Protective pathway in stressed cells not so helpful when it comes to prions

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Scientists at the National Institutes of Health (NIH) have discovered that an important cellular quality control mechanism may actually be toxic to some brain cells during prion infection. The research, published by Cell Press in the September 16th issue of the journal *Developmental Cell,* proposes a new general mechanism of cellular dysfunction that can contribute to the devastating and widespread neuronal death characteristic of slowly progressing neurodegenerative diseases.

Prions cause a number of untreatable and fatal neurodegenerative disorders, including bovine spongiform encephalopathy ("mad cow disease") in cattle and Creutzfeldt-Jakob disease in humans. "We know that abnormal metabolism of a normal prion protein (PrP) is at the root of these diseases. However, the pathways that lead to selective neuronal death are unknown," explains senior author Dr. Ramanujan S. Hegde from the National Institute of Child Health and Human Development in Bethesda, Maryland.

The endoplasmic reticulum (ER) is a membrane-bound subcompartment of the cell that helps fold newly-made proteins and route them to their final destinations within or outside the cell. When protein folding or trafficking is temporarily compromised, the ER experiences "stress" and compensates using a specific ER stress response.

Previous work demonstrated that part of the ER stress response is to re-route the trafficking of many proteins, including PrP. Instead of being transported into the ER, these proteins are sent to the cytosol to be

destroyed. The phenomenon, termed pre-emptive quality control (pQC), protects cells in the short term by reducing the protein burden on the ER during times of compromised function. "Whether such re-routing of PrP for long time periods might contribute to neurodegenerative phenotypes in prion disease has been unclear," says Dr. Hegde.

Dr. Hegde and colleagues designed a series of experiments to investigate a potential pathway linking prion infection, ER stress, pQC and neurodegeneration. The researchers found that prion infection induced ER stress, and consequently reduced transport of PrP into the ER. They then engineered transgenic mice to express a form of PrP that isn't efficiently transported into the ER; this approach mimics what happens to PrP during ER stress. In fact, the re-routed PrP caused mild neurodegeneration, even in the absence of prion infection or ER stress.

The results establish a previously unappreciated link between ER stress, pQC and PrP-induced neuronal damage, showing that an ordinarily helpful quality control pathway can be detrimental over long periods of time. "We believe that one mechanism of prion-mediated neurodegeneration might involve an indirect and surprisingly subtle effect on PrP biosynthesis and metabolism," concludes Dr. Hegde. He is quick to note that the neurodegeneration caused by pQC of PrP may very well be the lesser of two evils. "The consequences of not re-routing PrP for degradation during ER stress might be even worse for neurons."

Hegde says that his lab is now investigating why PrP exposed to the cytosol via this pathway is harmful: "Our working hypothesis is that PrP in the wrong part of the cell makes inappropriate interactions with other proteins to compromise their function."

Source: Cell Press