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Membrane protein of SARS-CoV-2 plays a pivotal role in the availability of active testosterone through its interaction with AKR1C2 enzyme leading to the upregulation of TMPRSS2 protease expression

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the coronavirus disease (COVID-19) and ongoing pandemic that has devastated humankind. During the COVID-19 pandemic, it was noticed that the mortality rate in men is higher than that in women. The membrane (M) protein of SARS-CoV-2 plays a pivotal role in the viral life cycle regulating intracellular trafficking and processing of spike (S) protein. In infected individuals, M protein inhibits the conversion of active testosterone to its inactive form through its interaction with Aldo-keto reductase family 1 member C2 (AKR1C2) protein. This leads to the high availability of active testosterone and boosts the formation of its complex with an androgen receptor that in turn promotes the transcription of the transmembrane protease serine 2 (TMPRSS2) gene. TMPRSS2 is known to play a pivotal role in the priming of S protein that is necessary for the SARS-CoV-2 entry into the host cell. Therefore, the interaction of the M protein of SARS-CoV-2 with AKR1C2 eventually leads to the upregulation of the transcription of the TMPRSS2 gene that results in an enhanced viral infection and in turn higher mortality in men. The interaction of M protein with AKR1C2 could be a possible target for SARS-CoV-2 antiviral drug design.

Keywords: SARS-CoV-2, membrane protein, AKR1C2, TMPRSS2, testosterone, pandemic

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Viruses of the *Coronaviridae* family are spherical enveloped particles with a large (27-32 kb) single strand RNA(+) genome encoding four main structural and sixteen non-structural proteins [1]. They have been known to infect humans, bats, cattle, horses, swine, dogs, cats, turkeys, rabbits, chickens, rats, and mice, causing gastroenteritis and respiratory tract diseases in their hosts [2]. Human HKU1, NL63 (alphacoronaviruses), and 229E, OC43 (betacoronaviruses) have been known to cause mild respiratory disease in humans. In 2002, a novel severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1, betacoronavirus) crossed over from bats to humans through palm civet cats as the intermediary host [3]. A decade later in 2012, another betacoronavirus – Middle East Respiratory Syndrome (MERS) crossed over from bats to humans through dromedary camels [4]. In 2019, a novel betacoronavirus had crossed over from bats to humans using Malayan pangolins (*Manis javanica*) as the intermediate host [5]. This virus was designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 causes a severe respiratory tract infection and has led to a global pandemic resulting in millions of deaths worldwide. As of September 2021, more than 221 million confirmed cases of SARS-CoV-2 infection were reported globally and has led to more than 4.5 million deaths [6].

Interactions of the SARS-CoV-2 proteins with the host cell receptors, proteins, and organelles are in the focus of intensive research. One of the areas is the regulation of expression of the cell proteins and enzymes by the viral particles. Previously, it was found that SARS-CoV spike (S) protein downregulates the expression of the angiotensin-converting enzyme 2 (ACE2), which is the main receptor for SARS-CoV-2 entry to the cell [7]. Here, we hypothesize that SARS-CoV-2 can upregulate the expression of transmembrane serine 2 protease (TMPRSS2) that is necessary for priming S protein by means of membrane (M) glycoprotein interaction with Aldo-keto reductase family 1 member C2 (AKR1C2) enzyme.

It is noteworthy that the mortality rate from COVID-19 for males is higher than that for females [8]. The higher mortality rate observed in males can be due to several lifestyle factors. Men have higher rates of tobacco use and alcohol consumption compared to women and, therefore, that could be linked to higher rates of COVID-19 infection and mortality [9]. Moreover, women have two X chromosomes containing immune related genes while men have one X chromosome. Due to incomplete gene silencing on the second X chromosome, women tend to have a stronger innate and adaptive immune response compared to men [10]. In addition, it was shown recently that the plasma concentrations of ACE2 receptor, which SARS-CoV-2 uses to enter the cell, are higher in males than in females [11]. On the other hand, the higher mortality rate of males from COVID-19 has led scientists to speculate that testosterone might also play a role in disease severity.

SARS-CoV-2 has been shown to reduce serum testosterone levels [12, 13]. The M protein is the most abundant envelope protein of SARS-CoV-2 that plays a key role in the assembly of viral particles by interacting with all of the other structural proteins [14]. During the early stage of infection, the M protein of SARS-CoV-2 targets the Leydig cells. This leads to a drop in the ratio of serum testosterone and luteinizing hormone [15]. Androgen receptor activity is stimulated by testosterone and 5α-dihydrotestosterone [16]. The activated androgen receptor was shown to regulate the expression of TMPRSS2 known to prime the S protein of SARS-CoV-2 providing the cleavage at the S1/S2 and the S2' sites necessary for the fusion of viral and cellular membranes [16]. Protease TMPRSS2 plays an important role in SARS-CoV-2 infection because it is expressed in epithelial cells, lining the respiratory tract including nose, trachea, alveoli, and type II pneumocytes – the entry ways for the virus into the organism [17].

AKR1C2 enzyme, which belongs to Aldo-keto reductase superfamily, deactivates the potent androgen [18-20]. Recently, the high-confidence proximity interaction between the viral M protein and human AKR1C2 was detected by applying proximity-dependent biotinylation (BioID) with the fast-acting miniTurbo enzyme to SARS-CoV-2 proteins *in vitro* [21] (not peer reviewed preprint). In the healthy cell, testosterone is converted to 5α-dihydrotestosterone by the enzyme 5α-reductase. The obtained 5α-dihydrotestosterone is an active form of testosterone that is converted to inactive testosterone by the enzyme AKR1C2 [20, 22]. The availability of the active testosterone in the healthy cell is controlled by the feedback loop mechanism. As a result, the availability of active testosterone is maintained at an optimum level. The active testosterone binds to the androgen receptor and activates it. The activated androgen receptor in turn promotes the transcription of the TMPRSS2 gene [23]. By binding to AKR1C2 protein, SARS-CoV-2 M protein inhibits the conversion of active testosterone to its inactive form catalyzed by AKR1C2. As a result, the concentration of active testosterone in the cell increases. That makes the interaction of the viral M protein with AKR1C2 enzyme pivotal for the availability of active testosterone in the cell. This interaction eventually leads to the upregulation of the transcription of the TMPRSS2 gene, enhanced viral infection, and in turn higher mortality in men, since they have a much higher testosterone level than women. The discovery of small drug molecules specifically blocking this interaction will counteract the strategy employed by SARS-CoV-2 and lead to the development of new antiviral agents that can help to suppress the spread of the infection.

Here, for the first time, we trace the link between the viral M protein and the changes in the concentration of active testosterone that eventually lead to the upregulation of cell TMPRSS2 expression in the course of a SARS-CoV-2 infection. Since the level of the testosterone in males is significantly higher than in females [24], the action of M protein could lead to much higher concentrations of active testosterone in males that eventually leads to their higher mortality rates from SARS-CoV-2.

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