FAST BREAKING PAPERS - 2009

April 2009

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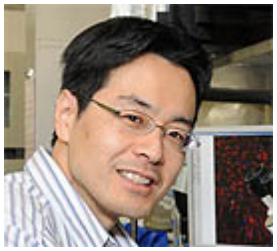
Koji Yamanaka & Don W. Cleveland talk with *ScienceWatch.com* and answer a few questions about this month's Fast Breaking Paper in the field of Neuroscience & Behavior. The authors have also sent along images of their work.



Article Title: Astrocytes as determinants of disease progression in inherited amyotrophic lateral sclerosis

Authors: Yamanaka, K;Chun, SJ;Boillee, S;Fujimori-Tonou, N;Yamashita, H;Gutmann, DH;Takahashi, R;Misawa, H;Cleveland, DW

Journal: NAT NEUROSCI, Volume: 11, Issue: 3, Page: 251-253, Year: MAR 2008

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(addresses have been truncated)

SW: Why do you think your paper is highly cited?

Glial cells have long been regarded as a supporting player of neurodegenerative diseases, which are characterized by a progressive, selective death of a certain group of neurons. However, our research identified a specific glial cell type, the astrocyte, as a therapeutic target for amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's disease), a neurodegenerative disease affecting adult motor neurons. This finding has a broad impact on other neurodegenerative disease research such as that regarding Alzheimer's , Parkinson's and Huntington's disease in which causative gene products are expressed ubiquitously (that is, in both neurons and their neighboring glial cells).

Furthermore, recent advances in stem cell research will make it feasible to treat neurodegenerative diseases using renewable cells, including astrocytes. Our research provides a proof-of-principle for the transplantation of healthy astrocytes (or astrocyte precursors) to slow disease progression in ALS.

Coauthor:
Don W. Cleveland

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

Familial forms of ALS are associated with dominant mutations in the gene for Cu/Zn superoxide dismutase (SOD1). Human ALS disease is well recapitulated in the mouse expressing an ALS-linked mutant SOD1 gene. While the mutant SOD1 gene is expressed in all cells, mutant SOD1 mice develop selective motor neuron death.

To identify the cell types which are crucial for neurodegeneration, we developed a new ALS mouse model carrying a mutant SOD1 transgene that can be removed by the

action of Cre recombinase. We initially published this mouse in 2006 (Boillée S, Yamanaka K, *et al.* "Onset and progression in inherited ALS determined by motor neurons and microglia," *Science* 312 [5778]: 1389-92, 2006) and used selective gene inactivation in motor neurons and microglia to identify mutant damage within them as key determinants of disease onset and progression, respectively. In our current paper, we identified astrocytes as a key determinant of disease progression.

SW: Would you summarize the significance of your paper in layman's terms?

Figure 1: +details

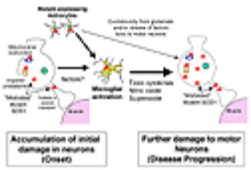
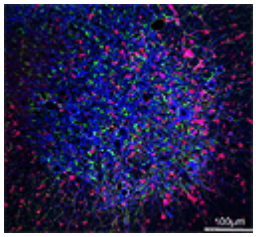


Figure 2:



ALS-linked SOD1 mutations provoke toxicity to motor neurons through an unknown mechanism. Although expression of mutant SOD1 in all cell types causes selective motor neuron death, the key damage from the mutant protein had been widely predicted to arise within the motor neurons.

What we have shown is that two types of glia cells, astrocytes, a supporting cell type that plays a principal role in brain repair and maintenance, and microglia, the resident immune cells within the nervous system, develop the damage responsible for accelerating disease progression.

This inflammatory process was further exacerbated in the environment where more mutant astrocytes were populated, leading to accelerated disease progression. Our results document that an appropriate therapy targeting either astrocytes or microglia would slow disease progression.

SW: Where do you see your research leading in the future?

In the short term, we will try to uncover exactly how the mutant SOD1 damages astrocytes and microglia so as to drive rapid disease progression. This is a crucial goal for devising therapies to ameliorate the underlying damage.

SW: Do you foresee any social or political implications for your research?

ALS is one of the most intractable diseases and no viable therapy is currently available. There is increasing demand to find a cure for ALS, not only from the patients' point of view but also from society and politics, since a significant amount of cost and personnel resources are required for ALS patient care. Our research provided an important key step to find a cure for ALS: identifying glial cells as attractive targets for a treatment that can slow disease progression.

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KEYWORDS: MOTOR-NEURONS; EXTEND SURVIVAL; RAT MODEL; ALS; MICE; MICROGLIA.

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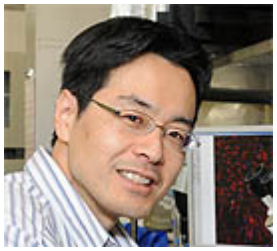

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Figures and descriptions:

Figure 1:

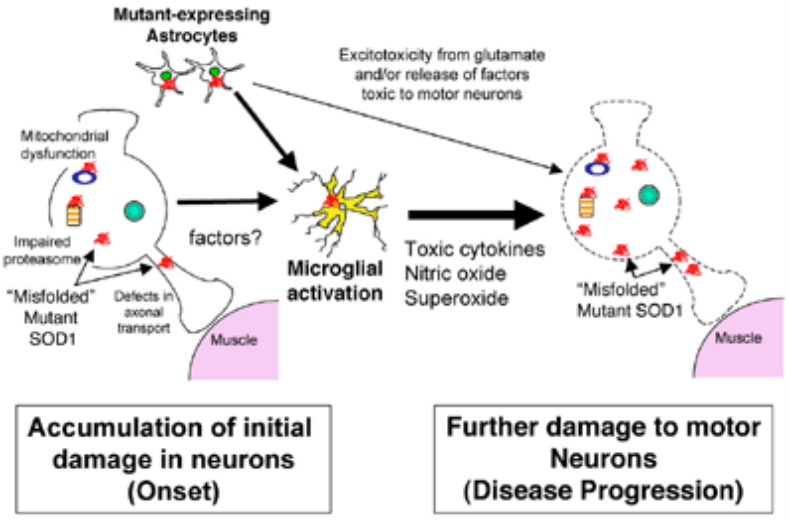

Figure 1:
Fluorescence staining of lumbar spinal cord section from symptomatic mutant SOD1 mouse. Prominent activation of microglia (anti-Mac2: red), and astrocytes (anti-GFAP: green) are detected. Neurons and their process stained with SMI-32 (non-phosphorylated neurofilament: blue).

Figure 2:

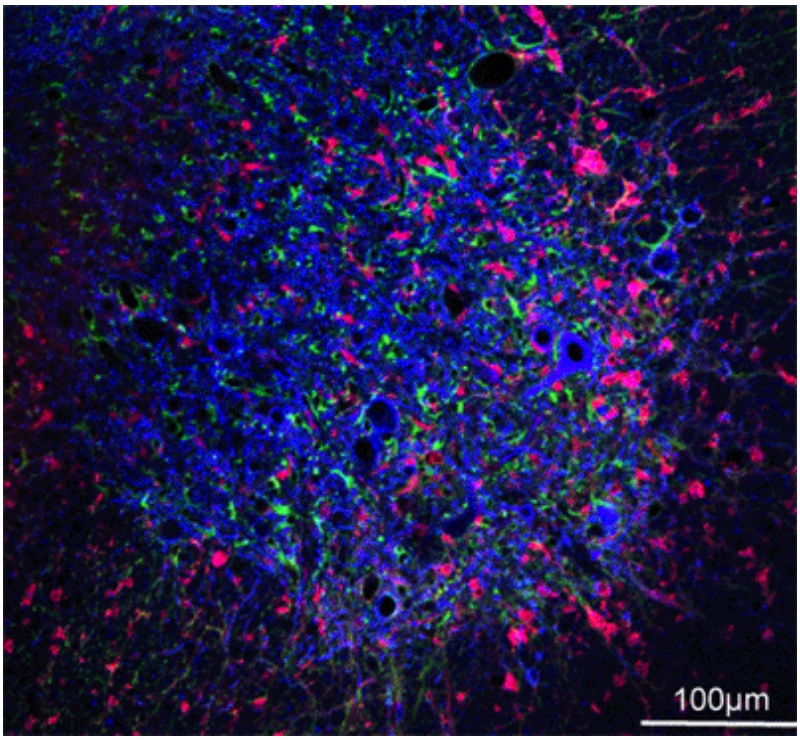

Figure 2:
Accelerated disease progression from mutant SOD1-mediated toxicity within astrocytes and microglia driving non-cell-autonomous motor neuron death. Initial damage within motor neurons including age dependent accumulation of an as yet unidentified mutant SOD1-mediated toxicity. Unidentified factors derived from damaged motor neurons or astrocytes cause activation of mutant-expressing microglia. Abnormal activated microglia produce high levels of nitric oxide and superoxide together with secretion of toxic cytokines to motor neurons. A combination of damage from mutant microglia and astrocytes cause further damage to motor neurons, thereby driving rapid disease progression.

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