

## EDITORIAL

# Androgen hazards with COVID-19

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(2020) **27**, E1–E3

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019 spurred the coronavirus disease 2019 (COVID-19) pandemic. A notable finding in many affected countries is that men have worse clinical outcomes and COVID-19 deaths compared with women (Grasselli *et al.* 2020, Moalem 2020). Sex differences in smoking do not appear to account for poorer outcomes (Cai 2020). Why then are there worse clinical outcomes for men compared with women? Although the etiology is probably multifactorial, the physiological effects of androgens are one possible reason that may explain these sex-specific differences in outcomes. There are at least two plausible mechanisms by which androgens may drive clinical outcomes in COVID-19. The first possible mechanism is linked to the expression of TMPRSS2, a cellular co-receptor required for SARS-CoV-2 infection (Hoffmann *et al.* 2020). The second possibility is androgen-driven immune modulation. Androgen regulation of the immune response may also partake in notable geographic variations in COVID-19-associated clinical outcomes. Here, we discuss these possible mechanistic scenarios by learning from examples of androgen manipulation in prostate cancer and other disease processes.

SARS-CoV-2 viral entry is known to require two host cellular proteins (Hoffmann *et al.* 2020). First, the virus uses angiotensin converting enzyme-2 (ACE2) to enter into the host cell. Second, the viral spike protein is primed by the TMPRSS2 protease. Separate from viral infections, TMPRSS2, in fact, has a widely recognized role in prostate cancer pathogenesis, as approximately half of all tumors

harbor a translocation that places the TMPRSS2 regulatory element in front of an ETS-family oncogene (Tomlins *et al.* 2005). The androgen-regulated nature of TMPRSS2 is what permits testosterone or dihydrotestosterone-driven oncogene expression in this scenario via the androgen receptor (AR) (Dai *et al.* 2017). In part, because of its oncogene-driving function, TMPRSS2 now serves as a canonical readout of AR-dependent transcription in prostate cancer models and tissues. While benign prostate and prostate cancer are clearly androgen-regulated tissues, this is not as clearly the case for pulmonary tissues. However, there are pulmonary disease processes, including asthma as one example, in which there are sex-dependent differences in clinical outcomes and severity (Zein & Erzurum 2015). TMPRSS2 is regulated by both androgens and glucocorticoids in a lung-derived cell line model (Mikkonen *et al.* 2010). Nevertheless, it is not known if TMPRSS2 expression in the normal human lung is regulated by androgens in physiological settings. If the answer is yes, and TMPRSS2 suppression impedes viral entry or activation, inhibition of (gonadal +/- adrenal) androgen synthesis or direct AR blockade with prostate cancer therapies, including enzalutamide or apalutamide, should be tested clinically.

Androgen modulation of the immune response is the second possible mechanism that may drive clinical outcomes by way of a compromised antiviral immune response to SARS-CoV-2. Generally, androgens have an immune suppressive effect. This is made apparent by several lines of evidence. First, women are disproportionately affected with inflammatory disease

processes compared to men. For example, in the case of asthma, boys generally have worse asthma than girls, and a sex switch occurs after puberty with a surge of gonadal sex steroids, with better outcomes in men and worsening severity in women (DeBoer *et al.* 2018). Second, gonadal testosterone deprivation (i.e. medical or surgical castration) has immune stimulatory effects (Drake *et al.* 2005). Third, suppressed peripheral tissue availability of potent androgens synthesized from adrenal precursor steroids is associated with worse clinical outcomes in inflammatory disease (Zein *et al.* 2020).

This last line of evidence is worth expanding because it may relate to geographical variations in androgen-associated clinical outcomes. In addition to the gonadal source for androgens, the adrenal reticularis synthesizes and secretes abundant, but not directly active, androgens in the form of dehydroepiandrosterone (DHEA) and DHEA-sulfate. DHEA is converted to potent androgens in peripheral tissues in a pathway that is initiated and regulated by 3 $\beta$ -hydroxysteroid dehydrogenase-1 (3 $\beta$ -HSD1; encoded by *HSD3B1*) (Auchus & Sharifi 2020). There are two major known functional forms of *HSD3B1* that correspond to two different human alleles (Chang *et al.* 2013, Sabharwal & Sharifi 2019). The adrenal-restrictive *HSD3B1*(1245A) allele encodes for an enzyme that is rapidly degraded and limits conversion from DHEA to downstream potent androgens. In contrast, the adrenal-permissive *HSD3B1*(1245C) allele encodes for an enzyme that is resistant to degradation, resulting in high steady-state levels of 3 $\beta$ -HSD1 and enabling more rapid potent androgen synthesis from DHEA. Adrenal-permissive and adrenal-restrictive *HSD3B1* allele inheritance confer clinically significant phenotypes as is most clearly evident by multiple studies of prostate cancer treated with medical castration, in which rapid extragonadal androgen synthesis enables more rapid progression to castration-resistant prostate cancer (CRPC) and slower synthesis is linked to delayed progression to CRPC, respectively (Hearn *et al.* 2020).

Do *HSD3B1* alleles and their consequences on peripheral adrenal androgen metabolism confer immune regulation phenotypes? The answer appears to be yes. In low DHEA and DHEA-sulfate physiological states (in this case, exogenous glucocorticoid administration which suppresses DHEA and DHEA-sulfate by 70%), *HSD3B1* genotype correlates with clinical outcomes in two cohorts with severe asthma (Zein *et al.* 2020). Specifically, adrenal-restrictive *HSD3B1* allele inheritance, which impairs potent androgen synthesis, is associated with worsened outcomes in asthma as assessed by multiple clinical

measures and absolute neutrophil count (Zein *et al.* 2020). This observation is consistent with an androgen-mediated immune suppressive effect. Stress and/or infection may also lead to low adrenal androgens in circulation, particularly in DHEA-sulfate (Arlt *et al.* 2006, Foster *et al.* 2020). The asthma data discussed above suggests that divergent functions of *HSD3B1* alleles may become phenotypically clear in the setting of adrenal androgen suppression, in which the substrate for 3 $\beta$ -HSD1 becomes limiting, specifically for the enzyme encoded by the adrenal-restrictive *HSD3B1* allele.

Interestingly, Italy and Spain, European countries most severely affected by COVID-19 at this time, are places that have the highest frequency of the adrenal-permissive *HSD3B1* allele in the general population, as per the 1000 Genomes Project (Sabharwal & Sharifi 2019). Is this attributable, in part, to an immune suppressive role of augmented androgen synthesis with inheritance of the adrenal-permissive *HSD3B1* allele? To test this directly, germline *HSD3B1* information should be interrogated in affected patients.

A broad range of clinical approaches are being deployed against COVID. They range from blockade of ACE2, a key binding site in the lungs, to antimalarial drugs and standard antiviral agents. Observations about the role of TMPRSS2 and its known androgen dependence have prompted questions arising from prostate cancer treatment paradigms. Potential strategies range from evaluating the therapeutic potential of medical castration to blockade of the androgen receptor through available oral agents.

Novel therapies targeting the androgen receptor transformed outcomes of prostate cancer patients in the last decade. These novel, highly potent AR antagonists are enriched for activity against an amplified androgen receptor emergent through treatment-mediated selection pressure and are often accompanied by structural variants capable of ligand-independent agonism. It is unlikely that such adaptations exist in alveolar epithelial cells, or that such potent approaches would be necessary. It is not known whether pharmacological blockade of the androgen receptor or interrupting the luteinizing hormone releasing hormone axis, or both, is optimal in this setting. Such questions are the goal of planned clinical investigations.

An anti-COVID approach targeting androgen-mediated TMPRSS2 expression requires a more pliable approach than prostate cancer strategies. For one, COVID is an acute illness that evolves rapidly through immediate post exposure, symptom onset and lethal ARDS.

An AR-targeted approach may exert benefit only in one of these phases, most likely early onset. Testing this will require early detection of COVID infection and targeting the receptor, as later in the disease course such interventions may be overwhelmed by the inflammatory process. Careful consideration of patient selection is critical to adequately assess this interaction and therapeutic intervention.

#### Declaration of interest

Nima Sharifi has been a consultant for Celgene and Charles Ryan has been an adviser for Bayer. Cleveland Clinic has patents on *HSD3B1*.

#### Funding

This work was supported by grants from the National Cancer Institute (R01CA172382, R01CA190289, and R01CA236780) and the Prostate Cancer Foundation.

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Received in final form 10 April 2020

Accepted 17 April 2020

Accepted Manuscript published online 17 April 2020