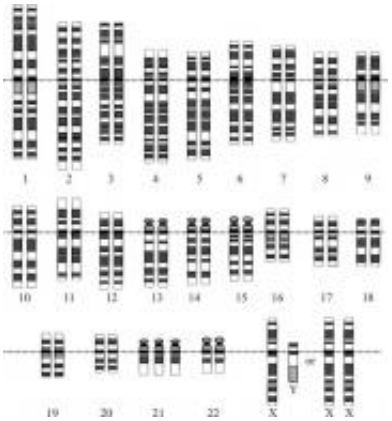
Medical Xpress

'Support' cells in brain play important role in Down syndrome

July 18 2014



Karyotype for trisomy Down syndrome. Notice the three copies of chromosome 21. Courtesy: National Human Genome Research Institute

Researchers from UC Davis School of Medicine and Shriners Hospitals for Children – Northern California have identified a group of cells in the brain that they say plays an important role in the abnormal neuron development in Down syndrome. After developing a new model for studying the syndrome using patient-derived stem cells, the scientists also found that applying an inexpensive antibiotic to the cells appears to correct many abnormalities in the interaction between the cells and developing neurons.

The findings, which focused on support cells in the brain called astroglial cells, appear online today in *Nature Communications*.

"We have developed a human cellular model for studying brain development in Down syndrome that allows us to carry out detailed physiological studies and screen possible new therapies," said Wenbin Deng, associate professor of biochemistry and molecular medicine and principal investigator of the study. "This model is more realistic than traditional animal models because it is derived from a patient's own cells."

Down syndrome is the most common chromosomal cause of mild to moderate intellectual disabilities in the United States, where it occurs in one in every 691 live births. It develops when a person has three copies of the 21st chromosome instead of the normal two. While mouse models have traditionally been used in studying the genetic disorder, Deng said the animal model is inadequate because the human brain is more complicated, and much of that complexity arises from astroglia cells, the star-shaped cells that play an important role in the physical structure of the brain as well as in the transmission of nerve impulses.

"Although neurons are regarded as our 'thinking cells,' the astroglia have an extremely important supportive role," said Deng. "Astroglial function is increasingly recognized as a critical factor in neuronal dysfunction in the brain, and this is the first study to show its importance in Down syndrome."

Creating a unique human cellular model

To investigate the role of astroglia in Down syndrome, the research team took skin cells from individuals with Down syndrome and transformed them into stem cells, which are known as induced pluripotent stem cells (iPSC). The cells possess the same genetic make-up as the donor and an ability to grow into different cell types. Deng and his colleagues next induced the stem cells to develop into separate pure populations of astroglial cells and neurons. This allowed them to systematically analyze

factors expressed by the astroglia and then study their effects on neuron development.

They found that a certain protein, known as S100B, is markedly increased in astroglial cells from patients with Down syndrome compared with those from healthy controls. S100B released by astroglial cells promotes harmful astroglial activation (astrogliosis) and adversely affects neurons, causing them to die at increased rates or develop in multiple dysfunctional ways.

The investigators obtained further evidence of the critical role of astroglial cells in Down syndrome by implanting the skin-cell derived astroglial cells from Down syndrome patients into mice. Those mice then developed the neuropathological phenotypes of Down syndrome, while mice implanted with Down syndrome neurons did not.

Neuroprotective effects of antibiotics

The research team also screened candidate drugs using a 'disease-in-a-dish' model. When they administered minocycline—a tetracycline antibiotic with anti-inflammatory properties commonly used to treat bacterial infections, acne and arthritis—many of the abnormalities in the astroglial cells were corrected and there were more healthy interactions between the astroglia and neurons compared to the control cells without the defect.

"The advent of induced pluripotent stem cell technology has created exciting new approaches to model neurodevelopmental and neurodegenerative diseases for the study of pathogenesis and for drug screening," said David Pleasure, professor of neurology and pediatrics and a co-author of the study. "Using this technology, the study is the first to discover the critical role of astroglial cells in Down syndrome as well as identify a promising pathway for exploring how a drug such as

minocycline may offer an effective way to help treat it."

Pleasure, who is research director at Shriner's Hospital for Children Northern California and also directs the Institute for Pediatric Regenerative Medicine, noted that considerable research interest has arisen about the use of minocycline for diseases of the central nervous system because of the increasing evidence about its neuroprotective effects. Unlike many drugs, minocycline can cross from the bloodstream into the brain so that it can act on the astroglial cells. The drug has never been tested as a treatment for Down syndrome, and both Pleasure and Deng cautioned that its safety and efficacy will require clinical trials in people with Down syndrome.

Currently, Deng's laboratory is conducting additional preclinical studies using the human-derived stem cells from Down syndrome patients and mouse models to determine whether cellular and behavioral abnormalities can be improved with minocycline therapy and other candidate drugs.

"The abnormalities we identified occur in the early stages of Down syndrome," said Deng. "While much more research is needed, it is exciting to consider that pharmacological intervention in these cellular processes might help slow or even prevent disease progression."

More information: "Role of astroglia in Down's syndrome revealed by patient-derived human-induced pluripotent stem cells," *Nature Communications*, 2014.

Provided by UC Davis