

Scientists show 'lifeless' prions capable of evolutionary change and adaptation

December 31 2009

Scientists from The Scripps Research Institute have determined for the first time that prions, bits of infectious protein devoid of DNA or RNA that can cause fatal neurodegenerative disease, are capable of Darwinian evolution.

The study from Scripps Florida in Jupiter shows that prions can develop large numbers of mutations at the protein level and, through natural selection, these mutations can eventually bring about such evolutionary adaptations as drug resistance, a phenomenon previously known to occur only in bacteria and viruses. These breakthrough findings also suggest that the normal [prion protein](#) - which occurs naturally in human cells - may prove to be a more effective [therapeutic target](#) than its abnormal toxic relation.

The study was published in the December 31, 2009 issue of the journal *Science Express*.

"On the face of it, you have exactly the same process of mutation and adaptive change in prions as you see in viruses," said Charles Weissmann, M.D., Ph.D., the head of Scripps Florida's Department of Infectology, who led the study. "This means that this pattern of Darwinian evolution appears to be universally active. In viruses, mutation is linked to changes in nucleic acid sequence that leads to resistance. Now, this adaptability has moved one level down - to prions and protein folding - and it's clear that you do not need nucleic acid for the process of evolution."

Infectious prions (short for proteinaceous infectious particles) are associated with some 20 different diseases in humans and animals, including [mad cow disease](#) and a rare human form, Creutzfeldt-Jakob disease. All these diseases are untreatable and eventually fatal.

Prions, which are composed solely of protein, are classified by distinct strains, originally characterized by their incubation time and the disease they cause. Prions have the ability to reproduce, despite the fact that they contain no nucleic acid genome.

Mammalian cells normally produce cellular [prion](#) protein or PrPC. During infection, abnormal or misfolded protein - known as PrPSc - converts the normal host prion protein into its toxic form by changing its conformation or shape. The end-stage consists of large assemblies (polymers) of these misfolded proteins, which cause massive tissue and cell damage.

"It was generally thought that once cellular prion protein was converted into the abnormal form, there was no further change," Weissmann said. "But there have been hints that something was happening. When you transmit prions from sheep to mice, they become more virulent over time. Now we know that the abnormal prions replicate, and create variants, perhaps at a low level initially. But once they are transferred to a new host, natural selection will eventually choose the more virulent and aggressive variants."

Drug Resistance

In the first part of the study, Weissmann and his colleagues transferred prion populations from infected brain cells to culture cells. When transplanted, cell-adapted prions developed and out-competed their brain-adapted counterparts, confirming prions' ability to adapt to new surroundings, a hallmark of [Darwinian evolution](#). When returned to brain, brain-adapted prions again took over the population.

To confirm the findings and to explore the issue of evolution of drug resistance, Weissmann and his colleagues used the drug swainsonine or swa, which is found in plants and fungi, and has been shown to inhibit certain prion strains. In cultures where the drug was present, the team found that a drug-resistant sub-strain of prion evolved to become predominant. When the drug was withdrawn, the sub-strain that was susceptible to swainsonine again grew to become the major component of the population.

Weissmann notes that the findings have implications for the development of therapeutic targets for prion disease. Instead of developing drugs to target abnormal proteins, it could be more efficient to try to limit the supply of normally produced prions - in essence, reducing the amount of fuel being fed into the fire. Weissmann and his colleagues have shown some 15 years ago that genetically engineered mice devoid of the normal prion protein develop and function quite normally (and are resistant to prion disease!).

"It will likely be very difficult to inhibit the production of a specific natural protein pharmacologically," Weissmann said, "You may end up interfering with some other critical physiological process, but nonetheless, finding a way to inhibit the production of normal prion protein is a project currently being pursued in collaboration with Scripps Florida Professor Corinne Lasmezas in our department."

Quasi-Species

Another implication of the findings, according to the study, is that drug-resistant variants either exist in the prion population at a low level prior to exposure or are generated during exposure to the drug. Indeed, the researchers found some prions secreted by infected cells were resistant to the drug before exposure, but only at levels less than one percent.

The scientists show that prion variants constantly arise in a particular population. These variants, or "mutants", are believed to differ in the way the prion protein is folded. As a consequence, prion populations are, in fact, comprised of multiple sub-strains.

This, Weissmann noted, is reminiscent of something he helped define some 30 years ago - the evolutionary concept of quasi-species. The idea was first conceived by Manfred Eigen, a German biophysicist who won the Nobel Prize in Chemistry in 1967. Basically stated, a quasi-species is a complex, self-perpetuating population of diverse and related entities that act as a whole. It was Weissmann, however, who provided the first confirmation of the theory through the study of a particular bacteriophage - a virus that infects bacteria - while he was director of the Institut für Molekularbiologie in Zürich, Switzerland.

"The proof of the quasi-species concept is a discovery we made over 30 years ago," he said. "We found that an RNA virus population, which was thought to have only one sequence, was constantly creating mutations and eliminating the unfavorable ones. In these quasi-populations, much like we have now found in prions, you begin with a single particle, but it becomes very heterogeneous as it grows into a larger population."

There are some unknown dynamics at work in the prion population that leads to this increased heterogeneity, Weissmann added, that still need to be explored.

"It's amusing that something we did 30 years has come back to us," he said. "But we know that mutation and natural selection occur in living organisms and now we know that they also occur in a non-living organism. I suppose anything that can't do that wouldn't stand much of a chance of survival."

More information: The joint first authors of the Science study,

"Darwinian Evolution of Prions in Cell Culture," are Jiali Li and Shawn Browning of The Scripps Research Institute. Other authors include Sukhvir P. Mahal and Anja M. Oelschlegel also of The Scripps Research Institute. Weissmann notes that after the manuscript was accepted by Science, an article by Ghaemmanghami et al. appeared in PLoS Pathogens that described emergence of prions resistant to a completely different drug, quinacrine, providing additional support to the Scripps Research team's conclusions.

Provided by The Scripps Research Institute

Citation: Scientists show 'lifeless' prions capable of evolutionary change and adaptation (2009, December 31) retrieved 17 April 2024 from <https://medicalxpress.com/news/2009-12-scientists-lifeless-prions-capable-evolutionary.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.