



Researchers are trying to establish whether Zika virus causes the birth defect microcephaly.

PUBLIC HEALTH

Zika highlights role of fetal-tissue research

Controversial tissue studies could prove crucial to probing link between virus and birth defects.

BY ERIKA CHECK HAYDEN

A protein that helps Zika virus infect adult skin cells might also give the virus access to stem cells that make brain cells, suggests a study carried out on donated human fetal tissue.

The result — published on 30 March in *Cell Stem Cell*¹ — is part of a growing body of research that seeks to determine how Zika might cause birth defects, but that requires a type of tissue that is increasingly controversial for researchers in the United States.

Recent advances in neuroscience and cell technology have given hints as to why some babies born to Zika-infected mothers have abnormally small heads — a condition called microcephaly — and other birth defects. But to fully understand what is happening in the womb, some scientists say that they need to study tissue from fetuses, which can be donated by couples who terminate pregnancies.

Researchers already knew that a protein called AXL enabled Zika to enter human skin cells. Now, Arnold Kriegstein, a neuroscientist at the University of California, San Francisco,

(UCSF) and his colleagues show that the protein is also made by cells in the fetus that form the eyes and the brain. AXL could provide a means for Zika virus to infect these cells.

Two other studies published this month^{2,3} showed that Zika specifically targets and kills neuron-forming cells, including those in organoids — brain-like structures derived from reprogrammed human skin cells. These studies suggest that Zika causes microcephaly by damaging fetal cells that make the brain, says neuroscientist Patricia Pestana Garcez of the Federal University of Rio de Janeiro, Brazil, who led one of the studies.

Kriegstein's study used fetal tissue donated by patients treated at UCSF medical facilities. But such material may get harder to come by, because the collection and use of fetal cells is under renewed scrutiny in the United States. Last July, an anti-abortion group called the Center for Medical Progress in Irvine, California, released video of employees from

the non-profit health-care provider Planned Parenthood discussing the sale of fetal tissue from abortions for research. Members of the US House of Representatives are now investigating the use of fetal tissue in research.

Scientists in the United States worry that the controversy could hamper essential research on the Zika virus. “Many fewer people are willing to donate, and it’s slowing us down,” says Susan Fisher, a stem-cell and developmental biologist at UCSF.

Fisher is studying how Zika virus is transmitted from mother to baby. She has found AXL in fetal cells called trophoblasts that anchor the placenta, which supplies a fetus with blood and nutrients, to the mother’s uterus. These cells are known to transmit infections such as cytomegalovirus from mother to baby. “This suggests that the placenta is extremely capable of transmitting Zika,” says Fisher, whose studies rely on fetal tissue donated from terminated and full-term pregnancies.

Carolyn Coyne, a virologist at the University of Pittsburgh in Pennsylvania, says that fetal tissue is particularly crucial for studies of Zika because the virus seems to be able to harm a fetus throughout pregnancy⁴. “It is absolutely essential to study Zika infection in human fetal tissue,” says Coyne. “These types of studies need to extend to all stages of pregnancy.”

Because abortion is illegal or highly restricted in many Latin American countries, laboratory research on neural development in the regions hit hardest by Zika relies mainly on other types of human tissue, such as organoids. Researchers in Brazil, for example, are studying the lethality of different Zika viruses in neurons and organoids derived from cord blood.

Both Fisher and Kriegstein are planning further studies to test how Zika infects developing brain and placental cells. They argue that such studies are crucial to establish why the virus damages babies’ brains, and whether this can be prevented.

The scientists will also use organoids and animal models, but they note that neither of these is a perfect substitute for human fetal tissue. For instance, researchers aren’t sure how faithfully the growth of brain organoids replicates human brain development. “It’ll be important to demonstrate in human tissue exactly how the virus is creating the pattern of damage that is emerging,” Kriegstein says. “In situations like this, where there’s considerable time pressure to try to unravel what’s going on and to protect the developing human brain, it’s especially important.” ■

1. Nowakowski, T. J. *et al.* *Cell Stem Cell* <http://dx.doi.org/10.1016/j.stem.2016.03.012> (2016).
2. Garcez, P. P. *et al.* *PeerJ Preprints* **4**, e1817v3 (2016).
3. Tang, H. *et al.* *Cell Stem Cell* <http://dx.doi.org/10.1016/j.stem.2016.02.016> (2016).
4. Brasil, P. *et al.* *N. Eng. J. Med.* <http://dx.doi.org/10.1056/NEJMoa1602412> (2016).