Zika virus study reveals possible causes of brain pathology

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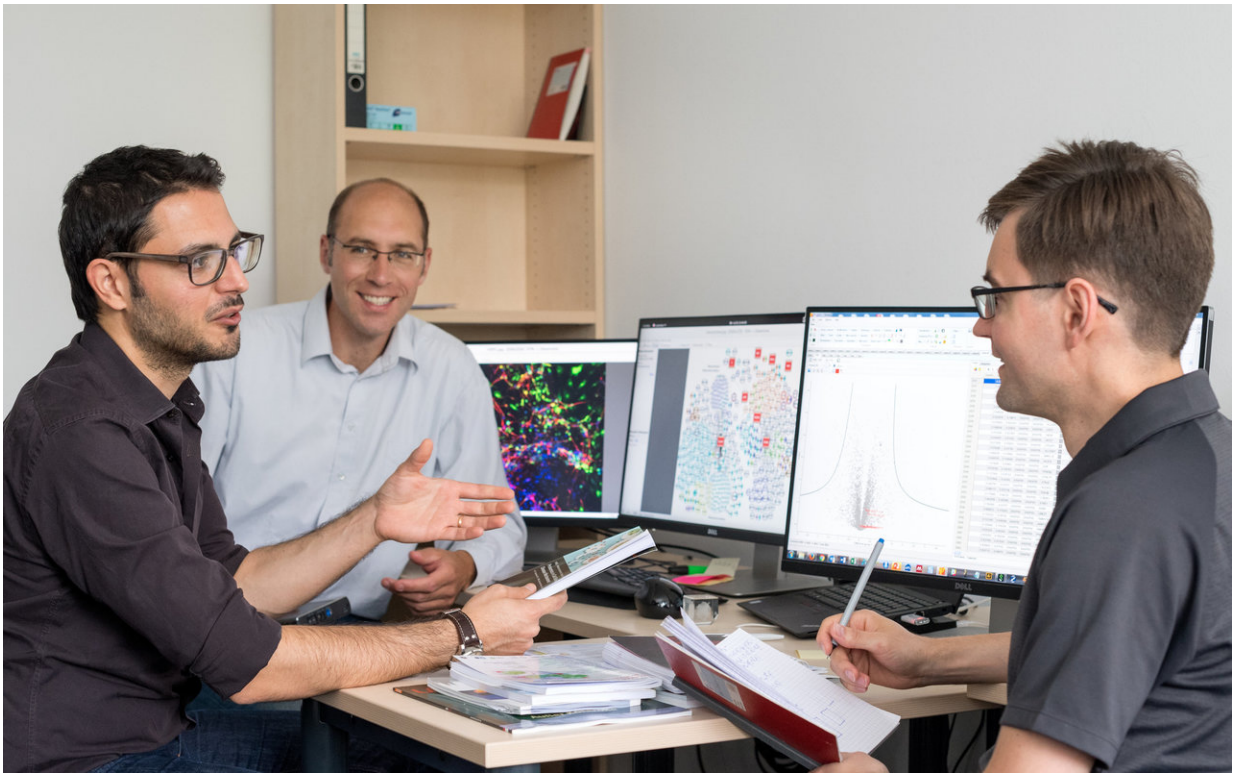

The scientific team of the Zika virus study (from left to right): Pietro Scaturro, Prof. Andreas Pichlmair and Dr. Alexey Stukalov. Credit: Astrid Eckert / Technical University of Munich

In healthy individuals, the Zika virus causes flu-like symptoms. If a pregnant woman becomes infected, the unborn child can suffer from

severe brain abnormalities as a result of mechanisms that have not yet been explained. A study by the Technical University of Munich (TUM) and the Max Planck Institute of Biochemistry (MPI-B) shows that Zika virus proteins bind to cellular proteins that are required for neural development.

A few years ago, Zika virus spread across South America, posing a health issue with global impact. A significant number of South American women who contracted the virus via mosquito bite at the start of their pregnancy subsequently gave birth to children with severe disabilities. The babies suffered from a condition known as microcephaly, causing the underdevelopment of the brain. This can lead to intellectual disabilities and other serious neurological disorders.

Scientists proved that these deformities are caused by Zika virus infections, but so far, they have been unable to explain why. Andreas Pichlmair, Chair for Viral Immunopathology at TUM, and his team from the TUM Institute of Virology and MPI-B have examined how Zika virus influences human brain cells. They identified the virus proteins with the potential to affect neuronal development in the developing brain.

Dangerous side-effect of virus replication

"Zika virus is closely related to the hepatitis C virus and certain tropical diseases such as Dengue and West Nile virus. It is, however, the only virus that causes brain damage in newborns," explains Pichlmair, who headed the recent study published in the science journal *Nature*.

The researchers discovered that the virus uses certain cellular proteins to replicate its own genome. These molecules are also important neurological factors in the process of stem cells developing into nerve cells. "Our findings suggest that the virus takes these factors away from

brain development and uses them to replicate its genome, which prevents the brain from developing properly," explains the virologist.

When the team headed by Pichlmair removed the factors in the cells, it was harder for the virus to replicate. The researchers were able to demonstrate which virus proteins come in contact with these development factors, causing brain defects. "Previous studies revealed the virus proteins necessary for the packaging or replication of the viral genome, but it was enigmatic to understand how these proteins influence neuronal development. It appears that viral proteins are responsible for causing the serious defects in the unborn—unintentionally, we presume," says Pichlmair.

Clear picture of the virus infection

In their comprehensive proteomics survey, the research team identified cellular proteins that were altered chemically or numerically by the virus or which bound to virus proteins. In this way, they were able to illustrate possible reasons for the caused deformities, and also obtained a very clear picture of how the virus reprograms the cell to use it for its own replication.

The influence of Zika virus on the cell was found to be dramatic: Nine percent of all cellular proteins were chemically altered, and virus proteins interacted with more than 380 cellular proteins. "Our comprehensive dataset will hopefully lead the way for other scientists to develop therapeutic approaches for the elimination of Zika or related viruses," says Pichlmair.

More information: Pietro Scaturro et al, An orthogonal proteomic survey uncovers novel Zika virus host factors, *Nature* (2018). DOI: 10.1038/s41586-018-0484-5