Blocking inflammation in the brain: New therapeutic target for the treatment of amyotrophic lateral sclerosis

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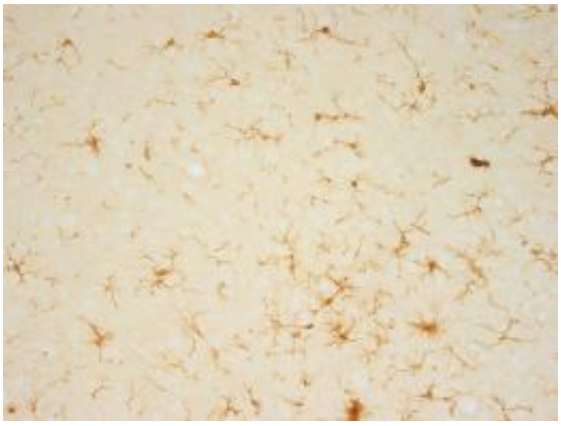

Section of a spinal cord of a mouse. In brown are microglia, the cells that sense SOD1 and produce IL-1ß. Image: MPI for Infection Biology/Meißner/Molawi/Zychlinsky

(PhysOrg.com) -- Amyotrophic lateral sclerosis (ALS) is a common and fatal motor neuron disease. It generates gradual and irreversible damage in the neurons that control movement. The cause of the disease is largely unknown; however, it appears to depend on both inherited and environmental factors. Inflammatory processes in the brain may also cause the death of neurons.

Scientists at the Max Planck Institute for Infection Biology in Berlin have now identified a signalling molecule that may be implicated in the

pathogenesis of ALS. Blocking this substance enhances motor performance and increases the life span in mice that have a disease similar to ALS. The results suggest that using this blocking agent to therapeutically intervene could have similar effects in ALS patients. (*PNAS*, online publication, June 28, 2010)

The research team working with Arturo Zychlinsky at the Max Planck Institute for Infection Biology is mainly interested in how inflammation begins in infectious diseases. They discovered that the enzyme superoxide dismutase 1 (SOD1) regulates inflammation by controlling the activity of another enzyme, caspase-1. This enzyme, in turn, splits the protein Interleukin-1 (IL-1ß) to activate it. The inflammation process begins.

Curiously, it is known that mutations in SOD1 cause a hereditary form of ALS. Moreover, ALS patients have an inflammation and show elevated levels of activated caspase-1. "Caspase-1 probably plays a similar role in ALS as it does in infectious diseases," says Arturo Zychlinsky.

In the course of further tests, the scientists were able to prove that in ALS misfolded SOD1 enzymes accumulate inside the neurons. This is a danger signal to which the cell reacts by activating caspase-1, which in turn, cleaves Interleukin-1ß and triggers inflammation (fig. 1). This inflammation gradually destroys the motor neurons. When mice carrying mutant SOD1 were treated with a protein that blocks Interleukin-1ß the inflammatory reaction was not only attenuated, the symptoms were also reduced and the animals' life span prolonged. Together with the ALS clinic at the Charité University Hospital in Berlin, the Max Planck group is now designing a clinical trial to test whether treating ALS patients with Interleukin-1 antagonist is feasible.

More information: Meissner F, Molawi K, Zychlinsky A, Mutant

superoxide dismutase 1-induced IL-1β accelerates ALS pathogenesis. PNAS 2010, June 28, 2010