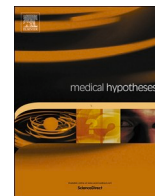




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# Mitochondrial hijacking: A potential mechanism for SARS-CoV-2 to impair female fertility

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## ABSTRACT

As well as causing respiratory lesions, the multi-organ complications caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are also well known. Combined with the epidemiological characteristics of SARS-CoV-2 with high transmission rate and low lethality, the impact of complications caused by its infection on infected individuals seems to be of greater concern. There has been evidence that viral infection is complicated by female reproductive impairment, but the mechanism by which SARS-CoV-2 impairs female fertility is unclear. In addition, RNA-GPS technology has revealed that the SARS-CoV-2 genome resides in mitochondria of the host cells and affects mitochondrial function. Considering the close relationship between mitochondria and female fertility, this paper takes mitochondrial hijacking as an entry point to elucidate the possible mechanisms by which SARS-CoV-2 affects female fertility through the mitochondrial hijacking pathway, which will be important for timely preventive measures and identification of therapeutic targets for infected women with reproductive needs, especially those with asymptomatic infection.

## Introduction

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, a global epidemic, has become a major public health emergency of global concern. As of December 29, 2021, there were more than 281 million confirmed cases and 5 million deaths worldwide [1]. Similar to other coronaviruses, SARS-CoV-2 is highly contagious, but by contrast, novel coronavirus is much less lethal [2]. So, the complications and sequelae caused by SARS-CoV-2 infection seem to have a more profound impact on people. Recent studies have found that at the organ level, SARS-CoV-2 appears to attack the endometrium more easily in women in the menstrual period or in older women [3]. As we all know, for women with reproductive dysfunction, the older they are, the longer the treatment time is, and the less likely they are to be successful. Nowadays fertility decline is a global issue, especially in countries with negative population growth, which will affect the development of the nation. Therefore, it is important to study how SARS-CoV-2 affects female fertility and this means that we will have a better chance of saving the fertility of infected women who have reproductive needs.

## The hypothesis

Previous evidence has shown that SARS-CoV-2 infection affects female pregnancy outcomes, SARS-CoV-2 resides and destroys mitochondria, and the function of mitochondria affects female fertility. Based on these, we assume that after SARS-CoV-2 infection in female, SARS-CoV-2 can damage cell mitochondria directly or indirectly, thereby further impact on female reproductive function and pregnancy outcome (Fig. 1).

## Effect of SARA-CoV-2 on female fertility

Although there are few related reports, the occurrence of SARS-CoV-2 detected in placenta tissue and vaginal secretions, as well as adverse pregnancy events such as premature birth and low birth weight, still suggest that SARS-CoV-2 infection will affect female fertility [4–6]. This may be because the expression of receptor angiotensin converting enzyme 2 (ACE2) and transmembrane protease serine 2 (TMPRSS2) which are necessary for SARS-CoV-2 infection is abundant in female ovarian tissues and endometrium, which makes the female reproductive system become the target of virus attack [4,7]. In addition, the

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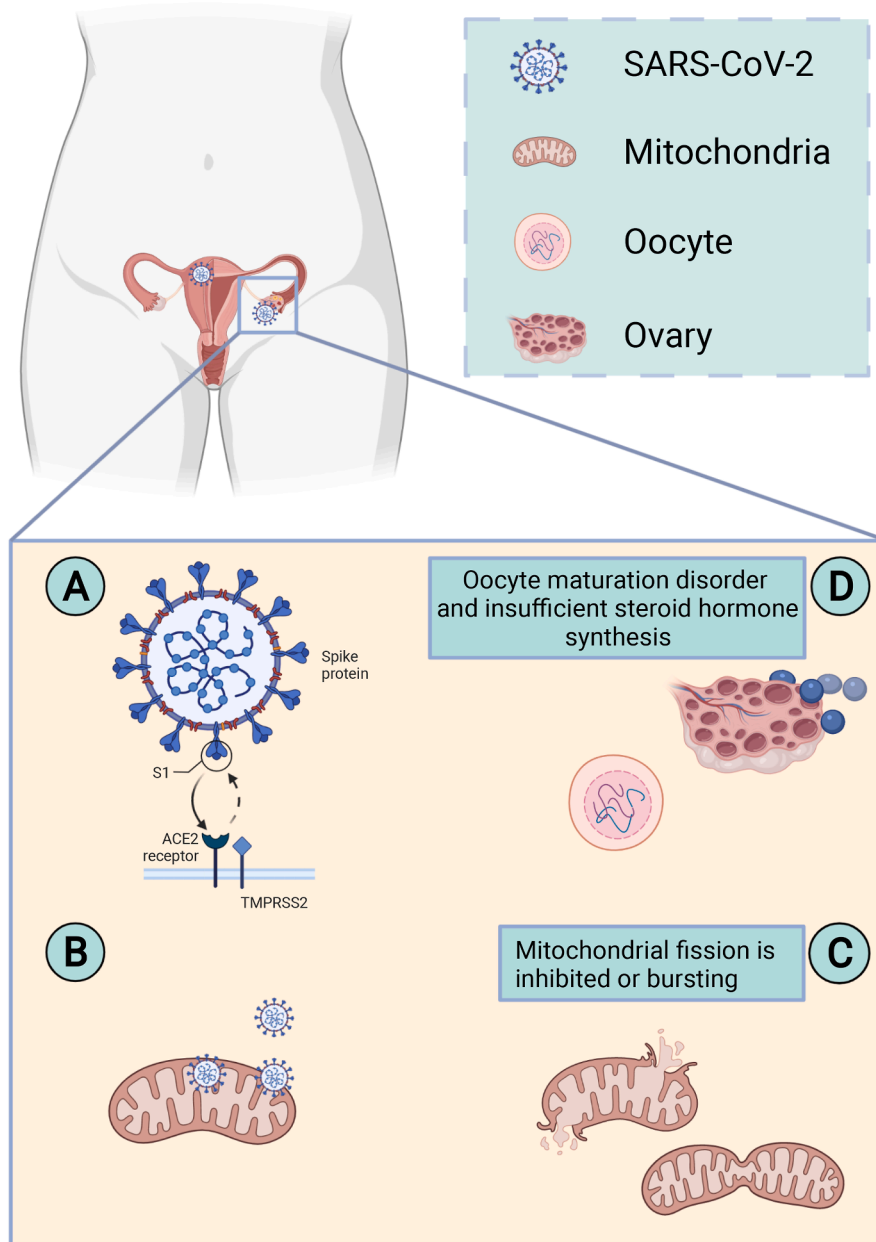
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expression of 17  $\beta$ -estradiol can increase the expression of SARS-CoV-2 receptor ACE2 [8]. And the increased estradiol (E2) during pregnancy and ovulation means that women may be more susceptible to SARS-CoV-2 attack during pregnancy and menstrual secretion, which is consistent with Abhari's findings [3].

In addition to the direct adverse pregnancy outcome caused by infection and damage of female reproductive system, SARS-CoV-2 will indirectly influence female reproductive outcome due to the radical changes of obstetrics and gynecology management under emergency caused by the COVID-19 pandemic. Although the test of SARS-CoV-2 in pregnant women near childbirth can help them to start clinical improvement as soon as possible and reduce the occurrence of adverse pregnancy outcomes [9], some pregnant women or women with reproductive needs are afraid of being infected with SARS-CoV-2 and unwilling to go to hospital to seek medical treatment, which will also

affect the detection rate of virus infection. In addition, due to the priority and inclination changes of medical resources during the COVID-19 pandemic, the screening of gynecological diseases was severely reduced or suspended, which makes the missed diagnosis rate of cervical cancer and other diseases increased significantly [10]. Patients with early pathological changes failed to be treated timely and thereby the condition aggravated. These changes in the management of obstetrics and gynecology have increased the missed diagnosis and the delay of patients' condition, which may endanger female fertility or even lives to varying degrees.



**Fig. 1.** Diagram of the hypothesis. (A) SARS-CoV-2 infects the female reproductive system through the combination of its S protein and ACE2. (B) SARS-CoV-2 locates and hijacks mitochondria after entering cells. (C) Mitochondrial dysfunction with bursting or fission decreased. (D) Oocyte maturation disorder and decreased synthesis of female reproductive hormone.

## SARA-CoV-2 hijacked the host mitochondria

### *SARS-CoV-2 infects host cells*

SARS-CoV-2 is a positive single-stranded RNA coronavirus with envelope [11]. The virus relies on the spike (S) protein on its envelope surface to mediate recognition and fusion between the virus and the host cell, thus causing infection [12]. The S protein of SARS-CoV-2 can be cleaved into S1 and S2 subunits by the action of host proteases, which are responsible for receptor binding and membrane fusion, respectively [13,14].

In fact, the S protein alone is not sufficient to cause infection, as SARS-CoV-2 infection of cells also requires the presence of host cell-expressed ACE2 and TMPRSS2 [15]. It has been recently reported that during SARS-CoV-2 infection, ACE2 can act as an entry point for viral infection and bind to the receptor binding domain (RBD) of the S1 subunit of the S protein to co-localize on the host cell surface, allowing SARS-CoV-2 to attach to the host cell surface [15–17]. TMPRSS2 is the promoter of virus entry into host cells, which cleaves at S1/S2 and S2' sites of S protein and activates the S2 subunit, which in turn drives the fusion of SARS-CoV-2 with the host cell membrane, thus mediating the entry of SARS-CoV-2 into the cell [15,18]. The infection process can be briefly summarized as follows: SARS-CoV-2 relies on its S protein and uses ACE2 on the host cell surface as an entry point, activates the S protein via TMPRSS2, and finally enters the cell. This result provides a direction to explore new targets of SARS-CoV-2 infection, which is important for the prevention of viral infection.

### *SARS-CoV-2 resides in mitochondria*

Mitochondria are not only important metabolic centers in cells, but also play a vital role in anti-viral defense responses. Recent studies found that cells infected with SARS-CoV-2 showed a significant increase in average mitochondrial size and impaired respiratory function [19,20]. In view of this, studying the relationship between SARS-CoV-2 and mitochondria will provide us with important information to study the mechanism of SARS-CoV-2 controlling hosts. Recent studies have shown that SARS-CoV-2 entering host cells targets mitochondria and exhibits a strong mitochondrial-resident signal [21,22]. Wu et al. [21] using RNA-GPS technology to predict the subcellular residency of the SARS-CoV-2 genome, found that SARS-CoV-2 exhibited a strong mitochondrial matrix residency signal, which appeared to be driven by the 5' leading sequence and 3' non-coding region of the SARS-CoV-2 genome driven. This general tendency of the SARS-CoV-2 genome to reside in mitochondria led us to note that the virus may cause host cell damage by hijacking host mitochondria.

However, in addition to the viral genome, we also found that the protein encoded by SARS-CoV-2 can also be localized to the host mitochondria. Among the peptides encoded by SARS-CoV-2 Open Reading Frames (ORFs), ORF-9b was found to interact with the mitochondrial outer membrane translocase 70 (TOM70) and co-localize on the mitochondrial surface [23,24]. In addition, SARS-CoV-2 ORF-9c is also known to interact with mitochondrial electron transport chain components [22,23]. In conclusion, both the physical localization of SARS-CoV-2 RNA to host cell mitochondria and the interaction between viral proteins and mitochondrial proteins suggest that SARS-CoV-2 has the ability to reside in host cell mitochondria. This close association between the virus and host mitochondria will provide clues to further explore the mechanism of damage after SARS-CoV-2 invades host cells.

### *SARS-CoV-2 affects host mitochondrial function*

After SARS-CoV-2 infection, host cell mitochondrial function is often impaired due to integration of the viral genome, activation of the inflammatory response, activation of the immune defense response, and the action of specific viral proteins [23,25,26]. Mitochondrial damage

caused by SARS-CoV-2 often manifests as impaired mitochondrial dynamics and energy metabolism. In Holder's research [27], it was found that mitochondrial fission was inhibited in patients with COVID-19, allowing fusion to be promoted in comparison, which in turn caused mitochondrial lengthening, which corresponds to the increased mitochondrial volume of SARS-CoV-2 infected cells found by Flynn under electron microscopy [20]. This altered mitochondrial dynamics prevents the timely removal of aged or damaged mitochondria by mitochondrial fission, resulting in the accumulation of dysfunctional mitochondria that eventually causes cellular dysfunction [28,29]. In addition, several recent systematic studies on SARS-CoV-2-infected individuals have also reported that mitochondria in virus-infected individuals show different levels of reduced coenzyme Q10 levels and impaired mitochondrial electron transport chain complexes I, III, and IV compared to healthy individuals, resulting in dysfunctional mitochondrial metabolism [30,31]. Although the exact mechanism by which SARS-CoV-2 virus affects mitochondrial dynamics and metabolism is not yet known, we must be aware that SARS-CoV-2 infection will be extremely disruptive to cellular bioenergetics.

Generally speaking, coronavirus infection can not only cause a strong inflammatory reaction, but also cause a "cytokine storm" due to over-activation of the immune response, which can cause serious damage to tissues and cells throughout the whole body [32]. In-depth studies revealed that SARS-CoV-2 can inhibit the antiviral response of host cells by hijacking mitochondria, while immune escape occurs, further causing virus replication within the host cells [33–35]. Jiang et al. [33] found through experiments that, similar to severe acute respiratory syndrome coronavirus (SARS-CoV), SARS-CoV-2 ORF-9b can be co-located with the outer membrane of mitochondria of host cells through interaction with TOM70. As a receptor for mitochondrial antiviral signaling (MAVS) protein, TOM70 binds to heat shock protein 90 (HSP90) after binding to MAVS and initiates recruitment of interferon regulatory factor 3 (IRF3), which in turn promotes transcription of type I interferon [34]. SARS-CoV-2 ORF-9b binds tightly to TOM70 due to its high affinity for TOM70, thus inhibiting the production of type I interferon and reducing the antiviral defense response of mitochondria. SARS-CoV-2 reduces the role of mitochondria in the innate immune response through the interaction of viral proteins with mitochondria, making possible persistent viral infection, and promotes viral replication and packaging within the host cell, further causing cellular damage.

In fact, SARS-CoV-2 has an indirect effect on mitochondrial function through ACE2 since it binds to ACE2 and infects host cells [24]. As the mechanism of SARS-CoV-2 infection has been studied in depth, more and more clues suggest that SARS-CoV-2 can cause cell damage by downregulating ACE2 and thus inhibiting mitochondrial function [36,37]. This may be because, on the one hand, the SARS-CoV-2 S protein causes ACE2 destabilization by down regulating AMP-activated protein kinase (AMPK) and up regulating mouse double minute 2 (MDM2), resulting in loss of ACE2 [36]. On the other hand, the loss of ACE2 allows for a decrease in the cleavage of angiotensin II (Ang II) into angiotensin 1–7 (Ang1-7) [38]. The increased Ang II allows increased production of reactive oxygen species (ROS), causing mitochondrial fragmentation as well as loss of mitochondrial membrane potential [38].

Whether by direct action of viral proteins or indirect damage through down regulation of ACE2, these findings suggest that SARS-CoV-2 can cause host cell injury by hijacking mitochondria. Although further studies are needed on the mechanism by which SARS-CoV-2 hijacks mitochondria to cause host pathogenesis, it may serve as a key target to help limit further disease progression as well as the exploration of etiology.

## Effect of mitochondria on female fertility

### *Mitochondrial function affects oocyte quality*

As the site of intracellular energy synthesis, storage and supply,

mitochondria are extremely abundant in oocytes [39]. Oocytes are highly energy-dependent, and a series of complicated changes before ovulation and fertilization usually require the use of adenosine triphosphate (ATP) provided by mitochondrial oxidative phosphorylation (OXPHOS) [40]. Therefore, we found that mitochondria play an important role in affecting the quality of oocytes and regulating female fertility. After deeply understanding the mechanism of oocyte's energy utilization, we know that oocyte's ability to absorb and metabolize glucose is actually weak, and its energy production depends on an energy metabolism pathway which uses pyruvate as a substrate and produces ATP through mitochondrial oxidative phosphorylation [41]. However, only relying on its own glycolysis is not enough to meet the needs of metabolic substrates. Oocytes also need glycolysis from follicular cells located in cumulus, and provide metabolic support for oocytes through their special gap junctions [40–43]. Once the function of mitochondria is damaged, the normal development of oocytes will be seriously affected.

Oocyte maturation is a critical step in the formation of fertilizable ovum and mitochondria play an integral role in this process by participating in oocyte metabolism, spindle formation and segregation of homologous chromosomes [39,44,45]. On the one hand, mitochondria can be dynamically distributed around microtubules to provide ATP for spindle formation [44,46], and the absence of mitochondria-derived ATP often predicts oocyte spindle disintegration [45]. On the other hand, mitochondria clustered around the spindle not only produce ATP to satisfy the maintenance of spindle integrity and spindle motility, but mitochondria can also exert counteracting forces on the spindle due to their directional migration and asymmetric distribution, further driving spindle motility [39,44]. Therefore, mitochondrial damage is often indicative of oocyte dysplasia.

#### *Mitochondrial function affects granulosa cell steroid hormone levels*

Besides the influence of oocyte quality, female fertility is largely related to various hormone levels. E2 promotes oocyte cytoplasmic maturation [47], while progesterone (P4) plays an important role in restoring the meiotic capacity of oocytes and embryonic development [48]. These steroid hormones affect the maturation of oocyte, and their levels is an index of ovarian reserve capacity, reflecting female fertility. Mitochondria are not only the center of energy metabolism in granulosa cells, but also important centers of steroid synthesis. It plays an important role as a bridge between granulosa cells and oocytes, and affects the quality of oocytes. [49]. A recent report [50] on the role of mitochondria in female fertility stated that cholesterol can be converted to pregnenolone by cytochrome P450<sub>sc</sub> (CYP11A1) in the mitochondrial inner membrane, which in turn promotes progesterone synthesis. When mitochondrial function is disturbed, the ability of granulosa cells to synthesize steroid hormones is often inhibited, which often predicts a poor pregnancy outcome.

#### **The possibility of SARS-CoV-2 affecting female fertility by hijacking mitochondria**

Although the highly contagious characteristics of SARS-CoV-2 are frightening, the multiple organ system complications caused by this virus are actually much more serious than those of COVID-19. Complications of nervous system, digestive system, kidney and heart are constantly reported in various diseases of SARS-CoV-2 [51,52], which is inextricably linked to the non-respiratory transmission of SARS-CoV-2 [52] and the high expression of ACE2 in other tissues and organs [53–55].

The exact mechanism by which SARS-CoV-2 causes these complications is not clear, and neuromodulation, immune response, and inflammatory response are all potential possibilities. However, as a mitochondrial resident virus, the influence of SARS-CoV-2 on mitochondrial function seems to be more closely related to complications. In

a study by Stefano et al. [26], it was found that selective neuronal mitochondrial functional impairment induced by SARS-CoV-2 infection affects cognitive performance. Kaundal [56] also found that mitochondrial dysfunction correlated with neurological symptoms in patients with COVID-19. This is not a coincidence, but suggests a link between the mitochondrial hijacking effect of SARS-CoV-2 and complications in infected patients.

Whether the porcine parvovirus (PPV) infection can damage mitochondria [57] and thus damage placental in animal studies or the adverse pregnancy outcome due to mitochondrial dysfunction in pregnant women infected with human immunodeficiency virus (HIV) [58,59], both have shown that viral infection can impair female fertility by inducing changes in mitochondrial function. In view of this, could the mitochondrial-localized virus SARS-CoV-2 also affect female fertility through its mitochondrial damage effects? Unlike males, due to nature selection, the defective and harmful mitochondria in females can be eliminated during ovum maturation. However, the mitochondrial fusion/fission balance in the cells infected with SARS-CoV-2 was broken, making the aging and damaged mitochondria unable to be cleared through mitochondrial fission in time [27], which meant that it was completely possible for the virus to affect female fertility by hijacking mitochondria.

We found that the probability of adverse pregnancy outcomes such as premature delivery, pre-eclampsia and intrauterine hypoxia increased after the infection of SARS-CoV-2 in pregnant women, so can we use our hypothesis to explain these results? SARS-CoV-2 can infect the female reproductive system by recognizing ACE2. Especially, the increase of E2 secretion during ovulation and pregnancy promotes the expression of ACE2, and thereby promotes the virus infection. Viruses entering the host cells further hijack mitochondria by recognizing its specific proteins and integrating genome. Mitochondrial defects cause trophoblast differentiation and maternal vascular dysfunction, which further leads to placental hypoxia and dysfunction [60], and finally leads to pre-eclampsia, premature delivery, intrauterine hypoxia and growth restriction of newborns. For non-pregnant women, mitochondrial dysfunction can also lead to inhibited oocyte maturation, insufficient steroid hormone synthesis, and ultimately affect their reproductive function.

#### **Summary**

Although the mechanisms of how SARS-CoV-2 affects female fertility are not yet clear, it is important to understand that the impairment of female fertility by SARS-CoV-2 may be a long-term and consequential effect. For those infected women with fertility needs, especially those with asymptomatic infection, only early knowledge of SARS-CoV-2 damage to the female reproductive system may allow timely means to prevent or treat it and thus avoid adverse fertility outcomes. We use mitochondrial hijacking as a bridge to explore the mechanisms by which SARS-CoV-2 impairs female fertility, which will provide important information for the exploration of related etiology and limit further disease progression.

#### **Consent statement/Ethical approval**

Not required.

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## 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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The authors consider that the first two authors should be regarded as joint First Authors. Fig. 1 was created with BioRender.com and obtained the publishing license.

## References

- [1] World Health Organization, WHO Coronavirus (COVID-19) Dashboard. <https://covid19.who.int/>, 2021 (accessed January 1, 2022).
- [2] Petersen E, Koopmans M, Go U, Hamer D, Petrosillo N, Castelli F, et al. The Lancet. Infect Dis 2020;20(9):e238–44. [https://doi.org/10.1016/s1473-3099\(20\)30484-9](https://doi.org/10.1016/s1473-3099(20)30484-9).
- [3] Abhari S, Kawwass J. Endometrial susceptibility to SARS CoV-2: explained by gene expression across the menstrual cycle? Fertil Steril 2020;114(2):255–6. <https://doi.org/10.1016/j.fertnstert.2020.06.046>.
- [4] Morelli F, Meirelles L, de Souza M, Mari N, Mesquita C, Dartibale C, et al. COVID-19 Infection in the Human Reproductive Tract of Men and Nonpregnant Women. Am J Tropical Med Hygiene 2021. <https://doi.org/10.4269/ajtmh.20-1098>.
- [5] Zaigham M, Holmberg A, Karlberg M, Lindsjö O, Jokubkiene L, Sandblom J, et al. Intrauterine vertical SARS-CoV-2 infection: a case confirming transplacental transmission followed by divergence of the viral genome. BJOG Int J Obstetr Gynaecol 2021. <https://doi.org/10.1111/1471-0528.16682>.
- [6] Dubej P, Reddy S, Manuel S, Dwivedi A. Maternal and neonatal characteristics and outcomes among COVID-19 infected women: An updated systematic review and meta-analysis. Eur J Obstetr Gynecol Reprod Biol 2020;252:490–501. <https://doi.org/10.1016/j.ejogrb.2020.07.034>.
- [7] Jing Y, Run-Qian L, Hao-Ran W, Hao-Ran C, Ya-Bin L, Yang G, et al. Potential influence of COVID-19/ACE2 on the female reproductive system. Mol Hum Reprod 2020;26(6):367–73. <https://doi.org/10.1093/molehr/gaaa030>.
- [8] Chaudhry F, Lavandero S, Xie X, Sabharwal B, Zheng Y-Y, Correa A, et al. Manipulation of ACE2 expression in COVID-19. Open Heart 2020;7(2):e001424. <https://doi.org/10.1136/openhrt-2020-001424>.
- [9] Carugno J, Di Spiezio Sardo A, Alonso L, Haimovich S, Campo R, De Angelis C, et al. COVID-19 Pandemic. Impact on Hysteroscopic Procedures: A Consensus Statement from the Global Congress of Hysteroscopy Scientific Committee. J Minim Invasive Gynecol 2020;27(5):988–92. <https://doi.org/10.1016/j.jmig.2020.04.023>.
- [10] Scioscia M, Noventa M, Palomba S, Laganà AS. Effect of the COVID-19 pandemic on oncology screenings: it is time to change course. BJOG 2021;128(13):2213–4. <https://doi.org/10.1111/bjog.v128.1310.1111/1471-0528.16857>.
- [11] Synowiec A, Szczepański A, Barreto-Duran E, Lie L, Pyrc K. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection. Clin Microbiol Rev 2021;34(2). <https://doi.org/10.1128/cmr.00133-20>.
- [12] Casalino L, Gaieb Z, Goldsmith JA, Hjorth CK, Dommer AC, Harbison AM, et al. Beyond Shielding: The Roles of Glycans in the SARS-CoV-2 Spike Protein. ACS Cent Sci 2020;6(10):1722–34. <https://doi.org/10.1021/acscentsci.0c01056>.
- [13] Raghuvamsi P, Tulsian N, Samsudin F, Qian X, Purushotorman K, Yue G, et al. SARS-CoV-2 S protein:ACE2 interaction reveals novel allosteric targets. eLife 2021; 10. <https://doi.org/10.7554/eLife.63646>.
- [14] Arafah A, Ali S, Yattoo A, Ali M, Rehman M. S1 Subunit and Host Proteases as Potential Therapeutic Avenues for the Treatment of COVID-19. Arch Med Res 2020;51(7):718–20. <https://doi.org/10.1016/j.arcmed.2020.05.013>.
- [15] Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell 2020;181(2):271–280.e8. <https://doi.org/10.1016/j.cell.2020.02.052>.
- [16] Wang Q, Zhang Y, Wu L, Niu S, Song C, Zhang Z, et al. Structural and Functional Basis of SARS-CoV-2 Entry by Using Human ACE2. Cell 2020;181(4):894–904.e9. <https://doi.org/10.1016/j.cell.2020.03.045>.
- [17] Benton D, Wrobel A, Xu P, Roustan C, Martin S, Rosenthal P, et al. Receptor binding and priming of the spike protein of SARS-CoV-2 for membrane fusion. Nature 2020;588(7837):327–30. <https://doi.org/10.1038/s41586-020-2772-0>.
- [18] Seyedpour S, Khodaei B, Loghman AH, Seyedpour N, Kisomi F, Balibeglo M, et al. Targeted therapy strategies against SARS-CoV-2 cell entry mechanisms: A systematic review of in vitro and in vivo studies. J Cell Physiol 2021;236(4): 2364–92. <https://doi.org/10.1002/jcp.v236.410.1002/jcp.30032>.
- [19] Ajaz S, McPhail MJ, Singh KK, Mujib S, Trovato FM, Napoli S, et al. Mitochondrial metabolic manipulation by SARS-CoV-2 in peripheral blood mononuclear cells of patients with COVID-19. Am J Physiol Cell Physiol 2021;320(1):C57–65. <https://doi.org/10.1152/ajpcell.00426.2020>.
- [20] Flynn RA, Belk JA, Qi Y, Yasumoto Y, Wei J, Alfajaro MM, et al. Discovery and functional interrogation of SARS-CoV-2 RNA-host protein interactions. Cell 2021; 184(9):2394–2411.e16. <https://doi.org/10.1016/j.cell.2021.03.012>.
- [21] Wu K, Fazal F, Parker K, Zou J, Chang H. RNA-GPS Predicts SARS-CoV-2 RNA Residency to Host Mitochondria and Nucleolus. Cell Syst 2020;11(1):102–108. e103. <https://doi.org/10.1016/j.cels.2020.06.008>.
- [22] Gatti P, Ilamathi H, Todkar K, Germain M. Mitochondria Targeted Viral Replication and Survival Strategies-Prospective on SARS-CoV-2. Front Pharmacol 2020;11. <https://doi.org/10.3389/fphar.2020.578599>.
- [23] Miller B, Silverstein A, Flores M, Cao K, Kumagai H, Mehta HH, et al. Host mitochondrial transcriptome response to SARS-CoV-2 in multiple cell models and clinical samples. Sci Rep 2021;11(1). <https://doi.org/10.1038/s41598-020-79552-z>.
- [24] Singh K, Chaubey G, Chen J, Suravajhala P. Decoding SARS-CoV-2 hijacking of host mitochondria in COVID-19 pathogenesis. Am J Physiol Cell Physiol 2020;319(2):C258–67. <https://doi.org/10.1152/ajpcell.00224.2020>.
- [25] Chang R, Mamun A, Dominic A, Le N. SARS-CoV-2 Mediated Endothelial Dysfunction: The Potential Role of Chronic Oxidative Stress. Front Physiol 2020; 11. <https://doi.org/10.3389/fphys.2020.605908>.
- [26] Stefano G, Ptacek R, Ptackova H, Martin A, Kream R. Selective Neuronal Mitochondrial Targeting in SARS-CoV-2 Infection Affects Cognitive Processes to Induce 'Brain Fog' and Results in Behavioral Changes that Favor Viral Survival. Med Sci Monitor Int Med J Experimental Clin Res 2021;27. <https://doi.org/10.12659/msm.930886>.
- [27] Holder K, Reddy PH. The COVID-19 Effect on the Immune System and Mitochondrial Dynamics in Diabetes, Obesity, and Dementia. Neurosci Rev J Bring Neurobiol Neurol Psychiatry 2021;27(4):331–9. <https://doi.org/10.1177/1073858420960443>.
- [28] Houzelle A, Jørgensen JA, Schaart G, Daemen S, van Polanen N, Fealy CE, et al. Human skeletal muscle mitochondrial dynamics in relation to oxidative capacity and insulin sensitivity. Diabetologia 2021;64(2):424–36. <https://doi.org/10.1007/s00125-020-05335-w>.
- [29] Kaufman B, Li C, Soleimanpour S. Mitochondrial regulation of  $\beta$ -cell function: maintaining the momentum for insulin release. Mol Aspects Med 2015;42:91–104. <https://doi.org/10.1016/j.mam.2015.01.004>.
- [30] Gibellini L, De Biasi S, Paolini A, Borella R, Boraldi F, Mattioli M, et al. Altered bioenergetics and mitochondrial dysfunction of monocytes in patients with COVID-19 pneumonia. EMBO Mol Med 2020;12(12). <https://doi.org/10.15252/emmm.202013001>.
- [31] Gvozđjakova A, Klauco F, Kucharska J, Sumbalova Z. Is mitochondrial bioenergetics and coenzyme Q10 the target of a virus causing COVID-19? Bratisl Lek Listy 2020;121(11):775–8. [https://doi.org/10.4149/bll\\_2020\\_126](https://doi.org/10.4149/bll_2020_126).
- [32] Chau AS, Weber AG, Maria NI, Narain S, Liu A, Hajizadeh N, et al. The Longitudinal Immune Response to Coronavirus Disease 2019: Chasing the Cytokine Storm. Arthritis Rheumatol (Hoboken, N.J.) 2021;73(1):23–35. <https://doi.org/10.1002/art.v73.110.1002/art.41526>.
- [33] Jiang H-W, Zhang H-N, Meng Q-F, Xie J, Li Y, Chen H, et al. SARS-CoV-2 Orf9b suppresses type I interferon responses by targeting TOM70. Cell Mol Immunol 2020;17(9):998–1000. <https://doi.org/10.1038/s41423-020-0514-8>.
- [34] Kreimendahl S, Rassow J. The Mitochondrial Outer Membrane Protein Tom70-Mediator in Protein Traffic, Membrane Contact Sites and Innate Immunity. Int J Mol Sci 2020;21(19). <https://doi.org/10.3390/ijms21197262>.
- [35] Dominguez Andres A, Feng Y, Campos A, Yin J, Yang C, James B, et al. SARS-CoV-2 ORF9c Is a Membrane-Associated Protein that Suppresses Antiviral Responses in Cells. In: bioRxiv : Preprint Server Biol; 2020. <https://doi.org/10.1101/2020.08.18.256776>.
- [36] Lei Y, Zhang J, Schiavon C, He M, Chen L, Shen H, et al. SARS-CoV-2 Spike Protein Impairs Endothelial Function via Downregulation of ACE2. In: bioRxiv : Preprint Server Biol; 2020. <https://doi.org/10.1101/2020.12.04.409144>.
- [37] Du F, Liu B, Zhang S. COVID-19: the role of excessive cytokine release and potential ACE2 down-regulation in promoting hypercoagulable state associated with severe illness. J Thromb Thrombolysis 2021;51(2):313–29. <https://doi.org/10.1007/s11239-020-02224-2>.
- [38] Wang J, Chen S, Bihl J. Exosome-Mediated Transfer of ACE2 (Angiotensin-Converting Enzyme 2) from Endothelial Progenitor Cells Promotes Survival and Function of Endothelial Cell. Oxidative Med Cell Longevity 2020;2020:4213541. <https://doi.org/10.1155/2020/4213541>.
- [39] Wakai T, Harada Y, Miyado K, Kono T. Mitochondrial dynamics controlled by mitofusins define organelle positioning and movement during mouse oocyte maturation. Mol Hum Reprod 2014;20(11):1090–100. <https://doi.org/10.1093/molehr/gau064>.
- [40] Cecchino G, Seli E, Alves da Motta E, Garcia-Velasco J. The role of mitochondrial activity in female fertility and assisted reproductive technologies: overview and current insights. Reprod Biomed Online 2018;36(6):686–97. <https://doi.org/10.1016/j.rbmo.2018.02.007>.
- [41] Richani D, Dunning K, Thompson J, Gilchrist R. Metabolic co-dependence of the oocyte and cumulus cells: essential role in determining oocyte developmental competence. Hum Reprod Update 2021;27(1):27–47. <https://doi.org/10.1093/humupd/dmaa043>.
- [42] Richani D, Gilchrist R. The epidermal growth factor network: role in oocyte growth, maturation and developmental competence. Human Reprod Update 2018; 24(1):1–14. <https://doi.org/10.1093/humupd/dmx029>.
- [43] Johnson M, Freeman E, Gardner D, Hunt P. Oxidative metabolism of pyruvate is required for meiotic maturation of murine oocytes in vivo. Biol Reprod 2007;77(1): 2–8. <https://doi.org/10.1095/biolreprod.106.059899>.
- [44] Duan X, Li Y, Yi K, Guo F, Wang HaiYang, Wu P-H, et al. Dynamic organelle distribution initiates actin-based spindle migration in mouse oocytes. Nat Commun 2020;11(1). <https://doi.org/10.1038/s41467-019-14068-3>.
- [45] Zhang X, Wu X, Lu S, Guo Y, Ma X. Deficit of mitochondria-derived ATP during oxidative stress impairs mouse MII oocyte spindles. Cell Res 2006;16(10):841–50. <https://doi.org/10.1038/sj.cr.7310095>.

- [46] Li R, Albertini D. The road to maturation: somatic cell interaction and self-organization of the mammalian oocyte. *Nat Rev Mol Cell Biol* 2013;14(3):141–52. <https://doi.org/10.1038/nrm3531>.
- [47] Tesarik J, Mendoza C. Direct non-genomic effects of follicular steroids on maturing human oocytes: oestrogen versus androgen antagonism. *Hum Reprod Update* 1997; 3(2):95–100. <https://doi.org/10.1093/humupd/3.2.95>.
- [48] Nagy B, Poto L, Farkas N, Koppán M, Varnagy A, Kovacs K, et al. Follicular fluid progesterone concentration is associated with fertilization outcome after IVF: a systematic review and meta-analysis. *Reprod Biomed Online* 2019;38(6):871–82. <https://doi.org/10.1016/j.rbmo.2018.12.045>.
- [49] Lin P, Lin L, Li C, Kao P, Tsai H, Chen S, et al. CREB1 Combining Bioinformatics and Experiments to Identify as a Key Regulator in Senescent Granulosa Cells 2020;10. <https://doi.org/10.3390/diagnostics10050295>.
- [50] Sreerangaraja Urs D, Wu W, Komrskova K, Postlerova P, Lin Y, Tzeng C, et al. Mitochondrial Function in Modulating Human Granulosa Cell Steroidogenesis and Female Fertility. *Int J Mol Sci* 2020;21(10). <https://doi.org/10.3390/ijms21103592>.
- [51] Al-Harathi L, Campbell E, Schneider J, Bennett D. What HIV in the Brain Can Teach Us About SARS-CoV-2 Neurological Complications? *AIDS Res Hum Retroviruses* 2021;37(4):255–65. <https://doi.org/10.1089/aid.2020.0161>.
- [52] Maghool F, Valiani A, Safari T, Emami M, Mohammadzadeh S. Gastrointestinal and renal complications in SARS-CoV-2-infected patients: Role of immune system. *Scand J Immunol* 2021;93(4):e12999. <https://doi.org/10.1111/sji.12999>.
- [53] Aleksova A, Gagno G, Sinagra G, Beltrami A, Janjusevic M, Ippolito G, et al. Effects of SARS-CoV-2 on Cardiovascular System: The Dual Role of Angiotensin-Converting Enzyme 2 (ACE2) as the Virus Receptor and Homeostasis Regulator-Review. *Int J Mol Sci* 2021;22(9). <https://doi.org/10.3390/ijms22094526>.
- [54] Chadchan S, Popli P, Maurya V, Kommagani R. The SARS-CoV-2 receptor, angiotensin-converting enzyme 2, is required for human endometrial stromal cell decidualization†. *Biol Reprod* 2021;104(2):336–43. <https://doi.org/10.1093/biolre/ioaa211>.
- [55] Ding Q, Shults N, Gychka S, Harris B, Suzuki Y. Protein Expression of Angiotensin-Converting Enzyme 2 (ACE2) is Upregulated in Brains with Alzheimer's Disease. *Int J Mol Sci* 2021;22(4). <https://doi.org/10.3390/ijms22041687>.
- [56] Kaundal RK, Kalvala AK, Kumar A. Neurological Implications of COVID-19: Role of Redox Imbalance and Mitochondrial Dysfunction. *Mol Neurobiol* 2021;58(9): 4575–87. <https://doi.org/10.1007/s12035-021-02412-y>.
- [57] Fan Zhang, Liang Li, Wang Huo, et al. Porcine Parvovirus Infection Causes Pig Placenta Tissue Damage Involving Nonstructural Protein 1 (NS1)-Induced Intrinsic ROS/Mitochondria-Mediated Apoptosis. *Viruses* 2019;11(4):389. <https://doi.org/10.3390/v11040389>.
- [58] Guitart-Mampel M, Hernandez A, Moren C, Catalan-Garcia M, Tobias E, Gonzalez-Casacuberta I, et al. Imbalance in mitochondrial dynamics and apoptosis in pregnancies among HIV-infected women on HAART with obstetric complications. *J Antimicrob Chemotherapy* 2017;72(9):2578–86. <https://doi.org/10.1093/jac/dkx187>.
- [59] Morén C, Noguera-Julián A, Garrabou G, Rovira N, Catalán M, Bañó M, et al. Mitochondrial disturbances in HIV pregnancies. *AIDS (London, England)* 2015;29 (1):5–12. <https://doi.org/10.1097/qad.0000000000000486>.
- [60] Shi Z, Long W, Zhao C, Guo X, Shen R, Ding H, et al. Comparative proteomics analysis suggests that placental mitochondria are involved in the development of pre-eclampsia. *PLoS One* 2013;8(5):e64351. <https://doi.org/10.1371/journal.pone.0064351>. <https://doi.org/10.1371/journal.pone.0064351.g00110.1371/journal.pone.0064351.g00210.1371/journal.pone.0064351.g00310.1371/journal.pone.0064351.g00410.1371/journal.pone.0064351.t00110.1371/journal.pone.0064351.t00210.1371/journal.pone.0064351.t003>.