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# Molecular mimicry between SARS-CoV-2 and the female reproductive system

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## Abstract

**Introduction:** Oogenesis, the process of egg production by the ovary, involves a complex differentiation program leading to the production of functional oocytes. This process comprises a sequential pathway of steps that are finely regulated. The question related to SARS-CoV-2 infection and fertility has been evoked for several reasons, including the mechanism of molecular mimicry, which may contribute to female infertility by leading to the generation of deleterious autoantibodies, possibly contributing to the onset of an autoimmune disease in infected patients.

**Objective:** The immunological potential of the peptides shared between SARS-CoV-2 spike glycoprotein and oogenesis-related proteins; Thus we planned a systematic study to improve our understanding of the possible effects of SARS-CoV-2 infection on female fertility using the angle of molecular mimicry as a starting point.

**Methods:** A library of 82 human proteins linked to oogenesis was assembled at random from UniProtKB database using oogenesis, uterine receptivity, decidualization, and placentation as a key words. For the analyses, an artificial polyprotein was built by joining the 82 a sequences of the oogenesis-associated proteins. These were analyzed by searching the Immune Epitope DataBase for immunoreactive SARS-CoV-2 spike glycoprotein epitopes hosting the shared pentapeptides.

**Results:** SARS-CoV-2 spike glycoprotein was found to share 41 minimal immune determinants, that is, pentapeptides, with 27 human proteins that relate to oogenesis,

uterine receptivity, decidualization, and placentation. All the shared pentapeptides that we identified, with the exception of four, are also present in SARS-CoV-2 spike glycoprotein–derived epitopes that have been experimentally validated as immunoreactive.

**KEYWORDS**
autoimmunity, COVID-19, epitopes, molecular mimicry, oogenesis, SARS-CoV-2

## 1 | INTRODUCTION

Oogenesis, the process of egg production by the ovary, involves a complex differentiation program leading to the production of functional oocytes. The ovaries (or female gonads) are filled with follicles in which the oocyte grows to maturity. It is well documented that females do not make new eggs and that the pool of eggs presents in the ovary at birth represent the total numbers of oocytes that will continuously decline over the female's life. At the time of menopause, virtually no eggs remain. The large supplies of eggs within ovary are immature. They undergo growth and maturation each month.

The maturation program of oocytes comprises a sequential pathway of steps that are finely regulated.[1,2] There are numerous possible causes of female infertility. Genetic and abnormal immune responses are often presented as factors that may lead to infertility.[3] Infertility resulting from the effect of autoantibodies (autoAbs) has been a matter of many debates.[4–6] Certain autoAbs such as anti-phospholipid, anti-thyroid (anti-thyroperoxidase and/or anti-thyroglobulin), anti-nuclear, anti-annexin V, anti-prothrombin, anti-laminin, anti-follicle stimulating hormone Abs have been associated with infertility, especially due to premature ovarian insufficiency, in addition to pregnancy loss.[5,6] Anti-sperm Abs also seem to be more frequent in the population of infertile women. The direct pathological role of these autoAbs is generally unknown.

The question related to SARS-CoV-2 infection and fertility (in females and males) has been evoked for several reasons. First, it is well documented nowadays, that the angiotensin converting enzyme II (ACE2) is an entry receptor for SARS-CoV-2, the virus responsible for coronavirus disease 19 (COVID-19).[7,8] ACE2 is a type I-transmembrane metallocarboxypeptidase with homology to ACE, a key player enzyme in the renin-angiotensin system, and a target for the treatment of hypertension. It is highly expressed in the small intestine, kidneys, heart, thyroid, adipose tissue, and especially in testis, ovaries, uterus, vagina and placenta.[2,9,10] Although at a lower level, ACE2 is also present in other organs and tissues. It has therefore been postulated that *via* ACE2, SARS-CoV-2 might cause direct injury in these tissues,[2,10] (Table 1, Table S1). ACE2 regulates follicular development and ovulation, modulates luteal angiogenesis and degeneration, and affects the regular changes of endometrial tissue and embryo development.[10] The question has thus been raised to know whether COVID-19 might have an effect on female fertility.[2,10]

Second, as said above, over years, there is a decline in female fertility linked to a reduction in both the quantity and quality of the germline (oocytes). Recent advances have revealed that autophagy, in relation with oxidative stress, influences oocyte longevity.[11,12] It turns out that autophagy is especially involved in SARS-CoV-2 infection.[13,14] Any dysfunction of autophagy, in the case of COVID-19, might therefore have important consequences in oocyte maturation that *de facto* could influence ovulation and fertility.

Third, as shown in the case of numerous other infections, Abs generated against viral proteins could cross-react with common sequences shared by pathogens and self-components. This mechanism of molecular mimicry may lead to the generation of deleterious Abs, which could participate to the onset of an autoimmune disease in infected patients.[15–17] With this aim in mind, we carried out a systematic study to improve our understanding of the possible effects of SARS-CoV-2 infection on female fertility using the angle of molecular mimicry as a starting point. We identified a number of rather long linear sequences shared by the SARS-CoV-2 proteins and oogenesis-related proteins that might play a role in the production of possibly pathogenic cross-reactive Abs.

## 2 | METHODS

Peptide sharing between oogenesis-related human proteins and spike glycoprotein (NCBI, GenBank Protein Accession Id = QHD43416.1) from SARS-CoV-2 (NCBI:txid2697049) was analyzed using pentapeptides as sequence probes since a peptide grouping formed by five amino acid (aa) residues defines a minimal immune determinant that can (1) induce highly specific Abs, and (2) determine antigen-Ab specific interaction.[18,19]

A library of 82 human proteins linked to oogenesis was assembled at random from UniProtKB database (www.uniprot.org/)[20] using oogenesis, uterine receptivity, decidualization, and placentation as a key words. The 82 human proteins are listed in Table S1. For the analyses, an artificial polyprotein was built by joining the 82 aa sequences of the oogenesis-associated proteins.

The spike glycoprotein primary sequence was dissected into pentapeptides offset by one residue (i.e., MFVFL, FVFLV, VFLVL, FLVLL, and so forth) and the resulting viral pentapeptides were analyzed for occurrences within the polyprotein. Occurrences and the corresponding proteins were annotated.

**TABLE 1** Pentapeptide sharing between SARS-CoV-2 spike glycoprotein and 27 human proteins linked to oogenesis, placentation, or decidualization

| Shared Peptides[a] | Human proteins and associated function(s)/pathologies[b,c] | Refs |
|---|---|---|
| AAAYY, KRISN, PDDFT | *ASPM. Abnormal spindle-like microcephaly-associated protein.*<br>Altered Aspm protein causes a massive loss of germ cells, resulting in a severe reduction in testis and ovary size accompanied by reduced fertility. | 22 |
| VNQNA | *BMP2. Bone morphogenetic protein 2 precursor*<br>Involved in uterine decidualization | 23 |
| QAGST, **SALGKL** | *CXA1. Gap junction alpha-1 protein*<br>Involved in decidualization. Reduced expression of Cx43 transcript and protein in maternal decidua indicate the key role of Cx43 in recurrent early pregnancy loss | 24,25 |
| GAISS | *DIAP2. Protein diaphanous homolog 2.*<br>Function in oogenesis and implications for human sterility | 26 |
| PGQTG | *DMRT1. Doublesex- and mab-3-related transcription factor 1.*<br>Plays a key role in male sex determination; involved in sex reversal. Promotes oogenesis. Lack of DMRT1 in the fetal ovary results in the formation of many fewer primordial follicles in the juvenile ovary | 27–30 |
| **GRLQSL**, VLGQS | *ERCC1. DNA excision repair protein ERCC-1.*<br>Essential for normal spermatogenesis and oogenesis and for functional integrity of germ cell DNA. May also contribute to sperm DNA fragmentation and male infertility | 31,32 |
| YSNNS | *FIGLA. Factor in the germline alpha.*<br>Regulates the expression of oocyte-specific genes, including those that initiate folliculogenesis and those that encode the zona pellucida required for fertilization. Essential for oocytes to survive. Balances sexually dimorphic gene expression in postnatal oocytes by activating oocyte-associated genes and repressing sperm-associated genes during normal postnatal oogenesis | 33,34 |
| NQNAQ | *FMN2. Formin-2.*<br>Required for spindle relocation, that is,– essential for fertility; also, it is highly expressed in the developing and adult central nervous system | 35,36 |
| VLTES | *HTRA3. Serine protease HTRA3 precursor*<br>Regulates trophoblast invasion during human placentation | 37 |
| GAGAA, LSSTA, LAATK | *JUNB. Transcription factor jun-B*<br>Essential for mammalian placentation | 38 |
| LHSTQ | *KASH5. Protein KASH5.*<br>Function as meiotic-specific factor. Most oocytes are arrested at the germinal vesicle stage after depletion of KASH5. | 39,40 |
| LPPLL | *KDM1B . Lysine-specific histone demethylase 1B.*<br>Demethylase required to establish maternal genomic imprints. highly expressed in growing oocytes where genomic imprints are established. | 41 |
| **ANLAAT** | *KiSSR. KiSS-1 receptor*<br>Involved in follicular development, oocyte maturation, ovulation, and steroidogenesis. Regulator of puberty and its alterations can lead to precocious puberty, absence of or incomplete sexual maturation, dysfunction of reproductive function, hypogonadotropic hypogonadism with or without anosmia | 42–48 |
| QVAVL, IEDLL, PPLLT, AKNLN, LQELG | *KMT2D. Histone-lysine N-methyltransferase 2D.*<br>Required during oogenesis and early development for bulk histone H3 lysine 4 trimethylation. Essential for early embryonic development. | 49,50 |
| APATV | *MARF1. Meiosis regulator and mRNA stability factor 1.*<br>An endoribonuclease that controls oocyte RNA homeostasis and genome integrity. Essential for meiotic progression of oocytes | 51,52 |
| TLLAL | *MK. Midkine precursor.*<br>Maturation of mammalian oocytes in the context of ovarian follicle | 53 |
| SNLLL | *MK01. Mitogen-activated protein kinase 1*<br>Abnormal placentation and delayed parturition | 54 |
| NSNNL, EELDK | *PANX1. Pannexin-1.*<br>An ATP-permeable channel with critical roles in a variety of physiological functions such as blood pressure regulation1, apoptotic cell clearance2 and human oocyte development3. PANX1 alterations cause human oocyte death and female infertility. | 55,56 |

(Continues)

**TABLE 1** (Continued)

| Shared Peptides[a] | Human proteins and associated function(s)/pathologies[b,c] | Refs |
|---|---|---|
| PLVSS | *PAQR5. Membrane progestin receptor gamma.*<br>Plasma membrane progesterone (P4) receptor coupled to G proteins and implicated in oocyte maturation. | 57 |
| IITTD | *PCSK5. Proprotein convertase subtilisin/kexin type 5*<br>Essential for the differentiation of uterine stromal fibroblasts into decidual cells (decidualization) | 58 |
| TFGAG | *S6OS1. Protein SIX6OS1.*<br>Belongs to a transcription factor network that regulates oocyte growth and differentiation; when altered, can cause non-obstructive azoospermia and premature ovarian insufficiency in humans | 59,60 |
| ASALG | *SOLH1. Spermatogenesis- and oogenesis-specific basic helix-loop-helix-containing protein 1*<br>Essential for spermatogonial differentiation; regulate mouse oocyte growth and differentiation. | 61,62 |
| FGGFN, IVNNT | *SRC. Proto-oncogene tyrosine-protein kinase Src.*<br>Protein tyrosine kinase that plays a role during oocyte maturation and fertilization. | 63,64 |
| LSSTA | *SYCY2. Syncytin-2 precursor*<br>Participates in trophoblast fusion and the formation of a syncytium during placenta morphogenesis; correlates with the risk of severe preeclampsia | 65,66 |
| TESNK | *TDRD6. Tudor domain-containing protein 6.*<br>Transcription factor that balances sexually dimorphic gene expression in postnatal oocytes. | 34 |
| GDSSS | *VDR. Vitamin D3 receptor*<br>Recurrent pregnancy loss | 67 |
| LEPLV, ANLAA | *YTDC2. 3′-5′ RNA helicase YTHDC2.*<br>Plays a key role in the male and female germline by promoting transition from mitotic to meiotic divisions in stem cells | 68 |

[a]Hexapeptides derived from overlapping pentapeptides given bold.
[b]Human proteins given by Uniprot accession and name in italics.
[c]Functions and/or associated pathologies: data from Uniprot, Pubmed, and OMIM public databases .

The immunological potential of the peptides shared between SARS-CoV-2 spike glycoprotein and oogenesis-related proteins was analyzed by searching the Immune Epitope DataBase (IEDB, www.iedb.org/)[21] for immunoreactive SARS-CoV-2 spike glycoprotein epitopes hosting the shared pentapeptides.

## 3 | RESULTS

### 3.1 | Peptide sharing between SARS-CoV-2 spike glycoprotein and human proteins related to oogenesis

Quantitatively, SARS-CoV-2 spike glycoprotein was found to share 41 minimal immune determinants, that is, pentapeptides, with 27 human proteins that relate to oogenesis, placentation and/or decidualization. The shared pentapeptides are the oogenesis related proteins are described in Table 1.

### 3.2 | Immunological potential of the peptides shared between SARS-CoV-2 spike glycoprotein and oogenesis-associated proteins

Exploration of the Immune Epitope DataBase (IEDB, www.iedb.org/)[21] revealed that all the shared pentapeptides described in Table 1, with the exception of two (namely, VLGQS, QVAVL, ALGKL, and SNLLL), are also present in SARS-CoV-2 spike glycoprotein–derived epitopes that have been experimentally validated as immunoreactive (see IEDB, www.iedb.org/ for immunoassays and references).[21]

## 4 | DISCUSSION

Since its appearance, SARS-CoV-2 has rightly attracted the scientific-clinical attention on organs and functions that are object of the viral attack and contribute to the acute pathology associated with this disease, that is, respiratory failure and dysfunctional immune system.[69,70] However and of relevant importance, it also emerged the possibility that the virus can affect multiple functions and, among them, human fertility.[71,72] Evidences indicate that the virus can target human reproductive organs that express its main receptor ACE2, although it is as yet unclear if this has any implications for human fertility.[73]

Here, a mechanism, that is, cross-reactivity, and a molecular platform, that is, peptide sequences derived from infertility-related proteins and also present in SARS-CoV-2, are proposed as possible links between infertility occurrence and SARS-CoV-2 infection. Actually, already in 1998,[74] it was shown that the sharing of a short peptide between murine myelin basic protein and hepatitis B virus (HBV) could lead to pathogenic autoimmune cross-reactivity in animal models, so explaining the high incidence of demyelinating diseases that was observed following HBV infection. These studies and some others

**TABLE 2** Distribution among 84 experimentally validated SARS-CoV-2 spike glycoprotein-derived epitopes of 41 pentapeptides shared between SARS-CoV-2 spike glycoprotein and 27 human proteins linked to oogenesis, placentation, and/or decidualization

| IEDB ID[a] | EPITOPE[b] | IEDB ID[a] | EPITOPE[b] |
|---|---|---|---|
| 10112 | dsfk**eeldk**y | 1309563 | qtgkiadynykl**pddft**gcv |
| 26710 | **iittd**ntfv | 1309567 | rdlpqgfsa**leplv**dlpigi |
| 54725 | **rlqsl**qtyv | 1309574 | rssv**lhstq**dlflpffsnvt |
| 59162 | slid**lqelg**kyeqyikw | 1309578 | sf**iedll**fnkvtladagfik |
| 1073281 | **tesnk**kflpfqqfgrdia | 1309581 | slid**lqelg**kyeqyikwpwy |
| 1073938 | vqidrlit**grlqsl**q | 1309585 | sssgwtag**aaayy**vgylqpr |
| 1073956 | vvlsfellh**apatv**c | 1309598 | tvydplqpeldsfk**eeldk**y |
| 1074838 | aeiras**anlaatK** | 1309608 | vvniqkeidrlnev**aknln**e |
| 1074865 | a**ysnns**iaiptnftisv | 1310254 | aensva**ysnns**iaip |
| 1074952 | kl**pddft**gcv | 1310300 | a**ysnns**iaiptnfti |
| 1074967 | **leplv**dlpi | 1310303 | caqkfngltv**lppll** |
| 1074971 | lit**grlqsl**qtyv | 1310360 | eiy**qagst**pcngveg |
| 1074989 | **lsstasalgk** | 1310415 | fngltv**lpplltd**em |
| 1075039 | rqia**pgqtg**kiadynykl | 1310434 | **gaiss**vlndilsrld |
| 1075094 | v**lpplltd**emiaqyt | 1310437 | gcviaw**nsnnl**dskv |
| 1075117 | wtag**aaayy**vgy | 1310444 | g**ivnnt**vydplqpel |
| 1087679 | pikd**fggfn**fsqilpdps | 1310447 | gkiadynykl**pddft** |
| 1087693 | qmyktptlky**fggfn**fsq | 1310448 | gklqdv**Vnqnaq**aln |
| 1087780 | vkqiyktppikd**fggfn**f | 1310487 | iginitrfq**tllal**h |
| 1125063 | gltv**lppll** | 1310513 | itrfq**tllal**hrsyl |
| 1309125 | lid**lqelg**kyeqyi | 1310551 | **krisn**cvadysvlyn |
| 1309143 | yawnr**krisn**cvady | 1310586 | lit**grlqsl**qtyvtq |
| 1309418 | aeiras**ANlaatk**msecvlg | 1310606 | lnev**aknln**eslidl |
| 1309440 | atrfasvyawnr**krisn**cva | 1310611 | **lpplltd**emiaqyts |
| 1309441 | a**ysnns**iaiptnftisvtte | 1310612 | lpqgfsa**leplv**dlp |
| 1309447 | d**fggfn**fsqilpdpskpskr | 1310614 | lqpeldsfk**eeldk**y |
| 1309451 | dsfk**eeldk**yfknhtspdvd | 1310765 | rfasvyawnr**krisn** |
| 1309468 | ferdisteiy**qagst**pcngv | 1310785 | sa**leplv**dlpigini |
| 1309490 | iaw**nsnnl**dskvggnynyly | 1310827 | sv**lhstq**dlflpffs |
| 1309501 | kl**pddft**gcviaw**nsnnl**ds | 1310852 | tlvkqlssnf**gaiss** |
| 1309504 | kqiyktppikd**fggfn**fsqi | 1310865 | trfq**tllal**hrsylt |
| 1309515 | lhrsyltp**gdsss**gwtagaa | 1310899 | vll**plvss**qcvnltt |
| 1309516 | lit**grlqsl**qtyvtqqlira | 1310947 | w**TFgagaa**lqipfam |
| 1309518 | lnev**aknln**eslid**lqelg**k | 1311674 | faqvkqiyktppikd**fggfn**fsqi |
| 1309519 | lpdpskpskrsf**iedll**fnk | 1311676 | fk**eeldk**yfk |
| 1309523 | lssnf**gaiss**vlndilsrld | 1311810 | r**krisn**cv |
| 1309531 | ngltgtg**vltesNK**kflpfq | 1311944 | ynykl**pddft** |
| 1309532 | ngltv**lpplltd**emiaqyts | 1315180 | a**ysnns**iai |
| 1309534 | nitrfq**tllal**hrsyltpgd | 1321084 | **lpplltd**em |
| 1309554 | **qagst**pcngvegfncyfplq | 1323750 | ras**ANlaatk** |
| 1309558 | qfnsaigkiqds**lssta**sal | 1323919 | **rlqsl**qty |
| 1309561 | qrnfyepq**iittd**ntfvsgn | 1324400 | sfk**eeldk**y |

[a]Epitopes listed as IEDB ID number and detailed at IEDB (www.iedb.org).[21]
[b]Peptides shared between SARS-CoV-2 spike glycoprotein-derived epitopes and human proteins are given in capital letters.

in the same line were guided by the idea that amino acid sequence similarities between the pathogens and the human host may lead to autoimmune pathologies through cross-reactivity phenomena occurring after pathogen infection. Taken together, Tables 1 and 2 effectively document the possibility that SARS-CoV-2 infection might hit numerous fertility-linked proteins, including enzymes involved in the methylation program of histones, thus causing severe and numerous alterations of the reproductive function in humans. Citing only a few, we can list here the loss of germ cells, severe reduction in testis and ovary size, alteration in male sex determination, sex reversal, alteration of folliculogenesis, alteration of the balance of the sexually dimorphic gene expression, reduced fertility, alterations of puberty with precocious puberty, absence of or incomplete sexual maturation, dysfunction of reproductive function, non-obstructive azoospermia and premature ovarian insufficiency [see Table 1, and references therein].

Although the present data warrant in-depth experimental studies, especially by testing large series of sera collected from COVID-19-ill patients in dedicated arrays for human proteins related to oogenesis, they encourage us to be vigilant in the future on issues of possible infertility in patients who have been infected by SARS-CoV-2.

It should be emphasized that the molecular mimicry we found does not indicate female reproductive dysfunction in COVID-19 patients. Nevertheless, our findings suggest potential cross-reactivity between the homologous peptides that may result in the development of autoantibodies and new-onset of related autoimmune manifestations. Thus, in our perspective, detecting such autoantibodies should be attempted.

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## CONFLICTS OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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