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Eyes on coronavirus

Yan-Ping Li [a,1], Ya Ma [b,1], Ningli Wang [b], Zi-Bing Jin [b,*]

[a] Laboratory for Stem Cell & Retinal Regeneration, The Eye Hospital, Wenzhou Medical University, Wenzhou 325027, China
[b] Beijing Institute of Ophthalmology, Beijing Tongren Eye Center, Beijing Tongren Hospital, Capital Medical University, Beijing Ophthalmology & Visual Science Key Laboratory, Beijing 100730 China

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ABSTRACT

Recently, coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 has spread around the world and is receiving worldwide attention. Approximately 20% of infected patients are suffering from severe disease of multiple systems and in danger of death, while the ocular complications of SARS-CoV-2-infected patients have not been reported generally. Herein, we focus on two major receptors of SARS-CoV-2, ACE2 and CD147 (BSG), in human ocular cells, and interpret the potential roles of coronaviruses in human ocular tissues and diseases.

1. Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a new zoonotic coronavirus which came from bat species and has not been observed in humans. The outbreak of COVID-19 is caused by SARS-CoV-2 infection, and it has reached pandemic proportions within a very short time, leading to a health emergency. Since the first detection of the virus, more than 242,000,000 people have been infected worldwide, and more than 820,000 have died as of Aug 27, 2020 (https://coronavirus.jhu.edu/map.html). Although the transmission of SARS-CoV-2 has been illustrated in detail, the association of ocular diseases with viruses has not been extensively studied. We hope that this review will lead the way for more studies on coronavirus and ocular implications.

1.1. Coronavirus structure and host

SARS-CoV-2, identified in December 2019, is a member of the positive-sense single-stranded RNA virus family. The disease with severe pneumonia imputable to SARS-CoV-2 was named by the World Health Organization (WHO) as COVID-2019 (Guan et al., 2020; Wang et al., 2020a). Coronavirus can be divided into four genera, including *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. On the envelope of the coronavirus, there are crown-like surface projections - spike proteins (S proteins), and the virus is named after this crown-like appearance. Both SARS-CoV causing the 2003 outbreak and SARS-CoV-2 are derived from the same family of coronaviruses. It has been shown that SARS-CoV can transmit through the direct or indirect contact of infectious aerosols with mucous membranes (Peiris et al., 2003).

As we all known, coronaviruses are hosted and originated from bats (Fig. 1). The results from genome sequence showed that the novel virus has high sequence identity to a bat coronavirus—RaTG13 (approximately 96.2%) (Zhou et al., 2020). As a zoonotic virus, SARS-CoV-2 is most likely originated from bats and transmitted to human via the intermediate hosts (Junejo et al., 2020). It had been proposed that many species such as pangolins (Lam et al., 2020), minks (Enserink, 2020), snakes (Ji et al., 2020) and turtles (Liu et al., 2020) are the intermediate hosts, but the latter two are still in controversial and needed further confirmation (Luan et al., 2020; Zhang et al., 2020a). Additionally, in some case reports, domestic animals like dogs, cats (Chini, 2020), tigers and lions (McAloose et al., 2020) were positive for SARS-CoV-2 (Fig. 1). In such scenario, it is important to understand the virus hosts to prevent the spread of SARS-CoV-2.

1.2. Coronaviruses enter into host cells via ACE2

The metallopeptidase angiotensin-converting enzyme 2 (ACE2) is a functional receptor for coronaviruses to invade host cells (Hoffmann

* Corresponding author.
E-mail address: jinzb502@ccmu.edu.cn (Z.-B. Jin).
[1] Equal contribution.

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et al., 2020; Li et al., 2003; Wang et al., 2004). Yang et al. established human *ACE2 (hACE2)* gene overexpression mouse and *hACE2* was driven by endogenous mouse ACE2 gene promoter. In transgenic mouse, tissue distribution of hACE2 protein exhibited similar phenomena to human. After being infected with SARS-CoV, the transgenic mouse had more severe and typical pathological changes in lungs compared to the wild-type mouse. In addition, the genetically modified mouse showed extrapulmonary organs damage such as inflammation, degeneration, and necrosis. They illustrated that virus entry into the cell was a critical step (Yang et al., 2007). Besides, transmembrane serine protease 2 (TMPRSS2) is a serine protease that primes the S protein of SARS-CoV-2. The propagation of SARS-CoV-2 also depends on the activity of TMPRSS2 (Hoffmann et al., 2020), as a host cell factor, TMPRSS2 can be blocked by the inhibitor of the cellular serine protease-camostat mesylate (Kawase et al., 2012). Camostat mesylate can inhibit the entry of SARS-CoV-2 (Hoffmann et al., 2020) and is expected to be used in the treatment of SARS-CoV-2. In Japan, camostat mesylate has been approved for use in human. After the cell membrane fusion, RNA of SARS-CoV-2 begins viral replication in the intracellular environment. Li et al. found ACE2 expressed in many human tissues. Therefore, SARS-CoV-2 can target multiple organs and cause dysfunction of various organs. For example, Huang et al. uncovered cardiac injury in five SARS-CoV-2-infected patients (Huang et al., 2020). Holshue et al. detected SARS-CoV-2 from the stool of a patient with SARS-CoV-2 infection (Holshue et al., 2020). Shen et al. found coronaviruses in tear and conjunctival secretions obtained from a patient infected with SARS-CoV-2 (Xia et al., 2020). Apart from the understanding of different ACE2 expression in various tissues, Li et al. also confirmed that SARS-CoV-2 infection risks are equal among sexes, ages, and races (Li et al., 2020a). The above studies provided new insights into the role of ACE2 in this pandemic.

1.2.1. Structure of the ACE2 protein

ACE2 is a type I transmembrane protein consisting of a short C-terminal cytoplasmic tail and N-terminal domain with the active site intracellularly and extracellularly, respectively (Lambert et al., 2005). It belongs to the dipeptidyl carboxydipeptidase angiotensin-converting enzyme family. ACE2 is the primary regulatory enzyme of the vascular protective axis of the classic renin-angiotensin system (RAS). The protein, which has high homology with human angiotensin 1 converting enzyme, is capable of catalyzing angiotensin I into angiotensin 1–9 and degrading angiotensin II into angiotensin 1–7 peptides (Imai et al., 2008, 2005). Thus, the vasodilator angiotensin 1–7 counteracts the function of vasoconstriction caused by angiotensin II (Zisman et al., 2003). Both SARS-CoV and SARS-CoV-2 can invade into host cells by binding with ACE2 (Li et al., 2003; Wan et al., 2020b).

1.3. Coronaviruses enter into host cells via CD147

CD147 (cluster of differentiation 147) known as basigin or EMMPRIN (extracellular matrix metalloproteinase inducer), is a plasma membrane protein, encoded by *BSG* gene (Yurchenko et al., 2006). Lately, Wang et al. found that anti-CD147 humanized antibody Meplazumab can prevent SARS-CoV-2 from entering into host cells during *in vitro* antiviral tests (Wang et al., 2020b). And they uncovered a tight interaction between SARS-CoV-2 S protein and CD147 with the aid of co-immunoprecipitation, ELISA, and immunoelectron microscopy. They discovered a novel binding site of SARS-CoV-2 and led a new way for seeking therapies of COVID-19 (Fig. 2A). At present, the excitement is that Meplazumab, a new humanized anti-CD147 monoclonal antibody, for treating SARS-CoV-2 is carried out in China and is now in phase II clinical trials (ClinicalTrial.gov Identifier NCT04275245). It has been proved that intcrlcukclin-6 (IL-6) in plasma would increase significantly in severe CODIV-19 patients (Zeng et al., 2020a). Aghai et al. demonstrated azithromycin could suppressed IL-6 synthesis (Aghai et al., 2007). In terms of anti-virus, Gielen et al. found that azithromycin can reduce the replication and release of rhinovirus in primary human bronchial epithelial cells (Gielen et al., 2010). As an antibiotic, azithromycin is used in a variety of infectious diseases. Therefore, Ulrich and Pillat suggested that azithromycin can be used as a potential antiviral drug for SARS-CoV-2 treatment by targeting CD147 (Ulrich and Pillat, 2020).

1.3.1. Characteristic of the CD147/basigin

Basigin has two subtypes, basigin-1 and basigin-2. The former one is a retina-specific form that expresses in the surface of rod and cone cells (Aït-Ali et al., 2015). The latter one is a common form and usually named as basigin or basigin-2. And in the mature mouse eyecups' cryosections, Ochrietor et al. uncovered basigin-1 expressed in the apical and basal surfaces of retinal pigment epithelium (RPE), while basigin-2 was absent in the RPE (Ochrietor et al., 2003). Monocarboxylate transporters (MCTs) have the function of transporting lactic acid which is an essential nutrient for RPE development in mouse (Philp et al., 2003). They proposed that basigin is required for targeting MCTs to the membrane of plasma. And in $Bsg^{-/-}$ mice, the degeneration of photoreceptors was observed with MCTs decreased (Philp et al., 2003). In human retina, rod photoreceptors secret a truncated thioredoxin-like protein called rod-derived cone viability factor (RdCVF), which plays

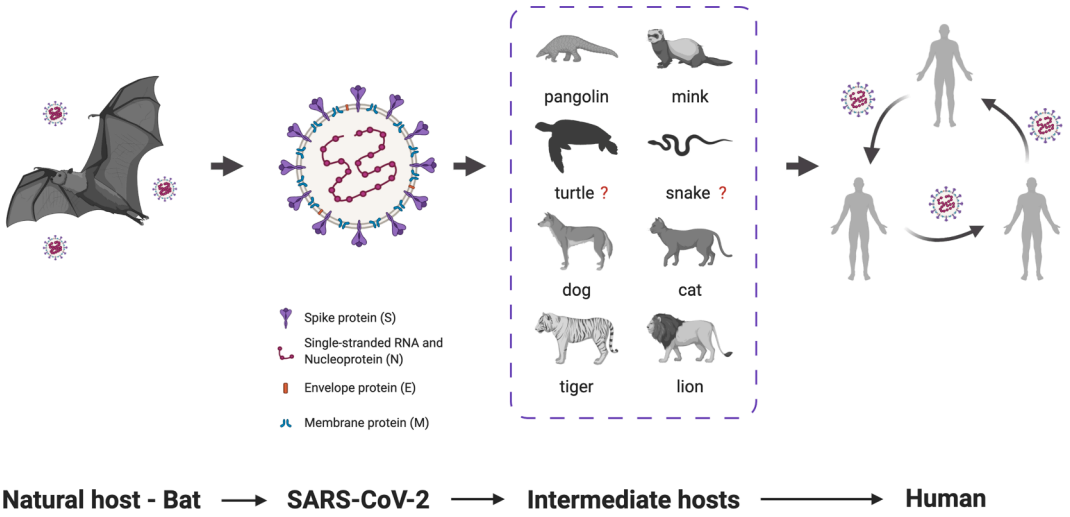

Fig. 1. The potential transmission of SARS-CoV-2. SARS-CoV-2 hosted and formed by bats, and then infected intermediate hosts. After contacting with animals carrying the virus, people are infected. It reaches pandemic proportions by close contact patients and virus-infected aerosols in human society.

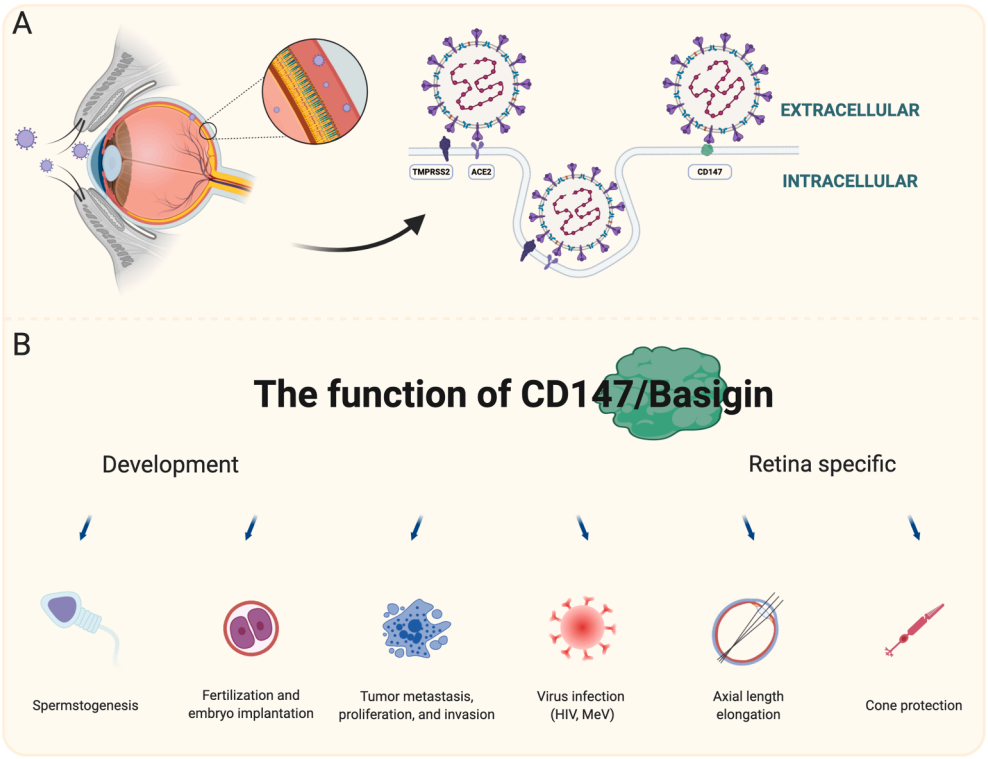

Fig. 2. SARS-CoV-2 invasion in the retina and the function of CD147/basigin. (A) The SARS-CoV-2 invades into host cells via cell membrane protein ACE2 and CD147/basigin in the retina. TMPRSS2 is a serine protease that primes the S protein of SARS-CoV-2.(B) The function of CD147/basigin. HIV, human immunodeficiency virus; MeV, measles virus.

a vital role in preventing cone photoreceptors from degeneration. RdCVF can bind to the extracellular components of basigin-1, thereby activating the glucose transporter GLUT1. GLUT1 can increase the intracellular glucose level to stimulate glycolysis for cone survival (Aït-Ali et al., 2015) (Fig. 2B). Therefore, as a new treatment, RdCVF can be used to treat retinitis pigmentosa patients with cone degeneration.

In a study on early-onset high myopia (EOHM), Jin et al. identified *de novo* mutations (DNMs) for EOHM by using trios (two normal parents and an EOHM children)-based whole-exome sequencing (WES). They discovered four DNMs in *BSG* gene (one nonsense mutation, two missense mutations, and one splice mutation), one of which was confirmed in BSG mutation knock-in mouse with axial length elongation (Jin et al., 2017) (Fig. 2B). This was the first time to verify a causative gene of EOHM using mouse model. Later, they found another four mutations in *BSG* gene in a cross-sectional study involving 731 high myopia patients (Cai et al., 2019). Notably, a recent national survey conducted in June 2020 showed that the rate of myopia among Chinese primary and middle school students increased by 11.7 percent in the first months of the year. Other than the conceivable ration of the longtime online learning and digital screen reading in at-the-home children, it is necessary to know whether the BSG (CD147) palys any roles in it.

Additionally, basigin also plays an important role in spermatogenesis (Akama et al., 2002), fertilization and embryo implantation (Chen et al., 2009) (Fig. 2B). Igakura et al. found that a null mutation in basigin leads to embryonic lethality (Igakura et al., 1998). CD147 expression not only associates with tumor metastasis (Li et al., 2020c), but promotes tumor proliferation (Peng et al., 2020) and invasion as well (Wang et al., 2020c) (Fig. 2B). In non-small cell lung cancer (NSCLC), CD147 exerts as an oncogene and expresses highly in NSCLC cells. The up-regulation of CD147 can promote NSCLC cells proliferation and inhibit cells apoptosis (Cheng et al., 2020). In infectious diseases, Crosnier et al. discovered malaria Plasmodium falciparum reticulocyte-binding protein homolog 5 (PfRh5) can bind to basigin to invade erythrocytes (Crosnier et al., 2011). And as a receptor for measles virus (MeV), basigin on epithelial cells can incorporate MeV cyclophilin B (CypB) for virus entry (Watanabe et al., 2010). Besides, basigin also acts as a receptor for cyclophilin A (CypA) in HIV-1 virions for HIV-1 early cellular infection (Pushkarsky et al., 2001) (Fig. 2B).

2. Ocular diseases caused by coronaviruses

In various clinical specimens, including bronchoalveolar lavage, nasal sputum, blood, and urine, SARS-CoV-2 has already been detected (Wang et al., 2020d). When exposed to a contaminated environment, the surface of eye is an another probable location of viral infection (Olofsson et al., 2005). In anatomical theory, Belser et al. described respiratory disease spread through the eye by means of the nasolacrimal system (Belser et al., 2013). As a result, virus-infected aerosols contact the eye surface and can later enter the respiratory system through the nasolacrimal system. As a mediator for virus enter into host cells, ACE2 receptor is also expressed in the retina, so it is possible that SARS-CoV-2 can harm the retina as well (Fig. 2A).

2.1. Virus-induced retina damage

Recently, Maria et al. detected SARS-CoV-2 viral RNA in three samples out of fourteen retinas from fourteen deceased patients with COVID-19 (Casagrande et al., 2020). The ophthalmological changes of infected patients were uncovered by Marinho et al. (Marinho et al., 2020). According to the optical coherence tomography (OCT) results, hyperreflective lesions were present not only at the ganglion cell level, but also at the inner plexiform layers of all COVID-19 patients. Additionally, four patients displayed cotton wool spots at the retinal arcade with microhemorrhages in color fundus photography and red-free imaging.

SARS-CoV-2 infection can lead to primary severe viral interstitial pneumonia in the lung, and 10% of these patients infected with COVID-19 develop acute respiratory distress syndrome (ARDS) (Conti et al.,

2020; Qiao et al., 2020). However, ARDS, a complication of COVID-19, has been shown to compromise the function of ocular tissue in ARDS pigs (Zadeh et al., 2019). Zadeh et al. constructed ARDS pig models by injecting lipopolysaccharide (LPS) into tracheas, and found endothelial dysfunction and increased ROS level in retinal arterioles. In addition, LPS-treated pigs developed blood-retina barrier damage and vascular rupture with obvious edema in the retina nerve fiber layer.

2.2. Virus-related conjunctivitis

CD147 is expressed in the epithelium and endothelium of the cornea and conjunctiva, and corneal stromal keratocytes (Määttä et al., 2006). Conjunctivitis is another complication of SARS-CoV-2 infection. Same as the respiratory tract, the ocular surface is an open pathway for virus entering. Based on the anatomic features of nasolacrimal duct (Maliborski and Rózycki, 2014), virus can be transported by tear from eye to nose. Zhang et al. (Zhang et al., 2020b) reported a nurse of Emergency Department who had conjunctivitis as the initial symptom, with positive test of the conjunctival and oropharyngeal swabs. In this case, the nurse was affected after the contaminated goggles touched her eyelids. Chen et al. (Chen et al., 2020) recruited 535 COVID-19 patients and found 27 of them presented with conjunctival congestion. Furthermore, frequent hand-eye contact was regarded as the risk factor for conjunctival congestion in this study. In a cohort study conducted by Zeng et al. (Zeng et al., 2020b), among 276 patients with COVID-19, 16 (5.8%) of them were myopia and wore spectacles more than 8 h per day. When compared with the peer prevalence of myopia in Hubei province (31.5%), the proportion of myopia patients with COVID-19 was smaller than that in general population. The authors postulated that wearing spectacles could prevent from hand-eye contact so that avoid virus transferring from the hand to the eye.

The prevalence of conjunctivitis in patients with COVID-19 range from 0.8% to 31.6% (Atum et al., 2020; Guan et al., 2020; Güemes-Villahoz et al., 2020; Wu et al., 2020a). Conjunctivitis manifested as conjunctival congestion, chemosis and epiphora in most cases (Wu et al., 2020a) and could happen prior to pneumonia or accompany with it. Nonetheless, cases of COVID-19 with conjunctivitis as the only symptom had also been reported (Ozturker, 2020; Scalinci and Battagliola, 2020; Wu et al., 2020b). Moreover, Navel et al. reported a case of COVID-19 manifested as hemorrhagic and pseudomembranous conjunctivitis 19 days after onset of cough (Navel et al., 2020). Therefore, it seems like that conjunctivitis could happen during the whole period.

Although conjunctiva shares the same receptor with the respiratory tract for SARS-CoV-2, it is still controversial whether conjunctiva is a gateway to transmit the virus. Researches had reported conjunctivitis in COVID-19 patients, but seldom of them detected SARS-CoV-2 RNA in tears and conjunctival secretions. The positivity rate of conjunctival swab RT-PCR range from 2.78% to 15.6% (Atum et al., 2020; Kaya et al., 2019; Wu et al., 2020a; Zhang et al., 2020b). The authors postulated that the low positive rate should be due to low viral load in tear, deficient sensitivity of PCR test and delayed sample collection. In the research of Seah et al., conjunctival swab samples of COVID-19 patients were obtained from different points of time, but the viral RNA was negative in tears through the course of disease (Seah et al., 2020). Therefore, due to low positive detection rate in conjunctival sac, some authors suggested that eyes are not the main transmission routes of SARS-CoV-2 (Guo et al., 2020; Liu and Sun, 2020).

2.3. Virus-induced ocular implications in animals

Additionally, the ocular implications of CoV-infected humans have not been completely elucidated. However, in various animals, such as cats and mice, ocular infection with CoVs has been well established (Doherty, 1971; Hök, 1993; Hooks et al., 1993; Robbins et al., 1990b).

Feline coronavirus (FCoV), one of the Coronaviridae family members, is the causative agent of feline infectious peritonitis (FIP) and consists of two pathotypes: avirulent and virulent (Pedersen, 2009). The latter always causes serious FIP, even leading to death in kittens, and there is no effective cure so far (Pedersen, 2009). Generally, FIP is divided into two forms: dry, or noneffusive, and wet, or effusive. Both types have common clinical symptoms, such as anorexia, lethargy, mild antibiotic-unresponsive fever, and abnormal weight loss (McReynolds and Macy, 1997). In addition, dry-type FIP always has ocular symptoms caused by the formation of granulomas in ocular tissue. Cats always have uveitis after FCoV infection, and pupil constriction occurs due to prostaglandin release with uveitis (Andrew, 2000). In addition, FCoV-induced vasculitis frequently leads to choroidal and retinal inflammation, which is called chorioretinitis. The most severe sign of chorioretinitis is retinal detachment (Doherty, 1971). Optic neuritis could also be seen in FCoV infection (Andrew, 2000).

Mouse hepatitis virus (MHV), strain JHM, is a member of the coronaviruses that causes acute and chronic eye diseases in BALB/c mice (Robbins et al., 1991, 1990b, 1990a). Wang et al. intravitreally injected MHV into BALB/c mice. They found infectious virus present in the retina and RPE, with immune cell infiltration and pro-inflammatory factors released in the early stage. In the late phase, they observed a decreased number of photoreceptor cells and ganglion cells and a thin neuroretina (Wang et al., 1996).

3. Clinical treatment and intervention

3.1. Dexamethasone

For the COVID-19 treatment, many drugs and agents are being investigated in clinical trials. Dexamethasone is a corticosteroid which exerts its anti-inflammatory and immunosuppressant effects in a wide range of conditions (Johnson et al., 2020). The recent RECOVERY (the Randomised Evaluation of COVID-19 therapy) trial (NCT04381936) at Oxford University in the UK showed that the use of dexamethasone in COVID-19 patients with invasive mechanical ventilation could reduce mortality by a third approximately. And the effect of dexamethasone among hospitalized patients on oxygen therapy without ventilators was also impressive: 20% reduction of mortality (The RECOVERY Collaborative Group., 2020). So far, dexamethasone is the first drug to improve survival rate in COVID-19, with a low cost and extensively available, the National Institutes of Health (NIH) in the US and the National Health Service (NHS) in the UK recommended the use of glucocorticoids for hospitalized patients with ventilators or oxygen therapy (National Health Service., 2020, National Institutes of Health., 2020).

The side effects of dexamethasone in eye include raised intraocular pressure, cataract, glaucoma, corneal or scleral thinning and conjunctivitis. But in RECOVERY trial, there are no effects or adverse effects on mild COVID-19 patients so far.

3.2. Chloroquine/Hydroxychloroquine

Chloroquine and its analog hydroxychloroquine used in human antimalarial treatment. It had been proved that these agents can result in under-glycosylated ACE2 expression to initiate antiviral mechanisms (Vincent et al., 2005). Gao et al. found chloroquine is positive for alleviating pneumonia of COVID-19 (Gao et al., 2020), and Gautret et al. discovered the combination of Azithromycin and hydroxychloroquine had more efficient in reducing SARS-CoV-2 vigour (Gautret et al., 2020), but the results of other clinical studies were inconsistent (Molina et al., 2020).

Some publications have pointed out the most adverse effect of chloroquine/hydroxychloroquine is macular retinopathy, and the risk of it depends on the cumulative dose rather than the daily dose (Savarino et al., 2003). Recent studies reported high dose in short therapy duration could also lead to retinopathy (with morbidity rate 25% to 40%) (Leung et al., 2015; Navajas et al., 2015). Additionally, because of methemoglobinemia and cardiac side effects were developed in COVID-19

patients, food and drug administration (FDA) revoked chloroquine/hydroxychloroquine emergency use authorization (EUA) (Revokes, 2020).

3.3. Clinical intervention

In the face of unprecedented epidemics, it is crucial to cutting off the transmission routes compared to the treatment, many leading experts developed a consensus on preferred practice patterns during clinical practice (Gupta et al., 2020; Areaux et al., 2020). To avoid overcrowding by a large number of patients in the hospital, the group encouraged the use of tele-counseling for triage and to stagger appointments (Kalavar et al., 2020; Wan et al., 2020a). They triage patients according to their urgency and severity. These measures not only provide more convenient and efficient medical services for patients but also reduce the probability of nosocomial infection caused by overcrowding in hospitals.

Indirect examinations and less time-consuming examinations are preferred in clinical practice, such as OCT and optical coherence tomography angiography (OCTA), which are replacements for dye-based angiography (Gupta et al., 2020).

Before emergency surgeries, confirmed or highly suspected patients are sent to a COVID-19-designated center. The instillation of 5% povidone iodine in the conjunctiva is necessary before surgery to eliminate virus on the ocular surface and conjunctival cul-de-sac (Eggers et al., 2015; Gupta et al., 2020).

3.4. The RAS in the eye

As one of the binding proteins of SARS-CoV-2, ACE2 is also a negative regulator in the vascular protective axis of the RAS. The RAS plays a role in regulating blood pressure, body fluid volume, electrolyte balance, and inflammation (Fig. 3A). And many peptidases, tangiotensin peptides, and receptors are involved in this system (Ferrão, 2014). As a part of the protective axis of RAS, ACE2/angiotensin-(1–7) [Ang-(1–7)]/Mas receptor can counterbalance the harmful effects of angiotensin II (Ang II) increase such as arteriole constriction (Santos et al., 2018). As one of angiotensin-converting enzyme family member, ACE2 has ability to cleave angiotensin II into angiotensin 1–7. As a vasodilator peptide (Ferrario et al., 1991), Ang-(1–7) plays a pivotal role in vasodilation, antioxidant activity, and antithrombosis through Mas receptors (Fig. 3B). The RAS comprises the circulatory RAS and local RASs, and the former exerts a vital role in controlling homeostatic arterial pressure.

Local RASs play a role in proliferation, angiogenesis, and apoptosis in numerous organs (Fyhrquist and Saijonmaa, 2008; Paul et al., 2006). Local production of RAS components occurs in various organs, including in the kidney, heart, brain, and eye (Holappa et al., 2017; Paul et al., 2006; Ribeiro-Oliveira et al., 2008). Recently, many components of the RAS have been found in the eyes of many species (Choudhary et al., 2017; Danser et al., 1994; Igić and Kojović, 1980; Paul et al., 2006; White et al., 2015). The (pro)renin receptor exists in Müller glia and retinal ganglion cells (RGCs). Angiotensinogen is expressed in RPE, Müller glia and ciliary body. ACE has been found in retinal microvessels (Ward et al., 1979). Additionally, ACE2 and chymases are expressed in vitreous fluids and retina (Holappa et al., 2015; Senanayake et al., 2007). Leonardi et al. found that the expression of ACE2 is in low level on the surface of conjunctiva and cornea (Leonardi et al., 2020). The intraocular RAS in retinal cells has been linked to various physiological functions and many blinding disorders, such as age-related macular degeneration (AMD), diabetic retinopathy (DR), and retinopathy of prematurity (ROP) (Choudhary et al., 2017; Moravski et al., 2000).

Both kinds of DR, including nonproliferative and proliferative DR, have increased retinal vessel permeability, developed microaneurysms, etc. In addition, the latter type of DR has concomitant retinal neovascularization that can cause hemorrhage, retinal detachment, and even visual loss (Prokofyeva and Zrenner, 2012). Strain et al. found that activation of the RAS promotes VEGF-mediated angiogenesis and retinal vessel permeability. The change in the RAS is responsible for DR development (Strain and Chaturvedi, 2002).

DR is one of serious complications of diabetes. Yang et al. verified that diabetes and hyperglycemia are independent predictors of SARS infected patients' mortality and morbidity (Yang et al., 2006). Two main reasons have contributed to the susceptibility of diabetics to virus infection. Firstly, diabetic patients have weakened immunity generally. A second reason is increased ACE2 in peripheral circulation. Patients with diabetes are usually administrated with the inhibitors of ACE (ACEis) or the angiotensin II receptor I blockers (ARBs) to treat complications of diabetes. As a result, ACE2 is increased to resisit AngI and AngII elevated by ACEi or ARB treatment (Ferrario et al., 2005). SARS or SARS-CoV-2 invades host cells by binding ACE2, therefore the diabetics have higher risk of virus infection (Fang et al., 2020) and the infected ones might have a poor prognosis. Additionally, Patel et al., found the expression level of circulating ACE2 is higher in man than women (Patel

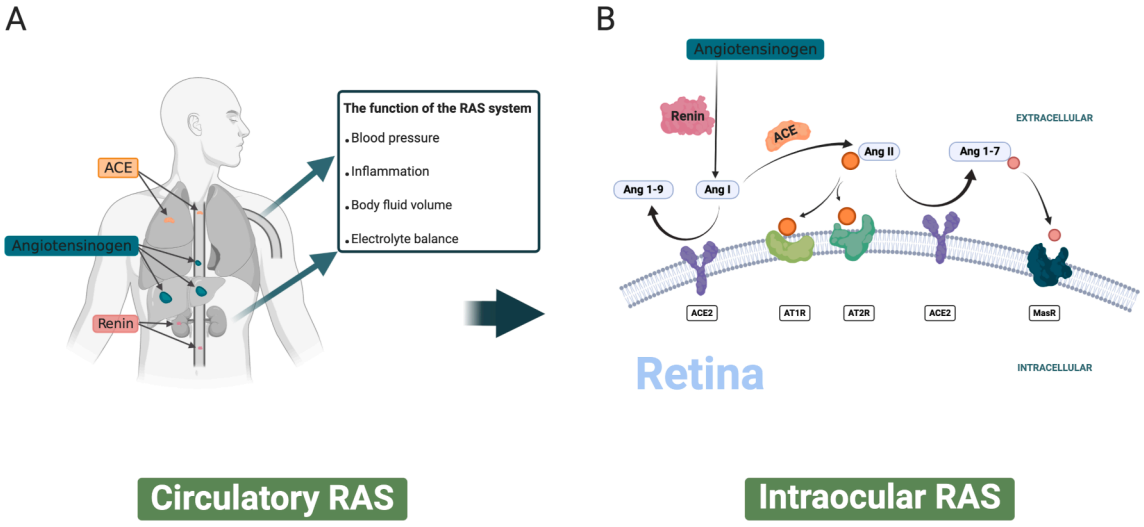

Fig. 3. Circulatory RAS and local RAS. (A) Origins of a part of the RAS components and the function of circulatory RAS. Renin is derived from the kidney, the liver is the main source of angiotensinogen in the circulation, ACE is expressed at high level in the lung. (B) The RAS cascade and the role of ACE2 in the axis of the RAS. Ang I, angiotensin I; Ang II, angiotensin II; Ang 1–7, angiotensin 1–7; Ang 1–9, angiotensin 1–9; ACE2, angiotensin-converting enzyme 2; AT1R, type1 angiotensin II receptor; AT2R, type2 angiotensin II receptor; MasR, MAS receptor.

et al., 2013). A recent study on COVID-19 has shown that male's mortality is 2.4 times higher than female, so gender is an another influencing factor for mortality of COVID-19 infected patients apart from diabetes (Jin et al., 2020). It has been proved that the organ involvement of SARS is related to the expression level of ACE2 in organs (Yang et al., 2010). In 2008, Niu et al., detected ACE2 is expressed in pancreas and participated in glucose homeostasis (Niu et al., 2008). Its expression in the pancreas suggest that SARS can attack islets and result in acute insulin dependent diabetes mellitus and mortality increaed (Yang et al., 2010).

AMD, one type of retinal degenerative diseases, leads to vision loss because of photoreceptor cells and RPE cells dysfunction. RPE cells have type1 angiotensin II (AT1) receptors, and their blockade is beneficial for preventing epithelial cells from damage and suppressing choroidal neovascularization (Nagai et al., 2006). In summary, the inhibition of the RAS is a novel strategy for AMD treatment (Satofuka et al., 2008).

ROP is a childhood disease resulting in blindness. Sarlos et al. uncovered that retinal vasculature development of rat pups is related to the RAS (Downie et al., 2010). The excessive activation of the retinal RAS may contribute to ROP progression.

The RAS is a key player in controlling water and electrolytes balance and the cardiovascular system. In retina, the local RAS plays a critical role in neurovascular function (Bader, 2010; Bader and Ganten, 2008; Paul et al., 2006). The character of the RAS in ocular tissues provides insight to retinal disease therapy. Amelioration of the progression of diabetes-related retinopathy by intraocular delivery of ACE2 via adeno-associated (AAV) can be seen in rodent models. Overexpression of ACE2 significantly reduced diabetes-induced complications such as oxidative stress, $CD45^{+}$ or $CD11b^{+}$ inflammatory cells infiltration, and acellular capillaries formation(Verma et al., 2012). It was indicated that ACE2 is a protective target in DR.

Moreover, as a key stage in the COVID-19, ACE2 is a mediator of SARS-CoV-2 infection. So, it becomes a very popular therapeutic target. Recombinant human ACE2 (rhACE2) is a soluble protein which can bind to SARS-CoV-2 as a decoy to inhibit virus infection ability (Li et al., 2020b). In the meantime, rhACE2 was reported to inhibit SARS-CoV-2 infected engineered human blood vessel organoids and human kidney organoids(Monteil et al., 2020). Thus, as a victim of virus, ACE2 also exerts a promising protective agent against catastrophic results of the SARS-CoV-2.

4. Conclusions

SARS-CoV-2 can be disseminated through tears and aerosols, but more studies on the ocular diseases of SARS-CoV-2 infections and pathogenic mechanisms are urgently needed in the near future. As the epidemic continues, more studies will be carried out, and a better understanding of SARS-CoV-2 will be developed. Both the ACE2 and CD147 (BSG) are particularly highly expressed in human eyes, indicating their potential role of the ocular complications in the affected patients. Meanwhile, it is necessary for health-care workers to wear personal protective equipment to prevent possible infections.

CRediT authorship contribution statement

Yan-Ping Li: Writing - original draft. **Ya Ma:** . **Ningli Wang:** . **Zi-Bing Jin:** Conceptualization, Funding acquisition, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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