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Progress on Human Coronavirus and Antiviral Drugs

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Abstract

Coronavirus (CoV) mainly causes local infection in birds and mammals, in recent decades, there is evidence that it can infect humans. Highly pathogenic coronavirus, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), are fatal zoonotic viruses, which have posed a major threat to public health. Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has also seriously endangered the health and safety of the human beings. These coronaviruses transmitted through close contact between people, resulting in the development of acute respiratory distress syndrome (ARDS) and multiple organ failure (MOSF), leading to higher morbidity and mortality. This article reviews the structure, epidemiology, immunology and treatment of coronavirus, hoping to provide reference for the prevention, control and treatment of the disease. Finally, we look forward to cyclosporine A as a new application in the treatment of SARS of CoV-2, also look forward to reduce the mortality caused by SARS-Cov-2.

Keywords: Coronavirus; Severe Acute Respiratory Syndrome; Middle East respiratory Syndrome; Severe Acute Respiratory Syndrome-Coronavirus-2; Epidemiology; Immunology; Clinical Treatment; Remdesivir; Cyclosporine A

Abbreviations: SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; ARDS: Acute Respiratory Distress Syndrome.

Introduction

In the past 20 years, severe acute respiratory syndrome broke out in 2003 and Middle East respiratory syndrome (MERS) appeared in 2012, which has posed a major threat to global public health; 29 countries have reported 8096 cases of SARS, including 774 deaths, with a fatality rate of 9.6%; 27 countries (including 12 from the Middle East) have reported 2499 cases of MERS, of which 861 cases died, with a fatality rate of 34.4%. In December 2019, coronavirus pneumonia occurred in Wuhan, China. Up to February 7 of 2020, there were 31211 confirmed cases in China, 4821 severe cases and 637 deaths; 270 confirmed cases and 1 death case occurred in 24 countries outside China. SARS CoV, MERS CoV and severe acute respiratory syndrome coronavirus-2 (SARS-cov-2) were all seriously pathogenic and could cause acute respiratory distress syndrome (ARDS) [1-6]. Coronavirus have aroused a lot of researchers' interest. In this paper, we reviewed the structure, epidemiology, immunology and treatment of coronavirus in order to provide reference for the prevention, control and treatment of this disease.

Constructor of Coronavirus

Highly pathogenic coronaviruses (SARS CoV, MERS CoV and SARS-cov-2) have been paid more and more attention.

Other coronaviruses have been found to have spread in humans for hundreds of years and can only cause mild respiratory diseases, such as 5% - 30% of the common cold. Coronaviruses belong to coronavirinae of coronaviridae, the order of nidoviralest, Coronaviruses (Nidovirales family), and it can be divided into four genera (α, β, γ and δ). Seven species of coronaviruses have been known to infect human beings, of which 2 species (HCoV-229E and HCov-Nl63) belong to alpha coronavirus, and five species (SARS CoV, MERS COV), HCoV-OC43, HCoV-HKU1 and SARS-CoV-2) are β – coronaviruses. γ - And δ- coronaviruses are not known human viruses, however, it is highly pathogenic to livestock. Animal epidemic coronavirus can cause a variety of respiratory, intestinal and nervous system diseases. Infectious diseases caused by SARS CoV, MERS CoV and SARS-cov-2 show that the coronavirus can cross the species barrier and infect humans with lethal characteristics There are four main structural proteins encoded by coronavirus genome: spike protein (S), membrane protein (M) and envelope protein (E) on the surface of virus envelope, and nucleocapsid protein (N) [7-10] located on the inner side of the envelope (Figure 1).

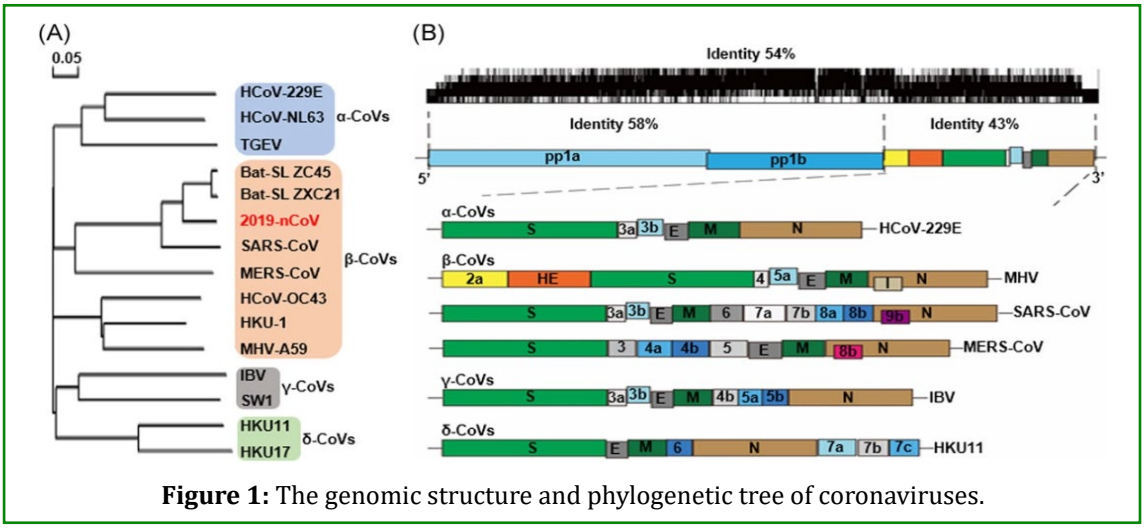

Figure 1: The genomic structure and phylogenetic tree of coronaviruses.

A. The phylogenetic tree of coronavirus. 2019 ncov is highlighted in red; B. the genome structure of coronavirus. Pp1a and pp1b represent two long polypeptides that can be processed into 16 nonstructural proteins. S, E, M and N represent four structural proteins [8]. Emerging coronaviruses: genome structure, replication, and pathogenesis. The only function of N protein is to combine with coronavirus genome ribonucleic acid (RNA) and form the Nucleocapsid) [11]. To a large extent, N protein participates in other aspects of virus genome cycle and host cell response to virus infection [11,12]. M protein is the most abundant structural protein that determines the shape of virus envelope and is the main organizer of virus structure, [9,13-15] teraction between S and M proteins is necessary for S protein to assemble new viruses in the Golgi complex of endoplasmic reticulum Golgi intermediate (ergic), ending of M protein and N protein stabilizes the nucleocapsid protein (n-protein-rna complex) and the inner core of the virus body, and finally promotes the viral assembly. M protein and E protein form the viral envelope together. The interaction of M protein and E protein can promote virus like particles (VLPs), [16-18,19,20]a kind of empty shell structure without viral nucleic acid.

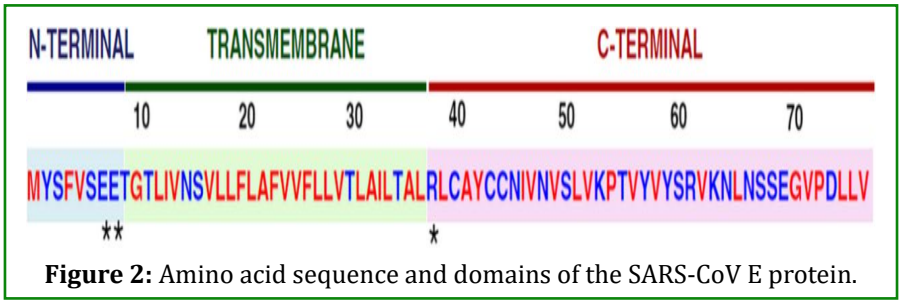

Figure 2: Amino acid sequence and domains of the SARS-CoV E protein.

Coronavirus E protein is a short complete membrane protein, containing 60-120 amino acids, the smallest among structural proteins (8.4-12 kDa), and also the most mysterious. E protein consists of a short hydrophilic amino

terminal (composed of 7-12 amino acids), a hydrophobic trans membrane domain (TMD, containing 25 amino acids), and a long hydrophilic carboxyl terminal (containing most proteins) (Figure 2) [21-24]. The hydrophobic region of TMD contains at least one amphiphilic α - helix, which forms an ion conducting pore in the membrane [25,26]. The total net charge of the peptide is zero, and the middle region is not charged. One side of the peptide is a negatively charged amino (n) terminal, and the other side is a variable charge carboxyl (c) terminal.

The amino (N)-terminal domain, the trans membrane domain (TMD), and the car boxy (C)-terminal domain. Amino acid properties are indicated: hydrophobic (red), hydrophilic (blue), polar, charged (asterisks) During the viral replication cycle, E protein was expressed in a large number of infected cells, but only a small part was integrated into the virus membrane. Most of the E proteins were located in the intracellular transport sites, which were involved in the assembly and binding of coronavirus targets, including estrogen receptor (ER), Golgi apparatus and ERGIC, It is suggested that E protein plays an important role in the process of virus assembly and maturation [27-32]. Some studies have found that SARS CoV E protein is related to virus virulence [19] and can form calcium ion permeable protein lipid channel in Golgi membrane.

The activity of E protein ion channel is closely related to lung injury, edema accumulation and death. IL-1 β - mediated inflammation is associated with lung injury and edema, but the relationship between IL-1 β and ion channel activity is not clear. Calcium concentration and pH value jointly regulate the pore charge and selectivity of E protein. Some studies have found that E protein ion channel activity is closely related to the activation of NLRP3 inflammatory bodies collusion, the ion disorder and infection caused by SARS CoV E protein ion channel at the cellular level are related to the immune pathological results and disease deterioration. The protein binding motif (PBM) of SARS CoV E protein is the last four amino acids (DLLV) at the C-terminal [33-35].

The PBM protein is closely related to the immune pathological results and disease progression. It is known that E protein interacts with five host proteins, namely BCL XL, pals1, multifunctional intracellular adaptor protein (syntenin), Na^++ K^+) ATPase α - 1 subunit and stoma tin like protein [28,36,37]. Teoh et al. [35] found that E protein interacted with PALS1 to destroy the tight junction of lung epithelial cells. It is suggested that SARS CoV virus particles can break through the alveolar wall and develop into systemic infection. Some studies have found that the interaction of E protein with Na^++ K^+ATPase α - 1 subunit and stoma tin like protein may be the reason for the decrease of human epithelial sodium channel level and activity. E protein is the determinant of SARS in animals [28,36]. By infecting mice with recombinant SARS CoV, it was found that E protein could lead to the redistribution of adaptor protein to the cytoplasm, induce the overexpression of inflammatory cytokines, thus aggravating the immune response, leading to tissue injury and edema, and eventually leading to typical acute respiratory distress syndrome (ARDS). Coronavirus E protein has at least three functions: ① the interaction between E protein and other proteins drives the production of virus like particles (VLPs) and participates in virus assembly [15,19,34]. ② TMD of E protein is crucial to the release of virus particles [31,38]. ③ E protein of SARS CoV is related to pathogenicity of SARS CoV [26,36], Some anti-coronavirus drugs may be closely related to E protein. (Figure: 3) illustrates the structure and genome organization of coronavirus with MERS cov as an example.

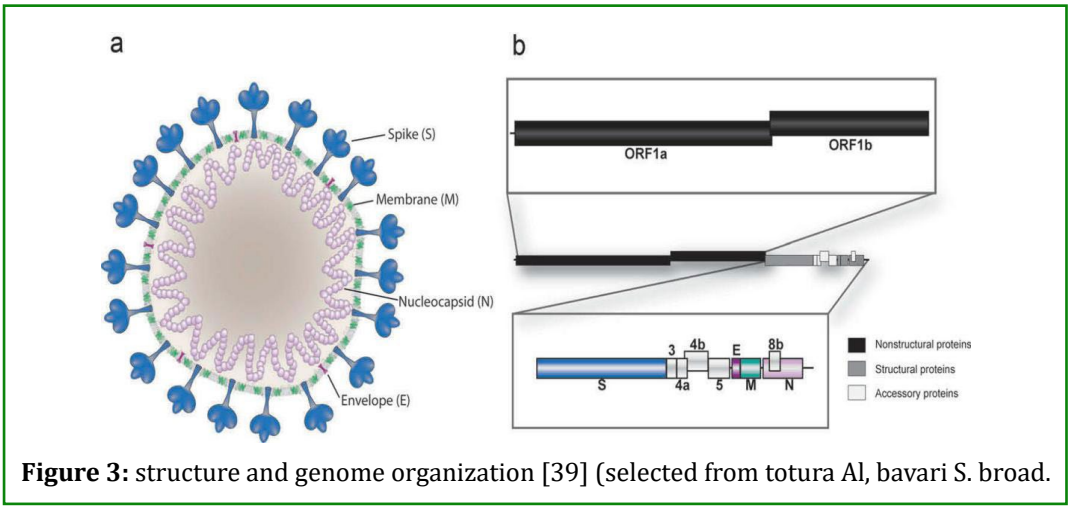

Figure 3: structure and genome organization [39] (selected from totura Al, bavari S. broad.

Spectrum coronavirus antiviral drug discovery. MERS CoV (GenBank jx869059) is used as the structural diagram of coronavirus particles and genomes. The virus particles exist in the form of enveloping virus particles, in which s protein,

M protein and envelope E protein modify the outer surface of the membrane. In the inner part of the virus, N protein can encapsulate the viral genome. The viral genome is composed of a single strand of positive strand RNA, A single multi protein open reading frame encodes a more conserved nonstructural protein (orf1a, ORF1b). At the 3 ′ end of the genome, viral specific helper proteins (ORF3, orf4a, orf4b, ORF5 and orf8b) are scattered among the conserved structural proteins that make up the viral body. The helper ORF proteins play an important role in the pathogenesis and infection of MERS CoV, such as activating interferon (IFN),The IFN pathway causes intense inflammation.

Epidemiological Characteristics

SARS CoV in 2002-2003, shortly after SARS appeared in southern China, SARS CoV was confirmed to be the cause of SARS. Human beings are the main source of infection of the disease. The animal source and intermediate host may be civet, bat, wild cat and other wild animals [1,40-44]. The incubation period is 4-20 (7.6 ± 3.4) days. The main transmission routes are respiratory droplets, contact transmission and hospital transmission ,The most common risk factors for SARS patients in China were age > 60 years (RR = 77.4%), The mortality of SARS patients under 60 years old was only 13.2%. Diabetes mellitus and / or heart disease were the important risk factors of death.

MERS cov since Saudi Arabia reported the first confirmed case of MERS in 2012, MERS cov has spread to more than 20 countries and regions, resulting in a large number of laboratory confirmed cases [2,3]. MERS outbreaks in Saudi Arabia, the United Arab Emirates and South Korea are the most serious. Typical MERS symptoms include fever, cough and shortness of breath; pneumonia is common, but not all patients exist; other symptoms include gastrointestinal symptoms, such as diarrhea. Some confirmed MERS cases are asymptomatic, which were found after positive contact tracking of confirmed cases, and about 35% of MERS patients died. Although most people infected with MERS CoV were due to human to human infection in the medical environment, the current scientific evidence shows that camels are the main host of MERS cov. At present, the exact transmission route of the virus in animals and humans is not clear.

SARS-cov-2 in December 2019, patients with unexplained pneumonia appeared in some medical institutions in Wuhan. Since the onset of SARS-cov-2 [4,45], as of February 7, 2020, there were 31211 confirmed cases in China, 4821 severe cases and 637 deaths; 270 confirmed cases and 1 death case occurred in 24 countries abroad. The cases in China accounted for 99% of the world's cases, including 22112 confirmed cases in Hubei Province. Bat, snake and pangolin may be hosts or intermediate hosts. SARS-cov-2 can be transmitted from person to person. Close contact transmission and respiratory droplet transmission are the main routes of transmission, and fecal oral transmission is also possible. People of all ages are generally susceptible, and most of them are adults, [46] ov-2 belongs to β - coronavirus, which is round or oval in shape, with a diameter of 60-140 nm. Its genetic characteristics are significantly different from those of SARS r CoV and MERSr cov, SARS-cov-2 can be detected in human respiratory epithelial cells in about 96 hours. At present, the source of the virus, the time of detoxification after infection and the pathogenesis are still unclear [47].

Pathogenesis

Type I trans membrane glycoprotein (S protein) of he trans membrane pathway is the main way for coronavirus to enter cells: the receptor binding domain (RBD) of MERS cov S protein is composed of S1 subunits, containing 367-606 amino acids, which can be divided into external subdomains and core domains. The RBD core of MERS cov S protein binds to cell receptors (mainly DDP4R) through special insertion rings and clamps in the lower and upper regions [48]. The virus can also produce membrane fusion through cell surface assisted pathway.

ER stress response unfolded protein reaction (UPR) and apoptosis. ER can withstand high protein content. When ER's ability to fold and process protein exceeds the limit, unfolded or misfolded proteins will accumulate rapidly in the lumen, thus activating ER stress response or UPR, Molecular chaperone and ER assisted degradation (ERAD) together constitute a variety of signal pathways of UPR. If UPR is prolonged and irreversible, it will initiate cell apoptosis. Virus infection can also trigger UPR by increasing the protein content of endoplasmic reticulum, this pathway can be used by host cells as an antiviral response [49-52]. Coronavirus E protein plays an anti-apoptotic role in infected cells by inhibiting UPR signaling pathway, which is likely to be a survival mechanism and can continue viral reproduction. So far, this function of E protein has only been confirmed in SARS CoV.

Immune response: inflammatory body activated viruses usually encode proteins to interfere with the immune system, thereby inhibiting one reaction or enhancing another as part of its pathogenicity. Some viral proteins destroy components of the immune response pathway to interfere with the destruction of the immune system and promote virus escape and disease occurrence, or regulate other cytokines, the immune mechanism of MERS CoV infected cells may be [53]: MERS cov binds to macrophages via DPP4 receptors, and then the macrophages present MERS cov antigen to Th0 cells. This process leads to T cell activation and differentiation,

including the production of cytokines related to other T cell subsets (i.e., Th1, Th2, and Th17), Although these cytokines, such as ifn-8, are activated by the cells to produce a large number of cytokines, such as ifn-8 and IFN - γ, which can be activated by the cells to produce a large number of cytokines, such as ifn-8, which can be activated continuously by cells, However, the long-term or short-term protective antibodies produced by MERS cov are not clear. MERS cov binds to the DPP-4 receptor of host cells through S protein, resulting in the emergence of genomic RNA in the cytoplasm. Immune response to dsRNA can be partially produced during the replication of MERS cov.

The cascade reaction of TLR-3 and signal pathway sensitized by dsRNA activates IRF and NF - κ B through traf3 and TRAF6, respectively, In order to promote the production of inflammatory cytokines, IL-12 and IFN - γ are essential to increase the release of antiviral proteins to protect uninfected cells. The helper protein of MERS cov can also bind to the dsRNA of MERS cov to interfere with TLR-3 signal transduction during replication, TLR-4 may recognize s protein and activate proinflammatory cytokines through MyD88 dependent signaling pathway. The interaction between virus and cells leads to the production of immune mediators. The cells infected with MERS cov secrete a large number of chemokine's and cytokines (MCP-1, IL10 and CXCL10), These chemokine's and cytokines in turn recruit lymphocytes and leukocytes to the site of infection (Figure 4).

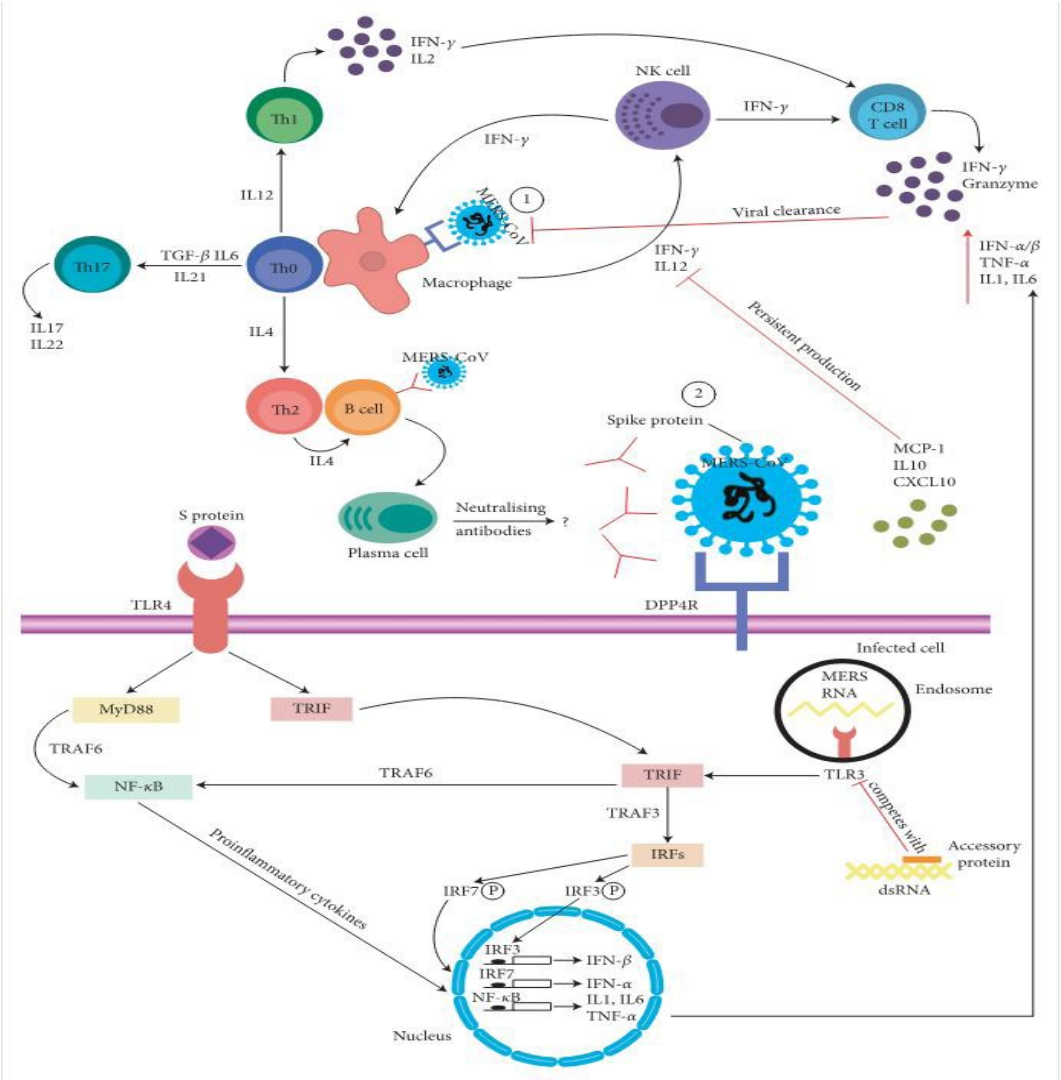

Figure 4: the proposed schematic representation of the immune response to MERS cov infection and how the invading virus is processed during an infection [53]. The red arrow shows the black effect.

Vaccine and Drug Prospect

At present, there is no specific vaccine or drug for the prevention and treatment of highly pathogenic coronavirus (SARS CoV, MERS CoV and SARS-cov-2) infection. Symptomatic and supportive treatment is mainly adopted. At present, the main anti coronavirus drugs and / or methods are as follows: ①targeting nonstructural protein drugs of coronavirus, such as Radcivir (gs-5734 class), ropinavir, ritonavir, ribavirin; 2;② In addition to coronavirus s protein, membrane (matrix) protein and other structural proteins may play an important role in the development of candidate vaccines, Targeting these viral proteins may contribute to the development of vaccines or drugs. ③ Essential host factors and immune regulation of coronavirus infection, such as cyclosporine, interferon and traditional Chinese medicine. Antiviral candidate drugs only show narrow-spectrum activity or are effective only in abnormally high-dose treatment; otherwise they will cause serious adverse effects or immunosuppression. In vitro cell culture or animal experiments, some drugs have shown the effectiveness of inhibiting this virus. Remdesvir (RDV, gs-5734) [54-58] is a broad-spectrum antiviral nucleotide analogue, In addition, it is also a new type of viral RNA, such as cov RNA, they are called nucleotide analogues, such as RDV.

Nucleotide analogues can replace NTP and bind to RdRp and insert into the RNA chain being synthesized. When the viral polymerase attempts to add the next NTP, it will be found that it cannot be added because of the different chemical structure of nucleotide analogues, which cannot polymerize with NTP, Recently, RDV has entered clinical trials in China Japan Friendship Hospital in Beijing. It has been found that immunosuppressant (cyclosporine A) can significantly inhibit coronavirus infection in vitro and animal experiments [59-62]. Cyclosporine A is a lipophilic cyclic polypeptide compound isolated from the culture medium of some hyphomycetes fungi, such as Cylindrocarpon lucidum and Tolypocladium fla chemical booktum, In the 20th century, it has been widely used as an immunosuppressive agent of immune T-2, which can prevent the immune response of other organs, and has been widely used as an immunosuppressive agent in the immune response, However, it has no effect on bone marrow, B cells and granulocyte survival.

The mechanism may be that cyclosporin A can bind to cyclophilin in immune cells; Cyclosporin A (CSA) can inhibit neurocalcin, calcineurin and nuclear translocation of NF-AT. Cyclosporine A also affects mitochondria by preventing MTP opening set of A and A may be used as a new immunotherapy strategy for the treatment of cancer, Cyclosporine A may inhibit viral replication (including Coronavirus) by binding with cyclophilin, thus inactivating its cis trans peptide proline isomerize [63-68,61]; it may also inhibit calcineurin and prevent MTP opening from affecting mitochondria, The results show that E protein plays an important role in viral replication and immune activation [36]. Other antiviral drugs such as ropinavir, ritonavir combined with IFN - β, convalescent plasma and monoclonal antibodies need further clinical evaluation; lycorine, etidine, monensin sodium, mycophenolate mofetil, mycophenolic acid, finapyridine and pyrrolidic acid have strong inhibitory effects on coronavirus replication in vitro.

Conclusion

In conclusion, CoVID-2019 caused by SARS-cov-2 is in an outbreak. In addition to active prevention and control, reducing the serious complications and mortality caused by SARS-cov-2 infection is the most important thing. It is urgent to carry out clinical research on drugs with definite effect in vitro and high feasibility as soon as possible. The clinical application of immunosuppressant cyclosporine A is safe, It may be a new ideal drug to fight CoVID -2019, but its clinical anti coronavirus effect needs to be further tested [56,69-71]. Some drugs containing fungal components in natural Chinese medicine may have some homology with cyclosporine, such as poria cocos.

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