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## Prion Protein Helps Healthy Neurons Make Proteins

Researchers have identified signaling pathways by which the normal prion protein (PrPC) switches on the general protein synthesis necessary to promote the growth and development of brain cells and protect them from harm.

Their results suggest, though they do not directly prove, that the neurodegeneration seen in “mad cow” and other rare devastating brain disease might be partly due to protein synthesis being shut down when abnormal prions (PrPSc) infect brain or nerve tissue.

These findings were published July 5, 2010, in *Proceedings of the National Academy of Science*. Howard Hughes Medical Institute international research scholar Vilma Martins and Glaucia Hajj, both from the Ludwig Institute for Cancer Research, Brazil are co-senior authors of this report. Martin Roffé, also at the Ludwig Institute, is the first author of the paper.

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**- Vilma R. Martins**

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Normal prion protein is relatively abundant in healthy brain tissue. When an abnormally folded, infectious prion protein enters cells it can convert these harmless proteins into their own awkward shapes. Martins acknowledges that in this form, prions are toxic to nerve cells and can kill them directly. But the misshapen prions are also unable to carry out their normal duties, and Martins thinks this contributes to neural degeneration, as well. “I think we have both things going on at the same time – toxicity of the prions and a loss-of-function of the normal PrPC protein,” she says.

For many years, the role of the normal prion protein was a mystery; animals in which the PrPC protein was eliminated remained healthy and appeared unaffected. But recently, a number of reports indicate that the protein has

important functions in development and maintenance of the nervous system. Closer examination of knockout mice has revealed subtle impairments in memory and cognition.

In their new work, Martins and colleagues add to that scene evidence that PrPC stimulates protein synthesis, particularly at the synaptic junctions between neurons, where information is stored and memories formed. They have determined how PrPC works with a chaperone protein called stress-inducible protein 1 (STI1) to control production of the pool of proteins a neuron needs to function properly. Switching on the synthesis of those proteins in the brain cells begins with the binding of STI1 to the PrPC protein on the cell's outer membrane. STI1 is secreted at high levels by astrocytes – large, star-shaped cells in the brain that have supportive and metabolic functions but, unlike neurons, don't carry information.

The binding event activates two signaling chains – the PI3K-Akt-mTOR pathway and the ERK1/2 pathways – which are turned on during learning and memory consolidation, Martins says. When she and her colleagues inhibited these signaling pathways protein synthesis in the cells slowed. They also showed that infecting cells with the abnormal prion, PrPSc, blocked PrPC-STI1's ability to ramp up protein synthesis in nerve cells grown in the lab. Since production of new proteins is critical to enable healthy signaling between neurons, this response might impair neuronal function in prion diseases like “mad cow” and Creutzfeldt- Jakob disease, the researchers say.

In the experiments with infected neurons, comments Martins, “we found that the neurons were unable to respond to STI1 and other nourishing factors. So the presence of the abnormal prion is altering the ability of the cells to respond to STI1, so that the neurons can't induce new protein synthesis, and this could be an important aspect of the neurodegeneration.”

Based on these findings, Martins says she also wants to study other types of neurodegeneration, such as that caused by stroke or Alzheimer's disease, in laboratory or animal models. “Perhaps we can use PrPC as a target in some way to increase survival pathways and protect those neurons against cell death,” she says.