First International Conference on Zika Virus

Cellular Targets and Receptors of Sexual Transmission of Zika Virus

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ZIKV in Semen

- Most recent data from Atkinson et al.* among the semen samples of 23 patients, Zika virus RNA was detected at high levels in ~60% and was not detected in ~40%

- After symptomatic infection, a substantial proportion of men have detectable Zika virus RNA at high copy numbers in semen during early convalescence, suggesting high risk for sexual transmission. Viral RNA clearance times are not consistent and can be prolonged up to 196 days.

*Emerg Infect Dis. 2017 Apr 15;23(4)
ZIKV in Semen and WHO

• The current World Health Organization (WHO) guidelines advise that male and female travelers abstinence to reduce the risk for sexual transmission for 180 days after leaving a country with ongoing Zika virus transmission*.

• The most recent data suggest that ZIKV RNA is detected belong ~6 month in male semen long after ZIKV RNA disappears from blood and urine.

Why Zika stays in Semen?

• Men’s Scutum is a privilege site, meaning that anti-Zika antibodies (Abs) are not efficient enough to destroy the virus
• Would the vaccine eliminate Zika?
• How one can counter this problem?
• In cases of HIV-1, HCV and GBV-C anti-viral Abs do not prevent sexual transmission*.

Once a person is infected, he/she is immune for life against Zika.
What cell types carry ZIKV in Semen

**Methodology**

**Fraction I:** Contained mostly spermatozoa (mature sperm)

**Fraction II:** Contained immature sperms, and leukocytes.

Infection were carried out with moi of 0.1 and 1.0

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In situ RT-PCR to determine the cell types infected with ZIKV

First major publication

• The first article was published in NEJM* to determine the % of PBMC infected with HIV-1

Thermocycler Designed for ISRTPCR

Infection of Spermatozoa (F1) moi 0.1
Infection of F II with 0.1
Spermatozoa

- Mature sperm cells are produced at a rate of 300 million/day
- Life expectancy once ejaculated is ~ 48 hrs
- 3 parts
  - Head, contains genetic material, acrosome
  - Midpiece, contains mitochondria
  - Tail, flagellum, locomotion
Infection of Spermatozoa (F1) moi 1.0
Real Time RT PCR

Amplification Plot

Cycle

ΔRn

Legend

A  B  C  D  E  F  G  H
TAM Family Receptors

- TAM stands for the first 3 letters of tyro3, Axl and Mer*.
- These are tyrosine kinase receptors.
- Sertoli cells express all three TAM receptors, involved in apoptosis of dead sperms.

Tyro Receptor and ZIKV
Why 180 days when sperm live for few days after ejaculation?

Possibilities

• 1) ZIKV infects immature sperms!
• Highly unlikely due to sertoli-cell barrier.
• Sertoli cells express all TAM receptors!

Testicular blood barrier
Why 180 days when sperm live for few days?

Possibilities

• 2) Spermatogenesis takes ~180 days to complete and the primary spermatids are infected!

• Unlikely! due to Testicular-Blood barrier

• Needs further investigation.

https://www.google.com/search?newwindow=1&hl=en&biw=1280&bih
Why 180 days when sperm live for few days?

Possibilities

• 3) ZIKV is protected from Zika Abs and the virus is protected and even a very small titer of the virus infecting mature sperms!

• Most likely, since low moi is infectious.
Are germ cells in danger

Possibilities

• 4) Only midpiece are infected and it does not penetrates the egg!

• NO DANGER TO GERM CELL

Germ cells are safe!
Unresolved Issues

• Detection of Zika virus RNA in semen samples does not necessarily indicate the presence of infectious virus.
• What other receptors are involved in ZIKV-sperm/Sertoli cells interactions?
• Do Sertoli cells serves as long term source for ZIKA in semen?
• Which stage of maturation sperm become permissive to ZIKV?
• At what stage of spermatogenesis tyro3 is expressed?
• What other types of receptors are expressed on male reproductive system?
Conclusions

• ZIKV appear to primarily infects the midpiece of live sperms.
• ZIKV can infect sperms at low moi (i.e. 0.1 moi)
• Between 6-30% of sperm were found to be infected, depending on moi (0.1 vs 1.0)
• Tyro3 is one of the receptors involved.
• Currently, we lack knowledge of viral persistence in semen. More data are urgently needed