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Focus on ACE2, find treatment strategies for new coronary pneumonia

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Since December 2019, the newly discovered coronavirus (2019-nCov) has caused an outbreak of pneumonia in Wuhan and caused great public concern. Coronavirus invades target cells via angiotensin-converting enzyme 2 (ACE2). A thorough understanding of the physiological characteristics of the protein and the mechanism of a series of physiological and physiological changes caused by the protein as the center after the virus invades the human body may help to discover and explain the corresponding clinical phenomenon and then deal with it in time. In addition, ACE2 is a potential Treatment target. This article will review the characteristics of the protein, target organ damage and treatment methods.
A prerequisite for coronavirus infection is its entry into host cells. In this process, spike protein (S protein) recognizes host cell receptors and induces fusion of viral and cell membranes. XU et al. [1] found that the S protein of Wuhan coronavirus is similar to the S protein of SARS coronavirus (SARS-CoV) through biological analysis. It can also interact with the ACE2 protein molecule on the surface of host cells through S protein to infect Epithelial cells of the host. Therefore, ACE2 molecule is the key molecule for 2019-nCoV infection, and it may affect the process of 2019-nCoV infection of human cells by binding to ACE2 molecule. In addition, Shi Zhengli's team from Wuhan Virus Research Institute published a paper [2], reporting that ACE2 is an essential protein for 2019-nCoV infected cells. This article will review the characteristics of the protein, target organ damage, and therapeutic drugs.

I. THE NEW CORONAVIRUS (2019-NCOV)

Coronavirus is a single-stranded positive-stranded RNA virus without segmentation. It belongs to the orthocoronavirinae subfamily of the Coronaviridae family of the order Nidovirales, and is divided into subfamilies of coronavirus according to serotype and genomic characteristics. a, β, γ and δ four genera. Coronavirus is a coronavirus belonging to the Coronaviridae family. It is named after a corolla virus that has protrusions that extend around.

Recently, ACEI/ARB drugs discontinuation for hypertensive patients with NCP associated with hypertension has attracted wide attention, mainly divided into the next two camps.

Firstly, ACEI / ARB drugs can improve the level of ACEII in the lung, thus opening a "convenient door" for the virus.

As result of that ACEI / ARB antihypertensive drugs should be stopped in patients with hypertension complicated with new coronavirus infection.

Secondly, in other hand, these drugs can reduce lung and cardiovascular damage.

Those who hold the opposite view think that ACE-2 will be down regulated, RAAS system will be activated, AT1 receptor will be over stimulated, pulmonary vascular permeability will be increased, and lung injury will be aggravated. This mechanism comes from the study of SARS CoV pneumonia, not new coronavirus pneumonia. Whether the two have the same mechanism of action is not confirmed by data at present. From the perspective of imaging and clinic, Lung injury is more likely to be caused by local virus infection.

In addition, if the lung injury is reflected by RAAS activation, the application of ACEI/ARB should obviously reduce the injury. At present, there is no specific drug for the new cronavirus pneumonia, and there is no evidence that the pneumonia patients who used this kind of drugs can prevent the progression of the disease.

One study showed that when ACEI receptor antagonists were applied to rats, the blood pressure decreased, while the level of ACE-2 increased by 4.7 and 2.8 times [1], respectively. Therefore, the application of ACEI / ARB has the risk of increasing ACE-2, which makes the virus more likely to invade cells.

Another study with 539 patients with viral pneumonia was retrospectively analyzed. It was found that ACEI and statins before hospitalization did not reduce mortality and intubation rate in patients with coronavirus pneumonia. It is likely that the result will also be in the new coronavirus pneumonia. In the absence of evidence to prove that ACEI/ARB is beneficial and potentially harmful to patients

with new coronavirurs pneumonia, it is not necessary to apply ACEI/ARB to those patients. At least, it should not be applied in a short time when virus infection is restored.

The similarities between new coronavirus and SARS.

The difference is mainly in four proteins, while the Spike protein and the Spike protein of SARS virus are highly similar. The difference between the two is only 4 amino acids. Spike protein can help the virus bind to the transmembrane receptor protein on the host cell membrane, thus helping itself to enter the host cell interior.

Bioinformatics analysis showed that the change of amino acids on the Spike protein of new coronavirus did not seem to affect the interaction between S- protein and receptor ACE-2 protein. Therefore, we have reason to believe that the new coronavirus is mediated through the binding of Spike protein to ACE-2 protein. Therefore, it can be considered that the spike protein of the two viruses has similar effect, that is, by reducing ACE-2, activating RAAS system, leading to lung injury.

Ferrario et al. Studied Lewis rats with normal blood pressure, and the conclusion can not be extended to hypertensive rats, nor to hypertensive population. In fact, the ACE-2 mRNA level in hypertensive rats was significantly reduced. The expression of ACE-2 protein will decrease in patients with hypertension, and if they are infected with the new coronavirus, they may cause more severe pulmonary failure. More than 40% of severe patients and dead patients have hypertension history, which also confirmed the relationship between the virus and ACE-2.

But their high mortality rate cannot be attributed to the use of RAAS blockers. The biggest reason is that the basic state of these patients themselves is very poor: old age and often combined with a variety of chronic diseases.

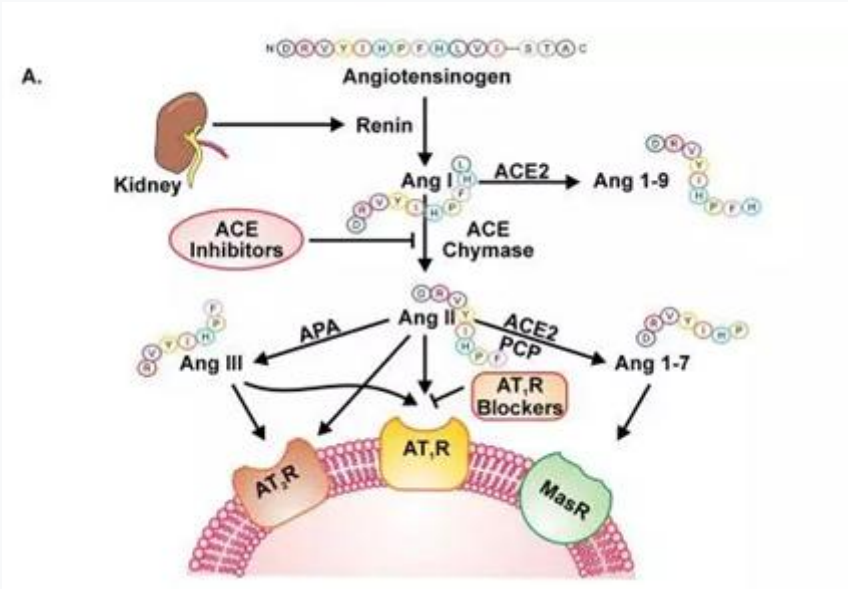
At present, we can not carry out clinical trials for verification, but some previous animal experiments may provide some references.

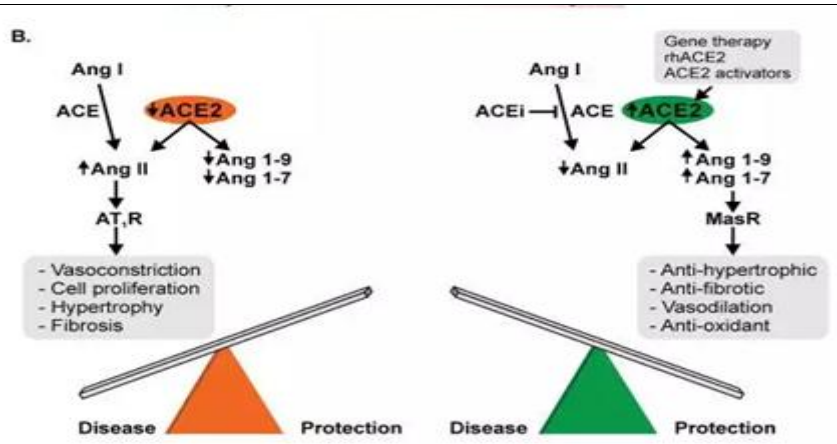
Some researchers used spike FC, a fragment of spike protein of SARS virus, to simulate the down-regulation of ACE-2 protein by the virus. The results suggest that spike FC can aggravate the acute lung injury caused by acid.

However, after the administration of AT1 inhibitor, this part of injury aggravated by spike FC can be relieved, even in the acid poisoning environment, this conclusion is still true.

Part1 Angiotensin-converting enzyme 2 (ACE2)

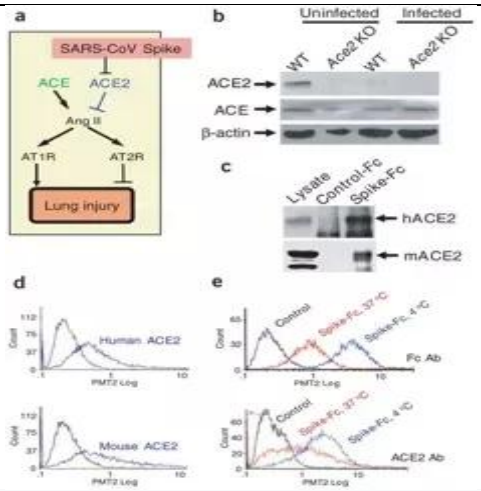
The renin-angiotensin system (RAS) is an important neuroendocrine system in the human body, including the classic angiotensin-converting enzyme (ACE) -angiotensin II (AngII) -angiotensin type II receptor (AT1R) axis, It is not the only pathway. Angiotensin-converting enzyme (ACE) congeners, angiotensin-converting enzyme 2 (ACE2), angiotensin 1-7 [Ang (1-7) and its receptor Mas, etc., constitute ACE2. -Ang （1-7） -Mas axis





In 2000, researchers found ACE2 in human heart left ventricle cDNA library and human lymphoma cDNA library prepared from explanted hearts of heart transplant recipients [3]. Like ACE, ACE2 belongs to the zinc metalloproteinase family. The sequence identity between ACE2 and ACE is 42%. The ACE2 protein is 805 amino acids in length and is encoded by the ACE2 gene located on chromosome Xp22. It consists of 4 parts, namely N-terminal signal peptide, catalytic extracellular domain, transmembrane domain and C-terminal intracellular domain. ACE2 is a type 1 membrane protein with a catalytic domain on the extracellular surface. ACE2 hydrolyzes the carboxy-terminal leucine from AngI to produce the non-peptide Ang (1-9), which can be converted into heptapeptide Ang1-7 by ACE and other peptidases [4]. In addition, ACE2 can directly degrade AngII to Ang (1-7). Ang (1-7) acts on Mas receptors to relax blood vessels, anti-proliferative, and anti-oxidative stress [5]. The ACE2-Ang (1-7) -Mas axis formed by the participation of Ang (1-7) can antagonize the ACE-Ang Ⅱ-AT1R axis, and the two together maintain the body's balance. Coronavirus specifically binds to which part of ACE2. Scholars used the sequence similarity between ACE2 subtypes to analyze the protein crystals of testicular ACE2 and Drosophila ACE2 homologs, and found that the enzyme catalytic region of ACE2 is located in a deep groove at the top of extracellular proteins. The pupae surrounding this deep groove are negatively charged and may have the ability to bind to the positively charged region of the S protein; several small patches of hydrophobic regions formed by hydrophobic residues around the pupae near the negative charge may also bind to the S protein. [6].

ACEII, the first human ace homolog discovered in 2000, is a zinc metalloproteinase, belonging to type 1 transmembrane protein. Its structure includes a signal peptide, a transmembrane domain and a metalloproteinase active site containing hexxh zinc binding domain. It can degrade ang I to form nine peptide ang 1-9, and degrade Ang II to form seven peptide ang 1-7 [1, 2]. ACEII was originally thought to be expressed only in the heart, kidney and testis. Later, it was also widely expressed in the lung, brain and digestive tract. In lung tissue, it is mainly distributed in type II alveolar cells (AT2 cells), but also in a small number of type I alveolar cells (AT1 cells), airway epithelial cells, fibroblasts, endothelial cells and macrophages [3].



Part 2 Target organ damage

1. Heart injury

ACE2 is highly expressed in the heart, which also provides the necessary receptors for the virus to invade the heart.

G.Y.Oudit et al. [7] found that mice infected with SARS-CoV can cause ACE2-dependent myocardial infection, and its ACE2 expression decreased significantly, confirming the important role of ACE2 in mediating cardiac SARS-CoV infection.

In addition, during the SARS outbreak in Toronto, SARS-CoV virus RNA was detected in 35% (7/20) of autopsy heart samples of patients who died from SARS.

- Macrophage-specific staining showed a marked increase in macrophage infiltration in patients with SARS-CoV in the heart and evidence of myocardial injury.

The presence of SARS-CoV in the heart is also associated with a significant decrease in ACE2 protein expression.

This will cause an increase in AngII. AngII regulates and participates in the growth of cardiomyocytes. It plays an important role in the pathophysiology of cardiovascular disease through intercellular and intracellular signaling mechanisms that affect intercellular communication, immunity, lipid peroxidation and insulin resistance Important role [8].

AntoniakS et al. [9] observed in WT mice for 28 days that infusion of AngII into mice will lead to aortic vascular remodeling, accompanied by increased medium thickness and enhanced fibrosis, eventually leading to the heart Hypertrophy, coagulation associated with fibrosis and inflammation of the heart is activated.

In addition, Ang (1-7) will be less, and its cardiovascular protection will be weaker or even disappear.

Therefore, SARS-CoV can mediate myocardial inflammation and myocardial ACE2 system down regulation-related damage. This may be the cause of myocardial dysfunction and adverse cardiac outcomes in patients with SARS.

The mechanism of 2019-nCoV invasion of cells is roughly the same as SARS, and 2019-nCoV may cause heart damage through similar mechanisms.

Huang et al. [10] released 5 of the earliest confirmed 41 patients with new-type coronavirus pneumonia in Wuhan (12%) who were diagnosed with virus-associated heart injury, mainly with an increase in hs-cTnI levels (> 28pg / mL) Four out of five people received ICU, accounting for 31% of the total number of ICU patients.

Hou Tao's analysis of 84 patients with novel coronavirus pneumonia from January 1, 2020 to January 22, 2020 also pointed out that myocardial enzymes increased during treatment, especially myocardial kinase (CK) And the increase of myocardial kinase isoenzyme (CKMB), suggesting that the patient's condition is serious and predicting that the patient's condition is worsening.

The recently released "Pneumonitis Diagnosis and Treatment Program for New Coronavirus Infection (Trial Fifth Edition)" pointed out that troponin increased in some newly critical patients. Although the current number of cardiovascular symptoms as the main manifestation is relatively small, from the current data, once the heart is involved, most patients are severely symptomatic. Its mechanism and processing method need to be

further studied. How to antagonize 2019-nCoV on ACE2-mediated myocardial cells and microenvironment is the key to improve myocardial injury. With the increase in the number of cases of 2019-nCoV pneumonia, the number of patients with heart injury cannot be ignored, and it needs to be detected and treated in time. Myocardial histopathology and changes in ACE2-related pathways can help us understand its mechanism and evaluate clinical treatment effects.

2. Lung injury

The lungs are the main target organs of the coronavirus, and most patients develop symptoms with respiratory symptoms.

Chen et al. [11] retrospectively analyzed the clinical data of 99 patients with new-type coronavirus in 2019. In chest imaging, 75% of patients had inflammatory changes in the lungs, which were manifested by high-density small patch patches and multi-lobal segments Ground-glass shadows, 17% of patients developed symptoms of acute respiratory distress. 76% of patients received oxygen therapy and 17% received mechanical ventilation (of which 13% were non-invasive and 4% were invasive). ACE2 is not only the invasion receptor of new coronavirus in lung tissue, but also may be involved in the occurrence and development of lung injury.

The results of ZUO et al. [12] showed that the expression of ACE2 receptors is mainly concentrated in a small group of type II alveolar epithelial cells (AT2) in the lung. This group of virus-susceptible AT2 cells accounts for 1.4% of all AT2 cells. ACE2 expression is minimal in others such as type I alveoli, bronchial epithelial cells, endothelial cells, fibroblasts and macrophages.

Kubal et al. [13] injected SARS-CoV spike protein into mice, which can cause acute acute lung failure, and this process can be weakened by blocking the renin-angiotensin pathway. In addition, ACE2 is a key negative regulator of severe pulmonary edema and acute lung failure.

Imai et al. [14] confirmed that ACE2 and type 2 angiotensin II receptor (AT2) protect mice from severe acute lung injury caused by acid inhalation or sepsis. However, other components of the renin-angiotensin system, including ACE, angiotensin II, and type 1a angiotensin II receptor (AT1a), promote the pathogenesis of the disease, induce pulmonary edema, and impair lung function. In addition, the deletion of the ACE2 gene also promotes TGF-β / Smad (TGF-β / Smad) signaling pathway-mediated tissue fibrosis and NF-κB-mediated inflammation.

The combination of the coronavirus S protein and ACE2 down-regulates the levels of ACE2 in the lungs, while ACE1 is not affected, Ang Ⅱ levels rise, AT1 receptors are overactivated, and the renin-angiotensin system is imbalanced in the lungs, leading to acute lung injury such as pulmonary edema Symptoms [15].

ACE2 plays a key role in the pathogenesis of acute lung injury, and it is inferred that it is also critical in 2019-nCoV-induced lung injury.

Although there are some opinions that ACE2 plays a protective role in ALI (acute lung injury), the lack of ACE2 in the lung may be one of the causes of ALI, but the mechanism is still not completely clear. The current research focuses on ACE2 enzyme activity and AngII substrate And its catalytic product, Ang1-7 [16]

2019-nCoV has invaded the body through ACE2 and caused severe lung injury. Exploring the pathophysiological mechanism downstream of ACE2 during the inflammatory storm is the key to solving the problem. Etiology, pathophysiology, and evaluation of therapeutic effects require extensive histopathological research. How to maintain the integrity of the alveolar interstitial between the alveoli and the alveoli, especially the integrity of the microvascular structure between the alveoli, is of great significance for the relief of interstitial exudation, and the role of Chinese medicine in it is worth exploring. The evaluation of relevant effective or harmful treatment effects needs to be confirmed based on the statistical results of relevant big data.

3. Intestinal injury

2019-nCoV infection clinical manifestations, fever and cough are the most common symptoms. In addition, it often causes severe intestinal symptoms such as diarrhea and nausea, and is even more severe than SARS-CoV and Middle East Respiratory Syndrome Coronavirus (MERS-CoV).

A scholar in the United States has reported on a patient who had diarrhea and abdominal discomfort in addition to a persistent fever and dry cough during his hospitalization. It is worth mentioning that a new coronavirus (rRT-PCR positive result) was also detected in stool samples of diarrhea [17].

Zhang et al. [18] found that the viral receptor ACE2 was highly expressed in esophageal stratified epithelial cells and ileal and colonic absorbable epithelial cells through analysis of genetic data, indicating that the digestive system is a potential infection route. The abnormal function and expression of ACE2 caused by the virus infection increased the Ang II with inflammatory stimulation to the intestine, and decreased Ang (1-7) that dilated blood vessels and inhibited inflammation and causes intestinal inflammation.

Hashimoto et al. [19] found that DSS-induced colitis mice with ACE2 gene knockout showed severe colon ulcer injury in mice, and the concentration of Ang Ⅱ in colon tissues increased significantly. After recombinant soluble ACE2 (rsACE2) was given, the Ang Ⅱ concentration decreased

Khajah et al. [20] found that DSS-induced colitis mice increased the expression of Ang Ⅱ and ACE2 in colonic mucosa, and the expression of Ang (1-7) also increased significantly. The expression of Ang Ⅱ decreased, and the phosphorylation of p38, ERK1 / 2, and Akt signaling pathways were significantly inhibited. At the histological level, colonic mucosal damage and ulcers improved. Ang (1-7) can also directly inhibit the activation of signal pathways such as ERK1 / 2 and NFκB through the Mas receptor, and reduce inflammatory damage of the intestine.

Therefore, intestinal symptoms of 2019-nCov infection may be related to invasion of intestinal epithelial cells expressing ACE2. The intestine is a possible target organ for the virus to invade the human body, and whether it can be transmitted through the digestive tract remains to be further studied. Whether we can give Ang (1-7) drug treatment or directly supplement Ang (1-7) is our basic and clinical research direction

Part3. ACE2 is a potential therapeutic target

1. Stop the virus

After SARS, there have been many drug developments targeting the viral receptor ACE2.

DongP. Han et al. [21] used alanine scanning mutagenesis to identify the key sites of ACE2 binding to SARS-CoV, and the results showed that the charged amino acid between residues 22 and 57 is important, especially K26 At positions 30 and D30, researchers used these amino acids to artificially synthesize related peptides and evaluate their role in antivirals. The two peptides (aa22-44 and aa22-57; P4 and P5) showed moderate antiviral activity, and their half inhibitory concentrations (IC50) were about 50 μM and 6 μM, respectively. In addition, a peptide (P6 peptide) synthesized by artificially connecting two discontinuous segments (aa22-44 and aa351-357) in ACE2 with glycine showed strong antiviral activity, and its IC50 was about 0.1 μM.

Huentelman et al. [22] based on the structure-based method, selected 140,000 small molecules through the docking of silicon molecules, and selected molecules with high binding capacity to further determine the ACE2 enzyme inhibitory activity and the ability to inhibit SARS coronavirus S protein-mediated cell fusion.

Studies have found a new human ACE2 inhibitor, NAAE. NAAE's ability to regulate ACE2 activity and prevent SARS-S protein-mediated cell fusion indicates that it is a potentially valuable lead compound. ACE2 derivatives (P4, P5, and P6) or small molecules (NAAE) are currently on the market. They are effective in blocking SARS-CoV invasion. The receptors for 2019-nCov are the same. Whether these drugs are effective or not remains to be confirmed.

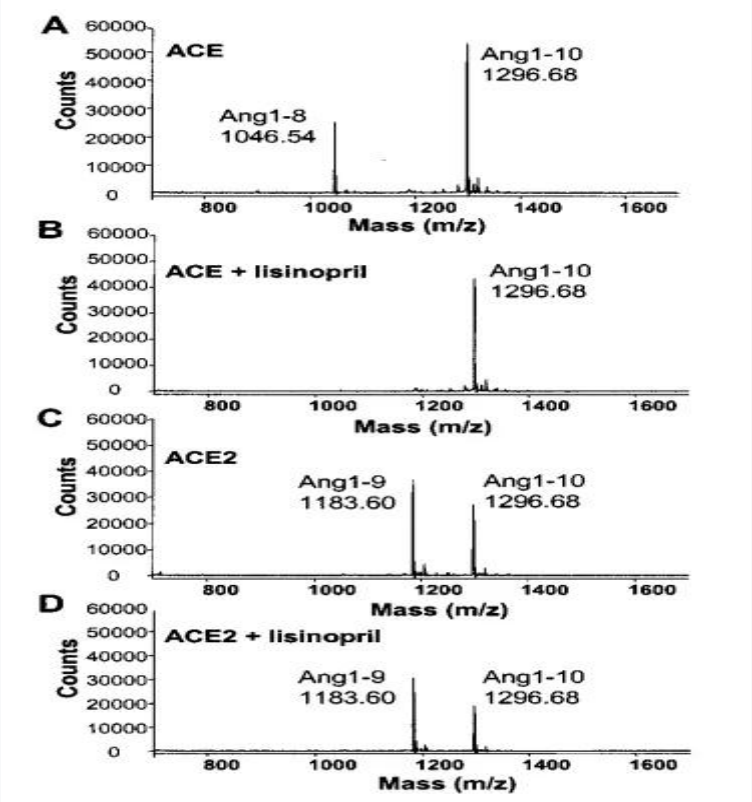
Studies [1] have confirmed that the 5 key amino acids of SARS virus S-protein interacting with ACE2, 4 of them have changed in 2019-nCov. S-protein is also required for the development of the above drugs. The protein structure of these two viruses is different and may affect the efficacy of the drug. However, using the same research method may develop effective targeted drugs.

2. Inhibits inflammation and reduces target organ damage

At present, many targeted drugs are in the clinical or even animal research stage. Symptomatic treatment is still the main method to suppress the occurrence and development of inflammation in a timely manner. Reduce the damage to the target organ by the virus, thereby improving the prognosis.

Low expression of ACE2 caused by virus infection activates the renin-angiotensin system (RAS) and aggravates lung injury [13]. Therefore, activating the ACE2-Ang (1-7) -Mas receptor pathway or inhibiting the ACE-Ang Ⅱ-AT1R receptor pathway may benefit patients.

In animal models, blocking angiotensin II receptor I (AT1R) can reduce SARS-CoVSpike protein-mediated lung injury. Studies by Henry et al. [23] suggest that ACEI and statins may have a certain effect on patients with viral pneumonia who are not coronavirus infected and have no underlying disease.



The use of ACEI in patients with novel coronavirus pneumonia is currently controversial. It can inhibit RAS and may play a role in protecting the lungs and controlling symptoms. Under normal physiological conditions, ACE2 and ACE are in equilibrium. Use of ACEI can inhibit ACE, leading to increased expression of ACE2, which increases the risk of infection

Ferrario et al. [24] showed that the inhibition of RAS by ACEI or AT1R blockers up-regulated ACE2 mRNA expression and ACE2 activity, but did not increase ACE2 concentration.

In addition, the expression level of ACE2 is inconsistent with the virus attack. For example, ACE2 is highly expressed in the heart and kidney, but serious lesions are rare in these organs, and the mechanism is still unclear. It is possible that viral infection also requires other receptors or cofactors.

Recently, in a phase II clinical trial of ARDS patients using recombinant human ACE2 (GSK2586881), this compound has been widely used in ARDS patients and can reduce AngII levels, increase Ang (1-7) and surfactant protein D Horizontal [25]. Tips for exogenous supplementation with ACE2 may be an effective method

3. Current research and application of drugs

scientists linked a human ACE2 extracellular region to the Fc region of human immunoglobulin IgG1 to construct a new recombinant protein. An ACE2 mutant (mACE2-Ig) with low catalytic activity was also used in the study. The fusion protein was then characterized. Fusion proteins have a wide range of potential neutralizing activities against coronaviruses. At the same time, ACE2 fusion proteins can also be used for diagnostics and research reagents for vaccine and inhibitor development [26]. Wang Yuedan and Chu Ming's team of Peking University School of Basic Medicine used artificial intelligence drug screening system to screen more than 4,100 drugs on the market. They found that common drugs such as statin may be ACE2 targeted therapeutic drugs.

PART 4 Summaries

ACE2 is an important protective protein in the human body and is also a necessary receptor for 2019-nCoV infection to invade the human body.

1. ACE2 is down-regulated after virus infection in humans, which reduces the degradation of Ang Ⅱ, which promotes the inflammatory response, reduces the production of Ang (1-7), which relaxes blood vessels,

improves endothelial function, and reduces proliferation. The ACE-AngⅡ-AT1R / AT2R axis is out of balance, and target organ damage occurs.

2. ACE2 is widely distributed, so 2019-nCoV can affect a variety of organs and show a variety of clinical manifestations. Those with atypical symptoms should pay more attention.

Heart damage, mostly in high-risk groups, is identified early and treated accordingly;

If gastrointestinal symptoms appear, the digestive system may be damaged. Pay attention to the possibility of fecal-oral transmission.

3. ACE2 is a potential therapeutic target, according to its structure, develop targeted drugs to block virus invasion in time; use ACE2-Ang (1-7) -Mas receptor pathway or inhibit ACE-AngⅡ-AT1R receptor pathway Drugs may inhibit inflammation and reduce target organ damage.

4. The role of ACE2 in 2019-nCoV infection needs further study

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