Hormonal control and therapeutic targeting of TMPRSS2 and ACE2 as a potential strategy to combat COVID-19

Background: The novel SARS-CoV-2 infection responsible for the COVID-19 pandemic is expected to have an adverse effect on the progression of multiple cancers, including prostate cancer, due to the ensuing cytokine storm associated oncogenic signaling. A better understanding of the host cell factors and their regulators will help identify potential therapies to block SARS-CoV-2 infection at an early stage and thereby prevent cancer progression. Host cell infection by SARS-CoV-2 requires the binding of the viral Spike S protein to ACE2 receptor and priming by the serine protease TMPRSS2 – encoded by a well-known androgen response gene and highly expressed in hormone-sensitive and castration-resistant prostate cancer. Epidemiological data showing increased severity and mortality of SARS-CoV-2 disease in men suggest a possible role for androgen in the transcriptional activation of ACE2 and TMPRSS2 in the lungs and other primary infection sites.

Methods: Experimental methods used are physical castration of mice, immunohistochemistry for AR, TMPRSS2 and ACE2 in multiple organs, qRT-PCR, ChIP-seq, immunoblotting, Co-IP, SARS-CoV-2 pseudovirus spinoculation, and viral entry reporter assays in prostate and lung cells.

Results: We present evidence for the transcriptional regulation of SARS-CoV-2 host cell receptor ACE2 and co-receptor TMPRSS2 by androgen in mouse organs (lungs and small intestine), and human prostate and lung cells. Additionally, we provide the first evidence for the endogenous interaction between TMPRSS2 and ACE2 in human cells. In an overexpression system as well as endogenous TMPRSS2 expression cells, camostat – a serine-protease inhibitor specific to TMPRSS2 - inhibited the cleavage of pseudotype SARS-CoV-2 surface Spike S protein without disrupting TMPRSS2-ACE2 interaction. Thus demonstrating a direct role of TMPRSS2 in priming the viral Spike S protein, a prerequisite for an active infection. Importantly, androgen deprivation, anti-androgens (enzalutamide/AR-PROTAC), or camostat attenuated the SARS-CoV-2 pseudovirus infection in lung and prostate cells.

Conclusions: Our preclinical data provide a strong rationale for clinical evaluation of TMRPSS2 inhibitors, androgen-deprivation therapy such as GnRH antagonist, and AR-signaling blockers alone or in combination with antiviral drugs as early as clinically possible. This will likely prevent progression to pneumonia, and multi-organ failure because of hyper-inflammatory responses in COVID-19 patients with or without cancer.