Exploiting Zika Virus Neurotropism:
A Potential Treatment for Glioblastoma

The Kids R.Kelly Peed On
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Background Information

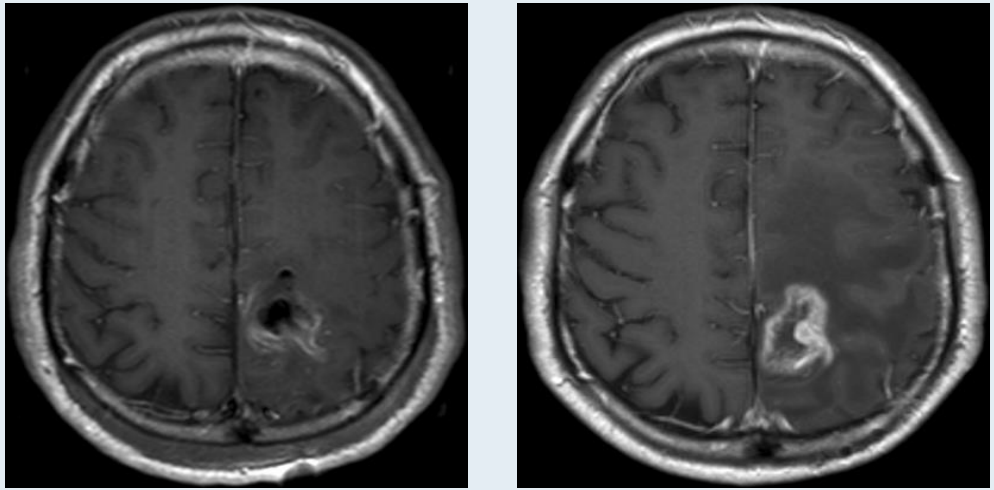
Glioblastoma

- Most common & most aggressive intrinsic brain tumor
- Always malignant!
- *Rarely* metastasize outside of the CNS
- **Derived from adult neural stem & progenitor cells**
- Lethal → average survival below 2 years
    - Very aggressive & very difficult to treat
    - No cure

(Zhu et al. 2017; mayoclinic.org)

Recurrent Glioblastoma

- Recur within 2cm of tumor margin in 90% of patients if surgically removed or shrunk by treatment



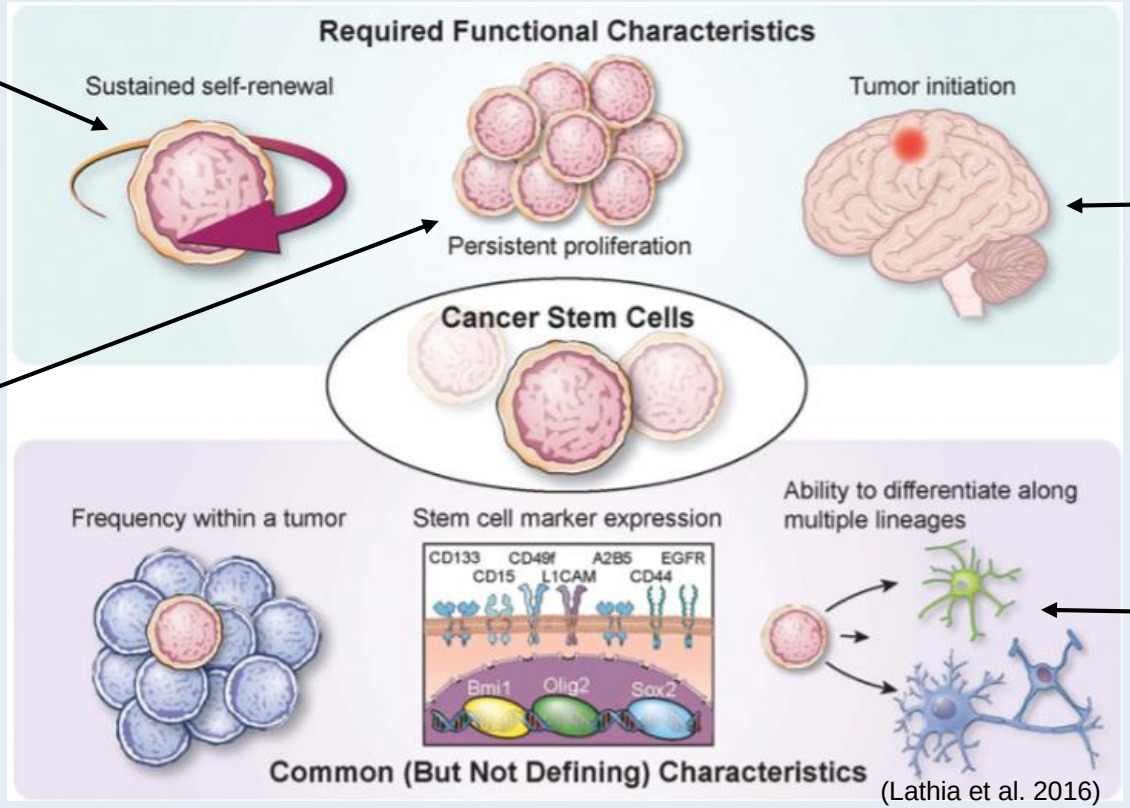
(Leitzen et al. 2016)

(Sontheimer 2015)

Glioblastoma Stem Cells (GSCs)

Self-renewal

Unregulated Proliferation



Tumor Initiation

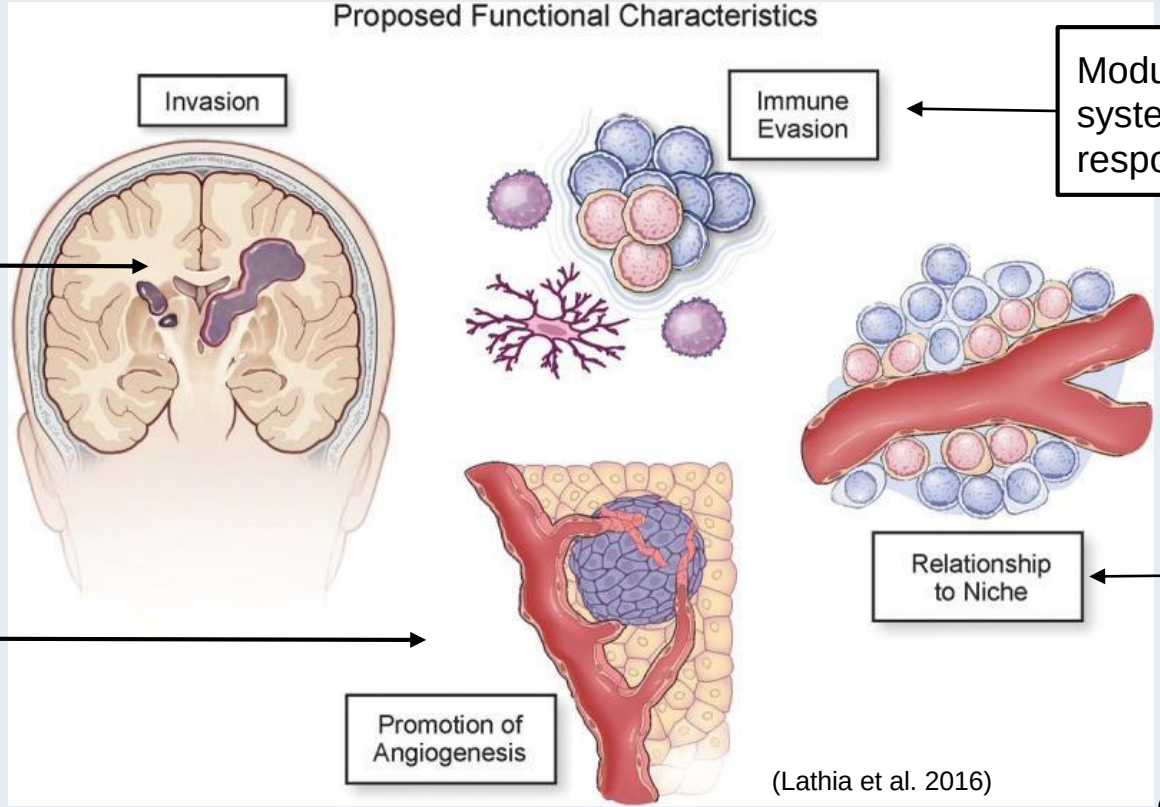
Differentiation

(Lathia et al. 2016)

Glioblastoma Stem Cells Drive Tumor Growth

Gliomas invade beyond tumor margin

Recruit blood vessels to provide nutrients for proliferation



(Lathia et al. 2016)

Modulates immune system to suppress response

Vascular niche factors sustain GSC population

(Gilbertson & Rich 2007)

Virotherapy Against Tumors

- Glioblastomas are uniquely aggressive due to GSCs
- This displays a need for localized treatment
  - Needs to infect and kill tumor cells specifically

(Zhu et al. 2017)

Virotherapies Against Glioblastoma in Progress

- Dr. Henry Friedman at Duke is working on recombinant polio/rhinovirus
  - Has shown success in clinical trial
  - FYI: he is on 60 minutes if you're interested
    - He is coming out w/ a massive paper soon
- Over 20 potential oncolytic viruses discovered:
  - Measels
  - Herpes simplex
  - Parvovirus
  - Adeno virus

Dogs get this :(

(Wollmann et al. 2012)

Benefit of Using Zika Virus

- Even in its natural state, it is less toxic to neurons
- Low levels of infection compared to other flaviviruses
- Zika virus has an advantage over dengue virus or West Nile because of cofactor of AXL ligands.

(Desasi et al. 2017l)

Zika Virus

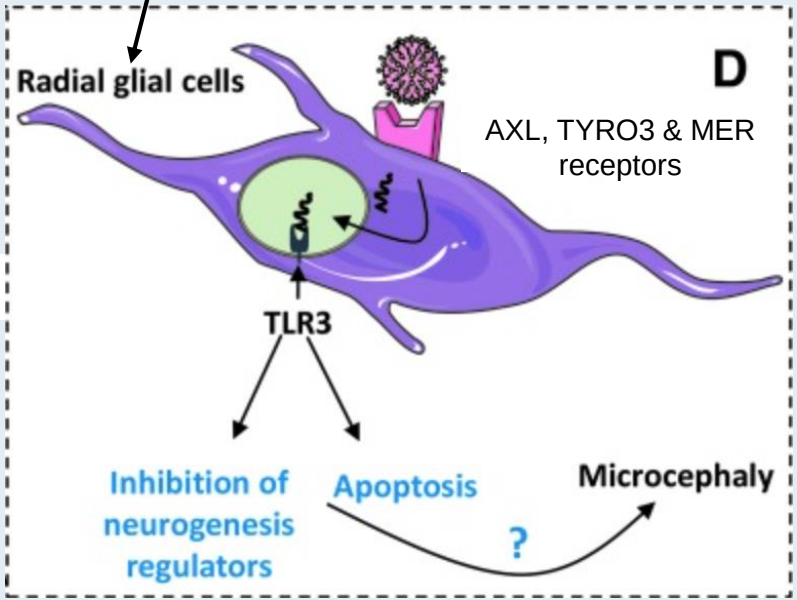
- RNA virus
- Flavivirus genus
- Most commonly transmitted by infected mosquito
- Mostly asymptomatic for adults
- Infection during/before pregnancy → fetal loss, congenital microcephaly or other severe brain abnormalities

(Center for Disease Control)

Zika Virus Targets Neural Progenitors

- ZIKV readily infects immature, undifferentiated neurons
  - Esp. radial glial cells
- Replicating and regenerating cells also vulnerable
- Adult neural cells (incl. stem cells) are protected

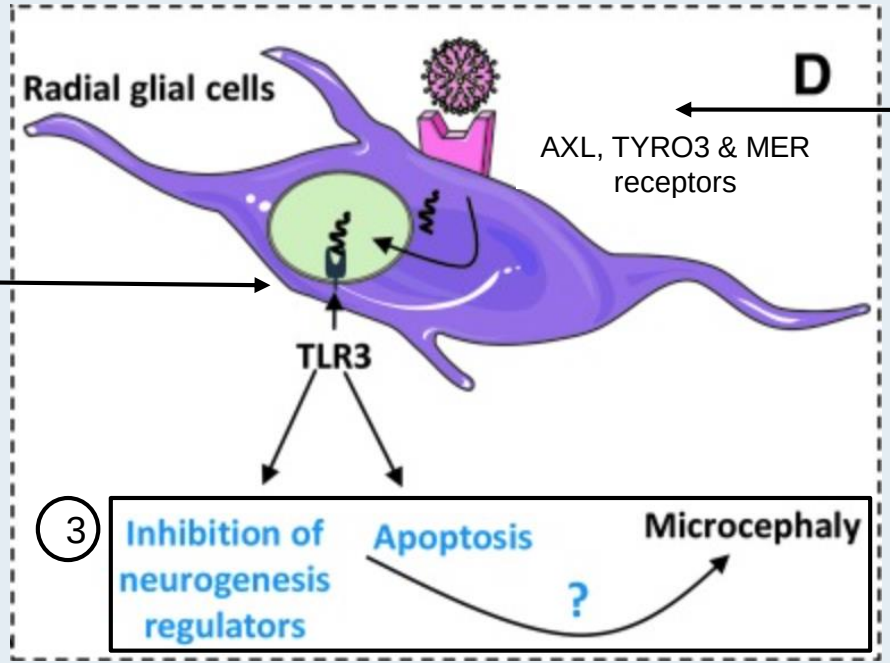
neural stem cells that generate neurons of different cortical layers



(Olagnier et al. 2016; Hughes et al. 2016; Ming et al. 2016)

Zika Virus Invades the CNS

ZIKV directly targets neural progenitors



1 Hypothesized mechanism of entry: TAM receptor tyrosine kinases

2 ZIKV activates TLR3-mediated immune response

(Olagnier et al. 2016; Hughes et al. 2016)

Zika Virus Has Oncolytic Activity Against Glioblastoma Stem Cells

Zhu et al. (2017)

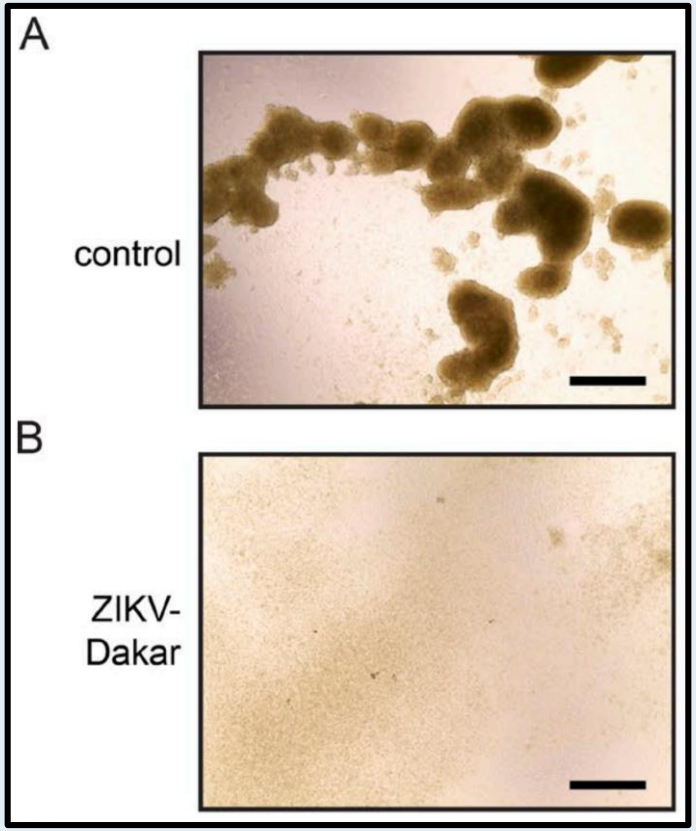
Zika Virus Has Oncolytic Activity Against Glioblastoma Stem Cells (Zhu et al. 2017)

Hypothesis

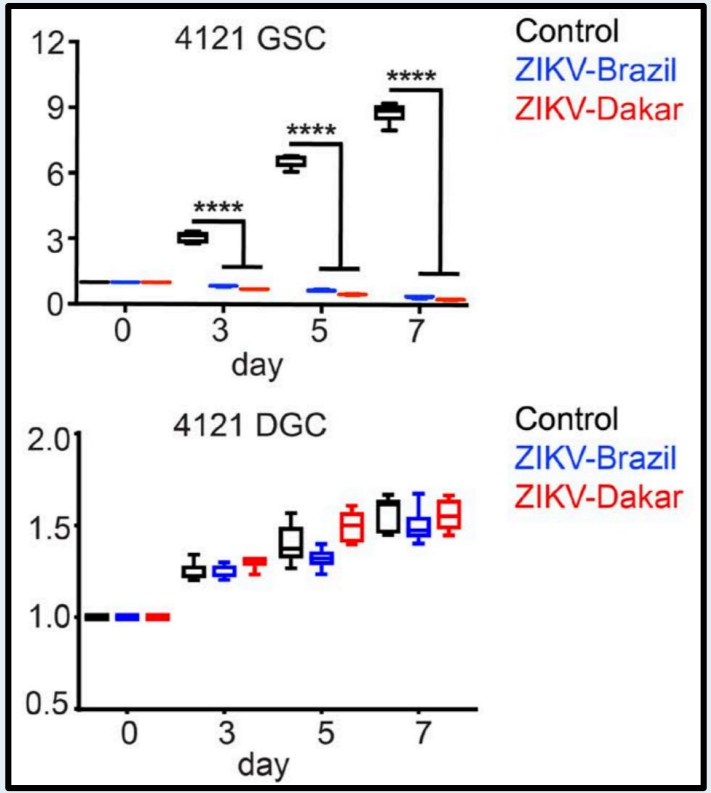
- Tropism of ZIKV for neural precursor cells can be leveraged against glioblastomas

Methods/Results

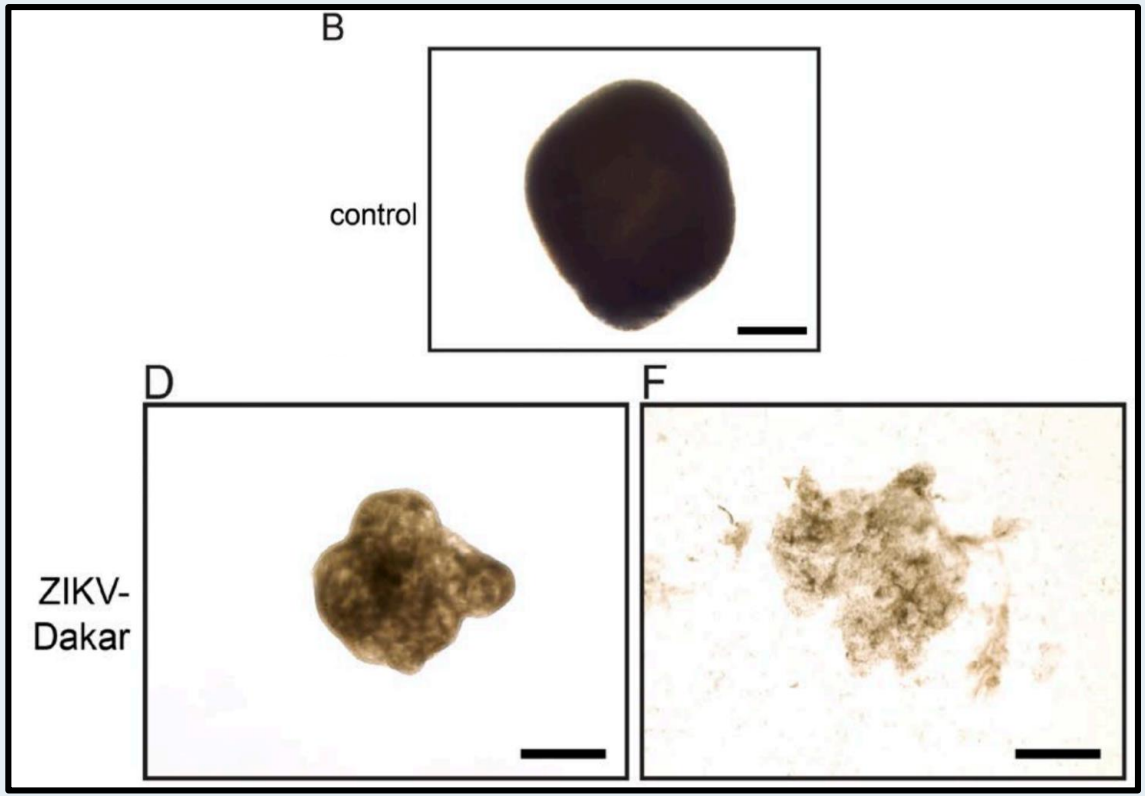
ZIKV infects human GSCs and inhibits proliferation



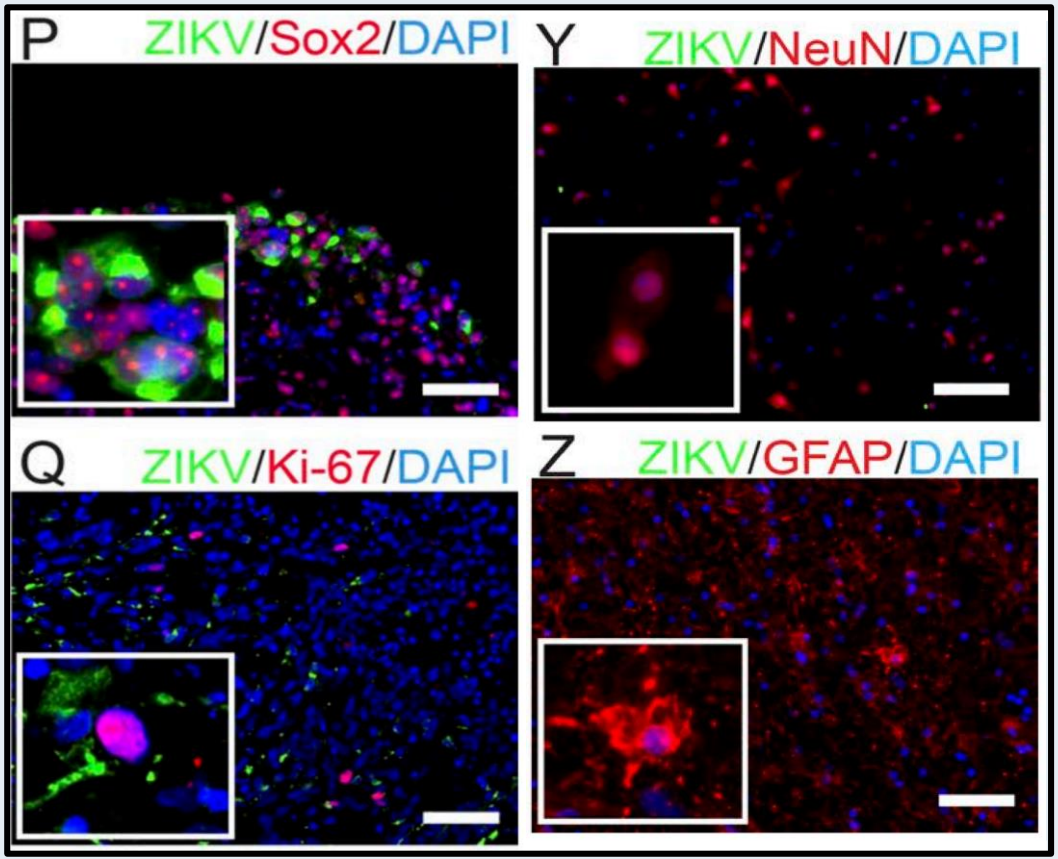
ZIKV Selectively infects GSCs



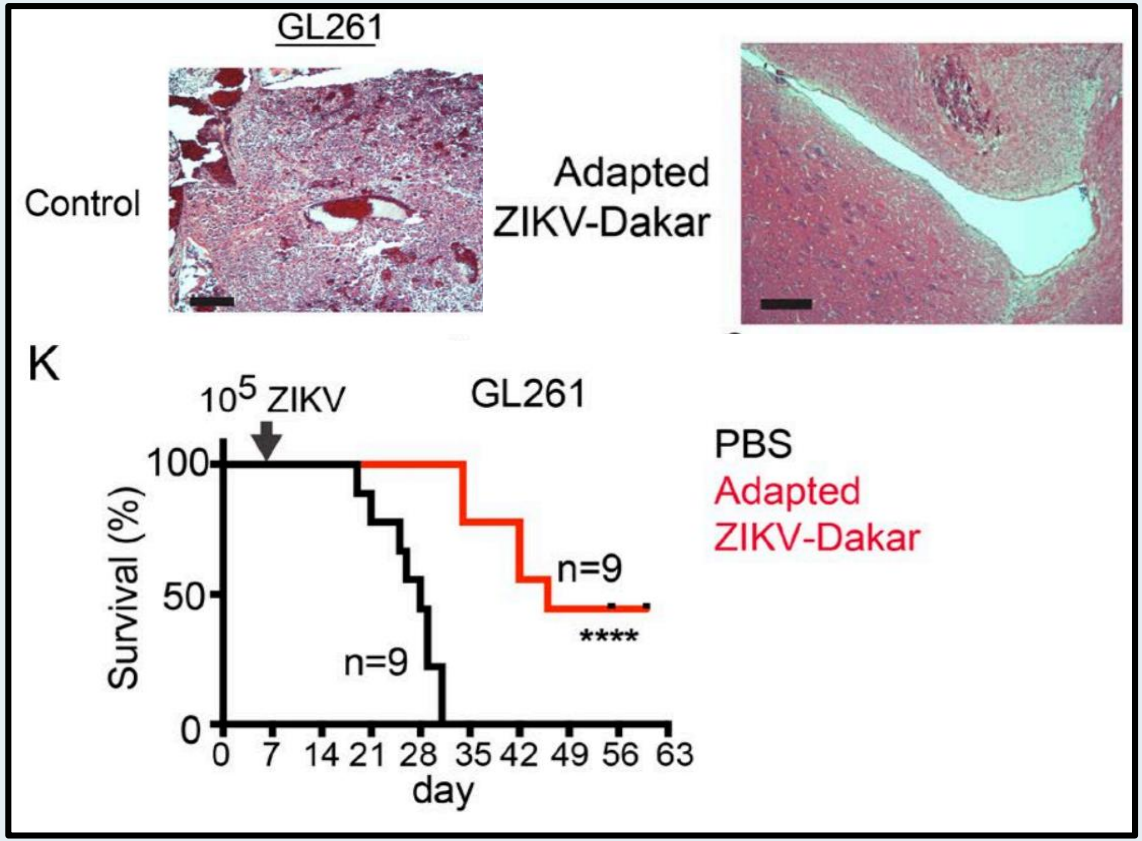
ZIKV prevents proliferation in glioblastoma organoids



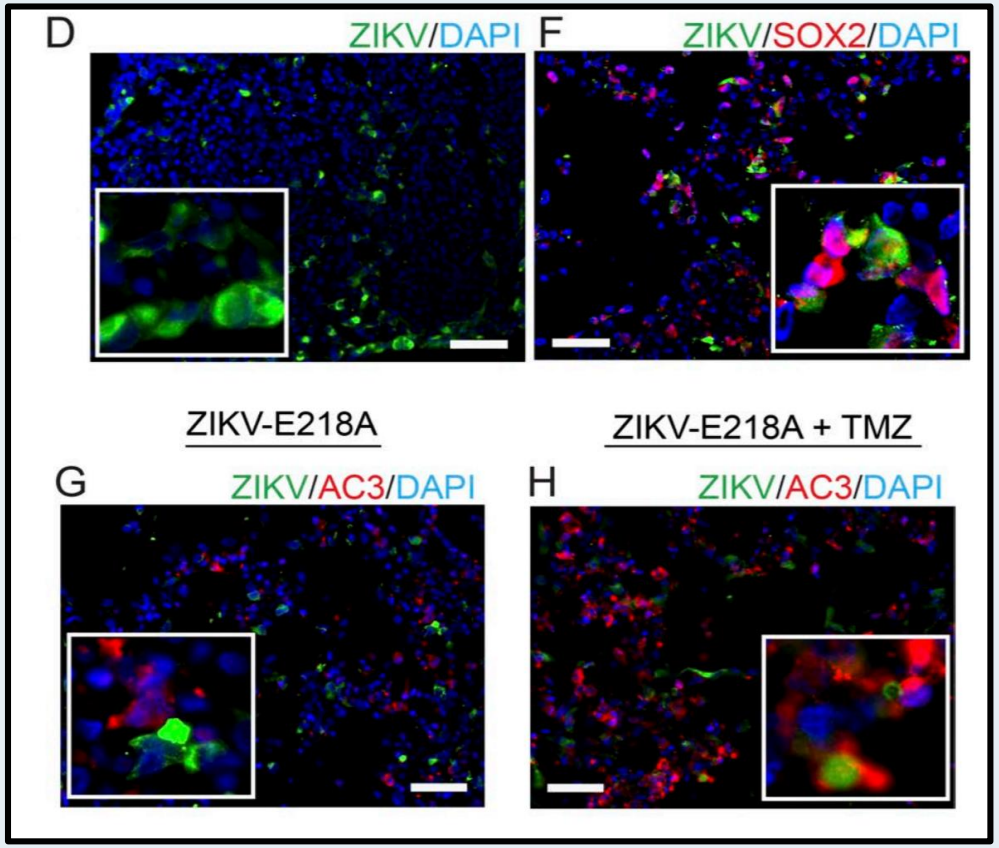
ZIKV targets GSCs in human tissue specimens



ZIKV attenuates glioma growth and prolongs survival



Mutated ZIKV maintains effectiveness against GSCs and has additive effects with temozolomide chemotherapy



How does ZIKV preferentially target GSCs for infection and trigger GSC death?

We don’t know!

GSCs Suppress Antitumor Immune Response

- Interferon (IFN) signaling increased in DGCs & suppressed in GSCs
  - IFNs: signaling proteins made/released by
- Immune response in DGCs protects against ZIKV infection
- ZIKV infects GSCs due to suppressed immune response
  - Pathway most activated by ZIKV infection → **IFN**
  - IFN activation by ZIKV → apoptosis of GSCs

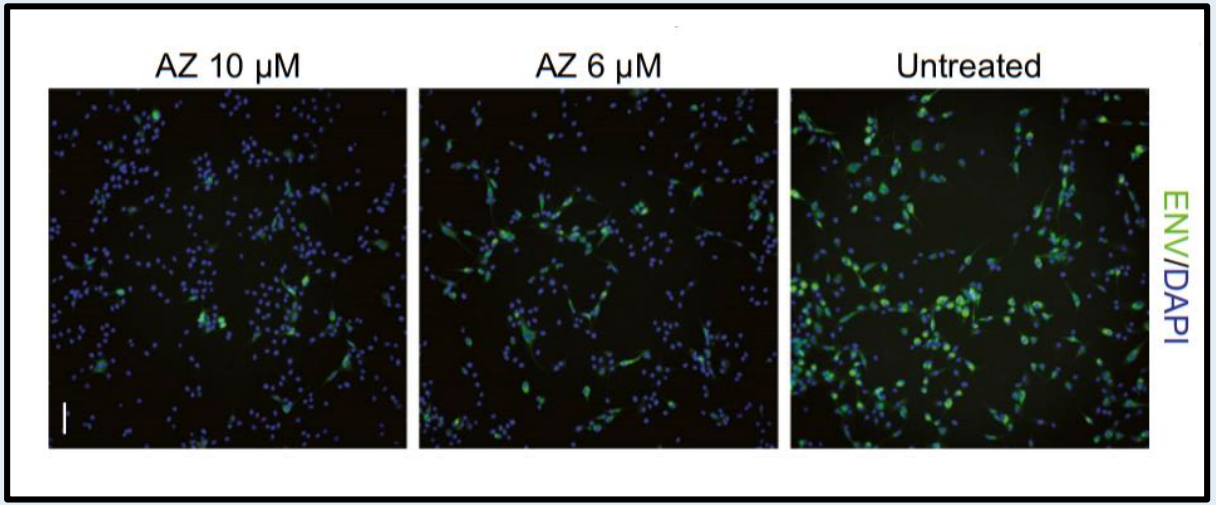
High AXL Receptor Expression in Glioblastomas

- AXL highly expressed on radial glia (neural stem cells)
- AXL highly expressed in glioblastomas
  - AXL = hypothesized mechanism of ZIKV entry into radial glial cells
- AXL might also play a role in tumor progression
  - Esp. angiogenesis, which is crucial to tumor cell proliferation

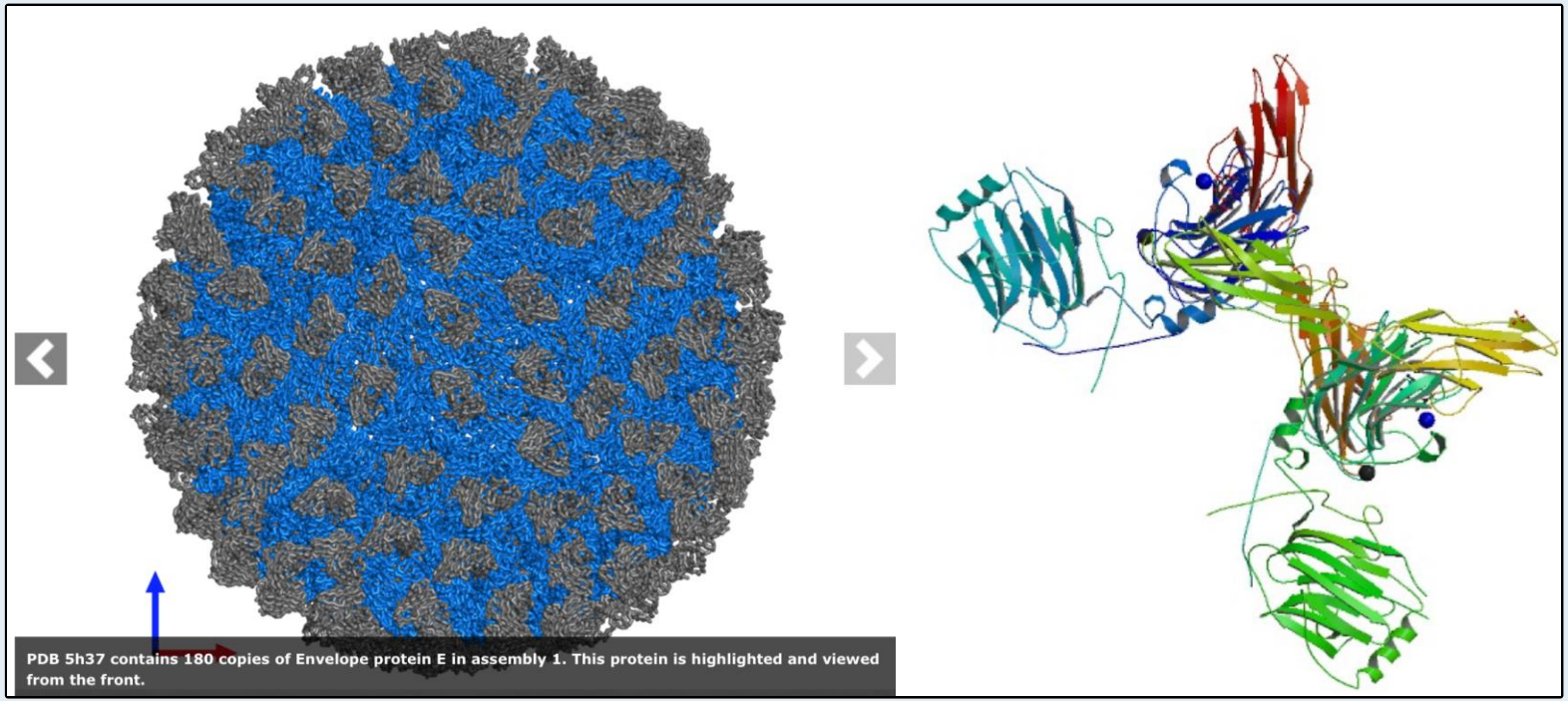
(Olagnier et al. 2016; Onken et al. 2017)

High AXL Expression in Glioblastomas

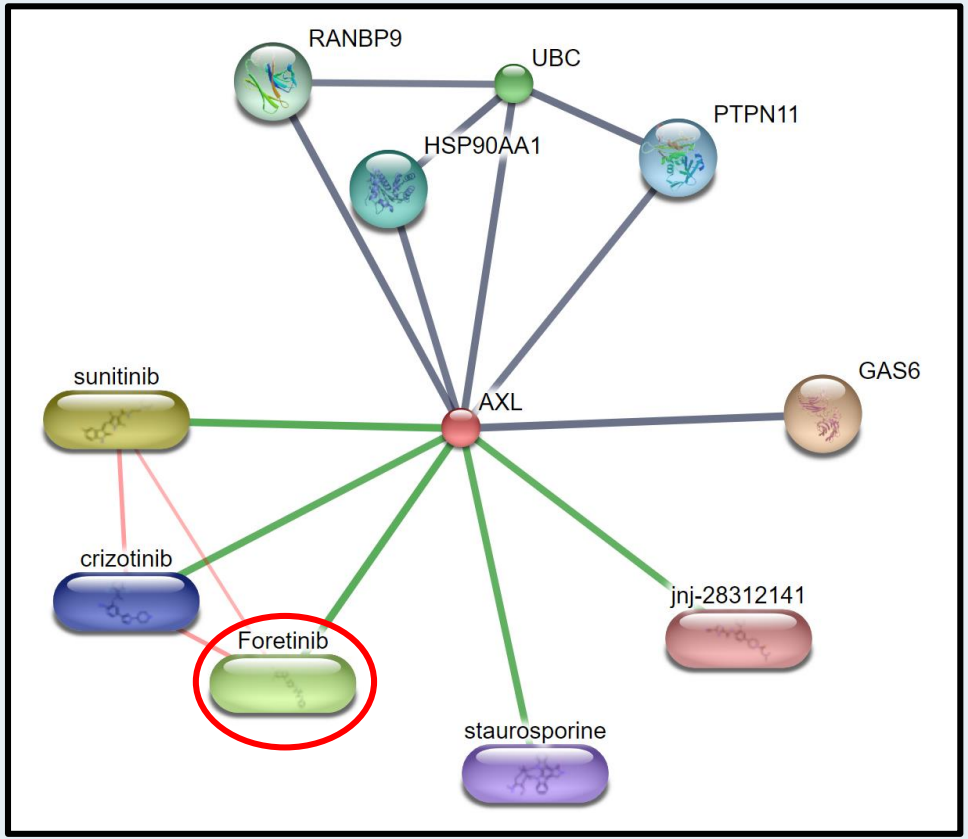
- Pharmaceutical blocking and genetic knockdowns of AXL receptors reduced ZIKA infection in glial stem cells



High AXL Expression in Glioblastomas



AXL is targeted by anti-cancer drugs



Limitations

- Mice are not natural hosts for ZIKV
- ZIKV pathogenesis studies have used immunocompromised mouse models
- This study used a mouse-adapted ZIKV strain
- ZIKV still infects non-tumor neural cells, just at a very low rate
  - Need to prevent toxicity to humans

(Zhu et al. 2017)

Difficulties with ZIKV

- There are two common strains of ZIKV- an African lineage and Asian lineage.
  - Genetic diversity between the two are important, as there is increased brain developmental abnormalities with the Asian lineage of the virus.
- It can be difficult to detect within individuals, as 80% of patients do not display clinical symptoms
  - This prevents diagnostic and surveillance methods

(Desai et al. 2017)

Future Direction

- Creating patient-derived glioblastoma models in more immunocompetent mice
- Further modification of ZIKV strain to reduce toxicity to non-tumor neural cells
- Evaluate efficacy of ZIKV in patient-derived GSCs in vivo
- Advancement in cancer treatment

Research that Needs to Happen First?

- Creating a better understanding of the ZIKV mechanism is crucial in order to push this kind of treatment through the FDA
- The rarity, high death rate and small advancement in Glioblastoma treatment, makes “radical” treatments more compelling.
- ZIKV could prove to be effective for other types or diseases and cancers.

Citations

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