An 'atlas' of the brain's choroid plexus across the lifespan

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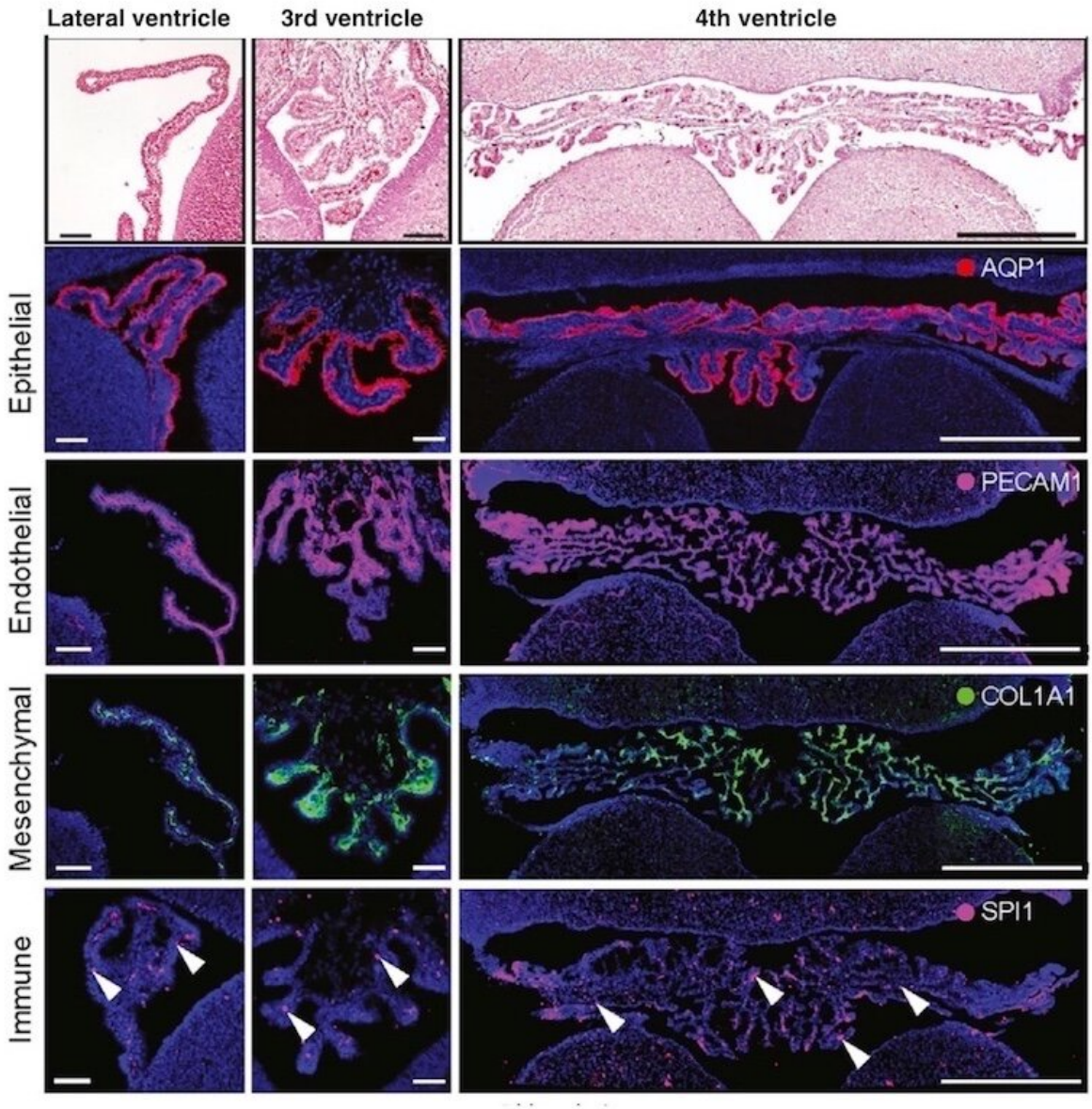


Cell types in the mouse embryonic choroid plexus, revealed by different stains. From left to right, choroid plexus from the lateral ventricle, third ventricle, and fourth ventricle. From the top, a pathologist's view, followed by epithelial, endothelial, mesenchymal, and immune cells. Credit: Dani N, Herbst RH, et al. Cell April 30, 2021, DOI 10.1016/j.cell.2021.04.003.

Once viewed merely as a producer of the cerebrospinal fluid (CSF) bathing the brain and spinal cord, the choroid plexus is now known to be a key player in brain development and immunity. These fronds of brain tissue, located in the CSF-filled brain cavities known as ventricles, secrete instructive cues into the CSF to regulate brain development. They also function as an important barrier between the brain and the rest of the body.

Maria Lehtinen, Ph.D., of Boston Children's Hospital has done much of the pioneering work in understanding this once-obscure tissue. In new work published in *Cell*, Lehtinen, Neil Dani, Ph.D., and other colleagues at Boston Children's and the Broad Institute created a cellular and spatial "atlas" of the choroid plexus during different life stages (early development, adulthood, old age).

The map provides a benchmark to accelerate future studies investigating the lifelong regulation of this diminutive but influential brain structure.

"To fully understand the choroid plexus and its functions, we needed to identify its constituent cell types and their molecular composition," says Dani, who was co-first author on the paper with Rebecca Herbst, a Ph.D. student at the Broad Institute. "Such insights had been missing in the community."

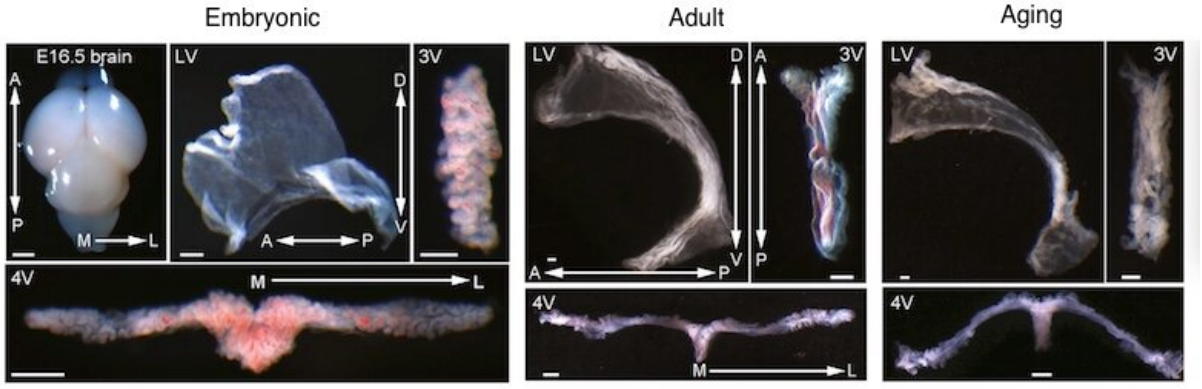
Extracting choroid plexus tissue

Isolating choroid plexus tissue from embryonic, adult, and aged mice was a job in itself. It required special micro-dissection approaches since these tissues lie deep within the brain's ventricles.

"Figuring out how to dissect out intact third-ventricle choroid plexus was particularly challenging," says Dani.

With tissue from each of the animals' three ventricles in hand, the researchers performed RNA sequencing of more than 98,000 cells and cell nuclei to compare their gene expression profiles (what genes were turned on or off). This enabled them to catalog different cell types and subtypes in choroid plexus from each ventricle, across different ages—the first time this has ever been done.

"We had previously done bulk RNA sequencing of choroid plexus tissue, but that was like putting everything in a blender," says Lehtinen, who was co-senior author on the paper with Naomi Habib, Ph.D. and Aviv Regev, Ph.D. at the Broad Institute. "We didn't know which cells were secreting what. Sequencing cell by cell gives us a blueprint of what cells are where over the course of the lifespan. Knowing the different types of cells, we can explore their roles and functions, how they are talking to each other, and how the tissue is built."



Choroid plexus from the lateral ventricle (LV), third ventricle (3V), and fourth ventricle (4V) of the developing, adult, and aging mouse brain. Credit: Dani H, Herbst RH et al. Cell 2021 Apr 30; DOI 10.1016/j.cell.2021.04.003.

A choroid plexus inventory

The investigations revealed a complex "architecture" of choroid plexus tissue specific to each ventricle. Gene expression varied especially among epithelial and fibroblast cells in the developing brain.

"We think the differences might have to do with helping guide the development of nearby brain regions," says Lehtinen. "There are different 'cocktails' of factors secreted into different ventricles, in different patterns."

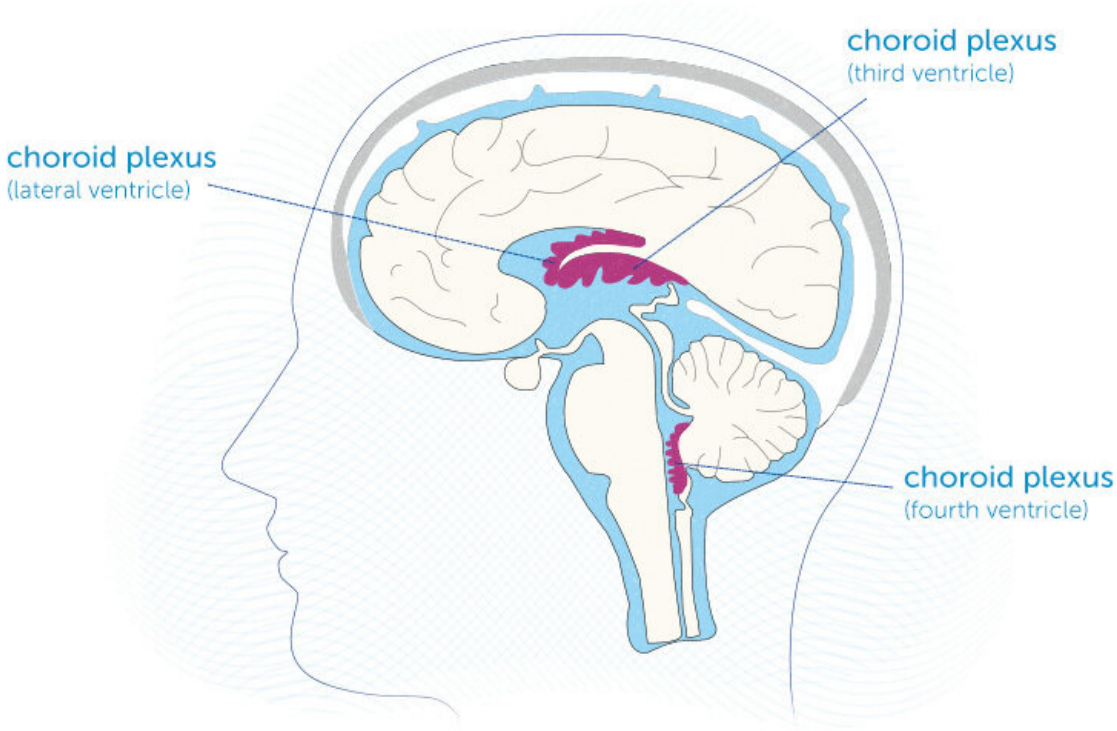
In addition to the core cell types, the researchers found several neuronal subtypes. "Typically, the choroid plexus is not thought to have too many neurons," says Lehtinen. "What they're doing in the choroid plexus is still up for discussion and experimentation."

The sequencing data also revealed differences in the cells' secretions and molecular makeup.

"We were intrigued by the expression of insulin in the epithelial cells of the developing third ventricle choroid plexus," says Dani. "Whether this is a viable and functional central source of insulin in the brain needs further investigation. We also found that some epithelial and mesenchymal cells expressed ACE2 receptors, which the SARS-CoV-2 virus uses to enter cells. This underscores the need to understand how the choroid plexus functions not just in health but in disease."

Defending the brain

The team found a great deal of immune activity in the choroid plexus, with several kinds of immune cells residing there, most commonly macrophages. Immune signaling activity varied with age, with more inflammatory signals picked up in samples from aged brains.



Choroid plexus tissue (shown here in pink) is anchored in each of the brain's ventricles and bathed in cerebrospinal fluid. Though small, the choroid plexus is a key player in brain development and immunity. Credit: Sebastian Stankiewicz, Boston Children's Hospital

"We can now start to analyze how different populations of immune cells are activated and how they respond to injury," says Lehtinen. "This gives

us a baseline and a set of molecular markers to start looking at."

Other findings revealed the arrangement of arteries, veins, and capillaries in the choroid plexus, and their organization in relation to adjacent brain regions.

"Some of these vessels expressed blood-brain barrier proteins, which was not described before" notes Dani. "Once we mapped them, we found them to be continuous with arteries from adjacent brain regions."

A therapeutic 'window'?

With this resource in hand, the scientific community now has much to explore. Lehtinen and Dani believe that once the choroid plexus is better understood, it could provide a target for neurologic drugs.

"Gene therapy directed toward the CSF and choroid plexus could be an exciting therapeutic approach," says Lehtinen. "It's not going to fix everything, but it could have a sizeable impact."

In other work, Lehtinen and colleagues recently showed that before birth, the choroid plexus can be a conduit for inflammation caused by maternal infection, paving the way for studies of neurodevelopmental conditions such as autism. Another study found that a protein in the choroid plexus helps reduce excess fluid levels in the brain, potentially providing a target for treating hydrocephalus.

More information: Neil Dani et al, A cellular and spatial map of the choroid plexus across brain ventricles and ages, *Cell* (2021). DOI: 10.1016/j.cell.2021.04.003

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