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Abstract

COVID-19 is an emerging acute communicable disease identified in patients with pneumonia in December 2019, which is declared as a pandemic in 11th March 2020 by World Health Organization. COVID-19 enters into target host cells by binding to ACE2(Angiotensin-converting enzyme 2) and modulates the expression of ACE2 in host cells. ACE2 is widely expressed in human tissues and considered as a pivotal component of RAS(renin-angiotensin system), exerts its physiological functions by modulating the levels of Ang II and Ang-(1-7). In this review, we focus on the distribution and functions of ACE2, thereby forecasting the possible infective targets and potential transmission pathways as well as the influence on female reproductive system.

Keywords: COVID-19, ACE2, Ang II, Ang-(1-7), Female reproductive system

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Reports of the emergence of COVID-19 appeared in December of 2019. The novel coronavirus virus has spread throughout the world with a rapid increase in cases and deaths. The number of reported cases has increased rapidly with 372,757 laboratory-confirmed cases and 16231 deaths as of March 24, 2020, which is an overwhelming health concerns on a globe scale(World Health Organization. Coronavirus disease (COVID-19) outbreak. <https://www.who.int/emergencies/diseases/novel-coronavirus-2019>). Epidemiologically, the genome of COVID-19 composed of 29891 nucleotides in size shared 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV(Chan et al. 2020). COVID-19 enters into target host cells by binding to angiotensin-converting enzyme 2(ACE2) through its surface Spike protein(Lu et al. 2020, Zhou et al. 2020), hence modulating the expression of ACE2 and causing severe injuries as severe acute respiratory syndrome coronavirus (SARS-CoV)(Kuba et al. 2005, Wang and Cheng 2020).

ACE2 is a human homolog of ACE(Angiotensin-converting enzyme), composed of 805 amino acids including a 17-amino acid N-terminal signal sequence and a C-terminal membrane binding domain(Tipnis et al. 2000), and hydrolyzes Ang II into Ang-(1-7)(angiotensin1-7)(Vickers et al. 2002). Ang II, the major component of ACE/Ang II/AT1(angiotensin II type 1) axis, facilitates vasoconstriction, contributes to cell proliferation(Campbell-Boswell and Robertson 1981, Ray et al. 1991, Hiruma et al. 1997, Bataller et al. 2000), and maintains the hydro-salinity balance(Hall et al. 1977, Johnson and Malvin 1977). Ang-(1-7) is an endogenous ligand for the G protein-coupled receptor Mas(Santos et al. 2003) and specifically inhibits Ang II by the antagonism of AT1 receptors, which is regarded as a key modulator of the human renin-angiotensin system(Roks et al. 1999). Moreover, Ang-(1-7) enhances vasodilation(Brosnihan et al. 1998, Oliveira et al. 1999), protects heart (Ferreira et al. 2001, Santos et al. 2004, Iwata et al. 2005) and alleviates metabolic syndrome(Giani et al. 2009, Liu et al. 2012).

Evidence has been accumulating that besides lung COVID-19 could also injury human heart(Huang et al. 2020, Wang et al. 2020, Zheng et al. 2020), liver(Chen et al. 2020, Zhang et al. 2020), kidney(Chen et al. 2020, Huang et al. 2020, Wang et al. 2020) and nervous system(Li et al. 2020, Mao et al. 2020). Recently cases of COVID-19 during pregnancy have been reported(Chen et al. 2020, Liu et al. 2020, Zhu et al. 2020), but the influence of COVID-19 on female reproductive system needs further investigation. Therefore, we focus this review mainly on the distribution and function of ACE2 in female reproductive system, provide an overview of the potential threaten of COVID-19 to the female fertility.

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ACE2 in ovary

Pereira et.al(2009) found that ACE2 presents in immature ovaries including stroma and granulosa cells as well as oocytes, the expression of which is enhanced in antral and preovulatory follicles subjected to eCG(equine chorionic gonadotropin) treatment(Pereira et al. 2009). ACE2 is also reported to be expressed in the theca cells and granulosa cells of cattle(Tonellotto dos Santos et al. 2012, Barreta et al. 2015). Notably, ACE2 mRNA transcripts were detected in ovaries from reproductive-age women and postmenopausal women(Reis et al. 2011). We analyzed ACE2 data from GeneCards (https://www.genecards.org/cgi-bin/carddisp.pl?gene=ACE2#protein_expression) database, and found that ACE2 is most abundantly expressed in ovary. In the meantime, data obtained in Bgee(https://bgee.org/?page=gene&gene_id=ENSG00000130234) showed that the expressional level of ACE2 in oocyte is relatively high. We therefore infer from the distributions of ACE2 that ovary and oocyte are potential targets for COVID-19.

ACE2, as the key converzyme in the axis, plays a synergistic role in balancing the levels of Ang II and Ang-(1-7). Ang II induces steroid secretion(Shuttleworth et al. 2002, Hayashi et al. 2003), facilitates follicle development(Shuttleworth et al. 2002, Ferreira et al. 2011) and oocyte maturation(Yoshimura et al. 1992, Giometti et al. 2005, Stefanello et al. 2006), contributes to follicular atresia(Tanaka et al. 1995, Kotani et al. 1999, Obermuller et al. 2004), influences ovulation(Pellicer et al. 1988, Kuo et al. 1991, Yoshimura et al. 1992, Yoshimura et al. 1993, Kuji et al. 1996, Acosta et al. 2000, Miyabayashi et al. 2005, Xu et al. 2005, Xu and Stouffer 2005, Ferreira et al. 2007, Guo et al. 2012) and maintains corpus luteum progression(Sugino et al. 2005). Ang-(1-7) promotes the production of estradiol and progesterone(Costa et al. 2003), enhances ovulation(Muthalif et al. 1998, Viana et al. 2011, Tonellotto dos Santos et al. 2012) and the resumption of meiosis in oocytes(Honorato-Sampaio et al. 2012). Recent study showed that the level of Ang-(1-7) is also associated with the oocyte maturation of human(Cavallo et al. 2017).

ACE2 in uterus and vagina

ACE2 mRNA has been identified in uterus of human(Vaz-Silva et al. 2009) and rat(Brosnihan et al. 2012). *Vaz-Silva et.al (2009)* claimed that ACE2 expression is more abundant in epithelial cells than in stromal cells, in the secretory phase than proliferative phase(Vaz-Silva et al. 2009). Moreover, we observed the presence of ACE2 in uterus and vagina by analyzing the data from the Human Protein Atlas portal(<https://www.proteinatlas.org/ENSG00000130234-ACE2/tissue>) and GeneCards. Noteworthy, despite of the high infection rate for 35 female COVID-19-patients' sexual partners(Cui et al. 2020), the confirmation of sexual transmission still needs extensive investigations.

Ang II plays a dual role in vascular beds and endometrium regeneration, and initiates the menstruation through spiral artery vasoconstriction(Ahmed et al. 1995, Li and Ahmed 1996, Li and Ahmed 1997). The balance between Ang II and Ang-(1–7) could regulate the endometrium regeneration process(Vaz-Silva et al. 2009) and myometrium activity(Deliu et al. 2011, Vaz-Silva et al. 2012). Moreover, Ang II increases the proliferation of uterus epithelial and stroma cells and enhances endometrial fibrosis, an effect of which is inhibited by Ang-(1-7)(Hering et al. 2010, Shan et al. 2014, Shan et al. 2015). Notably, the normal function of Ang II in endometrium is a necessity to the regular menstrual cycle, alteration in its distribution and the level of the receptors may be related to dysfunctional uterine bleeding associated with hyperplastic endometria(Li and Ahmed 1996). Furthermore, sets of evidence show that the aberrant expression of ACE2 and Ang II correlates with the metastasis and prognosis of endometrical carcinoma(Watanabe et al. 2003, Shibata et al. 2005, Delforce et al. 2017).

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ACE2 in pregnancy

ACE2 is widely expressed in human placenta and mainly in the syncytiotrophoblast, cytotrophoblast, endothelium and vascular smooth muscle of primary and secondary villi. In the maternal stroma, ACE2 is expressed in the invading and intravascular trophoblast and in decidual cells. ACE2 is also found in arterial and venous endothelium and smooth muscle of the umbilical cord(Valdes et al. 2006, Pringle et al. 2011). Of note, ACE2 reaches the highest level in early gestation(Pringle et al. 2011). During early gestation, ACE2 is expressed in the primary and secondary decidual zone and luminal and glandular epithelial cells. During late gestation, ACE2 staining was visualized in the labyrinth placenta and amniotic and yolk sac

epithelium(Neves et al. 2008, Ghadhanfar et al. 2017). Moreover, the increase of ACE2 in placenta of rat begins in the mid-gestation(Vaswani et al. 2015).

According to the TIGER Database Gene View(http://bioinfo.wilmer.jhu.edu/tiger/db_gene/ACE2-index.html) and GeneCards the expression of ACE2 in placenta is far more than that in lung, indicating the possible infection of placenta. Proof for intrauterine infection has yet appeared, but confirmed cases of newborns were reported. A newborn within 30 hours in Wuhan has been confirmed as positive in 5th February(D'Amore R. Can coronavirus pass from mother to baby? Maybe, but experts need more research. Global News. <https://globalnews.ca/news/6515302/coronavirus-mother-babytransmission/> Posted February 7, 2020. Accessed February 10, 2020.), and then a newborn in 13th March in London has tested positive for coronavirus(Shaun Wooller. Newborn baby in London has coronavirus as UK cases soar to 820 and 11 dead. <https://www.thesun.co.uk/news/11170653/newborn-baby-coronavirus-worlds-youngest-victim/>(accessed Mar 13, 2020).). Given that the identification of COVID-19 in cultured human airway epithelial cells requires at least 96 hours((National Health Commission of the People's Republic of China. The notice of launching guideline on diagnosis and treatment of the novel coronavirus pneumonia. (7th edition) (accessed Mar 4, 2020; in Chinese).), we believe in the possibility of intrauterine infection with COVID-19 and postulate that the fetus may have already been infected during the gestation. Additionally, the Human Protein Atlas portal and GeneCards database show the presence of ACE2 in breast. Although no reports of COVID-19 in milk has appeared, the chance of transmission of breast feeding still exists. Even if there is no virus in milk, contact transmission during breast feeding should be taken into account. Given the weaker immune system of newborns we strongly advise these confirmed pregnant patients avoid breast-fed way.

The main functions of Ang II, ACE2 and Ang-(1-7) during pregnancy are focusing on the regulation of blood pressure and fetus development as well as the engagement of whole pregnancy period. Ang II stimulates trophoblast invasion in rat and human cells(Hering et al. 2010). Ang-(1-7) and ACE2 may act as a local autocrine/paracrine regulator throughout pregnancy, participating in the early(angiogenesis, apoptosis, and growth) and late(uteroplacental blood flow) events of pregnancy(Neves et al. 2008). ACE2 hydrolyzes Ang II into Ang-(1-7) and thereby controlling the blood pressure and hydro-salinity balance of pregnant women(Pringle et al. 2011). The aberrant expression of Ang II, ACE2 and Ang-(1-7) may be involved in hypertension of pregnancy, preeclampsia and eclampsia(Merrill et al. 2002, Brosnihan et al. 2004, Anton et al. 2008, Anton et al. 2009, Sykes et al. 2014, Yamaleyeva et al. 2014). High expression of Ang II in placental villus during preeclampsia causes decreased blood flow and nutrition levels in fetus(Shibata et al.

2006, Anton et al. 2008, Anton et al. 2009). Meanwhile, low levels of ACE2 and Ang-(1-7) in placenta
associate with intrauterine growth restriction(Ghadhanfar et al. 2017).

ACE2 deficient mice show high blood pressure in gestation stage, decreased Ang-(1-7) in plasma and
increased Ang II within placenta, causing the abnormal placental functions including placental hypoxia and
uterine artery dysfunction, finally leading to fetal growth retardation(Bharadwaj et al. 2011, Yamaleyeva et
al. 2015). *Chen et.al (2014)* found that the maternal Ang (1-7)/Ang II ratio is independently associated with
gestational hypertension or preeclampsia factors causing preterm birth(Chen et al. 2014). The up-regulation
of ACE2-Ang-(1-7)-Mas prevents premature birth(Lumbers 2020). It is noteworthy that the involvement of
premature birth and intrauterine growth restriction with adult cardiovascular risk has already been well
documented(Irving et al. 2000). *Bessa et.al(2019)* reported that stimulation of the ACE2/Ang-(1-7)/Mas axis
in hypertensive pregnant rats could attenuate the cardiovascular dysfunction in adult offspring(Bessa et al.
2019), confirming the engagement of ACE2 axis in pregnancy.

COVID-19 infection poses a great threat to pregnant women and babies and causes premature
birth(50.0 %, 16/32) and fetal distress (39.3 %, 11/28) as well as premature rupture of fetal membranes
(21.4 %, 6/28) (Chen et al. 2020, Liu et al. 2020, Zhu et al. 2020), but whether it is ACE2 that causes the
dysfunction of placenta remains elusive and needs further evaluation. Moreover, just like SARS-CoV
patients, COVID-19 patients also have complicated acute renal impairment, renal dysfunction and renal
failure(Chu et al. 2005, Fan et al. 2020, Li et al. 2020, Li et al. 2020, Zhang et al. 2020). *Pacciarini
et.al(2008)* has found that SARS-CoV infects human tubular kidney cell(Pacciarini et al. 2008). Of note,
ACE2 level in the renal tubules of pregnant mice increases by 117%, which may contribute to the
maintenance of blood pressure(Brosnihan et al. 2003). We suppose that pregnant women with COVID-19
may be susceptible to renal injuries.

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Conclusion

COVID-19 may infect ovary, uterus, vagina and placenta through the ubiquitous expression of ACE2 within the female reproductive system. Therefore, we believe that apart from droplets and contact transmission the possibility of mother-to-child tract and sexual transmission also exist. Moreover, Ang II, ACE2 and Ang-(1-7) regulate follicle development and ovulation, modulate luteal angiogenesis and degeneration, influences the endometrial tissues' regular changes and the embryo development. Taking these functions into account, the regulation of COVID-19 to ACE2 may disturb the female reproductive functions and induce infertility, menstrual disorder and fetal distress. We suggest a following-up and evaluation of fertility after the healing, especially for the young female patients. Moreover, we should persistently pay close attention to the situation of pregnant patients and fetus and take timely and necessary measures. What's more, to decrease the incident of COVID-19 infection, special nursings should be conducted for healthy pregnant women, puerperants and newborn infants.

Authors' roles

C.F. and Y.J wrote manuscript. L.R, W.H, C.H., L.Y., G.Y. prepared the reference.

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Conflict of interest

None declared.

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