

The protein Srebp2 drives cholesterol formation in prion-infected neuronal cells

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Prions are causing fatal and infectious diseases of the nervous system, such as the mad cow disease (BSE), scrapie in sheep or Creutzfeldt-Jakob disease in humans. Scientists of Helmholtz Zentrum München and Technische Universität München, Germany, have now succeeded in elucidating another disease mechanism of prion diseases: The prion-infected cell changes its gene expression and produces increased quantities of cholesterol. Prions need this for their propagation.

Prions are infectious and transform the brains of humans and animals into sponge-like structures. Unlike a virus, a prion only consists of protein - called prion-protein in its pathological form (PrP^{Sc}). Until now, little was known about the processes that take place inside the infected neuronal cell. This made it difficult to develop effective drugs against prion diseases.

Using microarrays developed in the lab of Dr. Johannes Beckers, Christian Bach and colleagues from Helmholtz Zentrum München and Technische Universität made a genome-wide analysis of gene activity in prion-infected and healthy cells. The researchers found over 100 genes which are differentially expressed in infected and healthy cells. This has serious consequences for the [infected cells](#): "Several enzymes of cholesterol biosynthesis are affected", explained Christian Bach, first author of the study. As a consequence, the cholesterol level rises in the infected cells.

The cause of this development is the increased activity of the regulating

protein Srebp2. It switches on the genes that are involved in cholesterol biosynthesis and cellular uptake. To achieve this, Srebp2 binds to a special segment encoding the gene to be transcribed - the sterol regulatory element. This activates the gene, leading to the biosynthesis of the corresponding protein.

In every step of cholesterol biosynthesis Srebp2 switches on different genes, thus exactly controlling [gene expression](#), i.e. the translation of gene information into the corresponding protein. If cholesterol concentration is elevated in a healthy cell, Srebp2 remains in its inactive form and does not bind to the sterol regulatory element. This control mechanism is obviously disturbed in the infected cells, causing increased cholesterol synthesis. "Remarkably, only neuronal cells react in this way - microglia cells exposed to prions do not increase their cholesterol production," said Professor Hermann Schätzl of the Institute of Virology of Technische Universität München, who led the research together with Dr. Ina Vorberg. Further studies shall elucidate what role disturbed [cholesterol](#) regulation plays in neuronal cells for the development of prion diseases and shall thus point the way to new therapy approaches.

More information: Prion-Induced Activation of Cholesterogenic Gene Expression by a Sterol Regulatory Element Binding Protein (Srebp2) in [Neuronal Cells](#), *Journal Biological Chemistry* Vol 284, No. 45, pp 31260-31269 Nov 2009.

Source: Helmholtz Zentrum München

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