

Study reveals factors that can make placenta less capable of protecting fetus from zika

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Findings reported by Brazilian researchers in *PLOS Neglected Tropical Diseases* help explain why only some babies whose mothers are infected during pregnancy are born with microcephaly and other anomalies Credit: HUG-CELL/USP

Genetic factors that reduce the placenta's capacity to protect the fetus from the zika virus are described by Brazilian researchers in an article published in *PLOS Neglected Tropical Diseases*. According to the authors, the findings help explain why only some babies whose mothers are infected by zika virus during pregnancy are born with some kind of anomaly.

Since the 2015 epidemic at least 3,500 [babies](#) have suffered from [zika](#) congenital syndrome, which includes microcephaly, brain calcifications, and auditory and visual deficits, according to statistics available from the Brazilian Health Ministry. However, these cases are believed to

correspond to between 5% and 10% of all the fetuses exposed to zika in the first trimester, the riskiest period of pregnancy.

"We observed differences in the expression of two classes of genes in the [placenta](#) of the affected babies. One is associated with the placenta's capacity to invade and attach to the wall of the uterus. The other has to do with the production of certain molecules known as chemokines, which attract maternal immune cells to combat the virus in the placental barrier," said Sergio Verjovski , a professor in the University of São Paulo's Chemistry Institute (IQ-USP) and principal investigator for the study, which was supported by São Paulo Research Foundation—FAPESP .

The discovery was only possible thanks to a cellular reprogramming technique that enabled the researchers to recreate in the laboratory the cells that make up the so-called primitive placenta, which gives the fetus support in the first trimester.

These cells, called trophoblasts, were obtained from [blood samples](#) donated by three pairs of discordant twins—cases in which only one sibling was born with microcephaly although both were equally exposed to viral infection in the womb.

Because these children represent an ideal model for the study of [genetic factors](#) that increase susceptibility to congenital zika syndrome, they have been monitored for about four years by researchers affiliated with the Human Genome and Stem-Cell Research Center (HUG-CELL), one of the Research, Innovation and Dissemination Centers (RIDCs) funded by FAPESP. HUG-CELL's principal investigator is Mayana Zatz , a professor in the University of São Paulo's Bio-Science Institute (IB-USP) and a co-author of the article.

"First we reprogrammed the blood cells so that they returned to a stage

of pluripotency similar to that of embryo stem cells," Verjovski said. "Then we had these induced pluripotent stem cells [IPSCs] differentiate in vitro into primitive trophoblasts."

Next, two groups of placental cells were cultured, one to simulate the primitive placenta of babies born with microcephaly and hence most affected by zika, and the other to represent the placenta of twins resistant to viral infection.

All the cultured cells were infected with a Brazilian strain of the virus (ZIKV-BR), which circulated here during the 2015-16 epidemic. The researchers then used sequencing techniques to compare the two groups' transcriptomes (all RNA molecules expressed by their genes). The aim was to see in each case how the virus affected [gene expression](#) in placental cells.

"In the trophoblasts of the babies born with microcephaly, we observed decreased expression of several genes associated with the extracellular matrix. These genes are a key part of a process whereby the placenta, which is fetal tissue, invades and attaches to the uterus," Verjovski said. "This process is important for the placenta to nourish the fetus properly and act as a physical barrier against pathogens and toxins."

Analysis conducted 48 and 96 hours after infection showed statistically significant growth of chemokines RANTES/CCL5 (up to 4.6 times) and IP10 (up to 96 times) only in the trophoblasts from the resistant babies.

"These molecules are important signalers to the mother's immune defense in the placental barrier. They attract to the site maternal cells capable of destroying the virus," Verjovski said.

The results, therefore, suggest that the primitive placenta in resistant babies is able to prevent infection of fetal tissue more effectively.

"We would need to perform new experiments to confirm this hypothesis," Verjovski said. "One possibility would be placing the trophoblasts infected with zika in contact with blood samples from pregnant women, and observing whether placental cells of resistant babies are indeed able to attract more of the mother's immune cells. However, this isn't easy to do: we would need to obtain blood samples from pregnant women whose immune cells were compatible with the discordant twins' cells."

In any event, he continued, the identification of genes differentially expressed in babies with microcephaly paves the way for research that aims to develop interventions capable of preventing damage to the fetus by the virus. "We think it would be more feasible to develop a treatment that reinforces the placental barrier and prevents infection of the fetus than to invest, for example, in a drug that blocks damage by the virus directly in the fetal nervous system," he said.

More than genetics

In a study published in 2017 in *PNAS*, Verjovski and collaborators at the University of Missouri in the United States showed that the primitive placenta offers a far more favorable environment to infection by zika than the mature placenta because of increased first-trimester expression of several genes that encode attachment proteins that facilitate viral entry into fetal tissue. On the other hand, the mature placenta expresses more proteins associated with antiviral defense. This study involved primitive and mature trophoblasts also obtained by cellular reprogramming, but from embryonic stem cells (and hence not from children exposed to the virus during pregnancy).

"At the time we raised the hypothesis that the primitive placenta in fetuses susceptible to zika expressed more attachment receptors so that these babies were exposed to a higher viral load. We've now refuted this

theory with the new findings," Verjovski said.

The latest study showed, he added, that gene expression is initially the same in trophoblasts from twins born with and without microcephaly, but becomes different after viral infection. "For some unknown reason, the placenta responds differently to viral cell entry in susceptible and resistant babies," he said.

Other genetic factors associated with greater susceptibility to zika congenital syndrome were described by the HUG-CELL team in an article published in 2018 in *Nature Communications*. The researchers showed that zika replicated much more in neural progenitor cells (NPCs) from babies with microcephaly than in NPCs from their resistant siblings. Furthermore, NPCs from susceptible babies proliferated less and died more than NPCs from resistant babies. In this case, the NPCs were also generated by cellular reprogramming from blood samples donated by discordant twins.

A comparison of gene expression in the two groups brought to light differences in two important signaling pathways for brain development during the embryonic period—one mediated by the protein mTOR and the other by Wnt. These pathways regulate the proliferation and migration of central nervous system [cells](#), among other things.

Other factors that have been associated with a heightened risk of fetal anomalies besides genetics include maternal diet, gut microbiota composition, and maternal exposure to pollutants and other pathogens. One of the questions that remain open is why in some regions, such as the Northeast of Brazil, zika caused many more cases of microcephaly than in others where zika outbreaks also occurred.

"In the study published in 2017, we compared two different zika strains—one isolated in Uganda [in Africa, where the virus originated]

and another in Polynesia. The Brazilian strain derived from the latter," Verjovski said. "We found the African strain to be far more virulent in the primitive placenta. It's possible therefore that no cases of microcephaly occurred in Africa because the pregnant women infected there miscarried and the virus became less destructive as it mutated so that it was able to replicate for longer in the fetus and a larger number of infected women were able to take their pregnancies to term."

More information: Murilo Sena Amaral et al, Differential gene expression elicited by ZIKV infection in trophoblasts from congenital Zika syndrome discordant twins, *PLOS Neglected Tropical Diseases* (2020). [DOI: 10.1371/journal.pntd.0008424](https://doi.org/10.1371/journal.pntd.0008424)

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