell membrane that provides the entry point for the Sprotein(chloroquine and hydroxychloroquine inhibit endocytosis by increasing endosomal pH). Chloroquine can also inhibit RdRp by increasing intracellular zinc concentrations like remdesivir.

However, several key issues need to be emphasized: (1) The potential interaction of these antiviral drugs with other types of medications should be taken into account; (2) Side effects of two medication lopinavir/ritonavir should be considered(dyspepsia and liver damage); (3) Using three or more «antiviral» drugs with different mechanisms considering the side effects of some of them is controversial.

In addition to the medications listed above, research on the possibility of using antiviral antibodies in the plasma of recovered patientsis being carried out intensively. Plasma therapy is commonly used in viral diseases such as influenza A (H5N1), poliomyelitis, and Ebola [10,50].

Table. List of the medications used to treat COVID-19 and the targets for their action

Therapeutic Target	Function	Potential Medications	References
RNA-dependent RNA polymerase (RdRp)	Coronavirus genome replication	Remdisivir and ribavirin.They have an ability to inhibit RdRp.	[36, 44]
ThePapain-like proteasePLpro	Converts viral polyprotein into a functional enzyme.	Lopinavir, protease inhibitor that can inhibit viral protease: 3CLproorPLpro	[52]
The main protease 3CLpro	Converts viral polyprotein into a functional protein	Lopinavir	[21]
The Sprotein and TMPRSS2	The S protein of on the Virus surface that binds to the host surface ACE2 (angiotensin-converting enzyme/enzyme2) receptor.TMPRSS2 'supplements' the S protein to bind to theACE2 (angiotensin-converting enzyme/enzyme2) receptor.	Arbidol - It can prevent the interaction of the S protein and the ACE2 receptor and inhibit membrane fusion. Camostat mesylate inhibits TMPRSS2.	[33, 35]
ACE 2	A receptor on a host cell providing the entry point for the S-protein.	Chloroquine and hydroxychloroquine inhibit endocytosis byincreasing endosomal pH.	[30,42]

Given the above-mentioned facts, in order to stop the spread of coronavirus infections and to avoid their damaging effects, it is promising to inhibit the production of NSPs of the viral origin, which is possible by replacing nucleotides, in particular adenine, in the viral RNA translation phase. The improved models of adenosine analogs such as remdesivir and NITD008 should be used for this purpose [49, 50] because both of them try to inhibit the viral replication process by inhibiting RdRp. In addition, it is known that 3'-5 exoribonucleases of SARS-CoV2 block the inhibitory effect of remdesivir on RdRp, promoting further replication of the virus. Therefore, it is necessary to create new modified/improved versions of remdisivir and other adenosine analogs.

Conclusion. The cases of SARS-CoV were first reported in 2002 and the virus quickly spread to 32 countries around the world. Ten years later, MERS-CoV became widespread in 2012, and eight years later, in 2020, a new viral infection SARS-CoV-2 emerged. It has been proven that SARS-CoV-2 enters the cell with the help of the ACE2 receptors. The fact that this type of receptors is found not only in the respiratory system but also in the liver tissues, the digestive system (small intestine, duodenum), testicles and kidneys, makes these organs highly vulnerable to SARS-CoV-2.The different group of drugs have been proposed in complex treatment of COVID-19.Despite of this coronavirus is still associated with high incidence of various complications and fatal outcome worldwide .According epidemiologic studies the most susceptible are the patients with accompanying diabetes, cardiovascular ,respiratory system diseases and obesity.Potentially patients with intestinal microbiome disorders also may become vulnerable to COVID -19[32].

Given the global health threat caused by SARS-CoV-2, there is an urgent need for effective prevention and treatment of COVID-19 pneumonia, although finding drugs to treat pathogenic SARS-CoV-2 still remains a major problem. The medicines available to doctors around the world do not have a significant detrimental effect on the virus, as evidenced by the current epidemiological data.In initial stage the introduction of adenosine analog remdesivir against COVID-19 was considered as perspective drug[36].This agent was approved or authorized in about 50 countries, including USA and EU, but currently there are controversial views regarding its ability to reduce mortality in COVID 19.

We suppose that if the improved versions of adenosine analogs (NITD008, Remdesivir, etc.) with more efficacy and safety are developed, the virus will not be able to have a detrimental effect on host cells because they (the improved versions of adenosine analogs) will have the ability to inhibit the virus translation process rather than RdRp. As a result, the virus will no longer be able to produce non-structural proteins (nsps) so important for the manifestation of viral activity.

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SUMMARY

THE PECULIARITY OF COVID- 19 GENOME AND THE CORONAVIRUS RNA TRANSLATION PROCESS AS APOTENTIAL TARGET FOR ETIOTROPIC MEDICATIONSWITH ADENINE AND OTHER NUCLEOTIDE ANALOGUES (REVIEW)

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Despite the multifaceted effects of the medicines provided for COVID-19treatment, the number of the infected and mortality of patients increases which demonstrates the insufficient effectiveness of drugs used to fight coronavirus infections in medical practice, and clearly shows the need to develop new treatment tactics.In this review article are summarized and analyzed the literature data concerning specific features of COVID 19. Particular attention is given to genetic characteristic of this virus ,to mechanism of its invasion into the human organism, replication and interection with ACE-2 receptors ,as well as to the basic targets for the action of existing drugs with antiviral activity against COVID-19.

Currently, the following medications are used to treat COVID-19: remdesivir, chloroquine, hydroxychloroquine (HCQ), ribavirin, lopinavir/ritonavir. According to a recent theory of coronavirus treatment, the starting point for the mechanism of action of a potential etiotropic drug is the inhibition of the coronavirus main protease (Mpro/3CLpro) and the papain-like protease (PLpro). Among the drugs listed above, lopinavir acts through this mechanism but is characterized by severe side effects.It is emphasized that remdesivir as adenosine analog provides inhibitory action on RNA dependent RNA-Polymerase,but there are controversial views about reduction in mortality during using of this drug against COVID-19.

The present paper discusses the mechanism of action of a potential etiotropic drug against coronavirus, which implies the replacement of the nucleotides involved in the process of translation of the virus with their analogs with the aim to “inhibit” the ribosome and block the production of viral proteins.

Keywords:COVID-19, Genetic sequence**,** etiotropic drug, ribosome.

РЕЗЮМЕ

ОСОБЕННОСТИ ГЕНОМА COVID-19 И ТРАНСЛЯЦИОННЫЙ ПРОЦЕСС РНК КОРОНАВИРУСА КАК ПОТЕНЦИАЛЬНАЯ МИШЕНЬ ДЛЯ ЭТИОТРОПНОЙ ТЕРАПИИ АДЕНИНОМ И РАЗНЫМИ АНАЛОГАМИ НУКЛЕОТИДОВ (ОБЗОР)

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Несмотря на многочисленные эффекты лекарственных средств, применяемых для лечения COVID-19, количество инфицированных и смертность пациентов увеличивается, что свидетельствует о недостаточной эффективности препаратов, применяемых в медицинской практике для борьбы с коронавирусными инфекциями, и необходимости разработки новой тактики лечения.

В настоящей обзорной статье суммированы и проанализированы данные литературы, касающиеся специфических черт коронавируса. Особое внимание уделяется генетической характеристике этого вируса, механизму его инвазии в человеческий организм, репликации и взаймодействию с АКФ-2 рецепторами, также как и основным мишеням для действия существующих лекарств, обладающих антивирусной активностью против коронавируса.

В настоящее время для лечения COVID-19 используются следующие препараты: ремдесивир, хлорохин, гидроксихлорохин (HCQ), рибавирин, лопинавир/ритонавир. Согласно существующей теории лечения коронавируса, отправной точкой для механизма действия потенциального этиотропного препарата является ингибирование основной протеазы коронавируса (Mpro/3CLpro) и папаин-подобной протеазы (PLpro). Среди вышеперечисленных препаратов лопинавир действует повредством этого механизма, однако характеризуется серьезными побочными эффектами. В данной статье обсуждается механизм действия потенциального этиотропного препарата против коронавируса, который подразумевает замену нуклеотидов, участвующих в процессе трансляции вируса, их аналогами с целью «ингибировать» рибосомы и блокировать производство вирусных белков.

რეზიუმე

კოვიდ-19-ის გენომის თავისებურებანი და კორონავირუსის რნმ-ის ტრანსლაციური პროცესი, როგორც პოტენციური სამიზნე ადენინით და ნუკლეოტიდების სხვადასხვა ანალოგებით ეტიოტროპული თერაპიისთვის (მიმოხილვა)

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COVID-19-ის სამკურნალოდ მოწოდებული მედიკამენტების მრავალმხრივი ეფექტების მიუხედავად, ინფიცირებულთა რიცხვი და პაციენტთა სიკვდილიანობა მატულობს, რაც ცხადყოფს კორონავირუსის ინფექციებთან ბრძოლის სამკურნალოდ გამოყენებული მედიკამენტების არასაკმარის ეფექტურობას და მკურნალობის ახალი ტაქტიკის შემუშავების აუცილებობას. სტატიაში სუმირებული და გაანალიზებულია ლიტერატურული მონაცემები, რომლებიც ეხება კორონავირუსის სპეციფიკურ ნიშნებს, კერძოდ, განსაკუთრებული ყურადღება გამახვილებულია ამ ვირუსის გენეტიკურ მახასიათებლებზე, ადამიანის ორგანიზმში მისი ინვაზიის, რეპლიკაციის მექანიზმზე და ამფ-2 რეცეპტორებთან ურთიერთქმედებაზე, ისევე როგორც კორონავირუსის საწინააღმდეგოდ მოქმედი ანტივირუსული ეფექტის მქონე არსებული პრეპარატების ძირითად სამიზნეებზე.

ამჟამად COVID-19-ის სამკურნალოდ გამოიყენება შემდეგი მედიკამენტები: რემდესივირი, ქლოროქინი, ჰიდროქსიქლოროკინი (HCQ), რიბავირინი, ლოპინავირი/რიტონავირი. კორონავირუსის მკურნალობის ბოლოდროინდელი თეორიის თანახმად, პოტენციური ეტიოტროპული პრეპარატის მოქმედების მექანიზმის ამოსავალი წერტილი არის კორონავირუსის მთავარი პროტეაზას (Mpro/3CLpro) და პაპაინის მსგავსი პროტეაზას (PLpro) დათრგუნვა. ზემოთ ჩამოთვლილ მედიკამენტებს შორის ლოპინავირი მოქმედებს ამ მექანიზმის საშუალებით, მაგრამ მას ახასიათებს მწვავე გვერდითი მოვლენები.

წინამდებარე ნაშრომში განხილულია კორონავირუსის საწინააღმდეგო პოტენციური ეტიოტროპული პრეპარატის მოქმედების მექანიზმი, რაც გულისხმობს ვირუსის რეპლიკაციის პროცესში ჩართული ნუკლეოტიდების ჩანაცვლებას მათი ანალოგებით რიბოსომის "დათრგუნვის" და ვირუსული ცილების წარმოების ბლოკირების მიზნით.

LIVER EXTRACELLULAR MATRIX PECULIARITIES IN MAMMALS AND AVIANS

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The extracellular matrix - the connective tissue framework of the liver - on the one hand, determines the shape of the organ, and on the other hand, creates specialized compartments for blood and lymphatic vessels and nerves, as well as cell populations, the synergy of which determines the various functioning of the organ. The liver is the largest and heaviest parenchymal organ, and an appropriate matrix design is required to maintain its shape and fix it on the abdominal walls [1]. The liver has a dual blood supply (arterial and portal), and the connective tissue spaces containing these vessels are built with this factor in mind. Unlike other organs, in which there are three circulating fluids and, therefore, there are three compartments for the microcirculation, four fluids circulate in the liver: blood, bile, interstitial juice, and lymph [2]. At the same time, the liver produces more lymph than any other organ (up to 50% of the total amount of lymph in the body). Thus, the liver matrix forms a highly complex but strongly regulated labyrinth in which liver cells, blood vessels, bile ducts, lymphatic ducts, and tissue fluid have their own but closely interconnected compartments [3-5].

The study of the liver connective tissue skeleton dates back to the 17th century. Pursuant to Couinaud [6], in 1640 Walaeus described the connective tissue sheath, which wraps the portal vein, the hepatic artery, the bile duct, the lymphatic duct, and the nerves entering and leaving the liver connects to the capsule of the liver and hepatoduodenal ligament. Walaeus sheath originates from the vasculobiliary sheath (Glisson's capsule) and is not derived from the peritoneum or the capsule of the liver (Laennec's capsule). Besides, the separation between Laennec's capsule and the Walaeus sheath can be seen microscopically at the hepatic hilum [6], where the Walaeus sheath forms a thick plate at the inferior part of the liver referred to as the hilar (portal) plate [7].

The portal pedicle wrapped by the Walaeus sheath continues inside the organ, as the so-called Glissonian Pedicals [8].