idw - Informationsdienst Wissenschaft
Nachrichten, Termine, Experten

Pressemitteilung

Institute of Science and Technology Austria
Andreas Rothe

03.04.2025
http://idw-online.de/de/news849818

Forschungsergebnisse, Wissenschaftliche Publikationen
Biologie, Ernährung / Gesundheit / Pflege, Medizin
überregional

Pink Skies | ISTA researchers present new brain organoid model

Organoids have revolutionized science and medicine, providing platforms for disease modeling, drug testing, and understanding developmental processes. While not exact replicas of human organs, they offer significant insights. The Siegert group at the Institute of Science and Technology Austria (ISTA) presents a new organoid model that reveals details of the developing nervous system's response to viral infections, such as Rubella. This model could influence pharmaceutical testing, particularly benefiting drug safety for pregnant women.

Microglia are special cells in the human brain. Like a diligent ranger overseeing a forest and dealing with infestations and wildfires, microglia scan the brain environment for germs and initiate an anti-inflammatory response to remove them. They also monitor the quantity of neurons (nerve cells) and their connections to ensure optimal brain function in adulthood.

Sandra Siegert and her research group at the Institute of Science and Technology Austria (ISTA) focus on these microglia and their interplay with neurons during embryonic development. In their latest publication, the Siegert group introduces a new brain organoid model that, for the first time, incorporates microglia to mimic inflammatory reactions and their treatment. The results are published in the Journal of Neuroinflammation.

Rubella – the "German Measles"

Little itchy red dots that spread from the face across the body are a common experience for parents with children suffering from Rubella.

For kids and adults alike, the infection is mild; however, if contracted when pregnant, it can have serious implications. Rubella is classified into the so-called "TORCH-infections" (toxoplasmosis, others, rubella, cytomegalovirus, herpes simplex), which can be transmitted from a pregnant person to the developing fetus, causing malformations of the fetal brain and thus increasing the risk of schizophrenia in adulthood.

Understanding how such viral infections affect the development of the human brain is crucial. PhD student Verena Schmied, together with Professor Sandra Siegert and her research group at ISTA, set out to uncover some answers. Retinal organoids—one of the first established brain region-specific models with known developmental trajectories and cell architecture—proved to be highly useful.

3D structures that mimic the human brain

To get an organoid, you start, for instance, with skin cells from a person. These cells are then reprogrammed or 'set back to factory setting' to get versatile pluripotent stem cells—called human-induced pluripotent stem cells (hiPSCs). Given the right circumstances, hiPSCs can develop into any other cell type. With special growth factors, nutrients, and environmental constraints, hiPSCs cluster together and self-organize into mature retinal organoids in a Petri dish.

"Retinal organoids allow us to recapitulate important steps of early fetal brain development," says Schmied. To make accurate statements, these organoids must closely resemble the real thing. Recent brain-region organoid models to test viral infections during brain development, however, did not include microglia which are usually present from very early developmental stages.

To change that notion, the scientists added microglia into retinal organoids and used fluorescent colors and microscopes to verify their successful integration. Between the blue-stained neurons, the delicate bodies of microglia were prominently visible in bright pink. A beautiful moment for Siegert, who recalls, "Seeing an organoid full of integrated microglia and how they distribute themselves was really remarkable."

What happens after a viral infection?

The researchers then investigated how their organoids acted upon viral infection. "We mimicked viral infection with a synthetic molecule, that is recognized as a viral component and compared organoids with and without microglia," Schmied continues.
The viral infection distracts microglia properties, causing them to address this infection by inducing an inflammatory response. The shift results in an excess of dividing neurons, which could interfere with the proper assembly of the neuronal circuit, ultimately causing neurodevelopmental defects.

"The presence of microglia replicates the observed characteristics in an inflammatory condition and truly represents the negative consequences on the nervous system. This negative effect would not be seen when we would not have microglia in the system," explains Siegert.

Ibuprofen and the "off-label" dilemma during pregnancy

Although preventable by a vaccine, there is no specific antiviral treatment for Rubella other than anti-inflammatory drugs like ibuprofen. To see how ibuprofen affects the developing brain, the scientists administered the painkiller to the virus-infected organoids.

After administrating ibuprofen, the inflammatory-mediated changes were reduced and the normal neuronal environment was restored. This only happened in the presence of microglia, suggesting that ibuprofen exerts its protective effects during embryonic development by inhibiting two inflammatory enzymes—COX 1 and COX 2—of which COX 1 is specific for microglia.

"Our paper shows that it is critical to have microglia brain organoid models to mimic inflammatory reactions and their treatment. If microglia are missing, the effects might be overseen," summarizes Siegert.

A fact that is very important in the light of the recent development of brain organoid models and hIPSCs being used for drug testing and research: these models need to be as realistic as possible, and as now shown, this requires microglia. The Siegert group's new model could serve as a platform for further investigations, potentially benefiting expectant mothers. While commonly used painkillers like ibuprofen or paracetamol are considered safe for adults, they have not been tested in pregnant women. There are numerous reasons for this, including ethical concerns, cost implications, and

legal risks. The uncertainties that accompany them often result in “off-label” use.

-

Funding information
This project was supported by funding from the Gesellschaft für Forschungsförderung Niederösterreich (grant No. Sc19-017 to V. Schmied).

Originalpublikation:

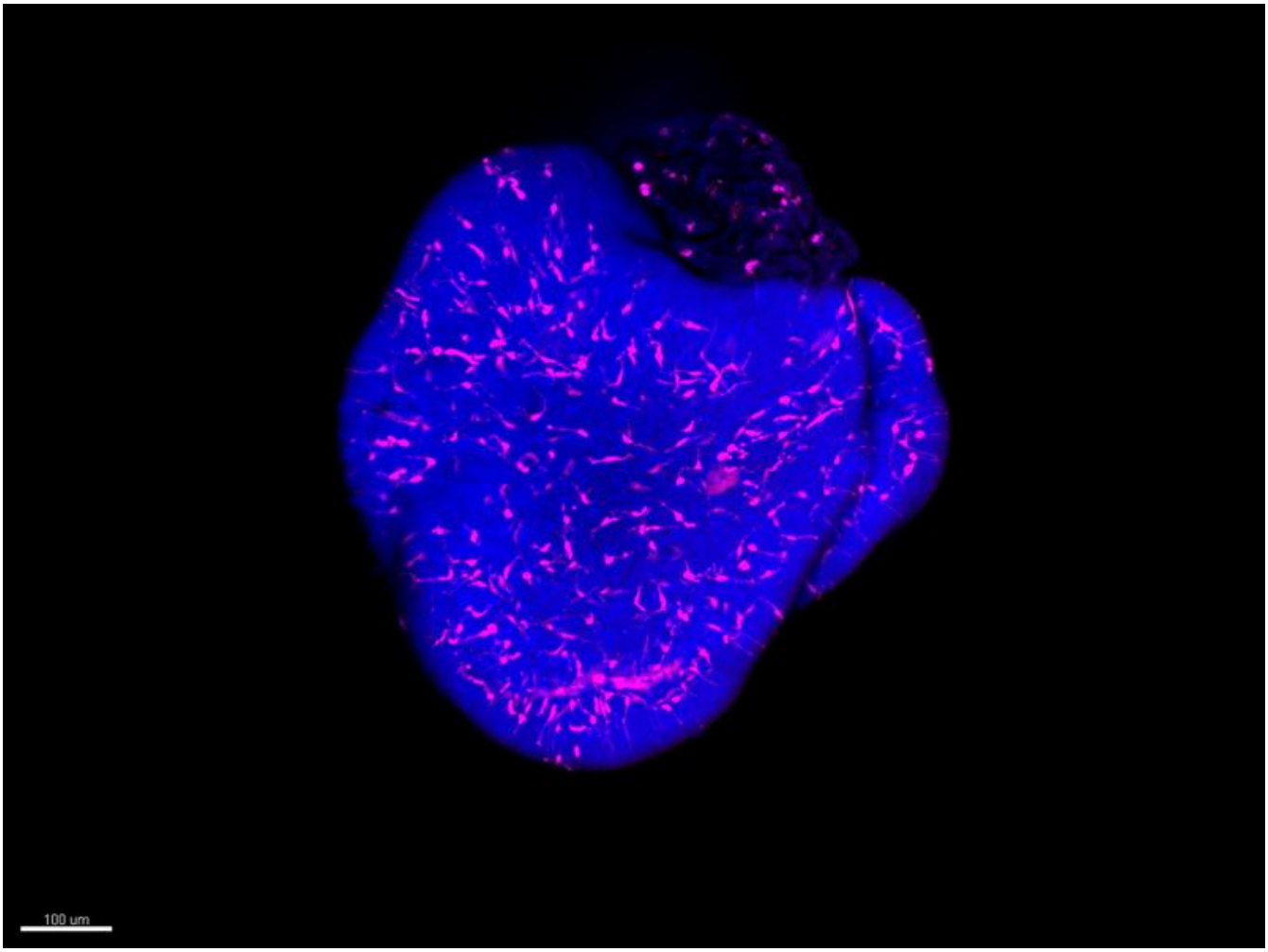
V. Schmied, M. Korkut-Demirbaş, J. P. Maya-Arteaga, A. Venturino & S. Siegert. 2025. Microglia determine an immune-challenged environment and facilitate ibuprofen action in human retinal organoids. Journal of Neuroinflammation. DOI: https://doi.org/10.1186/s12974-025-03366-x

URL zur Pressemitteilung: https://ista.ac.at/en/research/siegert-group/ "Microglia-Neuron Interaction" research group at ISTA

URL zur Pressemitteilung: https://pubmed.ncbi.nlm.nih.gov/37147251/ Recent development of brain organoid models and hIPSCs being used for drug testing and research

URL zur Pressemitteilung:
https://theconversation.com/why-is-it-so-hard-to-get-drugs-approved-for-use-during-pregnancy-238684 Off-label dilemma during pregnancy

Anhang Organoid with microglia. Microglia (magenta) integrated into retinal organoids (grey).
http://idw-online.de/de/attachment109342



Pink skies. Microglia (magenta) integrated into a retinal organoid. The cell nuclei of neurons are stained in blue.
© Schmied et al. / Journal of Neuroinflammation

Authors from the Siegert group, at the Institute of Science and Technology Austria (ISTA), from left to right: Sandra Siegert, Juan Pablo Maya-Arteaga, Alessandro Venturino, Verena Schmied and Medina Korkut-Demirbas.
© ISTA