Immediate remedies involving the inhibition of TMPRSS2 in SARS and SARS-CoV-2

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Abstract:

TMPRSS2 plays an integral role in the infection of host cells by SARS-CoV-2. Here I explore the role of TMPRSS2 in infection and look at potential inhibitors.

Introduction:

SARS and SARS-CoV-2 have an 86% genome similarity. Both likely jumped from bats to humans and both spread through coughing and sneezing by infected individuals. Both also infect epithelial cells in our lungs through the ACE2 receptor(The spike receptor binding domain of the spike protein binds to ACE2). TMPRSS2 is co-expressed with ACE2 and has been found to have a pivotal role in coronavirus infection.(1) By applying the vast amount of information available on SARS to SARS-CoV-2, new avenues for research can be opened and old ones can be repurposed. Here I explore the role of the TMPRSS2 in SARS and SARS-CoV-2 and reflect on practical, urgent remedies to the current situation.

Table 1. Experimental data on the role of airway proteases in the activation of influenza-, corona- and paramyxoviruses

Protease	Virus	*In vitro* evidence	*In vivo* evidence
TMPRSS2	Influenza A and B virus	The HA0s from H1N1, H2N2, H3N2 or influenza B are cleaved in cells overexpressing TMPRSS2 enabling trypsin-independent replication [25••, 36, 66]. Knockdown of TMPRSS2 in Calu-3 cells inhibits cleavage of H1N1 [67]	TMPRSS2-KO mice survive lethal infection with influenza H1N1 or H7N9 [15, 16]. In contrast, influenza B virus is lethal in TMPRSS2-KO mice [37]
	SARS, MERS and 229E coronaviruses	The coronavirus S-protein is cleaved when co-expressed with TMPRSS2 [31, 62•, 64, 68]	
	Metapneumovirus and parainfluenzavirus	The viruses efficiently replicate in cells overexpressing TMPRSS2 and their F protein is cleaved [58, 59]	

(1)

The Role of TMPRSS2:

TMPRSS2 is co-expressed with the ACE2 and HAT proteins. It is found primarily on the plasma membrane of epithelial cells in the prostate. However, here is plays a vital role in the lungs along with ACE2, a receptor for the spike glycoprotein of some beta-coronaviruses. TMPRSS2 has a role in many airway related viruses including influenza, MERS, and SARS.(1) In cell cultures, TMPRSS2 cleaves the SARS spike glycoprotein at two sites, mediating virus-cell fusion. The HAT protein which is also cleaves the spike glycoprotein(but only at one site) has been found to mediate cell-cell fusion(syncytium formation was 15 times more likely in HAT transfected cells), something not correlated with TMPRSS2. From this, we can reasonably state that TMPRSS2 plays a role in SARS infection in the lungs.(2) This can be applied to SARS-CoV-2 as well. SARS-CoV-2 infects cells in much the same way as SARS as evidenced by the effectiveness of a TMPRSS2 inhibitor in blocking host cell entry by SARS. TMPRSS2 plays a pivotal role in SARS-CoV-2 infection as well and is a prime target for drug development. I shall begin outlining inhibitors.

Potential Inhibitors:

In prostate epithelial tissue, where TMPRSS2 is primarily expressed, it is upregulated by androgens. While the 56% male infection rate for men vs 44% for women can be partially explained by variables such as susceptibility to other conditions or propensity to smoke, it lends slight credence to the role of androgen in the SARS-CoV-2.(3) Furthermore, smoking has been shown to increase androgen levels.(4) It was found that sulphoraphane, a naturally occurring compound found in cruciferous vegetables like broccoli and cabbage decreases the expression of TMPRSS2 by reducing androgen receptor signaling. Furthermore, it reduced infection of lung epithelial cells by Influenza A.(6)

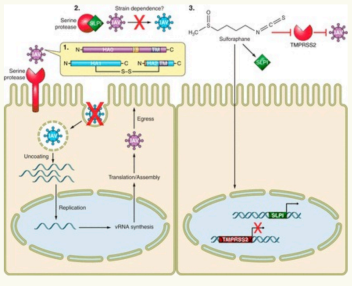

Fig. 3.

The protease/antiprotease balance regulates influenza A virus (IAV) infection and can be modulated by SFN supplementation. *1*: For entry into target host cells, the hemagglutinin (HA) protein on the IAV virion must be proteolytically cleaved from HA0 (purple) into fusoactive HA1 and HA2 proteins (blue). *2*: Respiratory serine proteases such as TMPRSS2 (TM), the human airway trypsin-like protease (HAT), and matriptase have been implicated in HA activation and IAV infection, which are likely to strain specific. Although antiproteases such as SLPI inhibit serine protease activity and protect against IAV infection, it remains unknown what HA-activating protease is inhibited by SLPI and how SLPI mediates these effects. *3*: Lastly, SFN supplementation can be used to increase SLPI secretion, reduce TMPRSS2 secretion, and decrease viral entry and downstream IAV infection.

(6)
Considering this link, testing of some Influenza drugs on SARS-CoV-2 may also be prudent. Nafamostat is a drug identified to inhibit TMPRSS2 action on the plasma membrane and in vitro was demonstrated to decrease the number of viral progeny following infection.(5) Furthermore, considering the importance of TMPRSS2 in Influenza infections, the repurposing of Influenza drugs for this new outbreak may be promising.

Conclusions:

A promising avenue for research is the effect of sulphoraphane on SARS-CoV-2 infections, something that has not yet been explored in great detail. Another promising avenue for research is Nafamostat. This seems to be the best option as of yet but more information on specific interactions with SARS-CoV-2 is required. TMPSRSS2 is a protease that plays a pivotal role in many lung related viral ailments, investing in research into drugs that can inhibit this protease effectively will be effective not only in the current pandemic but also in those of the future. More research is needed on specific interactions between SARS-CoV-2 and TMPRSS2 and more research is needed on the impact of drugs that have been isolated as TMPRSS2 inhibitors on the current outbreak.

Works Cited:

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