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Brain glia cells increase their DNA content to preserve vital blood-brain barrier

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The blood-brain barrier is essential for maintaining the brain's stable environment—preventing entry of harmful viruses and bacteria and isolating the brain's specific hormonal and neurotransmitter activity from that in the rest of the body.

In addition to nerve cells, the brain contains glia cells that support and protect the neurons. In the fruit fly, the blood-brain boundary is made by glia joined into an envelope sealed around the nerve cells. As the brain rapidly expands during development, the glial envelope must grow correspondingly to remain intact. However, little has been known about how the blood-brain barrier maintains its integrity as the brain it protects develops.

Now Whitehead Institute scientists report that as the developing larval fruit fly brain grows by cell division, it instructs subperineurial glia (SPG) cells that form the blood-brain barrier to enlarge by creating multiple copies of their genomes in a process known as polyploidization. The researchers report their work this month in the journal *Genes and Development*.

"We think that this may be the same developmental strategy that's used in other contexts, where you need an outer layer of cells to maintain a seal, yet you also need the organ to grow during development," says Whitehead Member Terry Orr-Weaver.

Like the larval fruit fly's blood-brain barrier, cell layers in the human

placenta and skin may employ polyploidization to respond to the need to expand while maintaining a sound boundary between the fetus and its surroundings, and the body and the outside world, respectively.

For preserving such barriers, polyploidy is ideal, as the cells forming the boundary enlarge without undergoing full cell division, a process that would break the tight junctions between cells.

In the larval fruit fly, polyploid SPG are necessary for maintaining the blood-brain barrier. When Yingdee Unhavaithaya, a postdoctoral researcher in Orr-Weaver's lab and first author of the Genes and Development article, prevented the SPG from making additional genome copies and becoming polyploid, the blood-brain barrier shattered as the brain continued to expand and the SPG was unable to accommodate its growth.

When allowed to progress naturally, polyploidy is flexible enough to accommodate even unusual brain expansion. After Unhavaithaya enlarged the brain by inducing a brain tumor, the SPG responded by increasing their ploidy and the blood-brain barrier remained unbroken.

This experiment also indicates that somehow the expanding brain mass is telling the SPG to increase their ploidy, but only as much as necessary to maintain the tight junctions between the SPG.

"It's a glimpse of communication between tissues during organogenesis," says Unhavaithaya. "We see different tissues trying to make a properly sized organ together. And one of the ways is by receiving instruction from the growing tissue so the other tissue can scale its size to properly conform to this tissue ratio for the organism."

For Orr-Weaver, Unhavaithaya's work could lead to additional exciting research.

"It has really opened up a whole new area to look at, so we can understand the mechanistic basis by which this communication happens," says Orr-Weaver, who is also an American Cancer Society professor of biology at MIT. "Does it happen at the organ level, or does it happen locally? There's really a lot to sort out."

More information: *Genes Dev.* 2012 Jan 1;26(1):31-6. www.ncbi.nlm.nih.gov/pubmed/22215808

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