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The hypothesis that SARS-CoV-2 affects male reproductive ability by regulating autophagy

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ABSTRACT

The outbreak of CoronaVirus Disease19 (COVID19) in December 2019 posed a serious threat to public safety, and its rapid spread caused a global health emergency. Clinical data show that in addition to respiratory system damage, some male patients with COVID-19 are also accompanied by abnormal renal function and even renal damage. As the main receptor of syndrome coronavirus 2 (SARS-CoV-2), angiotensin converting enzyme 2 (ACE2) is also found to be highly expressed not only in respiratory mucosa and alveolar epithelial cells, but also in renal tubule cells, testicular Leydig cells and seminiferous tubule cells. This suggests that SARS-CoV-2 has the possibility of infecting the male reproductive system, and the recent detection of SARS-CoV-2 in the patient's semen further confirms this theory. In previous studies, it has been found that ACE2 has the ability to regulate autophagy. Not only that, recent studies have also found that SARS-CoV-2 infection can also lead to a reduction in autophagy. All of these associate SARS-CoV-2 with autophagy. Furthermore, autophagy has been shown to have an effect on male reproduction in many studies. Based on these, we propose the hypothesis that SARS-CoV-2 affects male reproductive function by regulating autophagy. This hypothesis may provide a new idea for future treatment of COVID-19 male patients with reproductive function injury, and it can also prompt medical staff and patients to consciously check their reproductive function.

CoronaVirus Disease19 (COVID-19) is a new kind of infectious respiratory disease caused by syndrome coronavirus 2 (SARS-CoV-2). Like severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), SARS-CoV-2 is highly pathogenic and lethal [1]. According to the existing clinical data, some patients not only suffer from respiratory diseases, but also have complications such as acute renal injury and even renal necrosis [2–4], in addition, SARS-CoV-2 was also found in recent semen analysis of male patients [5]. These show that SARS-CoV-2 has a certain infection to the male reproductive system and may cause damage to male fertility. As a receptor protein of SARS-CoV-2, ACE2 not only mediates SARS-CoV-2 infection in host cells, but also is associated with the decrease of autophagy [6]. Moreover, recent studies have found that SARS-CoV-2 infection limits autophagy by interfering with multiple metabolic pathways [7]. The majority of studies have further found that autophagy is often associated with male reproductive ability [8,9]. Therefore, we associate SARS-CoV-2 infection with male reproduction and autophagy, and put forward the hypothesis that SARS-CoV-2 affects male reproductive function by regulating autophagy.

Epidemiological characteristics of COVID-19

The outbreak of COVID-19 in late December 2019 has attracted much attention because of its high infectivity. With the in-depth study of SARS-CoV-2, we found that the virus is more contagious than SARS-CoV and MERS-CoV [10]. In addition, according to survey data, of the 44,672 confirmed cases in mainland China, there were 1023 deaths, with a crude case fatality rate of 2.3% [11], which was lower than that of MERS-CoV (37%) and SARS-CoV (10%) [12]. It can be seen that compared with MERS-CoV and SARS-CoV, SARS-CoV-2 is more prominent in that it is highly contagious and the case fatality rate is relatively low.

1918–1919 influenza pandemic has similar characteristics to COVID-19. The case fatality rate of 1918–1919 influenza pandemic is less than 5%, but due to its wide spread, it has a great impact on society [13]. Besides, 1918–1919 influenza pandemic is accompanied by many complications and sequelae, which eventually cause a lot of irreversible damage to patients. Thus, in the face of this kind of highly contagious but relatively low mortality infectious diseases, we should not only pay attention to the treatment of the disease itself, but also pay attention to its complications and sequelae so as to avoid serious complications or

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sequelae in the course of clinical treatment or after cure.

Injury of non-respiratory system caused by SARS-CoV-2

Lung injury is considered to be the main damage of SARS-CoV-2 infection. The common symptoms of COVID-19 are fever and dry cough, followed by the most typical symptoms-respiratory distress, and severe patients can deteriorate rapidly and die of respiratory failure in a short period of time [14]. Nevertheless, in addition to respiratory diseases, liver biopsies from patients with severe COVID-19 death showed moderate microvascular steatosis, mild lobular and portal vein activity and other liver injury [15]. Moreover, complications such as acute renal injury, acute heart injury and myocarditis were also found in dead patients [2–4], suggesting that SARS-CoV-2 may cause damage to the non-respiratory system.

SARS-CoV-2 is similar to SARS-CoV in that it also uses ACE2 as its receptor [16]. ACE2 was found to be highly expressed not only in alveolar epithelial cells, but also in hepatic endothelial cells, making the liver a target for SARS-CoV. In addition, SARS-CoV may also induce hepatocyte apoptosis, resulting in liver injury [17,18]. In the study of SARS-CoV-2, it may lead to liver injury through direct cytopathic effect induced by virus or immunopathological effect caused by excessive inflammatory response [19]. Not only that, when using drugs to treat COVID-19, some drugs will also cause liver, kidney and other organ damage. All these further prove that SARS-CoV-2 has the ability to infect the non-respiratory system and can cause non-respiratory system damage.

Based on this, we can realize that from a clinical point of view, in addition to actively dealing with the primary disease caused by SARS-CoV-2 infection, we should also pay attention to monitoring the damage of other organs, such as liver, kidney and other non-respiratory organs. At the same time, it is also a kind of education for doctors and patients, reminding them to consciously check the organs of the non-respiratory system from time to time, so as to prevent other functional disorders of the body.

The potential possibility of SARS-CoV-2 affecting male reproductive ability by regulating autophagy

SARS-CoV-2 infects reproduction-related cells through ACE2

COVID-19 patients are not limited to respiratory injuries, but may also be accompanied by non-respiratory diseases. Previous clinical data have shown that in addition to respiratory diseases, some male patients with COVID-19 are accompanied by kidney damage and even renal failure [2,4], which suggest that SARS-CoV-2 may affect male fertility. At the same time, orchitis has been found to cause male reproductive dysfunction as a complication of SARS [20], which also supports this view. Similar to SARS-CoV, SARS-CoV-2, it can also infect host cells through ACE2. It is worth emphasizing that ACE2 exists not only in respiratory system cells such as alveoli and trachea, but also in testicular cells, seminiferous tubule cells, testicular Leydig cells, kidney cells and so on [4,21], indicating that SARS-CoV-2 is likely to invade the reproductive system.

Coronavirus spike protein (S protein) plays an important role in virus infection and pathogenesis。As the key surface localization glycoprotein of the virus, it mediates the invasion of the virus by binding to the host cell surface receptor [1]. The S protein of SARS-CoV-2 has the typical characteristics of coronavirus S protein, and its two subunits S1 and S2 are responsible for receptor recognition and membrane fusion, respectively. S1 subunit can be further divided into N-terminal domain (NTD) and C-terminal domain (CTD), both of which can play a role as ligands binding to receptors [22]. From this we can know that the signal recognition of SARS-CoV-2 in the process of entering host cells may be related to the NTD or CTD of S1 subunit. Wang Q et al. [22] found that for SARS-CoV-2, its S1 subunit CTD and ACE2 were co-located on the surface of host cells, and its NTD had no ability to bind to ACE2. These results suggest that the entry of SARS-CoV-2 into the host cell may be through the binding of its S1 subunit CTD to ACE2, thus invading the host cell.

To sum up, we can know that the existence of ACE2 on the surface of testicular cells provides the possibility for SARS-CoV-2 to infect the reproductive system, and it may induce SARS-CoV-2 to infect a series of reproduction-related cells by combining with the CTD sequence of S protein S1 subunit of SARS-CoV-2, and finally affect male fertility.

SARS-CoV-2 can regulate autophagy

In MERS-CoV-infected cells, autophagy is limited by a virus-induced AKT1-dependent activation of the E3-ligase S-phase kinase-associated protein 2 (SKP2) [23]. Similarly, recent studies have found an increase in the level of autophagy receptor SQSTM1/p62 in SARS-CoV-2-infected cells, suggesting a decrease in autophagy flux. ARS-CoV-2 infection also promotes AKT1/Skp2-dependent autophagy to initiate Beclin-1 (BECN1) degradation [7]. These results suggest that SARS-CoV-2 infection can limit the level of autophagy.

As the main receptor of SARS-CoV-2, angiotensin converting enzyme 2 (ACE2) not only mediates the entry of SARS-CoV-2 into host cells, but also has some relationship with autophagy. In previous studies, it was found that the level of autophagy decreased under the action of ACE2 [6,24], while the overexpression of ACE2 appeared in autophagy deficient cells [25]. The regulation of autophagy by ACE2 also confirms the effect of SARS-CoV-2 on autophagy from the side.

Effect of autophagy on male reproduction

Autophagy is a degradation system in eukaryotic cells, which can not only degrade intracellular aging-damaged organelles and unneeded metabolites to provide cell energy and nutrients, but also play an important role in the elimination of intracellular pathogenic microorganisms. Moreover, more and more studies have proved that autophagy is involved in a wide range of cellular events in the male reproductive system, affecting male reproductive ability. In the process of spermatogenesis, autophagy is very important to ensure the formation of specific structures and the degradation of some components in spermatogenesis [26].

In autophagy-deficientt mouse testis, due to the accumulation of a negative cytoskeleton organization regulator, PDLIM1, the cytoskeleton structure is disordered, the assembly of extracellular specialized (ES) is destroyed, and finally lead to sperm head deformity [26]. Besides, autophagy has also been shown to synthesize testosterone by promoting cholesterol uptake and degradation of intracellular low density lipoprotein, which may be involved in the metabolism and elimination of testosterone, as well as the production of other cholesterol-based hormones [8]. It can be seen that autophagy plays an active role in male spermatogenesis and endocrine process.

We know that SARS-CoV-2 may infect host cells by binding to ACE2 on the surface of reproduction-related cells such as Leydig cells. SARS-CoV-2 itself or ACE2 can cause cell dysfunction by regulating the level of autophagy, and some viral proteins can also directly induce or inhibit the autophagy pathway to achieve virus survival [27]. For example, the dual action of HIV and autophagy pathway increases virus production by using the early stage of autophagy and inhibiting the late stage of autophagy [28,29]. This information links SARS-CoV-2, autophagy and male fertility, leading us to speculate whether SARS-CoV-2 may eventually cause male reproductive disorders by regulating the level of autophagy in male germ cells.

The importance of SARS-CoV-2 affecting male reproduction

In the recent treatment of COVID-19, it was found that male patients had renal dysfunction and even renal injury [2,4]. Furthermore, clinical

data also show that the receptor protein ACE2 that mediates the entry of SARS-CoV-2 into host cells is not only expressed in alveolar cells, but also highly expressed in male renal tubular cells [4,21,30]. All these suggest that SARS-CoV-2 not only causes damage to the respiratory system of patients, but also has a certain impact on the reproductive system of male patients. Therefore, in the process of treating COVID-19 patients, clinicians should not only focus on respiratory diseases, but also pay attention to whether the reproductive function of male patients is normal, especially the fertility evaluation and appropriate intervention of young patients. In addition, when a male patient comes to see a doctor because of symptoms such as fever and reproductive system disorders, doctors need to consider whether the patient is likely to be infected by novel coronavirus and take timely protective measures.

Through education to make medical staff and patients understand the impact of SARS-CoV-2 on male reproduction, doctors can not only use drugs to protect male reproductive system in the process of clinical treatment, so as to reduce the impact of such complications on male reproduction, but also enable patients with fertility needs to consciously carry out fertility physical examination after rehabilitation, so as to avoid irreversible damage to their fertility because of sequelae.

The hypothetical mechanism that SARS-CoV-2 affects male reproductive ability by regulating autophagy can provide a new idea for the treatment of male COVID-19 patients with impaired reproductive ability in the future. Clinicians can treat reproductive function damage in male COVID-19 patients, or sequelae such as reproductive decline after recovery by regulating autophagy.

Conclusion

Through analysis, we systematically linked SARS-CoV-2, autophagy and male fertility, and realized that SARS-CoV-2 has the possibility of infecting male germ cells. SARS-CoV-2 can also cause some damage to male germ cells by regulating the level of autophagy, and finally affect male fertility.

Although the specific mechanism of injury is not clear, our hypothesis provides a new idea, suggesting that we can explain the effect of SARS-CoV-2 on male reproduction from the aspect of autophagy. For male patients with reproductive dysfunction, regulating autophagy may be a good treatment. Not only that, it is also a kind of education for medical staff and male patients, so that they can understand the impact of SARS-CoV-2 on male reproductive function, and enable them to consciously carry out semen and sex hormone tests, so as to prevent such complications or sequelae from damage to the reproductive function of male patients.

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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