DOI: 10.4274/MMJ.galenos.2025.40460
Medeni Med J 2025;40:101-109

Review

TMPRSS2: A Key Host Factor in SARS-CoV-2 Infection and Potential Therapeutic Target

TMPRSS2: SARS-CoV-2 Enfeksiyonunda Önemli Bir Konak Faktörü ve Potansiyel Terapötik Hedef

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ABSTRACT

The transmembrane serine protease 2 (*TMPRSS2*) gene plays a crucial role in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection by priming the viral spike protein for membrane fusion and facilitating viral entry into host cells. This review aims to explore the molecular function of TMPRSS2, its genetic variations, and its potential as a therapeutic target in corona virus disease 2019 (COVID-19) and other respiratory viral infections. TMPRSS2 is highly expressed in lung and prostate tissues and is regulated by androgens, which may contribute to sex-based differences in COVID-19 severity. Genetic polymorphisms in TMPRSS2 have been been associated with variability in disease susceptibility and severity across populations. Several TMPRSS2 inhibitors, including serine protease inhibitors, such as camostat mesylate and nafamostat, have demonstarted promise in blocking viral entry. In addition, RNA based strategies such as siRNA and clustered regularly interspaced short palindromic repeats offer potential approaches for downregulating TMPRSS2 expression. However, the development of selective inhibitors that avoid off target effects remains a challenge. The presence of *TMPRSS2-ERG* gene fusion, commonly found in prostate cancer, has also been linked to altered COVID-19 susceptibility, suggesting a complex interplay between viral infection and cancer biology. This review also discusses future perspectives, including large-scale genomic studies to identify high-risk individuals, the development of next-generation TMPRSS2 inhibitors, and potential broad-spectrum antiviral therapies targeting TMPRSS2.

Keywords: Transmembrane serine protease 2, Severe acute respiratory syndrome coronavirus 2, corona virus disease-2019, viral entry, therapeutic targets

ÖZ

Transmembran serin proteaz 2 (*TMPRSS2*) geni, membran füzyonu için viral spike proteinini hazırlayarak ve konakçı hücrelere viral girişi kolaylaştırarak şiddetli akut solunum yolu sendromu koronavirüs 2 (SARS-CoV-2) enfeksiyonunda önemli bir rol oynar. Bu derleme, *TMPRSS2*'nin moleküler işlevini, genetik varyasyonlarını ve koronavirüs hastalığı 2019 (COVID-19) ve diğer solunum yolu viral enfeksiyonlarında terapötik bir hedef olarak potansiyelini araştırmayı amaçlamaktadır. TMPRSS2 akciğer ve prostat dokularında yüksek oranda eksprese edilir ve androjenler tarafından düzenlenir, bu da COVID-19 şiddetinde cinsiyete dayalı farklılıklara katkıda bulunabilir. TMPRSS2'deki genetik polimorfizmler, popülasyonlar arasında hastalık duyarlılığı ve şiddetindeki değişkenlikle ilişkilendirilmiştir. Camostat mesilat ve nafamostat gibi serin proteaz inhibitörleri de dahil olmak üzere çeşitli TMPRSS2 inhibitörleri, viral girişin bloke edilmesinde umut vaat etmiştir. Buna ek olarak, siRNA ve kümelenmiş düzenli aralıklı kısa palindromik tekrarlar gibi RNA tabanlı stratejiler, TMPRSS2 ekspresyonunun aşağı regülasyonu için potansiyel yaklaşımlar sunmaktadır. Bununla birlikte, hedef dışı etkilerden kaçınan seçici inhibitörlerin geliştirilmesi bir zorluk olmaya devam etmektedir.

Prostat kanserinde yaygın olarak bulunan *TMPRSS2-ERG* gen füzyonunun varlığı da değişmiş COVID-19 duyarlılığı ile bağlantılıdır ve viral enfeksiyon ile kanser biyolojisi arasında karmaşık bir etkileşim olduğunu düşündürmektedir. Bu derlemede ayrıca, yüksek riskli bireyleri belirlemek için büyük ölçekli genomik çalışmalar, yeni nesil TMPRSS2 inhibitörlerinin geliştirilmesi ve TMPRSS2'yi hedefleyen potansiyel geniş spektrumlu antiviral tedaviler de dahil olmak üzere geleceğe yönelik perspektifler tartışılmaktadır.

Anahtar kelimeler: Transmembran serin proteaz 2, şiddetli akut solunum yolu sendromu koronavirüs 2, koronavirüs hastalığı 2019, viral giriş, terapötik hedefler

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Received: 02.02.2025
Accepted: 10.05.2025
Published: 26 June 2025

Cite as: Haily Liduin K, Salleh MN, Jelemie CS, Badrin MJQ, Prastiyanto ME, Ramachandran V. TMPRSS2: A key host factor in SARS-CoV-2 infection and potential therapeutic target. Medeni Med J.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to an unprecedented global health crisis, affecting millions of people worldwide[1,2]. SARS-CoV-2 primarily targets the respiratory system, with clinical manifestations ranging from mild flu-like symptoms to severe pneumonia, acute respiratory distress syndrome (ARDS), and multi-organ failure. Despite extensive research on viral pathogenesis and host-virus interactions, effective antiviral strategies remain limited[3,4]. One of the key factors influencing SARS-CoV-2 infection is the host protease *transmembrane serine protease 2* (*TMPRSS2*) (Figure 1), which plays a critical role in viral entry by facilitating spike (S) protein priming and fusion with host cell membranes[5].

TMPRSS2 is a *TMPRSS2* encoded by the TMPRSS2 gene located on chromosome 21q22.36.

Its role in viral infections was first recognized in influenza and other coronaviruses (e.g., SARS-CoV-1 and MERS-CoV,), where it enhanced viral entry by cleaving hemagglutinin (HA) and spike glycoproteins. In SARS-CoV-2 infection, TMPRSS2 functions in conjunction with *angiotensin-converting enzyme 2* (ACE2), the primary receptor for the virus. Upon binding of the viral S protein to ACE2, TMPRSS2 cleaves the S1/S2 site, triggering membrane fusion and viral entry, thereby bypassing the endosomal pathway[7].

Interestingly, TMPRSS2 is androgen-regulated, which may explain sex-based differences in COVID-19 severity, with males exhibiting higher susceptibility and worse outcomes than females. Furthermore, genetic polymorphisms in TMPRSS2 have been associated with variations in susceptibility to infection and severity across different populations. Additionally, TMPRSS2-*E26 transformation-specific-related gene* (*ERG*) fusion, commonly found in prostate cancer, has raised questions about the potential link between cancer, androgen signalling, and COVID-19 outcomes[8].

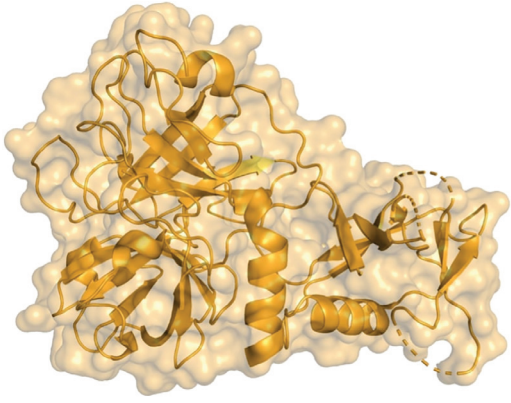

Figure 1. Illustration of TMPRSS2 protein structure from the PDB database.

TMPRSS2: Transmembrane protease serine 2, PDB: Protein Data Bank

The *TMPRSS2* gene plays a critical role in SARS-CoV-2 infection by helping the virus enter human cells. It does so by priming the viral spike protein, allowing it to fuse with the host cell membrane. This process is androgen-regulated, meaning it is influenced by male hormones. As a result, males tend to have higher levels of TMPRSS2 and may experience more severe outcomes from COVID-19 compared to females. Additionally, genetic variations in TMPRSS2 have been linked to differences in how individuals respond to the virus, with some populations being more susceptible to infection or severe disease[8].

An important genetic alteration associated with prostate cancer is the TMPRSS2-ERG fusion, where the TMPRSS2 gene fuses with the *ERG* gene. This fusion leads to overexpression of the ERG protein, which contributes to prostate cancer progression[9]. Since TMPRSS2 is essential for SARS-CoV-2 entry into cells, the *TMPRSS2-ERG* fusion could increase the susceptibility of prostate cancer patients to COVID-19, as they may have higher levels of TMPRSS2 expression. This potential link between prostate cancer, androgen signaling, and COVID-19 severity has raised important questions[10,11]. Prostate cancer therapies, such as androgen deprivation therapy (ADT), may affect the immune system and influence how patients respond to viral infections like SARS-CoV-2. Understanding how the TMPRSS2-ERG fusion impacts both cancer and COVID-19 can help identify high-risk patients and inform potential treatment strategies[12].

Given the critical role of TMPRSS2 in viral entry, it has emerged as a promising therapeutic target for COVID-19. Several pharmacological inhibitors-including serine protease inhibitors such as camostat mesylate and Nafamostat-have demonstrated the ability to block TMPRSS2-mediated SARS-CoV-2 entry[13]. Additionally, RNA-based approaches, such as siRNA and clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR)-Cas9, have been explored to downregulate TMPRSS2 expression. However, challenges remain in developing selective inhibitors that minimize off-target effects because TMPRSS2 also plays a physiological role in lung homeostasis.

This review aims to provide a comprehensive overview of TMPRSS2 in the context of SARS-CoV-2 infection, including its molecular function, genetic variability, and potential as a therapeutic target. We discuss emerging research on TMPRSS2 inhibitors, the impact of genetic polymorphisms on COVID-19 susceptibility, and future perspectives on targeting TMPRSS2 for broad-spectrum antiviral therapy. Understanding the interplay between

TMPRSS2 and SARS-CoV-2 may provide new insights into the disease mechanisms and pave the way for effective therapeutic interventions.

Structure and Function of *TMPRSS2*

The *TMPRSS2* gene encodes a *TMPRSS2* that plays a crucial role in various physiological and pathological processes, including viral infections and cancer progression[14]. This gene is highly expressed in epithelial tissues, particularly in the lungs, prostate, gastrointestinal tract, and kidneys, making it a key factor in respiratory viral infections[15].

TMPRSS2 is a membrane-bound serine protease that consists of several structural domains (Figure 2). The cytoplasmic domain (N-terminal region) is responsible for intracellular signalling. The transmembrane domain anchors proteins to the plasma membrane. The low-density lipoprotein receptor class A domain is thought to facilitate protein-protein interactions. The scavenger receptor cysteine-rich domain may be involved in ligand binding. A serine protease catalytic domain (C-terminal region) is responsible for cleaving and activating substrates, including viral glycoproteins[16]. The catalytic activity of TMPRSS2 depends on a conserved histidine (H), aspartic acid (D), and serine (S) catalytic triad, which is characteristic of serine proteases[17].

Beyond its involvement in viral infections, TMPRSS2 plays important roles in normal physiological processes. Particularly in lung homeostasis, TMPRSS2 is expressed in alveolar epithelial cells, where it regulates epithelial sodium channels, which are critical for lung fluid balance[18]. *TMPRSS2* is recognized for its regulation by androgens, particularly in the prostate, where its abnormal activity, such as fusion with the ERG oncogene, has been associated with the progression of prostate cancer. This regulation is mediated by the androgen receptor (AR)[19]. When androgens bind to AR, the complex translocates to the nucleus and enhances TMPRSS2 transcription by interacting with specific androgen-responsive elements within the gene's promoter region[20]. Although TMPRSS2 is clearly androgen-responsive, current evidence does not confirm whether postmenopausal women exhibit increased TMPRSS2 expression in the respiratory tract[21]. Nevertheless, the decline in estrogen levels after menopause may alter immune function, potentially affecting the response to viral infections. Further investigation is required to clarify TMPRSS2 expression patterns and their implications in this population[22,23]. TMPRSS2 expression in the gastrointestinal tract suggests a possible involvement in the regulation of digestive processes, while its presence in endothelial cells points to a potential role in maintaining vascular integrity and homeostasis[24,25].

TMPRSS2 in SARS-CoV-2 Infection

TMPRSS2 plays a crucial role in the early stages of SARS-CoV-2 infection by facilitating viral entry into the host cells (Figure 3). SARS-CoV-2, like other coronaviruses, relies on host proteases to cleave its spike (*S*) glycoprotein, which enables fusion with the host cell membrane. The viral spike protein is composed of two subunits: S1, which is responsible for receptor binding,

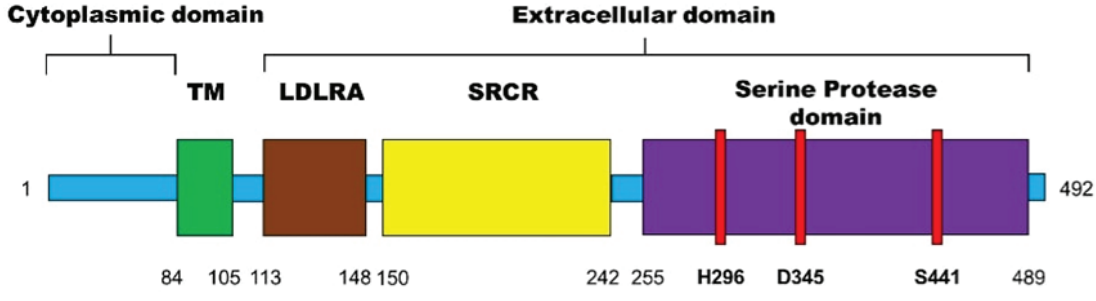

Figure 2. TMPRSS2 structural domains.

TMPRSS2: Transmembrane protease serine 2, LDLRA: Low-density lipoprotein receptor class A, SRCR: Scavenger Receptor Cysteine-Rich

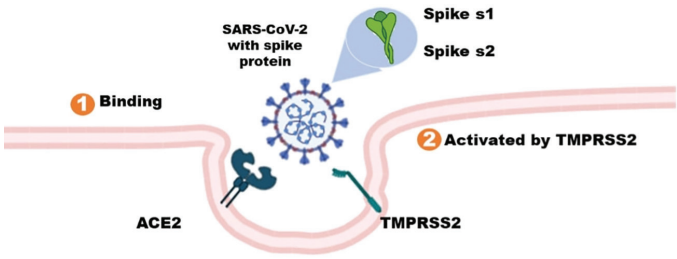

Figure 3. Illustration of TMPRSS2 protein structure from the PDB database.

TMPRSS2: Transmembrane protease serine 2, PDB: Protein Data Bank, ACE2: Angiotensin-converting enzyme 2, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

and S2, which mediates membrane fusion. *TMPRSS2* specifically cleaves the S1/S2 junction and the S2′ site of the spike protein, which is essential for viral-host membrane fusion and subsequent viral RNA release into the cytoplasm[16].

SARS-CoV-2 primarily uses the ACE2 receptor for host cell attachment. The interaction between the viral receptor-binding domain of S1 and ACE2 is a prerequisite for infection. However, ACE2 binding alone is not sufficient for viral entry, and proteolytic activation of the spike protein is required to expose the fusion peptide. TMPRSS2 cleaves and activates the spike protein at the cell surface, enabling direct fusion of the viral and host membranes, bypassing the need for endosomal processing[16].

In the absence of *TMPRSS2*, SARS-CoV-2 can enter cells via an alternative endosomal pathway that is mediated by cathepsin L/B. However, this route is generally less efficient and is more dependent on endosomal acidification. Studies have shown that TMPRSS2-expressing cells have significantly higher viral infectivity compared to those relying on cathepsins alone[17]. This explains why inhibitors of *TMPRSS2*, such as Camostat mesylate, effectively block SARS-CoV-2 infection, whereas cathepsin inhibitors have limited efficacy.

Notably, TMPRSS2 expression is regulated by androgens, leading to higher expression levels in males compared to females. This may contribute to the observed sex-based differences in COVID-19 severity, with males experiencing higher rates of severe disease and mortality. Studies suggest that ADT, commonly used in prostate cancer treatment, may reduce TMPRSS2 expression and lower COVID-19 severity in prostate cancer patients[26].

Additionally, *TMPRSS2* expression levels increased with age, particularly in lung tissue. This may partially explain why older individuals are more susceptible to severe SARS-CoV-2 infections, as higher *TMPRSS2* levels can enhance viral entry and replication.

TMPRSS2-Mediated SARS-CoV-2 Pathogenesis

In addition to viral entry, *TMPRSS2* may contribute to COVID-19 severity by promoting viral spread and tissue damage. Infected epithelial cells undergo apoptosis and inflammatory cytokine release, exacerbating lung injury and leading to ARDS in severe cases[27]. *TMPRSS2*'s role in facilitating direct viral entry rather than endosomal processing may also influence immune evasion strategies employed by SARS-CoV-2.

The role of TMPRSS2 is not unique to SARS-CoV-2; it also plays a crucial role in other coronaviruses. Similar to SARS-CoV-2, SARS-CoV-1 utilizes TMPRSS2 for spike protein activation and cell entry. *TMPRSS2* inhibition reduces SARS-CoV-1 infectivity. Unlike SARS-CoV-2, MERS-CoV primarily binds to dipeptidyl peptidase 4 instead of ACE2. However, TMPRSS2 is still involved in spike protein priming, playing a role in viral tropism and pathogenesis[28]. *TMPRSS2* also activates the HA protein of influenza A virus, facilitating viral entry into host cells. This highlights its broad role in respiratory viral infections, making it an attractive antiviral target beyond coronaviruses.

Genetic Variability and Population Susceptibility

Genetic variation in *TMPRSS2* has been implicated in the differential susceptibility to SARS-CoV-2 infection and COVID-19 severity across populations. Polymorphisms in TMPRSS2 can influence its expression levels, enzymatic activity, and interaction with the viral spike protein, affecting viral entry efficiency and disease outcomes (Table 1)[16,29-33].

Several single-nucleotide polymorphisms (SNPs) in *TMPRSS2* have been identified as potential modulators of SARS-CoV-2 infection. Genome-wide association studies have revealed that variants such as rs2070788 and rs383510 are associated with increased expression of TMPRSS2 in lung tissues, potentially enhancing viral entry and increasing disease severity[16]. Conversely, certain loss-of-function mutations may confer partial resistance to SARS-CoV-2 by reducing TMPRSS2-mediated spike protein cleavage[33].

A study by Asselta et al.[29] reported that the rs12329760 (V160M) SNP, a missense variant in TMPRSS2, is associated with reduced proteolytic activity, potentially leading to lower viral entry efficiency and milder COVID-19 symptoms. This variant is more prevalent in

Table 1. Key TMPRSS2 polymorphisms and their association with COVID-19.

Study	SNP (rsID)	Variant type	Effect on TMPRSS2 expression	Population distribution	Impact on COVID-19 susceptibility/severity	c.DNA locus
Hoffmann et al.[16] (2020)	rs464397, rs469390, rs383510 and rs2070788	Upstream variant	Increased TMPRSS2 expression in lungs	High in Europeans and Africans	Higher risk of severe COVID-19 due to increased viral entry efficiency	chromosome 21q22.3,
Asselta et al.[29] (2020)	rs2285666 (c.439+4G>A) and rs35803318 (p.Val749Val)	Upstream variant	Increased TMPRSS2 expression	High in Europeans	Higher susceptibility to SARS-CoV-2 infection	Xp22 in intron 3
Irham et al.[30] (2020)	rs12329760 (p.Val160Met))	Missense mutation	Reduced TMPRSS2 protease activity	Common in East Asians	Potential protective effect, lower viral entry efficiency	chr21:41480570
Adli et al.[31] (2022)	rs75603675 (p.Gly197Ser)	Missense mutation	Alters TMPRSS2 enzymatic activity	Higher in South Asian populations	Possible role in modifying COVID-19 outcomes	chr21:41507982
Zeberg and Pääbo[32] (2020)	rs8134378 (c.585+312T>C)	Intronic variant	Affects TMPRSS2 regulation	High in African populations	Linked to severe COVID-19 cases in some studies	Intron 6, chr21:41521831
Daniloski et al.[33] (2020)	rs35074065 (c.-74+475A>G)	Regulatory variant	Alters TMPRSS2 transcription	Present in multiple ethnic groups	Associated with lung tissue expression variability	chr21:41461593

COVID-19: Corona virus disease 19, TMPRSS2 The transmembrane serine protease 2, SNP: Single-nucleotide polymorphisms

East Asian populations, suggesting potential population-level differences in COVID-19 susceptibility[30]. Studies have shown that *TMPRSS2* expression varies significantly across ethnic groups, which may contribute to disparities in COVID-19 severity. For instance, higher expression levels have been reported in European and African populations compared to East Asians, correlating with the prevalence of high-expression SNPs such as rs207078824. This could partly explain the observed differences in COVID-19 hospitalization and mortality rates among different ethnic groups[31].

Furthermore, variations in *TMPRSS2* expression were influenced by the local genetic landscape and evolutionary pressure. The high prevalence of specific TMPRSS2 SNPs in certain populations may reflect historical adaptation to past pandemics involving coronaviruses or other respiratory pathogens[32].

Androgen Regulation and Sex-Based Differences

Sex-based disparities in COVID-19 outcomes have been widely documented, with males experiencing higher mortality rates than females[35]. One contributing factor is the androgen-regulated expression of *TMPRSS2*, which is significantly upregulated in male tissues, including the lungs and prostate[36]. The androgen response element within the TMPRSS2 promoter region enhances its transcriptional activity in response to circulating testosterone levels, leading to higher expression in males[37].

This regulation may provide a mechanistic explanation for the higher disease severity observed in male subjects. In contrast, female sex hormones such as estrogen have been suggested to downregulate TMPRSS2 expression, potentially offering a protective effect[38]. Clinical trials have explored the use of ADT to reduce TMPRSS2 expression and mitigate COVID-19 severity in high-risk male populations[39].

Cancer-Related Gene Fusions and Their Potential Role in COVID-19 Susceptibility

Gene fusions, such as the *TMPRSS2-ERG* fusion commonly observed in prostate cancer, have been linked to altered TMPRSS2 expression, potentially affecting viral entry and increasing susceptibility to SARS-CoV-2[37]. However, gene fusions are not exclusive to prostate cancer. Similar alterations have been observed in other cancers, including lung, breast, and cholangiocarcinoma, where changes in TMPRSS2 expression could influence

COVID-19 outcomes[40,41]. While cancer-related gene fusions may contribute to altered immune responses, the direct connection between these fusions and COVID-19 severity remains an area of ongoing research[42,43].

Patients with cancers, particularly aggressive or metastatic types, are generally at higher risk for severe COVID-19 outcomes due to factors such as immune dysregulation, tumor microenvironment, and pre-existing comorbidities. However, further studies are needed to clarify whether specific gene fusions in various cancers contribute directly to SARS-CoV-2 susceptibility or severity[44,45].

TMPRSS2 as a Therapeutic Target

Given its critical role in SARS-CoV-2 entry, *TMPRSS2* has emerged as a promising therapeutic target for COVID-19 treatment. Unlike endosomal entry mechanisms that rely on cathepsins, *TMPRSS2*-mediated viral entry occurs at the plasma membrane, facilitating direct fusion of the viral envelope with the host cell membrane. Blocking *TMPRSS2* activity effectively prevents spike protein cleavage, thereby inhibiting viral entry and reducing infection rates. Unlike ACE2, which has essential physiological functions in the renin-angiotensin system, TMPRSS2 is a non-essential protease, making it a safer therapeutic target with fewer systemic side effects[16].

Several serine protease inhibitors have been investigated for their ability to block *TMPRSS2* activity and prevent SARS-CoV-2 infections. Camostat mesylate, a synthetic serine protease inhibitor, was initially developed for the treatment of chronic pancreatitis and postoperative reflux esophagitis. It has been shown to effectively inhibit *TMPRSS2*-mediated spike protein priming and prevent SARS-CoV-2 entry *in vitro*. Early clinical trials suggested that Camostat mesylate might reduce viral load and improve outcomes in COVID-19 patients. However, its short half-life and need for frequent dosing present limitations for clinical use[46].

Nafamostat, a structurally related serine protease inhibitor, exhibited higher potency than camostat in inhibiting *TMPRSS2* activity. Due to its strong anti-coagulant properties, it has been explored as a dual therapy for COVID-19 patients with thrombotic complications. Nafamostat efficiently blocks spike protein processing at nanomolar concentrations, and has demonstrated promising results in preclinical studies. However, intravenous administration and potential bleeding risks limit its widespread use[47].

Bromhexine, an over-the-counter mucolytic drug, has been identified as an indirect *TMPRSS2* inhibitor. It reduces TMPRSS2 expression, and has been shown to be effective in decreasing viral replication in preliminary studies. While promising, further clinical validation is required to establish its role in COVID-19 treatment[48].

Gene-silencing technologies offer an alternative approach to inhibiting TMPRSS2, reducing its expression rather than directly targeting its enzymatic activity; siRNA-based therapeutics can selectively degrade TMPRSS2 mRNA, reducing protein expression and preventing SARS-CoV-2 entry. Several *in vitro* studies have demonstrated that *TMPRSS2*-targeting siRNAs effectively suppress viral infection. However, challenges such as efficient delivery, stability, and potential off-target effects remain significant barriers to clinical application[49].

CRISPR-Cas9 and CRISPR interference (CRISPRi) technologies have been explored for the selective knockdown of *TMPRSS2* expression. These genome-editing approaches could provide long-term resistance against coronaviruses, but face regulatory and ethical challenges before clinical translation[50].

Because *TMPRSS2* is regulated by androgens, hormonal modulation has been proposed as a strategy to reduce its expression and limit SARS-CoV-2 infection. ADT, which is commonly used for prostate cancer, has been suggested as a potential strategy for reducing *TMPRSS2* expression in COVID-19 patients. Drugs, such as bicalutamide and enzalutamide, which inhibit AR signaling, have shown promise in reducing *TMPRSS2* levels in lung tissues. Retrospective studies have suggested that prostate cancer patients receiving ADT have lower rates of severe COVID-19. However, broader clinical trials are needed to validate these findings[51].

Finasteride and dutasteride, used to treat benign prostatic hyperplasia, inhibit 5-alpha reductase, an enzyme that converts testosterone to its more active form, dihydrotestosterone (DHT). By lowering the DHT levels, these drugs may indirectly reduce *TMPRSS2* expression and viral entry. Clinical trials are currently underway to assess their efficacy against COVID-19. Several Food and Drug Administration-approved drugs have been investigated for TMPRSS2 inhibition, and aprotinin has shown efficacy in inhibiting SARS-CoV-2 entry. Aprotinin is a protease inhibitor used in surgeries to reduce bleeding. E-64d, a cathepsin inhibitor, has been explored in combination with *TMPRSS2* inhibitors to block both the membrane fusion and endosomal viral entry pathways. While *TMPRSS2* inhibitors prevent membrane fusion, ACE2-based therapies, such as soluble ACE2 decoys, can block viral attachment. Combining

TMPRSS2 inhibition with ACE2 blockade may enhance antiviral efficacy[52].

Challenges and Future Directions

Despite the promise of *TMPRSS2* inhibitors, several challenges remain to be overcome. Selective inhibition: *TMPRSS2* plays physiological roles in lung function, and complete inhibition may have unintended side effects. The development of highly selective inhibitors that target viral entry while preserving normal lung function is crucial. Delivery mechanisms: RNA-based therapies require efficient delivery systems that target lung epithelial cells. Advances in nanoparticle and lipid-based delivery systems could improve their clinical feasibility[53].

Clinical validation: many *TMPRSS2* inhibitors have shown efficacy in preclinical models, but large-scale clinical trials are required to confirm their safety and effectiveness in COVID-19 patients. Broad-Spectrum Antiviral potential: since *TMPRSS2* also facilitates infection by other coronaviruses (e.g., SARS-CoV-1, MERS-CoV) and influenza viruses, developing *TMPRSS2*-targeting drugs could provide protection against future pandemics[16].

CONCLUSION

TMPRSS2 plays a pivotal role in the pathogenesis of SARS-CoV-2 by facilitating viral entry through the cleavage of the spike protein. Its expression in lung and prostate tissues, combined with androgen regulation, may explain the sex-based differences in COVID-19 severity. Genetic variants of *TMPRSS2* contribute to the variability in disease susceptibility and severity, highlighting the need for personalized therapeutic strategies. Several *TMPRSS2* inhibitors, including serine protease inhibitors such as Camostat mesylate and Nafamostat, show promise in clinical trials for reducing viral entry and infection. Additionally, RNA-based approaches, such as siRNA and CRISPR, offer potential strategies for downregulating *TMPRSS2* expression. The association of *TMPRSS2* with prostate cancer underscores its dual role in viral infection and cancer biology, suggesting broader therapeutic implications. Future research should focus on large-scale genomic studies to identify high-risk populations and develop selective *TMPRSS2* inhibitors. These efforts will be key to advancing antiviral therapies for COVID-19 and preparing for future pandemics involving similar respiratory viruses. Targeting *TMPRSS2* offers a promising approach for managing COVID-19 and other viral infections.

Ethics

Author Contributions

Concept: M.N.S., V.R., Design: H.L.K., V.R., Data Collection and/or Processing: C.S.J., M.J.Q.B., M.E.P., Analysis and/or Interpretation: M.N.S., V.R., Literature Search: H.L.K., C.S.J., M.J.Q.B., Writing: H.L.K., M.E.P.

Conflict of Interest: The authors have no conflict of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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