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The Role of Genetic Sex and Mitochondria in Response to COVID-19 Infection

Malgorzata Kloc[a–c] Rafik Mark Ghobrial[a, b] Jacek Z. Kubiak[d, e]

[a]The Houston Methodist Research Institute, Houston, TX, USA; [b]Department of Surgery, The Houston Methodist Hospital, Houston, TX, USA; [c]Department of Genetics, M.D. Anderson Cancer Center, The University of Texas, Houston, TX, USA; [d]Laboratory of Regenerative Medicine and Cell Biology, Military Institute of Hygiene and Epidemiology (WIHE), Warsaw, Poland; [e]UnivRennes, UMR 6290, CNRS, Institute of Genetics and Development of Rennes, Cell Cycle Group, Faculty of Medicine, Rennes, France

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Abstract
The difference between the female and male immune response to COVID-19 infection, and infections in general, is multifactorial. The well-known determiners of the immune response, such as X and Y chromosomes, sex hormones, and microbiota, are functionally interconnected and influence each other in shaping the organism's immunity. We focus our commentary on the interplay between the genetic sex and mitochondria and how this may affect a sex-dependent immune response in COVID-19 infection. Realizing the existence of these interactions may help in designing novel methods or fine-tuning the existing and routine therapies to fight COVID-19 and other infections.

Introduction

Research and clinical studies indicate that the genetic sex of patients influences the immune response, and the course, and prognosis of many common noninfectious and infectious diseases. A similar correlation has also been observed recently in COVID-19-infected patients; the worldwide statistical analyses of COVID-19 cases indicate that the rate of infection and the direness of the outcome are much higher and severe in males than in females. The most popular explanation for this phenomenon is "the immunocompetence handicap model" proposing that in males, the testosterone-dependent secondary male sex traits develop at the expense of the immune response. Sex hormones are known to affect the innate and adaptive immunological response with the androgens being anti-inflammatory, and the estrogens both pro-inflammatory and anti-inflammatory [1, 2]. However, the mechanisms of these sex-related differences are multifactorial and depend on very complex reciprocal interactions between sex chromosome-encoded and regulatory factors, hormones, and microbiota inhabiting the human body. In the last decade, it became clear that the microorganisms inhabiting the human gastrointestinal tract differ, in the type and abundance of species, between the sexes. This sex-dependent microbiome, called the microgenderome, develops after puberty when the sex hormones kick in and regulates local and systemic inflamma-

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Malgorzata Kloc
Department of Transplant Immunology
The Houston Methodist Research Institute
6670 Bertner Ave, Houston, TX 77030 (USA)
mkloc@houstonmethodist.org

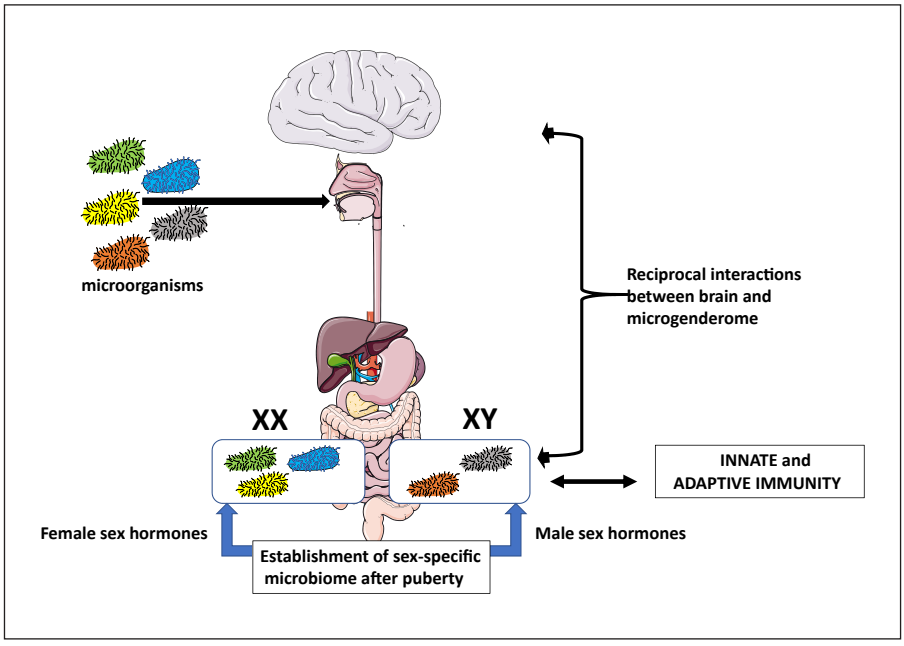

Fig. 1. Microgenderome effect on the immune system. The microorganisms acquired during birth, and from the environment (air and food) colonize the human body, especially the digestive system. After puberty, the sex hormones influence the abundance and variety of species inhabiting the male and female body; less variety in males than in females. The compounds produced by the microgendorome reciprocally influence the function of innate and adaptive immunity, and brain (adapted from Vemuri et al. [2]).

tion, and response to infection (Fig. 1) [1–3]. Recent studies also indicate that the sex-related difference in the immune response may depend on the sexually dimorphic populations of mitochondria. Below we give a short summary of how these different elements pitch in and shape the immune response to COVID-19 and other diseases.

X and Y Chromosome Regulation of Immunity

Although some differences between the female and male immune response are directly related to the number of X chromosomes (2 X in females vs. 1 X in males), and the effect of sex hormones on the functions of immune cells, the studies of last decade indicate that both Y and X chromosomes regulate immune cell transcription and translation (transcriptome and proteome) profiles.

X Chromosome

The Archive.ensabl.org 2017: http://mar2017.archive.ensembl.org/Homo_sapiens/Location/Chromosome?r=X [4] indicate that the human chromosome X consists of over 150 million DNA base pairs and contains more than 800 protein-coding genes, which include the highest number of the innate and adaptive immunity-related genes of the whole human genome, and several hundred non-coding genes. The immune response genes include fraktaline receptor CXCR3 (C-X-C motif chemokine receptor 3) that directs immune cells, including macrophages, movement into inflamed tissues, and organs; the gene for CD80 ligand that binds to the CD40 receptor on antigen-presenting cells, B cells, monocytes/macrophages, and dendritic cells, and through interaction with CD154 transduces signals for T-dependent B-cell activation; and the interleukin-1 receptor-associated kinase 1 (IRAK1) gene. The X chromosome also contains 10% of all genomic microRNA (miRNA) genes that regulate expression and degradation of autosomal gene products [5, 6]. Studies showed that the absence of, or extensive deletions in one of the X chromosomes, lead to a variety of autoimmune diseases (Fig. 2) [5, 6].

A higher rate of COVID-19 infection in males may be, in part, influenced by the X chromosome mosaicism in the female cells, due to the stochastic X chromosome inactivation [7]. For example, the angiotensin-converting enzyme 2 (ACE2), the receptor for β-type coronaviruses SARS-CoV-1 and SARS-CoV-2, is encoded by the ACE2 gene located on the X chromosome. It is possible that some alleles of this gene may code for the receptors with different efficiency of recognizing and binding the virus. Male cells always express a single ACE2 allele because all cells contain an identical X chromosome. In contrast, a female has a heterogenic ACE2 allele because of the mosaicism of X chromosomes, which are stochastically dis-

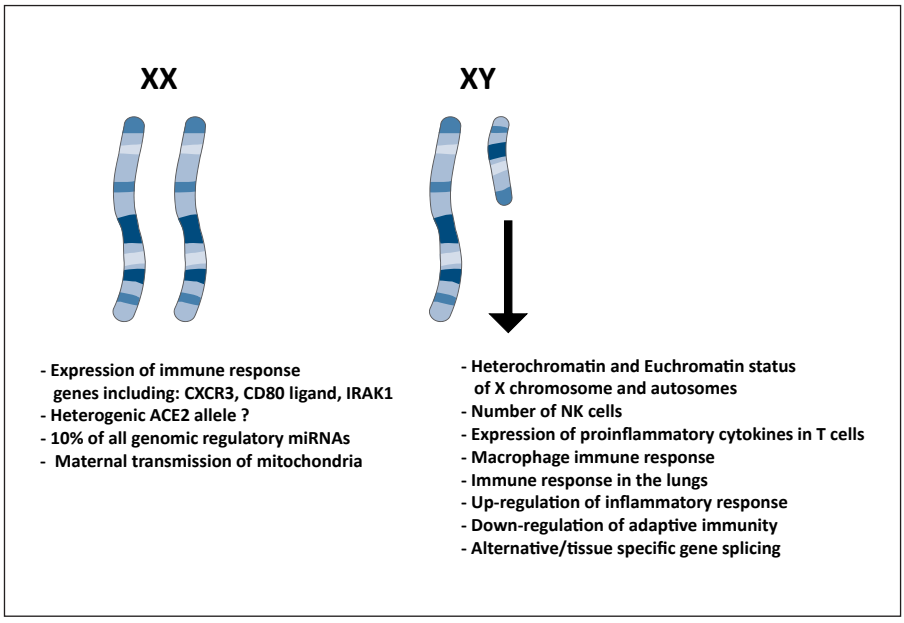

Fig. 2. Effect of sex chromosomes on the immune-related functions. The X chromosome contains many immune response-related genes and 10% of all genomic miRNAs that regulate transcription, splicing, and degradation of many genes. It also, through the specification of female identity, directs maternal purging and transmission of mitochondria. Because in the female cells, the inactivation of one of the X chromosomes is random, the female body may contain different alleles of the same gene. For example, different alleles of viral receptor ACE2 may have a different affinity to the virus, which will affect the antiviral immune response. The Y chromosome regulates many different immune-response functions, immune cell numbers, and immune cell phenotypes through the regulation of transcriptionally inert (heterochromatin) and active (euchromatin) status of X chromosome and autosomes.

tributed between the cells. Thus, in the female, a potentially more efficient form of ACE2 receptor would be present in only half of all cells. This may limit infectibility with SARS-CoV-1 and SARS-CoV-2 viruses and, to some extent, give females a relative resistance to the infection (Fig. 2). It has also been debated if such ACE2 polymorphism may have an impact on hypertension and other diseases [8, 9].

Y Chromosome

The human Y chromosome is much smaller than the X chromosome, consist of around 60 million DNA base pairs, and, in the majority of animals, its large portion is transcriptionally silent (heterochromatic). The Y chromosome is mainly composed of transposable elements, repeat sequences (comprising over 50% of its content), multicopy genes such as the polymorphic variants of the ribosomal genes, and a low number of protein-encoding genes, which are mainly male-specific and regulate sexual development, spermatogenesis, sex ratio, and fertility, and often evolved through the transposition/translocation from the autosomes. This male-specific region of the Y chromosome (MSY) does not recombine and, thus, remains unchanged between the consecutive male generations [10–13]. Studies showed that Y chromosome can regulate the heterochromatin/euchromatin status of the autosomes and X chromosomes and, thus, affects silencing/expression of various genes, including the immune response genes, and regulate the tissue-/cell-specific alternative gene splicing [10, 14–18]. Although the mechanism by which the Y chromosome influences heterochromatin/euchromatin content and thus the transcription of the other genes is largely unknown, one of the hypotheses postulates that the Y chromosome sequesters heterochromatinization factors and another that it affects the architecture of cell nucleus, which makes specific genes inaccessible to the transcription factors [19–22]. Phylogenetic studies showed that the males with the haplogroup I, which is one of the most popular European lineages of the Y chromosome, have upregulated inflammatory response, downregulated adaptive immunity, and a higher risk of coronary diseases [23–25]. In the murine models, Y chromosomes influence the number of natural killer T cells, the gene expression pattern in $CD4^+$ T cells, the immune response of macrophages, and the mortality rate following the infection with coxsackievirus [26–28], which argues for the strong impact of the Y chromosome on a large variety of immune cells and immune processes. Studies of Case et al. [10] showed that the copy number of the Y chromosome gene *Sly* and RNA-binding motif gene *Rbmy* inversely regulates the susceptibility to autoimmune disease. Studies in mouse influenza model [29] showed that certain genetic variants of chromosome Y result in higher susceptibility to influenza A infection, activate pro-inflammatory cytokine expression in T cells, and increase pathogenic immune response in the lungs (Fig. 2).

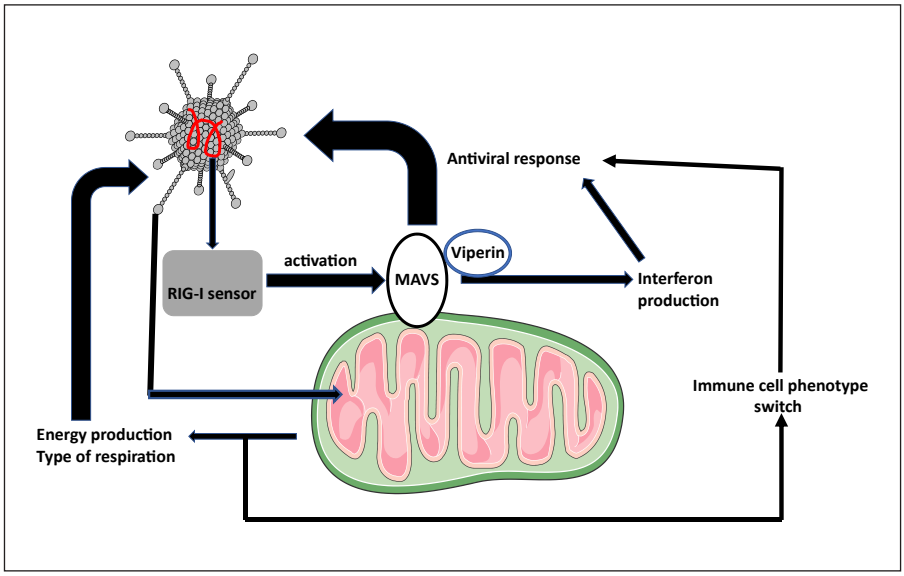

Fig. 3. Effect of mitochondria on the antiviral immune response. The presence of the virus is sensed by the RIG-I that is a major sensor of viral RNA. This activates anti-viral MAVS protein present in the mitochondrial membrane. Activated MAVS, through the interaction with the virus inhibitory protein, viperin, affects the level of interferon, which in turn regulates virus replication. In addition, viruses can directly affect mitochondrial functions such as aerobic or anaerobic respiration, which in turn affect immune cell phenotypes and responses.

Mitochondria

Studies of the past decades [30, 31] showed that mitochondria are not only the bioenergetic (they generate ATP) and biosynthetic (they generate components for the synthesis of various macromolecules) hubs but are also indispensable regulators of the innate and adaptive immune response, development, and maintenance/survival and activation of the specific phenotypes of immune cells. Mitochondria can also affect various signaling pathways and transcription in immune cells by changing the ATP level, alternating their metabolic pathways, and releasing the reactive oxygen species and mitochondrial DNA signals. By changing the type of respiration from the broken TCA cycle to β-Oxidation, the mitochondria can switch macrophage phenotype from the proinflammatory (M1) to the anti-inflammatory (M2). In addition, the localization of mitochondria in the proximity of endoplasmic reticulum membranes of the immune cells directly affects their metabolism and immune-related functions [30, 31]. Also, the outer membrane of mitochondria contains the mitochondrial antiviral signaling (MAVS) protein that is activated by the viral RNA sensor, the retinoic acid-inducible gene I (RIG-I) that senses the presence of viral RNA. MAVS can also act as an antiviral defense mechanism. In the macrophages infected with RNA viruses, MAVS interacts with the antiviral protein viperin, affecting the level of antiviral compound interferon (Fig. 3) [30, 32]. Proper functioning of mitochondrial MAVS response can be especially relevant and significant for COVID-19 infection where the SARS-CoV-2 virus directly infects alveolar macrophages inducing them to switch on the cytokine storm in the lungs [33]. Moreover, because the survival and replication of the virus depend on the energy produced by the host mitochondria, which in turn, are affected by the virus (Fig. 3); the novel antiviral strategies may include compounds that modulate mitochondrial bioenergetic functions [34].

All these data indicate that the healthy and properly functioning mitochondria are indispensable for the adequacy of the immune response. Thus, it is not surprising that one of the theories explaining the higher infection rate and severity of infections, such as COVID-19, in males relates to the maternal transmission of mitochondria, and substandard quality of mitochondria in the males. In mammals, including humans, mitochondria are maternally transmitted in the egg cytoplasm. Following fertilization, during early embryogenesis, maternal mitochondria replicate and enter the prospective somatic and germ cells [20]. Although there are some, very rare, examples of paternal transmission of mitochondria in humans [35], the concept of maternal inheritance of mitochondrial DNA in humans remains valid. During the formation and maturation of the mammalian egg, the mitochondria undergo the quality control [36] and those which are defective, or contain, harmful for the female, mutations, are eliminated. Because this mitochondrial culling is female-biased, the mitochondria remaining in the egg cytoplasm may con-

tain mutations harmful for the male. This so-called "mother curse" [20] may also influence the quality and caliber of a male immune response.

Recently, the melatonin was suggested as a potential adjuvant for COVID-19 treatment [37]. Melatonin has positive effects on mitochondrial homeostasis by scavenging toxic oxygen species and nitrogen-based reactants, enhancing anti-oxidative enzymes, facilitating the electron transport chain, limiting electron leakage, free radical generation, and stimulating ATP synthesis [38]. In light of our hypothesis that the quality of mitochondria may influence COVID-19 infection, the melatonin treatment of COVID-19 patients may be more beneficial for men than women. Although, at present, there is no proven effective remedy for the sex-biased outcome of COVID-19 and other microbial infections, the detailed knowledge of all mechanisms underlying the differences between female and male immune response should facilitate the development of new treatments and therapeutic approaches.

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Disclosure Statement

Authors do not have conflict of interest and have nothing to disclose.

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Authors Contributions

Malgorzata Kloc: concept, writing, and figures. Jacek Z. Kubiak: concept, writing, editing, and figures. Rafik Mark Ghobrial: writing and editing.

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