Seminars in Immunopathology (2019) 41:133–135
https://doi.org/10.1007/s00281-018-00728-x

INTRODUCTION

Sex differences in immunity

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Received: 15 November 2018 / Accepted: 19 November 2018 / Published online: 7 February 2019

The immune system defends us from environmental threats, such as infections, and detects and removes abnormal cells that can potentially lead to malignancies. Optimal immunological homeostasis is achieved when the threat is removed with high efficiency and at low cost (collateral tissue damage) for the host. The nature and strength of immune responses differ between women and men, resulting in sex-specific differences in the prevalence, manifestations, and outcomes of malignancies and autoimmune and infectious diseases. While women are in general able to mount a more vigorous immune response to infections, vaccinations, and some malignancies, they also suffer more from inflammatory and autoimmune diseases. Growing data indicate that common biological pathways leading to inflammation and immune activation are involved in the pathophysiology of autoimmune and infectious diseases, and that these pathways are regulated by sex-linked factors, including sex hormones and sex-chromosome-encoded genes. A better understanding of the fundamental processes that regulate sex-specific differences in immune responses is required to optimize prevention and treatment strategies for women and men in a first step toward personalized medicine.

In the current supplemental issue of *Seminars in Immunopathology*, review articles address our current level of understanding of these differences and identify gaps in our knowledge related to sex differences in immunity, and their consequences for a number of diseases highly relevant for human health. Increasing evidence suggests that the functioning of our immune system is already shaped by the intrauterine environment early during immune ontogeny, and that altered prenatal development can have a significant impact on the risk for infectious and autoimmune diseases later in life. Zazara et al. [1] review the developmental origins of higher susceptibility to infections and immune diseases during childhood and throughout life, and discuss how these prenatal events can contribute to sex-specific differences in the functioning of the immune system. Several genes that play a critical role in regulating immune responses in humans, including the genes encoding for FoxP3, CD40L, TLR7, TLR8, and IL2 receptor subunit gamma, are located on the X chromosome. Souyris et al. [2] review recent exciting data demonstrating that escape from X-chromosome inactivation can result in different expression levels of TLR7 between women and men, and discuss the implication of these findings for the predisposition of women to TLR7-driven autoimmune diseases, such as systemic lupus erythematosus. Continuing with the theme of autoimmune diseases, Schwinge et al. [3] discuss sex-specific differences in immunity that might underlie the female predominance in two autoimmune liver diseases: autoimmune hepatitis and primary biliary cholangitis. Gold et al. [4] review the immunological mechanisms that drive inflammatory diseases of the central nervous system, including multiple sclerosis, neuromyelitis optical spectrum disorders, and neuronal autoantibody-mediated autoimmune encephalitis, all of which occur more frequently in women compared to men.

While most autoimmune diseases are more frequent in women, sex differences in the incidence and clinical manifestations of infectious diseases show a more heterogeneous picture. Vom Steeg et al. [5] review differences between women and men in the outcome of influenza A virus infections, which depend significantly on the age of the host and the causing viral strain. The authors discuss growing evidence that sex steroid hormones can directly impact immune responses during influenza A virus infection, resulting in sex-specific differences in disease manifestations and outcome. Another viral infection that shows significant differences in disease

This article is a contribution to the special issue on Sex differences in immunity - Guest Editors: Hanna Lotter and Marcus Altfeld

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manifestations between women and men is HIV-1 infection. Rechtien et al. [6] discuss recent evidence suggesting that the type I IFN pathway might be responsible for these differences between the sexes, as innate immune cells from women produce significantly more IFN-α in response to HIV-1 compared to men. Büttner et al. [7] review sex disparities in HBV-related liver diseases that occur with a clear male bias and discuss the implications of recent data suggesting that sex hormones are involved in the regulation of HBV replication. Taken together, clinical and immunological data from these three important viral infections affecting millions of individuals worldwide clearly emphasize the critical role of sex-specific differences in immune responses for disease outcomes, which should be taken into account to optimize treatment strategies for women and men.

But not only are the manifestations of viral infections affected by sex, but also the incidence and outcome of parasitic infections. Sellau et al. [8] describe the impact of androgens on the immune system that lead to a male bias in parasitic diseases like amebiasis, leishmaniasis, and helminth infections, in which monocytes and macrophages are critical key players between control and induction of immunopathology. Hertz et al. [9] review sex differences in the prevalence and disease outcome of *Mycobacterium tuberculosis* infection, one of the most prevalent bacterial infections in humans that over-proportionally affect men, and discuss the effects of gender-related and sex-related factors that might contribute to these differences. Finally, the significant contribution of sex to modulating vaccine-induced immune responses has gained increasing attention in the last years, and Fischinger et al. [10] discuss the immune pathways that might be responsible for these sex differences, with a special focus on the role of sex as a modulator of humoral immunity.

Sex differences in the prevalence and manifestation of human diseases are not limited to infectious and autoimmune diseases, but also affect cancers, the leading cause of death worldwide. Many solid cancers in non-reproductive organs occur more frequently in men, and also hematological malignancies exhibit sex-biased differences. Ben-Batalla et al. [11] discuss data on the mechanisms that might result in these sex-biased imbalances in the incidence and outcomes of cancer, with particular focus on leukemia, including differences in the response to immune checkpoint inhibitor treatments. Furthermore, the understanding of the critical role of the microbiome in regulating immune processes has increased over the past years. Vemuri et al. [12] review recent studies demonstrating the significant effects that the sex of a host can have on the composition of the gastrointestinal tract microbiome, and refer to this as the "microgenderome". The authors discuss the role of the microgenderome in driving sex differences in immunity and manifestations of human diseases, and the possible implications for treatments aimed at manipulating the microbiome, including fecal microbial transplants.

Taken together, this collection of review articles addresses sex-specific aspects of a broad spectrum of different human diseases and discusses common biological principles, such as the effects of X-chromosomal gene expression, immune ontogeny, and the microbiome, that might contribute to these sex differences. Overall, these articles provide a comprehensive

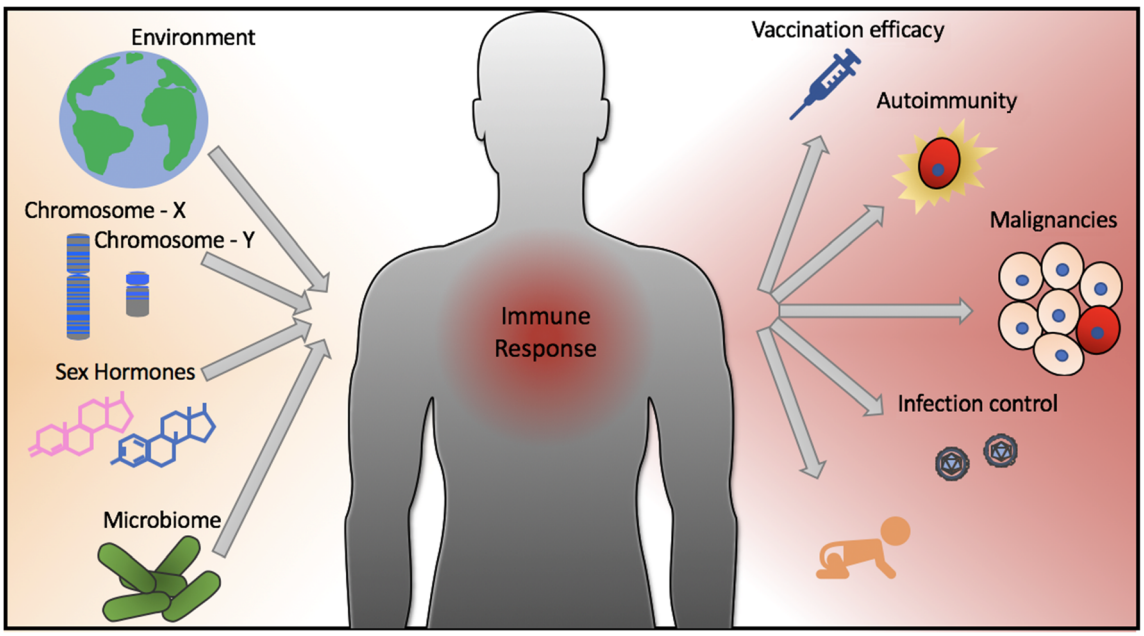

Fig. 1 The immune system is determined by external and internal factors. Sex-chromosome encoded genes and sex hormones modulate the immunity either directly or via the microbiome. These influences alter the immune response toward vaccination, affect autoimmunity, malignancies, susceptibility to infections, and the prenatal immune development in a sex-specific manner

view on the significant effects that sex-specific factors have on the incidence, manifestations, and outcome of infectious diseases; autoimmune diseases; and malignancies. While it is now well established that sex represents an important variable in these diseases, significant gaps remain in our understanding of the precise mechanisms mediating sex-biased immune responses and how this affects the outcome of human diseases. Future research is required (i) to define the pathways that are mediating these sex-specific differences, (ii) to dissect the effect of sex hormones on different compartments of the immune system, (iii) to determine the role of sex chromosome-encoded genes, and (iv) to assess the contribution of sex-differences in the microbiome. Clinical studies should not only take the sex, but also the age, reproductive status, and use of exogenous hormones into account when interpreting outcomes. Studies both in animals and humans have to be designed accordingly. A better understanding of the mechanisms that regulate differences in host immunity between females and males will enable the development of individualized treatment concepts that take sex-specific host factors into account (Fig. 1).

References

1. Zazara DE, Arck PC (2018) Developmental origin and sex-specific risk for infections and immune diseases later in life. Semin Immunopathol. https://doi.org/10.1007/s00281-018-0713-x
2. Souyris M, Mejía JE, Chaumeil J, Guéry JC (2018) Female predisposition to TLR7-driven autoimmunity: gene dosage and the escape from X chromosome inactivation. Semin Immunopathol. https://doi.org/10.1007/s00281-018-0712-y
3. Schwinge D, Schramm C (2018) Sex-related factors in autoimmune liver diseases. Semin Immunopathol. https://doi.org/10.1007/s00281-018-0715-8
4. Gold SM, Willing A, Leypoldt F, Paul F, Friese MA (2018) Sex differences in autoimmune disorders of the central nervous system. Semin Immunopathol. https://doi.org/10.1007/s00281-018-0723-8
5. vom Steeg LG, Klein SL (2018) Sex and sex steroids impact influenza pathogenesis across the life course. Semin Immunopathol. https://doi.org/10.1007/s00281-018-0718-5
6. Rechtien A, Altfeld M (2018) Sexual dimorphism in HIV-1 infection. Semin Immunopathol. https://doi.org/10.1007/s00281-018-0704-y
7. Büttner N, Thimme R (2018) Sexual dimorphism in hepatitis B and C and hepatocellular carcinoma. https://doi.org/10.1007/s00281-018-0727-4
8. Sellau J, Groneberg M, Lotter H (2018) Androgen-dependent immune modulation in parasitic infection. Semin Immunopathol. https://doi.org/10.1007/s00281-018-0722-9
9. Hertz D, Schneider B (2018) Sex differences in tuberculosis. Semin Immunopathol. https://doi.org/10.1007/s00281-018-0725-6
10. Fischinger S, Boudreau CM, Butler AL, Streeck H, Alter G (2018) Sex differences in vaccine-induced humoral immunity. https://doi.org/10.1007/s00281-018-0726-5
11. Ben-Batalla I, Vargas-Delgado ME, Meier L, Loges S (2018) Sexual dimorphism in solid and hematological malignancies. Semin Immunopathol. https://doi.org/10.1007/s00281-018-0724-7
12. Vemuri R, Sylvia KE, Klein SL, Forster SC, Plebanski M, Eri R, Flanagan KL (2018) The microgenderome revealed: sex differences in bidirectional interactions between the microbiota, hormones, immunity and disease susceptibility. Semin Immunopathol. https://doi.org/10.1007/s00281-018-0716-7