Zika virus damages the male reproductive system and leads to infertility in mice

Subject Code: H07

With the support by the National Natural Science Foundation of China, a collaborative study by the research groups led by Prof. Gao Fu (**高福**) from the Institute of Microbiology, Chinese Academy of Sciences and Prof. Li Xiangdong (**李向东**) from China Agricultural University demonstrates that Zika virus infection causes testis damage and leads to male infertility in mice, which was published in *Cell* (2016, 167(6): 1511—1524).

Zika virus (ZIKV) is a mosquito-borne pathogen from the family *Flaviviridae*. The virus rapidly spread worldwide after its outbreak in Brazil in 2015, with 69 countries/territories reported evidence of ZIKV transmission from 2015 onwards. Most individuals infected with ZIKV are asymptomatic or have mild symptoms, such as fever, malaise, rash and conjunctivitis. In some cases, ZIKV infections are associated with microcephaly in newborns and Guillain-Barré Syndrome in adults. In addition, ZIKV RNA has been detected in semen two months after initial symptoms, and the sexually transmitted Zika cases have been reported, suggesting a new route of infection.

Our group found that ZIKV could cross the blood-testes-barrier and infect the reproductive tract in male mice. Testicular interstitial hyperemia, acute orchitis/epididymis along with a substantial decrease in organ sizes, as well as decreased levels of testosterone was observed at 8 days after infection. At 16 days, death was observed in a large percentage of sperm cells, and further damage was observed in the testes as well as the vas deferens. At 30 days after infection, a breakdown in the morphology of the testes and disruption of the seminal vesicles could be observed, resulting in completely atrophied testes and seminal vesicles by 60 days after infection.

Further studies showed that Zika virus could infect the testes and epididymis, but not the prostates or seminal vesicles. Specifically, ZIKV induced innate immune responses in Leydig, Sertoli, and epididymal epithelial cells, resulting in the production of pro-inflammatory cytokines/chemokines. However, ZIKV did not induce a rapid and abundant cytokine production in peritubular cell and spermatogonia, suggesting that these cells were vulnerable to ZIKV infection and could be the potential repositories for ZIKV.

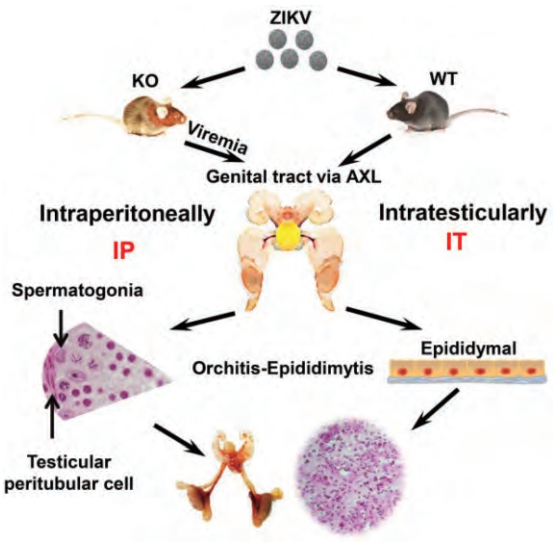

Figure ZIKV causes orchitis-epididymitis inmice leading to male infertility.

These findings provide new insight into the pathogenic mechanisms of ZIKV and support sexual transmission hypothesis. However, more studies are needed to completely understand all mechanisms of ZIKV pathogenesis.