Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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NLRP3 inflammasome: A joint, potential therapeutic target in management of COVID-19 and fertility problems

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ABSTRACT

To overcome COVID-19 long-term consequences, one possible approach is to control inflammasomes activation, because SARS-CoV-2 can induce humoral and cellular immune responses. In this opinion article we hypothesized that if it is proven with convincing and unmistakable evidence that firstly, SARS-CoV-2 can enter cells and damage them through its common receptors in the reproductive tissues, and secondly, inflammasome pathway activation is responsible for the damages caused, then the inflammasome inhibitors might be considered as suitable candidates in preventing the pathological effects on the germ cells and reproductive tissues and subsequent fertility.

1. Introduction

Coronavirus disease 2019 (COVID-19) was thought to affect only the respiratory system. However, studies have progressively revealed that severe acute respiratory syndrome–coronavirus 2 (SARS-CoV-2) damages different organs and tissues through its receptors and factors responsible for virus entry/replication. The scientific community in reproductive biology currently focuses on the study of possible impacts of the virus on male and female reproductive organs, (in) fertility, and most importantly, its potential influence on the next generation.

Recently, investigators have evaluated previously generated high-throughput gene and protein expression data by inquiring online repositories and proposed that several reproductive tissues are suspected sites for SARS-CoV-2 contamination (Sun, 2020; Youssef and Abdelhak, 2020).These suggestions are based on the distribution of angiotensin-converting enzyme 2 (ACE2, as its entry receptor) and transmembrane serine protease 2 (TMPRSS2, a host protease that cleaves the viral S protein to allow virus spreading in the cell) in the genital tract, and detection of cells which express both receptors. Co-expression of ACE2 and TMPRSS2 genes is necessary for mediating membrane fusion between the virus and target cells (Song et al., 2020). However, there have been some controversy and several unanswered questions/ issues in the literature.

ACE2 receptor is highly expressed by testicular cells (Sertoli, Leydig, spermatogonial stem cells, seminiferous duct cells, and germ cells at different stages) and by cells of seminal vesicles and prostate (Song et al., 2020; Wang and Xu, 2020). A recent finding showed that its expression in testicular tissue is the highest compared to lung and also other male urogenital organs including prostate, kidney, and bladder tissues (Al-Benna, 2021). Moreover, TMPRSS2 expression is confirmed in spermatogonial stem cells, elongated spermatid, epididymis, and luminal epithelial cells of the prostate. Thus, these tissues could act as host in the case of exposure to the virus. Structural changes of the testis and epididymis, genital complaints such as scrotal discomfort, germ cell depletion and apoptotic death, increased serum LH, decreased ratio of T/LH and FSH/LH in men, and even in a case of reversible cryptozoospermia, are implicated in COVID19 pathogenesis as well (Song et al., 2020; Illiano et al., 2020; Basourakos and Schlegel, 2021; Barbry et al., 2020). Although it is controversial, the presence of SARS-CoV-2 virus in semen samples of infected patients has numerously been reported

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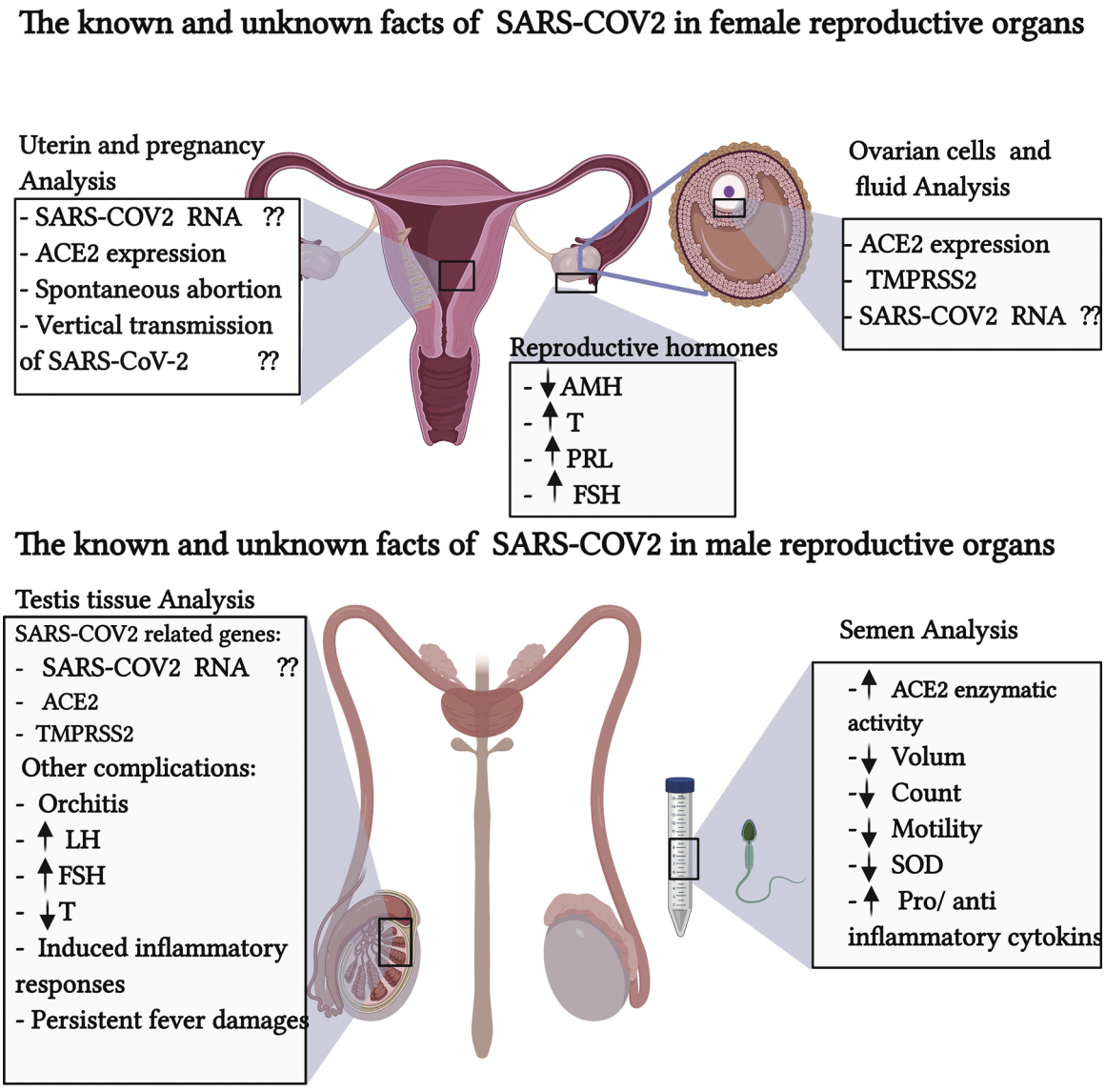

Fig. 1. The known and unknown facts of SARS-COV2 in female and male reproductive organs. Created with BioRender.com.

(Saylam et al., 2021; Vahedian-Azimi et al., 2021).

Some putative receptors (e.g. ACE2) for virus infection were reported in different human female reproductive organs, including fallopian tube cells (ciliated and endothelial), ovary, cervix, and endometrial cells of the uterus. In a preliminary case report investigating the possibility of vertical transmission of the virus, 16 oocytes from two asymptomatic SARS-CoV-2 positive women were analyzed in which RNA for N gene of the virus was undetectable (Zupin et al., 2020; Hikmet et al., 2020).

Moreover, during assisted reproductive procedures such as preparation, handling and cryopreservation of gametes and embryos, preparing of culture media and storing the samples in liquid nitrogen, the oocytes and sperms may be exposed to or contaminated by SARS-CoV-2 (Anifandis et al., 2021a).

Interestingly, it has been demonstrated that disparities exist in the susceptibility to infection by SARS- CoV-2 between females and males, originated from differential gene expression at the genetic or epigenetic levels according to gender, which resulted in a much higher mortality rate in men in comparison to women (Anifandis et al., 2021b).

Some known and unknown effects of SARS−COV-2 on male and female reproductive organs are summarized in Fig. 1.

Since SARS-CoV-2 can induce humoral and cellular immune responses, to overcome COVID-19 long-term consequences, one possible approach is to control inflammasomes activation. NLRP3, as the most important and the best studied inflammasome, detects and binds to inflammatory factors, then activates caspase-1 pathways and induces the secretion of the proinflammatory cytokins IL-1β and IL-18. Moreover, there is a second signal which causes the direct activation of these multiprotein complexes by cellular signaling events such as increased reactive oxygen species (ROS) generation or lysosomal damage. The final events in this step, like the first, are the production of cytokines IL-1β and IL18 as well as formation of Gasdermin D (GSDMD) pores in cell membranes which is followed by a cascade of downstream events, eventually inducing an inflammatory type of programmed cell death called pyroptosis (Shah, 2020; Latz et al., 2013) (Fig. 2 A).

If these immune responses are not adequately monitored, extensive cell and tissue damages can occur in multiple systems of the human body. Recently, it has been shown that the excess activation of inflammasomes and their signaling pathways in male and female reproductive systems can culminate in an imbalance among the inflammatory and pro-inflammatory cytokines and increase the incidence of infertility, miscarriage, preeclampsia, gestational diabetes, preterm labor, reproductive aging and endometriosis (Walenta et al., 2018; de Rivero Vaccari, 2020; Fang et al., 2021). In addition, the role of NLRP3 in immune response of testicles has been demonstrated. The expression of the

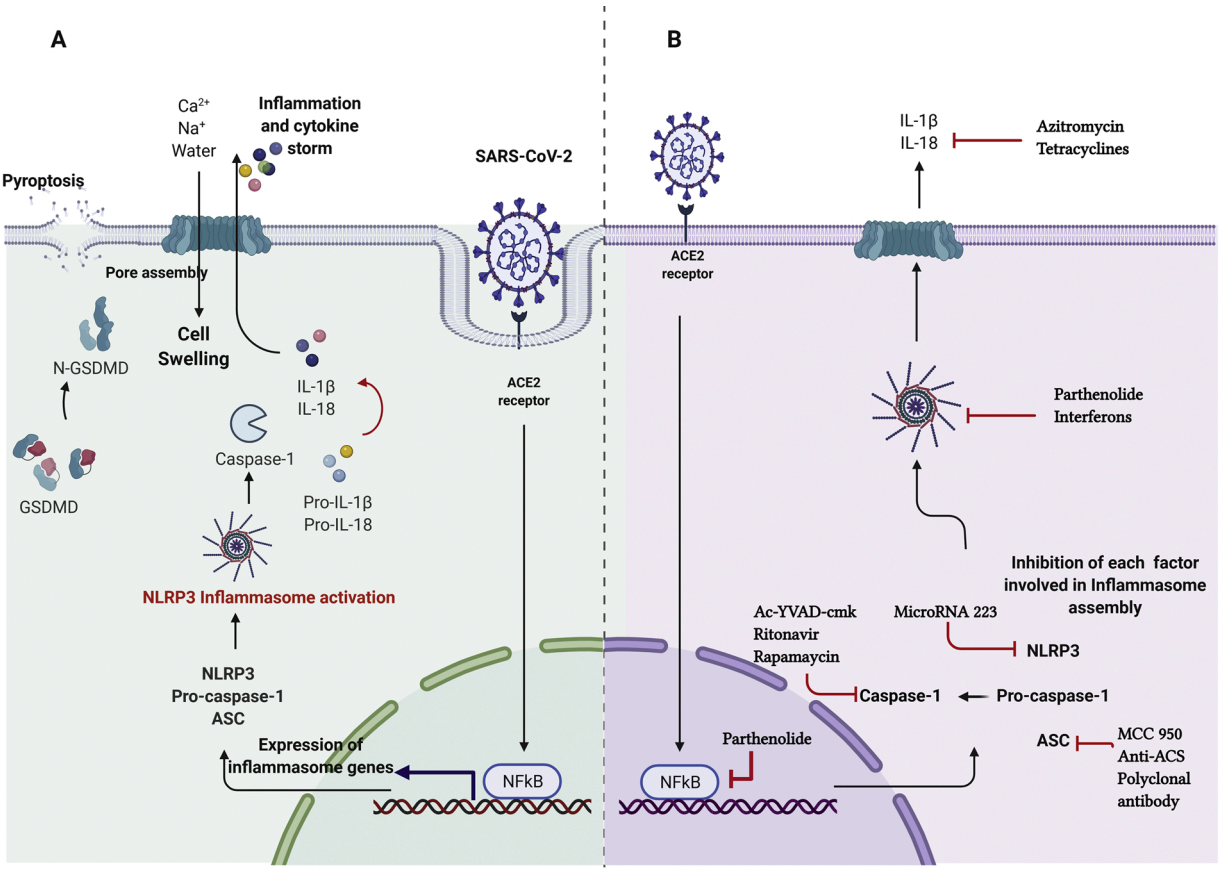

Fig. 2. A: Cell exposure to SARS-CoV2 leads to inflammasome activation resulting in membrane rupture, cell death, and inflammation.B: Inhibitors can directly target the NLRP3 protein; or the other components and products of the inflammasome pathway. ACE2, angiotensin-converting enzyme 2; SARS-CoV, severe acute respiratory syndrome coronavirus; Created with BioRender.com.

inflammasome proteins increases in the sperm of patients with spinal cord injury (Zhang et al., 2013). Elevated expression of the inflammasome is associated with decreased sperm motility which can be improved by blockade of the inflammasome with anti-ASC (Ibrahim et al., 2014).

It is logical that the secretion or release of immune mediators in the reproductive tissues or biological fluids would be accompanied by multisystem infections, thereby increasing the risk of infertility. Therefore, targeting the inflammasomes to decrease the proinflammatory environment could be a promising approach against SARS−COV-2. They can be tracked in reproductive cells in order to identify the intensity of immune responses after multiorgan infection.

Numerous inhibitors have been introduced for each component of the inflammasome signaling pathway until now; some of them specifically inhibit only one component such as the MCC950, which blocks the release of IL-1β induced by NLRP3 activators. It acts exclusively on the NLRP3 pathway; Ac-YVAD-cmk, a potent irreversible inhibitor of caspase-1, exhibits anti-inflammatory, anti-apoptotic, and anti-pyroptotic effects. Some inhibitors are also able to act on two targets, such as Parthenolide which is a broad-spectrum inhibitor with many anti-inflammatory properties. Its targets include NF-κB, caspase-1, and various inflammasomes such as NLRP1, NLRP3, and NLRC4 (Lin et al., 2018; Zahid et al., 2019; Xu et al., 2019).

If it is proven with convincing and unmistakable evidence that firstly, the virus can enter cells and damage them through its common receptors in the reproductive tissues, and secondly, inflammasome pathway activation is responsible for the damages caused, then inflammasome inhibitors might be considered as suitable candidates in preventing the pathological effects on the germ cells, reproductive tissues and subsequent fertility (Fig. 2B).

Declaration of Competing Interest

The authors declare no conflict of interest.

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