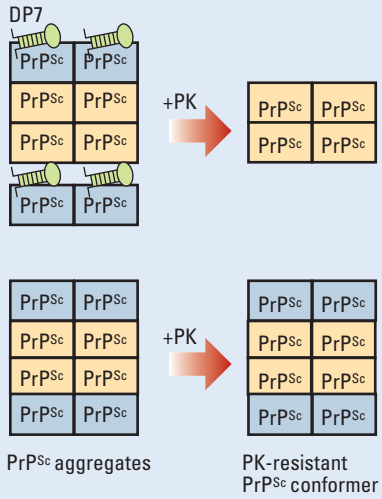
Aptamer apt for prion?

While the major human-infecting prion disorder, Creutzfeldt–Jakob disease (CJD), is somewhat rare, it is fatal—about 770 have died of CJD in the United Kingdom since 1990, according to the U.K. CJD Surveillance Unit. There are currently no available treatments for the underlying disease, but scientists from the University of Munich and the University of Bonn in Germany may now have demonstrated a new therapeutic approach.

The pathogenesis of prion diseases is thought to be associated with the interaction between normal cellular prion protein (PrP^{C}) and its abnormal isoform (PrP^{Sc}) and the subsequent formation of insoluble PrP^{Sc} aggregates (amyloids) that have enhanced resistance to proteinase K (PK) digestions. The German scientists are approaching the problem of inhibiting the formation of such aggregates with RNA aptamers, which are sequences with highly specific binding properties reminiscent of those of monoclonal antibodies.

The team performed in vitro binding assays between aptamer libraries and a human prion protein peptide sequence that has been implicated as functionally important for disease conversion (*ChemBioChem* **2002,** *3,* 717–725). The highest-affinity aptamer, DP7, was identified and tested against full-length prion proteins, to which it showed binding activity.



DP7, it is proposed, precludes the formation of proteinase K–resistant PrP^{Sc} aggregates.

To probe the biochemical usefulness of this binding behavior, DP7 was placed in a culture with a persistently prion-infected cell line. Negative control cultures with either untreated cells or with unselected aptamers from the library screen were prepared in parallel. One-half of the cultures were treated with PK before isolation and analysis of prion proteins, while the rest were not. For the non-PK treated samples, the amount of insoluble PrP^{Sc} was not significantly affected by the presence of DP7 compared to the controls. However, the relative proportion of insoluble protein after PK treatment is much reduced in the presence of DP7—indicating a reduction in PK resistance. The researchers propose a model in which DP7 initially binds to PrP^{C} and sterically disrupts the formation of PK-resistant, high-molecular-weight, tightly folded PrP^{Sc} aggregates originating from a pre-existing crystal seed (see figure).

Although side effects, bioavailability, and blood–brain barrier permeation of these aptamers are unknown, the German team believes that DP7 could represent the first of a novel class of therapeutic or prophylactic agents against prion diseases.

—DAVID FILMORE

Delete gene, avoid fat

Cake, pasta, cookies, filet mignon, and pie—imagine eating all of these delectable delights and more without worrying about gaining weight or developing diabetes. Thanks to the findings of researchers at the University of Wisconsin (UW)–Madison and Rockefeller University (New York), eating rich, fatty foods without consequences may be possible in the future. James M. Ntambi, professor of biochemistry and of nutritional sciences at UW–Madison, reports that mice who have had the gene SCD-1 deleted and who are given a rich, high-fat diet do not gain fat deposits or excess sugar in the blood.

The gene SCD-1 is responsible for producing an enzyme known as stearoyl-CoA desaturase-1 (SCD) that is necessary for the body to make the major fatty acids that reside in fat tissue. In a UW press release, Ntambi says, "The idea was to make them fat, but the mice lacking the SCD-1 gene never got up there despite a diet that contained nearly 15% fat."

The human equivalent of SCD-1 was recently identified, and Ntambi's group is studying that gene's function in tissue culture. The mice that lacked the SCD-1 gene didn't accumulate fat in the liver or other tissue where it would normally gather, causing health problems related to obesity (*Science* **2002,** *297,* 240–243).

Ntambi and Makoto Miyazaki, a biochemist at UW–Madison and coauthor, acknowledged that the elimination of SCD-1 caused side effects in the mice, most commonly skin and eye problems as the animals got older. The researchers then conducted a second study of mice with half the level of the enzyme SCD due to heterozygosity, and those mice did not suffer from any side effects. These findings might suggest that it is possible to develop drugs to suppress the fatty acids produced by the SCD-1 gene and protect from obesity and diabetes while minimizing troublesome side effects.

—FELICIA M. WILLIS

PHOTO: PHOTODISC

Advertiser