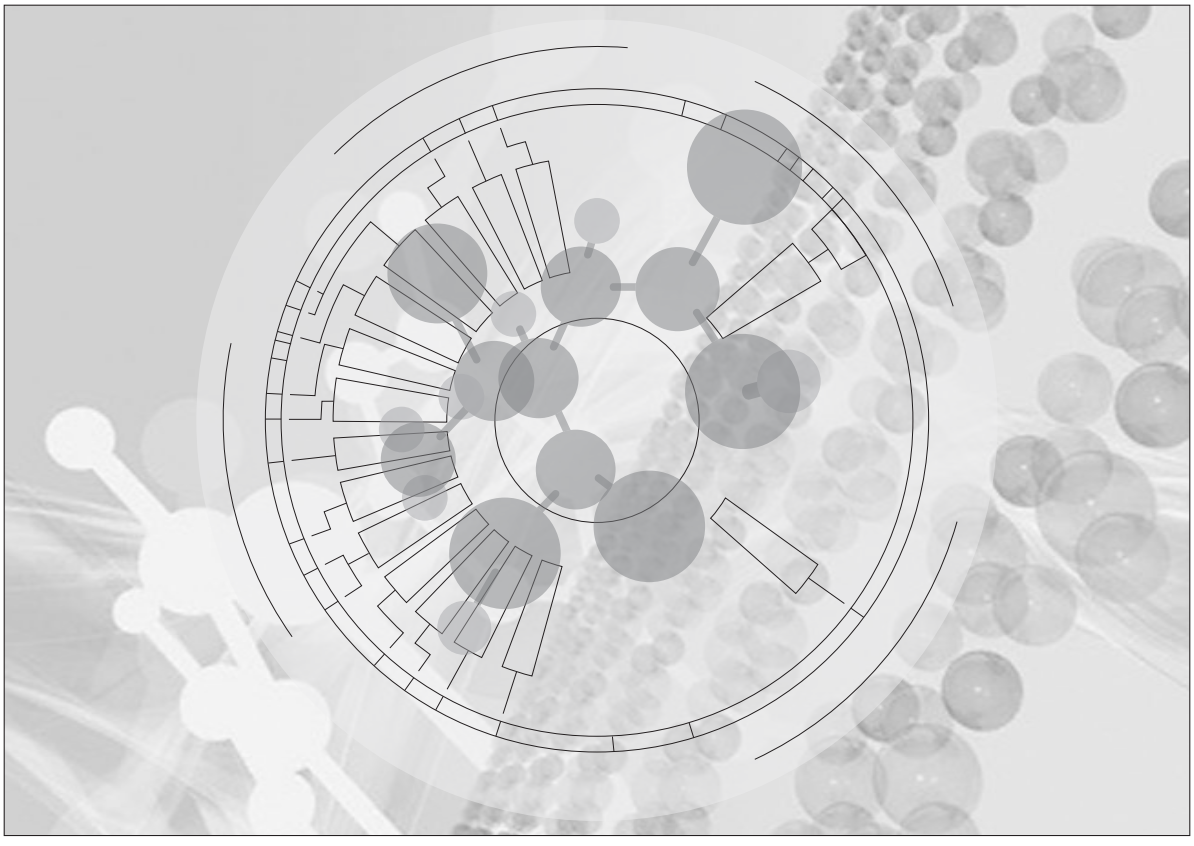

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Prions Mutate and Adapt to Host Environment

Scientists from the Florida campus of The Scripps Research Institute have shown that prions, bits of infectious protein that can cause fatal neurodegenerative disease such as Bovine Spongiform Encephalopathy (BSE) or "mad cow disease," have the ability to adapt to survive in a new host environment.

In this regard, although they lack DNA and RNA, they behave much like viruses, producing distinct self-perpetuating structural mutations that provide a clear evolutionary advantage.

The study was published this week in the online Early Edition, the journal Proceedings of the National Academy of Sciences.

"We found that when a particular prion strain is transferred from brain cells to a different cell line, its properties gradually change, giving rise to a variant strain that is better adapted to this new cellular environment," said Charles Weissmann, M.D., Ph.D., the Head of Scripps Florida's Department of Infectology, who led the study. "If those same prions are subsequently transferred to another cell line, they change again, adapting to these new host cells. And if returned to the brain, the prions gradually regain their original properties. We found physical evidence that, at least in one case, the fold of the prion changed when its properties changed."

Darwinian Evolution Without DNA

These new findings come approximately one year after Weissmann and colleagues published a study in the January 1, 2010 edition of the journal Science that showed that prions were capable of Darwinian evolution.

That earlier study also showed that prions can develop large numbers of mutations and that these mutations can bring about such evolutionary adaptations as drug resistance, a phenomenon previously known to occur only in bacteria and viruses. This study also suggested that the normal prion protein -- which occurs naturally in mammalian cells -- may prove to be a more effective therapeutic target than its abnormal toxic relation.

"Because prions can adapt to changing environments, it now becomes clear that it will be more difficult than originally thought to find drugs that will work against them," Weissmann said. "But if you could develop a drug that inhibits formation of the normal prion protein, you could, in essence, starve the infectious prions and prevent them from reproducing. This approach to treatment, although technically demanding, can be envisaged because, as we have shown earlier, deprivation of PrP is not detrimental to health -- at least to the health of mice."

Folding and Misfolding

Prions, which are composed solely of protein, are classified by distinct strains, characterized by their incubation time and the disease they cause. In addition to BSE/mad cow disease in cattle, diseases caused by prions include scrapie in sheep, chronic wasting disease in deer, and variant Creutzfeldt-Jakob disease in humans. 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 sheets (polymers) of these misfolded proteins, which causes massive tissue and cell damage.

"The infectious prion protein can fold in different ways, and depending on the fold, a different prion strain results," Weissmann said. "As long as prions are maintained in the same host, they retain their characteristic fold, so that strains breed true."

When prions multiply, however, that fold is not always reproduced correctly, so a prion population contains many variants, albeit at low levels.

The new study found that when a prion population is transferred to a different host, one of the variants may replicate faster -- an evolutionary advantage -- and become the dominant strain. This new population also contains variants, one of which may be selected over others when transferred to a different host.

"The result is that prions, although devoid of genetic material, behave similarly to viruses and other pathogens, in that they can mutate and undergo evolutionary selection," Weissmann said. "They do it by changing their fold, while viruses incur changes in their nucleic acid sequence."

Diverse Yet Related

The new study suggests that prion populations constitute a "quasi-species" similar in nature to RNA viruses and retroviruses, such as flu viruses and HIV.

The idea of a quasi-species was first conceived by Manfred Eigen, a German biophysicist who won the Nobel Prize in Chemistry in 1967. Basically, a quasi-species is a complex, self-perpetuating population of diverse and related entities that act as a whole. It was Weissmann, however, who in 1978 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.

But that's where the comparison ends, Weissmann said.

"The fact that they behave like viruses doesn't mean they're anything like a virus," he said. "A bicycle is like a car in that it gets you from one place to the other, but they're not the same. The end effect is the same, however. Prions and viruses are both able to change their structure to survive."

The first author of the study is Sukhvir P. Mahal of Scripps Research. Other authors include Shawn Browning, Jiali Li, and Irena Suponitsky-Kroyter, also of Scripps Research.

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S. P. Mahal, S. Browning, J. Li, I. Suponitsky-Kroyter, C. Weissmann. Transfer of a prion strain to different hosts leads to emergence of strain variants. Proceedings of the National Academy of Sciences, 2010; DOI: 10.1073/pnas.1013014108