Deconvolution of Anti-host and Anti-viral Genomic Responses in Zika Virus-infected and Bystander Human Macrophages

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Zika virus (ZIKV) disease

Symptoms:
- Conjunctivitis
- Fever
- Joint pain
- Rash

Baby with Microcephaly
Baby with Typical Head Size

CDC.Gov
Carteaux G et al NEJM 2016
Dos Santos T et al NEJM 2016
A fundamental question in the field

• ZIKV infects macrophages
• Macrophages should protect us from viral infections
• Begs the question: how does ZIKV infect macrophages?
Current limitation to answering this question

- Often difficult/impossible to achieve high levels of infection *in vitro*

Where is the signal coming from? Mixing can decrease sensitivity and specificity

Highly susceptible cell lines are often deficient in important anti-viral responses

Modified viruses are significantly less virulent
Impossible to study patient derived viruses
Isolation of ZIKV+ and ZIKV- populations more accurately identifies virally regulated genes.
ZIKV suppresses inflammatory signaling
ZIKV degrades STAT2 blocking type I interferon (IFN) signaling

Type I IFN

↓

STAT1-P – STAT2-P

↓

IRF9

↓

IFN-stimulated genes
ZIKV suppresses RNA polymerase 2 (RNApol2) transcription disproportionately affecting core macrophage genes.
ZIKV targets transcription to block macrophage responses

Infect 1° human MPs and FACS separate

Bystander ZIKV-

Infected ZIKV+

Genome-wide transcriptomics epigenomics

Identify ZIKV regulated responses

Anti-viral pathways

Pro-viral pathways

Biochemical Functional Validation

IRF9

STAT1

STAT2

RPB1

RNApoly2
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