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Neurological Disorder Impacts Brain Cells Differently

Al La Spada, MD, PhD

In a paper published in the November 9 issue of *The Journal of Neuroscience*, researchers at the University of California, San Diego School of Medicine and University of Washington describe in deeper detail the pathology of a devastating neurological disorder, but also reveal new cellular targets for possibly slowing its development.

Spinocerebellar ataxia type 7 (SCA7) is an inherited neurological disorder in which cells in the cerebellum and brainstem degenerate, resulting in progressive loss of physical coordination and possible blindness. Its pathology is similar to other neurodegenerative diseases like Parkinson's, Huntington's and amyotrophic lateral sclerosis. And like them, it's currently incurable.

The scientists, led by Al La Spada, MD, PhD, chief of the division of genetics in the UC San Diego department of pediatrics, and professor of cellular and molecular medicine, neurosciences and biological sciences, used a variety of transgenic mouse models to show that SCA7 results from genetic dysfunction not just in affected neurons, but also in associated non-neuronal support cells.

"The central nervous system is quite complicated, with neurons interacting with each other and with other cell types. So it shouldn't be a surprise that the disease process is similarly complex," said La Spada, who is also associate director of the UC San Diego Institute for Genomic Medicine. "We show that dysfunction in a variety of cell types contributes to SCA7, and that if you can improve function in any of these cell types, you have a reasonable chance of improving treatment of the disease."

La Spada and colleagues created a transgenic mouse in which the key gene mutation that causes SCA7 could be easily manipulated. The mouse was then bred with other mouse models that eliminated the mutant gene protein from specific cell types affected by SCA7: Purkinje

neurons (large cells in the cerebral cortex responsible for motor coordination), Bergmann glia (support cells found in the cerebellum) and cells in the olivary complex (part of the brainstem controlling body movement).

By creating and comparing mice that expressed the mutant gene only in targeted cells, La Spada said the scientists made two unexpected discoveries: First, when the gene mutation was eliminated from Bergmann glia, neurodegeneration continued unabated and still involved dysfunction and degeneration of the Bergmann glia themselves. Second, when the mutation was excised from Purkinje neurons and the olivary complex, there was significantly less neurological damage and Bergmann glia remained intact.

“The first result highlights the relatively new idea that degeneration goes both ways,” said La Spada. “It isn’t just neurons becoming affected when their support cells dysfunction. The Bergmann glia didn’t express the mutant gene, but they still degenerated. This shows the bilateral relationship between neurons and non-neuronal cells. They’re equal partners, in both normal functioning and in disease.

“The second result underscores the relevance of Purkinje cells and the olivary neuron circuit in the brainstem to SCA7. When it’s dysfunctional, degeneration occurs. This is crucial for our understanding of this disease, and should enable us to develop more specific therapeutic approaches. Although we have our work cut out for us, we now have a better idea of what we’re up against.”

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