

Mini Review

Different roles of sex hormones in inflammation may lead to sex-disaggregation of COVID-19 pathology

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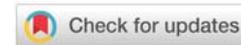
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Abstract

Severe acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the single strain RNA virus, infection causes the global pandemic coronavirus disease 2019 (COVID-19), in which the immune escape ability of SARS-CoV-2 has an important role by inhibiting antiviral innate immunity. Pattern-Recognition Receptors (PRRs), such as Retinoic acid-Inducible Gene I (RIG-I), induce antiviral innate immune responses by sensing viral nucleotides and producing type I interferons. Epidemiological investigation reveals there is sex disaggregation in that males experience more severe symptoms and suffer higher mortality from COVID-19 than females. This review discusses the different roles of sex hormones in the immune response to SARS-CoV-2 infection to explain the mechanism of sex disaggregation and explore novel preventive strategies.

The Pattern-Recognition Receptors (PRRs), including Toll-Like Receptors (TLRs) in the endosome and retinoic acid-inducible (RIG)-1-Like Receptors (RLRs) in the cytoplasm, sense viral infection by binding the RNA of SARS-CoV-2 and induce antiviral innate immunity through producing type I interferons and inflammatory cytokines [1]. Efficient type I interferon production and antiviral immunity will eliminate invading SARS-CoV-2 and block infecting other organs by hematogenous dissemination at the early stage upon infection. On the other side, overactivation of inflammation through nuclear factor κ B (NF- κ B) signal pathway with more inflammatory cytokines, such as interleukin 1, 6 and tumor necrosis factor α , will also aggravate infection and multiple organs dysfunction syndrome at the late stage. RIG-I-induced TBK-IRF3 activation was responsible for cytoplasmic viral RNA from the receptor (ACE2) mediated invasion of SARS-

CoV-2. Lysosome localized TLR7 was responsible for detecting endosome-lysosome viral RNA from lipid raft mediated invasion of SARS-CoV-2 [1].

However, SARS-CoV-2 has a strong immune escape ability by decreasing RIG-I and TLR7 activation and inhibiting antiviral innate immunity through its open reading framework proteins and non-structure proteins to proliferate in host cells [1,2]. When exceeding viruses replicates, the host cells, such as the branch and lung epithelia cells will undergo panoptosis or pyroptosis. These dirty cell death patterns will release Damage-Associated Molecular Patterns (DAMP), such as ATP, histone and HMGB1, et al. activate TLRs and induce IL-1, IL-6 and TNF α expression and secretion, which induces further inflammation and organs dysfunction [1,2]. We speculate that DAMP-induced inflammation will have a critical role in the pathology of SARS-Cov-2.



There are similar numbers of COVID-19 cases in people identifying as men and women [3-5], which indicates that the sex hormones may not have a function in the antiviral innate immunity to SARS-Cov-2. However, numerous clinical data analyses and meta-analyses have shown that men were more likely to develop severe illness, longer hospitalization periods and have higher case fatality rates, especially when older than 60 years [3-5], which indicates that sex hormone may have a function in the cell death induced inflammation of SARS-Cov-2 pathology.

Sex hormones were found to have different liver carcinogenic effects twenty years ago and were supported with increasing evidence by regulating inflammation. Estrogen and testosterone have immune-modulatory properties and roles in the sexual disaggregation of the immune system. Toll-Like Receptor (TLR) 7/8, the important sensors for viral or cytoplasmic RNA locate on the X chromosome. Females also have approximately eight times risk more common than males Systemic Lupus Erythematosus (SLE) with more expression of TLR7 and type I interferon production, on which antiviral innate immunity is dependent. ER α signaling in the pDC promotes IFN α levels following TLR stimulation, which also increases antiviral innate immunity in females. Females are more resistant to shock, trauma and sepsis-mediated immune dysfunction, and organ injury than males. Oestrogen induces neutrophil survival in both females and males and testosterone potentiates neutrophil activation [3-5].

Specific knockout of Androgen Receptor (AR) expression in hepatocytes only decreased both the frequency and volume of DEN-induced Hepatic Cell Carcinoma (HCC) [6]. Mechanism research revealed that androgen could promote IL-6 signal transduction and increase IL-6-induced hepatic cell proliferation, which ultimately increases HCC initiation and development. On the other side, the protective role of estrogen in female HCC was also found. Estrogen attenuated NF- κ B activation and decreased IL-6 production in Kupffer cells, which decreases liver inflammation and protects hepatocytes from malignant transformation [6]. The most important inflammatory cells, such as monocytes, macrophages and neutrophils, all express ARs and ERs. In accordance with the above results, AR has a positive role, while ER has a negative role in the inflammation of these cells through epigenetic and signal transduction ways [7].

Taking into account the discussed above pathological progress of SARS-CoV-2 and the function of sex hormones in inflammation, we speculate that the antiviral innate immune responses, typically the activation of RIG-I and TLR7 were similar in men and women, which lead to similar infection incidence between men and women. However, the DAMP-induced inflammation was tightly regulated by sex hormones, typically the positive role of androgen and the negative role of estrogen in IL-6 transcription and signal pathway. We also raised the question of whether the sex disaggregation in clinical patients of SARS-Cov-2 resulted from the different roles of androgen and estrogen in NF- κ B and IL-6 signal pathways, which needs to be further addressed.

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