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Mini Review

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

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

However, SARS-CoV-2 has a strong immune escape ability by decreasing RIG-I and TRL7 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 TNFα 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.

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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. ERα signaling in the pDC promotes IFNα 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].

Specifical 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-κB 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-κB and IL-6 signal pathways, which needs to be further addressed.

References

1. Liu G, Gack MU. Insights into pandemic respiratory viruses: manipulation of the antiviral interferon response by SARS-CoV-2 and influenza A virus. Curr Opin Immunol. 2022 Oct;78:102252. doi: 10.1016/j.coi.2022.102252. Epub 2022 Sep 14. PMID: 36215931; PMCID: PMC9472579.

2. Vabret N, Britton GJ, Gruber C, Hegde S, Kim J, Kuksin M, Levantovsky R, Malle L, Moreira A, Park MD, Pia L, Risson E, Saffern M, Salomé B, Esai Selvan M, Spindler MP, Tan J, van der Heide V, Gregory JK, Alexandropoulos K, Bhardwaj N, Brown BD, Greenbaum B, Gümüş ZH, Homann D, Horowitz A, Kamphorst AO, Curotto de Lafaille MA, Mehandru S, Merad M, Samstein RM; Sinai Immunology Review Project. Immunology of COVID-19: Current State of the Science. Immunity. 2020 Jun 16;52(6):910-941. doi: 10.1016/j.immuni.2020.05.002. Epub 2020 May 6. PMID: 32505227; PMCID: PMC7200337.

3. Ho JQ, Sepand MR, Bigdelou B, Shekarian T, Esfandyarpour R, Chauhan P, Serpooshan V, Beura LK, Hutter G, Zanganeh S. The immune response to COVID-19: Does sex matter? Immunology. 2022 Aug;166(4):429-443. doi: 10.1111/imm.13487. Epub 2022 May 3. PMID: 35470422; PMCID: PMC9111683.

4. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol. 2020 Jul;20(7):442-447. doi: 10.1038/s41577-020-0348-8. Epub 2020 Jun 11. PMID: 32528136; PMCID: PMC7288618.

5. Casimir GJ, Lefèvre N, Corazza F, Duchateau J. Sex and inflammation in respiratory diseases: a clinical viewpoint. Biol Sex Differ. 2013 Sep 1;4:16. doi: 10.1186/2042-6410-4-16. PMID: 24128344; PMCID: PMC3765878.

6. Kur P, Kolasa-Wołosiuk A, Misiakiewicz-Has K, Wiszniewska B. Sex Hormone-Dependent Physiology and Diseases of Liver. Int J Environ Res Public Health. 2020 Apr 11;17(8):2620. doi: 10.3390/ijerph17082620. PMID: 32290381; PMCID: PMC7216036.

7. Chlamydas S, Markouli M, Strepkos D, Piperi C. Epigenetic mechanisms regulate sex-specific bias in disease manifestations. J Mol Med (Berl). 2022 Aug;100(8):1111-1123. doi: 10.1007/s00109-022-02227-x. Epub 2022 Jun 29. PMID: 35764820; PMCID: PMC9244100.

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