Protein identified that can disrupt embryonic brain development and neuron migration

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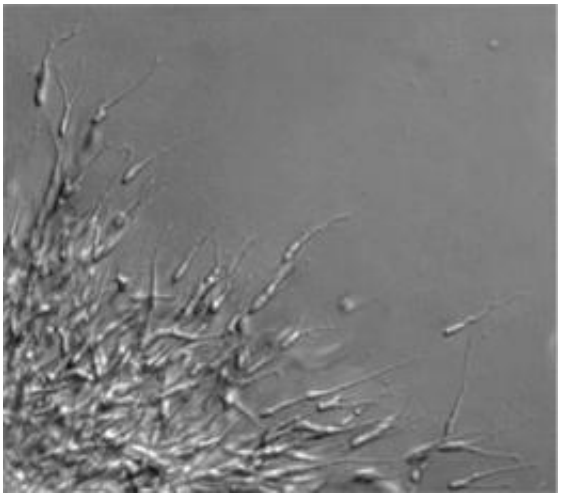

Interneurons (moving from bottom-left to top-right in this image) use tiny arms to pull themselves out of a piece of embryonic brain tissue that has grown for two days in a petri dish. Credit: KU Leuven

Interneurons – nerve cells that function as 'dimmers' – play an important role in the brain. Their formation and migration to the cerebral cortex during the embryonic stage of development is crucial to normal brain functioning. Abnormal interneuron development and migration can eventually lead to a range of disorders and diseases, from epilepsy to Alzheimer's. New research by Dr. Eve Seuntjens and Dr. Veronique van den Berghe of the Department of Development and Regeneration (Danny Huylebroeck laboratory, Faculty of Medicine) at KU Leuven (University of Leuven) has identified two proteins, Sip1 and Unc5b, that

play an important role in the development and migration of interneurons to the cerebral cortex – a breakthrough in our understanding of early brain development.

Two types of nerve cells are crucial to healthy brain functioning. Projection neurons, the more widely known of the two, make connections between different areas of the brain. Interneurons, a second type, work as dimmers that regulate the signalling processes of projection neurons. A shortage or irregular functioning of interneurons can cause short circuits in the nervous system. This can lead to seizures, a common symptom of many brain disorders. Interneuron dysfunction even appears to play a role in schizophrenia, autism and neurodegenerative diseases such as Alzheimer's, Parkinson's and ALS.

Trailblazers

Researchers have only recently understood how different kinds of neuron are formed during embryonic development. During early brain development, stem cells form projection neurons in the cerebral cortex. Interneurons are made elsewhere in the brain. These interneurons then migrate to the cortex to mix with the projection neurons. Dr. Eve Seuntjens of the Celgen laboratory led by Professor Danny Huylebroeck explains: "The journey of interneurons is very complex: their environment changes constantly during growth and there are no existing structures—such as nerve pathways—available for them to follow."

The question is how young interneurons receive their 'directions' to the cerebral cortex. Several proteins play a role, says Dr. Seuntjens. "We changed the gene containing the production code for the protein Sip1 in mice so that this protein was no longer produced during brain development. In those mice, the interneurons never made it to the cerebral cortex—they couldn't find the way.

That has to do with the guidance signals – substances that repel or attract interneurons and thus point them in the right direction – encountered by the interneurons on their way to the cerebral cortex. Without Sip1 production, interneurons see things through an overly sharp lens, so to speak. They see too many stop signs and become blocked. That overly sharp lens is Unc5b, a protein. Unc5b is deactivated by Sip1 in healthy mice. There are several known factors that influence the migration of interneurons, but Unc5b is the first protein we've isolated that we now know must be switched off in order for interneuron migration to move ahead smoothly."

The next step is to study this process in the neurons of humans. "Now that there are techniques to create stem cells from skin cells, we can mimic the development of stem cells into interneurons and study what can go wrong. From there, we can test whether certain drugs can reverse the damage. That's all still on the horizon, but you can see that the focus of research on many brain disorders and diseases is increasingly shifting to early child development because that just might be where a cause can be found."

More information: www.sciencedirect.com/science/ … ii/S0896627312010008

Provided by KU Leuven