ZIKA Virus and Male Infertility

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Zika virus (ZIKV) has been reported by several groups as an important virus causing pathological damage in the male reproductive tract. ZIKV can infect and persist in testicular somatic and germ cells, as well as spermatozoa, leading to cell death and testicular atrophy. ZIKV has also been detected in semen samples from ZIKV-infected patients. This has huge implications for human reproduction. Global scientific efforts are being applied to understand the mechanisms related to arboviruses persistency, pathogenesis, and host cellular response to suggest a potential target to develop robust antiviral therapeutics and vaccines. Here, we discuss the cellular modulation of the immunologic and physiologic properties of the male reproductive tract environment caused by arboviruses infection, focusing on ZIKV. We also present an overview of the current vaccine effects and therapeutic targets against ZIKV infection that may impact the testis and male fertility.

Keywords: Sertoli cells ; Leydig cells ; ZIKA virus ; arboviruses ; infertility ; immunology

1. Introduction

The testis is a reproductive gland that is part of the internal structures of the male reproductive tract (MRT) and is involved in spermatogenesis and steroidogenesis. Each testis is composed of a tangle of tubes, the seminiferous ducts. These ducts are formed by Sertoli cells (SCs) and the germinal epithelium, which is responsible for ensuring protection and nutrition to accurate spermatogenesis. Leydig cells (LCs) are found in the testis interstitium, adjacent to the seminiferous tubules. LCs promote steroidogenesis through the secretion of male sex hormones, especially testosterone, responsible for the development of male genital organs and secondary sexual characters [1,2].

The testis is considered an immune-privileged organ [3]. This is essential to ensure the immunogenic germ cell protection against immune system activation during spermatogenesis. This is mainly provided by the combination of a local immunosuppressive environment and systemic immune tolerance [4,5,6]. It has long been assumed that the blood-testis barrier (BTB) constitutes the main mechanism of the immune-privileged status of the testis [7]. In addition to BTB and anatomical impairment of external cells' and molecules' entrance to the testis, SCs also provide anti-inflammatory mediator secretion aiming to maintain the tolerogenic microenvironment [8]. However, many local immune modulators, including macrophages, dendritic cells (DCs), natural killer cells (NKs), mast cells, and T-lymphocytes, contribute to the intercommunication among testicular components [9,10,11,12].

The testis is commonly exposed to pathogens derived from blood, trauma, or through the genitourinary tract. To protect itself against all these pathogens, the testis also needs the ability to overpower immune privilege. This is achieved by inducing local innate immune responses [3]. Even counting this frontline protection, some pathogens have an immune escape mechanism that leads to infection and persistence in the MRT. Reproductive tract infections (RTI) can be caused by bacterial, parasitic, and viral pathogens [13]. RTI promoted by viral infections is notorious, as shown by the World Health Organization (WHO) in 2006, which estimated that 500 million people live with genital herpes, 300 million women have human papillomavirus (HPV), and approximately 240 million people suffer from chronic hepatitis B [14]. In 2016, the WHO also estimated that over 17 million people are living with HIV on antiretroviral therapy. However, the number of HIV-positive cases is increasing worldwide [15].

2. Discussion

Some diseases can persist a long time in human semen. Ebola [16], Zika virus (ZIKV) [17], HIV [18], and 27 other types of viruses that contaminate humans have been found in semen and testis for differing periods [19]. Despite the knowledge that various types of viruses can be found in semen, their sexual transmission capacity is still poorly understood. Some of these are not considered sexually transmitted diseases because this route is not the main form of contagion. However, ZIKV has already been confirmed by the WHO to have sexual transmission (World Health Organization, 2016) and considered to be the first arbovirus reported to be associated with sexual transmission [20,21]. Due to this fact, attention is being turned to the possibility that other arboviruses may be present in the MRT. Compared to ZIKV, the literature

regarding this effect is scarce, and the available data suggests that arbovirus sexual transmission is a relevant point of concern. The presence of ZIKV in the male genital tract and its ability of sexual transmission leads to unanswered questions such as (1) has the ZIKV a tropism for any specific cell in the male reproductive system?, (2) what features may favor the ZIKV persistence in testicles when compared to other arboviruses?, (3) can the spermatozoa harbor the virus?, (4) how long does the virus remain viable in the male genital tract?, (5) how can the prolonged presence of ZIKV in the male genital tract cause infertility?, (6) is this ZIKV-induced testicular damage reversible? Based on these questions, it is clear the importance of continuing to investigate the role of ZIKV in the male reproductive system. In addition, a vaccine against ZIKV may be the best way to protect the population from infection and control the disease and its consequences. The vaccination should protect against the future and possible damage to the male genital tract, avoiding fertility-related problems.