Blood test detects prions

For the first time, researchers have developed an *in vitro* technique to detect the presence of prions in blood samples. An effective blood test for these lethal brain diseases could allow for early diagnosis as well as for curbing their transmission.

Prion diseases—including variant Creutzfeldt-Jakob disease (vCJD), the human form of mad cow disease—arise through an accumulation of misfolded, self-replicating proteins in the brain that results in neurodegeneration and death. These diseases can incubate for decades before symptoms appear.

Since the first wave of vCJD occurred in the United Kingdom in the late 1990s, the medical community has been looking for a quick and reliable test for diagnosis of prion diseases. However, the prion proteins, which concentrate in the brain, are present in undetectable levels in the blood. No one has yet developed a biochemical test; definitive diagnosis of vCJD occurs only at autopsy.

Now, Claudio Soto of the University of Texas Medical Branch (Galveston, TX) and his colleagues have devised a way to amplify and detect the presence of prions in blood samples (*Nat. Med.*, September). Upon incubation of a minute amount of the prion protein PrP^{Sc} with an excess of the normal protein PrP^{C}, the prion protein changes the conformation of the surrounding normal proteins, causing the formation of protein aggregates in the sample. Sonication causes the aggregates to break up, releasing more PrP^{Sc}, which form the basis of new PrP^{Sc} clusters.

Soto's group tested the effectiveness of the assay using blood samples taken from hamsters showing symptoms of the prion disease scrapie. They ran 140 cycles and, using western blot, detected the prion protein 89% of the time, with no false positives.

Soto's group is now using this amplification method to determine the earliest point during the incubation period at which prion proteins can be detected in the blood.

In addition, they are adapting the technique to detect prions in humans and cattle.

A reliable blood test for prion detection would have several important uses, including prevention of accidental transmission through blood transfusion and organ transplant and large-scale screening to prevent the entry of diseased animals into the food supply.

Tanja Schub

RODENTS REVEAL METASTASIS MYSTERIES

Recent research has revealed two genes that may engender a predisposition to increased risk of metastasis in individual patients or specific tumor types—potentially important developments in the fight against cancer.

Tumor metastasis has bleak implications for patient survival and is recognized as the primary cause of cancer mortality. Unfortunately, it has proven difficult to confidently identify genes or mutations involved in the progression to metastatic disease. However, two articles published recently in *Nature Genetics* may offer important progress in this continuing search.

In the first article, researchers led by Kent Hunter of the National Cancer Institute (Bethesda, MD) analyzed a chromosomal region previously linked to metastasis of mammary tumors in mice (published online 4 September; doi: 10.1038/ng1635). By comparing this region in different mouse strains with especially high or low metastatic efficiency, the researchers identified 23 candidate genes, which they first prioritized in terms of their probable role in tumor progression and then analyzed in terms of expression patterns and strain-specific sequence variations. This led the team to the gene encoding Sipa1, a signaling protein with a specific mutation in metastasis-prone mouse strains that prevents it from interacting with a key repressor.

Mice implanted with mammary tumor cells with reduced *Sipa1* expression showed a significant decrease in metastatic progression; moreover, when cultured, these cells showed enhanced adhesion properties. On the other hand, mice implanted with cells overexpressing *Sipa1* showed double the number of metastases seen in mice implanted with unmodified tumor cells. The authors suggest that *Sipa1* could function importantly in regulating cell morphology and adhesion, and that patients harboring mutations in this gene could face a congenital disadvantage subsequent to the onset of cancer.

In the same issue, Massachusetts Institute of Technology (Cambridge, MA) investigator Robert Weinberg and his colleagues examine melanoma, a cancer type known for its potential to metastasize rapidly (doi: 10.1038/ng1634). During development, dermal melanocyte precursors migrate from the neural crest, and Weinberg's group speculated that these migratory properties could predispose melanocytes to form highly metastatic tumors. Mice subcutaneously injected with retrovirally transformed melanocytes developed tumors that readily metastasized to a wide variety of tissues; when examination of the resulting nodules revealed that metastasis did not seem to result from gross genomic alterations, Weinberg's team looked at the expression patterns of genes linked to neural crest cell migration. One such gene, encoding the transcription factor Slug, seems to regulate the expression of other migration-related genes; when mice were injected with melanocytes in which Slug levels were sharply reduced through RNA interference, there was a reduction by an entire order of magnitude in the extent of metastasis, suggesting that dysregulation of this developmental pathway may be a key step in melanoma metastasis.

Michael Eisenstein