MICROBIOLOGY

Focuses on the impact of Zika virus infection on the male reproductive tract

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Since the outbreak of Zika virus (ZIKV) in Latin American countries in 2015, many studies investigating the effects of the virus on pregnant women have been published and focused global attention. In addition to transmission by mosquitoes, ZIKV can be detected in these men of affected males for extended periods of time and transmitted sexually [1]. However, the impact of ZIKV on the male reproductive system has been much less documented.

The testis produces sperm and sex hormones. Spermatogenesis is a highly complex cell differentiation process necessary for the production of haploid spermatozoa [2]. Mature sperm progress to the epididymis, where the developing gametes get mature and are stored until ejaculation. Maintenance of qualitatively and quantitatively normal spermatogenesis is absolutely essential for male fertility.

In a recent publication in *Cell*, a team led by Prof. Xiangdong Li and Prof. George Fu Gao from China conducted a longitudinal study to demonstrate that ZIKV causes testis damage and male infertility in mice [3]. Firstly, they inoculated IFNα/β receptor-deficient mice (lacking a critical component of the innate antiviral immunity) with ZIKV and performed morphological, hormonal and histopathological analysis of the male genital tract to confirm that ZIKV infects testis/epididymis, but not the prostate/seminal vesicle. Consistently, AXL, a putative ZIKV entry cofactor, is expressed in testes and epididymides, but not in the prostate or seminal vesicle. Secondly, the presence of ZIKV specifically in testicular peritubularmyoid (PTM) cells and some spermatogonia is confirmed using a monoclonal antibody Z6. Thirdly, ZIKV significantly induces cytokine secretion by Sertoli and Leydig cells, while no cytokine secretion is observed with PTM and germ cells, indicating that PTM and germ cells (spermatogonia) are susceptible to ZIKV infection.

On 31 October 2016, Michael Diamond and colleagues published a back-to-back study in *Nature* [4] to assess the effects of ZIKV infection on the reproductive tract of male mice. ZIKV preferentially infects spermatogonia, primary spermatocytes and Sertoli cells in testes, using a mouse-adapted African ZIKV strain (Dakar 41519). There is a noticeable decrease in testis size and fertility ability among ZIKV-infected animals compared to controls, as well as damage to the seminiferous tubules of the testis and tissue injury to the epididymis. The authors also suggest reduced levels of testosterone and inhibin B—two hormones important for the production of sperm.

These great findings open up the idea that ZIKV could impact people other than pregnancy. Men could also be at risk of getting infected. However, several important considerations remain. Firstly, susceptibility and degree of injury of male reproductive tract in mice vary among different studies. Secondly, the reasons for eventual testicular disruption in ZIKV-infected male mice are inconsistent. Impact and mechanism of ZIKV infection on different testicular cells, such as spermatogonia, spermatocytes, spermatozoa, Sertoli cells, Leydig cells and PTM cells, need further investigation. Lastly, further work is needed to determine whether these results in mice can be translated to humans. If so, longer-term investigation of clinical follow-up data regarding all ZIKV-infected men is recommended. It is obvious that it will be hard to compare sperm counts before and after a Zika infection.

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