Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Reproductive Immunology 141 (2020) 103154

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jri

SARS-CoV-2 (Covid-19): Interferon-epsilon may be responsible of decreased mortality in females

Covid-19 disease which started in Wuhan, China has became a pandemic now (Ahn et al., 2020). According to descriptive analysis in different populations, it seems that males have higher mortality than females (Guan et al., 2020; Livingston and Bucher, 2020; Grasselli et al., 2020). We want to argue about this fact according to the reservoir of the virus and by discussing about interferon (IFN) epsilon (ε).

Pangolins which are unique mammals, are thought to be a natural reservoir of SARS-CoV-2-like CoVs (Zhang et al., 2020). IFNε is particularly expressed in epithelial cells and it is essential in skin and mucosal immunity (lung, intestines and reproductive tissues) of all African and Asian pangolin species (Choo et al., 2016). The production of IFN-I or IFN-α/β is the basic natural immune defense response against viral infections (Ye et al., 2020). IFNε, like the other type I IFNs, might be responsible of decreased mortality in females because of its antiviral effects. The pangolin immune system evolved differently than in other mammals, the single copy intronless IFNε gene is pseudogenised in pangolin species (Choo et al., 2016). This might play a role in pangolin's mild symptoms during coronovirus infections and their immun response to viral infections.

Furthermore; IFNε protects the female reproductive tract from viral and bacterial infections, especially from HIV-1 infection (Fung et al., 2013). IFNε is constitutively expressed by reproductive tract epithelium and regulated by hormones during the menstruel cycle, reproduction, and menopause and by exogenous hormones (Marks et al., 2019). IFN-ε regulates mucosal immunity against viral and bacterial infections, and can suppress HIV replication and its expression correlates negatively with progesterone levels (Li et al., 2018). In females, IFNε has limited role in the reproductive tract and it has no role in any other organ. This can be a reason why females have less mortality rather than males. On the other hand, in a new report, higher mortality rates in males was found to be associated with lower ACE2 receptor levels (Sharma et al., 2020). Other IFNs, such as IFN-λ may be an ideal treatment for covid-19 because it reduces the viral load and improves the clinical symptoms of patients. However, it has no effect on mortality (Ye et al., 2020).

Covid-19 patients can have darkness/rash in their skin in severe cases (Estébanez et al., 2020) and there is a report which shows a decrease in spermatogenezis in covid patients (Zhengpin and Xiaojiang, 2020). IFNε is present in both tissues and there is another report which argues that covid infection is likely to be androgen mediated (Wambier and Goren, 2020).

It has been shown that IFNε also exerts its biological activity by stimulating immune mediators and activating the JAK-STAT signal pathways in vitro and in vivo (Zwarthoff et al., 1985). The JAK/STAT pathway responds to type I IFN secreted from neighboring cells and SARS-CoV proteins have been shown to affect this pathway before (Frieman and Baric, 2008). Another arguement is about the furin like cleavage of the S protein of the virus. Furin is especially expressed in differentiated Th1 cells in a Stat4-dependent manner. Expression of furin enhances IFN-γ secretion, whereas inhibition of furin interferes with IFN-γ production (Pesu et al., 2006). Transcription through the JAK?STAT signalling pathway activated by IFNs, leads to the upregulation of many IFN-controlled genes that quickly kill viruses in infected cells (Pesu et al., 2006). JAK?STAT signal blocking by baricitinib (a selective JAK1 and JAK2 inhibitor) produces an impairment of IFN-mediated antiviral response, with a potential facilitating effect on the evolution of SARS-CoV-2 infection. The initial sensing of coronaviruses by the innate immune machinery might be the critical step in protecting the host from infection, especially in men.

Declaration of Competing Interest

The authors declare that they have no conflicts of interests.

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https://doi.org/10.1016/j.jri.2020.103154
Received 23 April 2020
Available online 02 June 2020

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