LETTER TO THE EDITOR

Clock genes may drive seasonal variation in SARS-CoV-2 infectivity: Are we due for a second wave of COVID-19 in the fall?

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To the Editor,

Over the course of late spring Coronavirus Disease 2019 (COVID-19) diagnosis and hospitalizations have declined in the subtropical northern hemisphere, while in the subtropical southern hemisphere, they have increased. An important question for healthcare preparedness and public policy makers is 'to what extent is COVID-19 seasonal?' Viral respiratory infections such as influenza follow a seasonal outbreak cycle; however, it is not known whether severe acute respiratory syndrome coronavirus (SARS-CoV)-2 infection follows a seasonal pattern.

SARS-CoV-2 infectivity is dependent on proteolysis of its spike protein by the TMPRSS2 enzyme expressed on the surface of type II pneumocytes in human lung tissue (1). In humans, the only known promoter of the TMPRSS2 gene is an androgen response element (2). In our recent publications, we have presented evidence that males with androgen sensitivity are more likely to exhibit severe symptoms following COVID-19 infection (3). It is important to note that androgen sensitivity denotes a genetic predisposition for genes under the control of the androgen receptor (AR) to be susceptible to the presence of androgens; this is distinct from the level of androgens present. For example, in androgenetic alopecia both the presence of the androgen sensitivity genotype and high levels of testosterone are required to produce the male pattern baldness phenotype.

A genetic predisposition for androgen sensitivity in males leads to androgenetic alopecia (male pattern hair loss) and increased risk of prostate cancer (4, 5). We have recently reported that among hospitalized men with COVID-19, 79% were diagnosed with androgenetic alopecia compared to the expected prevalence of 31-53% in aged matched controls of similar ethnicity (3). Further, Montopoli et al. (6) observed that COVID-19 infection rates were lower in prostate cancer patients receiving androgen deprivation therapy (ADT) *versus* prostate cancer patients not receiving ADTs (OR 4.05; 95% CI 1.55-10.59). Taken together, it appears that SARS-CoV-2 infectivity is likely to be mediated by androgen sensitivity and may respond to ADT. We are currently exploring this in several studies.

SARS-CoV-2 infection is likely to follow a similar chronobiological pattern. Since a strong dependence on androgen sensitivity has been

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implied by the epidemiology of severe COVID-19 infections, we hypothesized that seasonal expression of proteins that affect androgen receptor function may provide an explanation. One such gene is the period circadian protein homolog 1 (Per1). Per1 is primarily expressed in the superchaismatic nucleus (SCN) located in the hypothalamus; the SCN acts as the primary circadian clock and produces signals that keep the body on an approximate 24-h schedule (7). Environmental cues, most importantly light, are required to reset the circadian clock; the SCN is synchronized via specialized photosensitive ganglion cells (photosensitive retinal ganglion cells) present in the retina. Per1 expression follows the circadian cycle of the SCN and is mediated by the seasonality of available light. Sumova et al. (8) demonstrated that rats exposed to a longer photoperiod (16 hours light and 8 hours darkness) exhibited at least 4 additional hours of Per1 expression compared to rats exposed to a shorter photoperiod (8 hours light and 16 hours darkness).

Per1 expression has been demonstrated to mediate androgen receptor function. Cao et al. demonstrated that Per1 inhibited transactivation of the AR. Moreover, they showed that overexpression of Per1 diminished the expression of androgen-sensitive genes following the addition of dihydrotestosterone. Finally, the overexpression of Per1 in prostate cancer cells inhibited their growth and led to apoptosis (7).

Other seasonally expressed genes have also been demonstrated to affect the androgen receptor. Dopico et al. (9) demonstrated large seasonal immune and endocrine variation in the expression of clock genes; they reported increased expression of estradiol receptor genes during summer and increased expression of IL-6 receptor genes in the winter. IL-6 regulates androgen receptor activity by causing ligand and synergistic activation of the AR. Such effect is down-regulated by nonsteroidal antagonists of the AR (10). Additionally, prostate specific antigen (PSA) levels have been shown to vary seasonally (11).

Taken together, longer day light associated with spring and summer months are likely to reduce androgen sensitivity. Reduced androgen sensitivity would lead to lower expression of TMPRSS2 and subsequently may reduce SARS-CoV-2 infectivity. Conversely, the lower available daylight associated with fall and winter months is likely to increase SARS-CoV-2 infectivity. While it is postulated that influenza's seasonal infectiveness rate is mediated by changes in immune response, it is important to note that influenza entry into lung cells is also dependent on the TMPRSS2 enzyme (12) and, as such, may be influenced by variation in the length of the daylight. It would be interesting to study the degree of variation in influenza's seasonal infectivity as a function of geographic latitude, i.e., would smaller annual variations in length of day (e.g., at the equator) lead to a broader distribution of annual influenza infection rates. In conclusion, because both SARS-CoV-2 and influenza are dependent on TMPRSS2 for infectivity, it is likely that SARS-CoV-2 will have a similar seasonal cycle; thus, the fall and winter are likely to see an increase in COVID-19 cases.

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