

Vascular development may be at risk in autism

July 13 2020



A Canadian collaboration led by Dr. Baptiste Lacoste has undertaken the first ever in-depth study of vasculature in the autistic brain. Credit: The Ottawa Hospital

A Canadian collaboration led by Dr. Baptiste Lacoste has undertaken the first ever in-depth study of vasculature in the autistic brain. The product of four years of work, a paper published today in *Nature Neuroscience* lays out several lines of novel evidence that strongly implicate defects in endothelial cells—the lining of blood vessels—in autism.

Dr. Lacoste, a scientist at The Ottawa Hospital and an assistant professor in the University of Ottawa's Faculty of Medicine and Brain and Mind Research institute, heads a lab that specializes in neurovascular interactions in health and disease. In collaboration with researchers at McGill University, Laval University, and the National Research Council of Canada, Dr. Lacoste's team used a [mouse model](#) with one of the most common genetic mutations found in [autism spectrum disorder](#)—16p11.2 deletion, or "16p" for short.

The team, in which Dr. Lacoste's graduate student Julie Ouellette and research associate Dr. Xavier Toussay played prominent roles, also used [cells](#) derived from the tissue of human autistic adults who carry the 16p mutation.

Nerves and blood vessels not in synch

"If you imagine you have a luxury car—a Ferrari—and it's beautiful, sitting in your garage. But if you don't put gas in the tank, the car won't drive," says Dr. Lacoste. "It's exactly the same with the brain. It's the

most complex organ, but if you don't have [blood supply](#), the brain just doesn't work properly."

Normally, when brain cells light up, [blood](#) rushes to the active brain region, a phenomenon called 'neurovascular coupling'. But when neurons of mice with the 16p deletion are stimulated, this study found that vascular responses in those brain regions were delayed and weaker.

This disconnect—or 'neurovascular uncoupling'—was shown to originate in the blood vessels themselves: Arteries isolated from these mice and kept alive in a medium also showed a weak and sluggish response to chemicals that induce dilation of blood vessels. The team further isolated the source of the deficit in the endothelium, as opposed to the other cell types, such as muscle cells, that surround blood vessels.

Difficulties in development

Dr. Lacoste's work further shows that problems with blood vessels begin very early in life for those who carry the 16p deletion. In a petri dish, both human-derived and mouse endothelial cells with the mutation were unable to sprout the extensions that normally connect blood vessels to each other, allowing the vascular network to expand and grow. Endothelial cells in the brains of newborn autistic mice had the same problem.

By adolescence, the mice still showed reduced vascular density in their brains. Interestingly, in contrast to the problems in the [circulatory system](#), the researchers found that the neurons in the brains of these young mice appeared to be surprisingly well organized.

As the mice grew, other cells in the brain compensated for their dysfunctional endothelial cells, so that by adulthood they had developed a full network of blood vessels. However, as the researchers' previous

experiments showed, these blood vessels remained dysfunctional in adult mice.

"It's a bit like if a plumber comes to your house and does a bad job installing the pipes," says Dr. Lacoste. "You will have trouble getting the right water pressure in your sink from then on."

Blood vessels and autistic behavior

When a person or mouse carries a 16p mutation, that genetic difference is replicated in every cell in their body. This makes it harder to pin down the cause of systemic developmental differences.

To address this difficulty, Dr. Lacoste's team generated mice that only expressed the mutation in their [endothelial cells](#)—so-called "conditional mutants". These mice showed similar deficits in their vascular development as whole-body mutants.

Remarkably, although every other cell in their [brain](#) and body was genetically normal, these conditional mutants displayed some behavioral signs of autism: hyperactivity, stereotypic movements, and motor learning impairment.

This indicated that the problems in the blood vessels contributed to neuronal dysfunction, which in turn led to the outward signs and symptoms of autism.

Further avenues of inquiry

The researchers used an equal number of male and female mice and found more pronounced effects in male [mice](#), suggesting that females may have other tools, such as estrogen, that either compensate or mask

the deficits. They suggest this as an avenue of inquiry, as well as the role of [blood vessels](#) in a broader range of neurodevelopmental disorders, which could lead to novel diagnostics and therapeutics.

More information: Vascular contributions to 16p11.2 deletion autism syndrome modeled in mice, *Nature Neuroscience* (2020). [DOI: 10.1038/s41593-020-0663-1](#)

Provided by The Ottawa Hospital

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