can bind to anti-myelin antibodies[13]. Many other viruses—including herpesviruses such as Epstein–Barr virus—also bind to DR2. Thus, microbial peptides could trigger an autoimmune response against myelin in humans. The inflammatory response may be self-perpetuating after an infectious agent has been cleared (or has become latent), because MBP and other myelin proteins are released as the result of myelin destruction. This may explain why Soldan *et al.*[2] could amplify HHV-6 DNA from only 15 of 50 MS patients.

Molecular mimicry provides a scheme whereby viral sensitization in the blood leads to activation of T cells. These enter the brain where they may cause destruction when they encounter their cognate mimic in myelin (see figure). Molecular mimicry also allows for reconciliation of the "genes versus the environment" debate: the most important gene in determining susceptibility to MS—that is, HLA—is critical for selecting the appropriate mimic and presenting it to the immune system. Moreover, many different viruses mimic various parts of the myelin sheath, so inflammation in the white matter of the brain may ensue from an immune response to a variety of microbes. Thus, the hope of finding *the* virus that triggers MS may remain elusive forever.

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Puzzling over prion partners

Stefan Weiss

To understand what goes wrong in disease, we often need to know how the biological systems usually operate and work backward from there. The study of transmissible spongiform encephalopathies (TSEs)—such as bovine spongiform encephalopathy, Creutzfeldt–Jakob disease and scrapie—is no exception. Here, the search hinges on the normal function of the cellular prion protein PrP^C, and two papers in this issue may provide a means to that end by identifying possible receptors for this protein.

The main principle of the "protein-only" hypothesis is that a cell-membrane glycoprotein called PrP^C is converted to a misfolded, pathological form designated PrP*. The conversion is almost always accompanied by the formation of a protease-resistant molecule (PrP^{Sc}), and the ultimate result is cell death. But how and why does this happen? And what does PrP^C normally do?

Found in the brains of all vertebrates examined so far, PrP^C is anchored to the plasma membrane by a glycosyl-phosphatidylinositol moiety. So it comes as no surprise that both of the newly identified putative PrP^C receptors are membrane-bound proteins. In the first study, Martins *et al.* (page 1376) used a technique called complementary hydropathy—the theory being that peptides encoded by complementary DNA strands will bind one another—to make a 16-amino-acid complementary peptide to the neurotoxic region of PrP^C. By raising antibodies against this peptide and probing mouse neurons, they identified a 66-kDa membrane protein that binds PrP^C both *in vitro* and *in vivo*.

Rieger *et al.* (page 1383) took a different approach, using a yeast two-hybrid screen to identify proteins that interact with PrP^C. They pulled out the 37-kDa laminin receptor precursor protein (LRP)—a membrane-bound protein that mediates the action of laminin on neurons, and is highly conserved among mammals. Shown in the picture are neuroblastoma cells incubated with anti-LRP antibodies (the dense circle around the cells indicates that LRP is localized to the surface). LRP was found in all of the organs that are associated with prion propagation, and increased concentrations of LRP correlated with the accumulation of PrP^{Sc} in mice and hamsters.

Size alone indicates that the receptors identified by Martins *et al.* and Rieger *et al.* are probably not the same, although the LRP is thought to homodimerize *in vivo* to form the 67-kDa high-affinity laminin receptor. At present, it's impossible to say whether either of these proteins is *the* physiological receptor for PrP^C, or even to speculate what PrP^C may do when it interacts with them. But, as long as we don't know what the function of PrP^C is, any of its molecular interactions are very relevant to the study of prion diseases.

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