Is There Still Hope After Prions Have Spread Within the Brain?

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(See the article by Relaño-Gines et al, on pages 1038–45.)

Prion diseases are devastating neurological conditions of the central nervous system that affect animals and human beings. They are inexorably fatal and, so far, incurable. The initial event is the conversion, which can be either sporadic, genetic, or infectious, of a normal host-encoded glycoprotein termed cellular prion protein (PrP C) into a rogue misfolded isoform, the scrapie prion protein (PrPSc), which forms highly toxic aggregates and amyloid-like deposits [1]. Fortunately, Creutzfeldt–Jakob disease (CJD), the human form of prion diseases, is rare (fewer than 2 new patients per million per year), but the possibilities that CJD-associated prions may be transmitted via contaminated biomedical products and that animal prions may pass into humans through meat consumption are real public health issues that call for effective treatments.

In the wake of the Mad Cow Disease crisis, considerable efforts have been invested in the search for effective antiprion therapies that would halt the progression of the infectious agent in lymphoid and neural tissues [2]. At the same time, similar efforts have been made in other neurodegenerative conditions such as Alzheimer’s disease, Parkinson’s disease, or amyotrophic lateral sclerosis, which are also caused by toxic accumulation of misfolded proteins. Limited but encouraging results have been reported in those conditions, in particular through passive or active immunotherapy. Significant regression of the amyloid deposits is commonly observed together with a slowing of functional impairments such as the cognitive decline in mice developing Alzheimer’s manifestations [3–7]. In prion diseases, the therapies so far tested are effective only in peripherally infected mice, and only if started 1–4 weeks after prion inoculation [8]. For reasons that are still not clear, prions are sensitive to therapeutic agents, including antibodies, so long as they stay in secondary lymphoid tissues, but become resistant to the same agents once they have entered the brain [9]. At variance with most neurodegenerative diseases that appear to be still therapeutically manageable while developing in the nervous system, prions in the brain seem to indicate a point of no return.

The article by Relano-Gines et al in this issue of the Journal suggests that this occurrence may not be absolute and that there are ways to manage prion diseases at the neural stage [10]. The authors show that mouse embryonic stem cells grafted around the hippocampus area and lateral ventricles of mice infected with a scrapie agent, by intracranial route, can slow the course of the disease. The time of engraftment experimentally tested was 100 days after inoculation, that is, only 2–3 weeks before clinical manifestations are usually expected, and at a time when prions have massively colonized the brain. Under such conditions, clinical onset is delayed by 20% and survival is extended by 10%–15%. The outcome improvement is still modest, the relief is of limited duration, and all the treated mice do ultimately succumb. Moreover, the engraftment of neural stem cells 20 days later, when mice are on the verge of showing clinical manifestations, does not further modify the course of the disease. However, the findings reported by Relano-Gines et al represent a first breach of the general idea that prion diseases are intractable once the infectious agent has settled in the central nervous system or has been directly injected into the brain. The translation of this discovery into clinical treatment of CJD patients will require substantial improvements in the capacity of stem cells to repair massive damage and exert long-term protection. In this respect, the experience accumulated over the past 10 years on neural stem cell grafts in Huntington’s and Parkinson’s patients is extremely important [11]. Even though Relano-Gines et al do not observe acute signs of immune rejection, the minor genetic disparities between donor and host generate a rampant immune response which in the long term may damage the grafted cells [12]. Another difficulty regarding the long-term preservation of
neural cell grafts is the capacity of misfolded amyloid to infect in a prion-like mode, and by cell-to-cell contiguity, the grafted tissues [13]. It would be surprising if prions themselves were an exception to the prion-like rule and did not, sooner or later, invade the graft. In the present study, it did not seem to make a difference whether the grafted stem cells were prion-infectable or not, but in the long term it should. A third important parameter that affects the success of neural stem cell grafts is the relationship the graft establishes with local glial cells: astrocytes and microglia. For reasons that are still poorly understood and poorly controlled, the outcome of the crosstalk between graft and glia may be beneficial or detrimental. It may favor long-term engraftment and dampen inflammation, as suggested in the present study, but it may, as well, exacerbate inflammation and accelerate neuronal loss. In order to improve antiprion therapies, it will be essential to have a more precise understanding of the factors, including lymphokines, chemokines, blood-borne monocytes/macrophages, and activated T cells, that dictate the behavior of astrocytes and microglial cells.

In conclusion, the study by Relano-Gines et al [10] upsets dogma and proves the concept that prion diseases are tractable, even when prions are expanding in the brain. This is encouraging news for all those who work in the field of prion diseases and are searching for efficient therapies against what remains a dreadful threat.

**Funding**

Funded by the European Union (FOOD-CT-2006-023144); Association France Alzheimer; INSERM; and Pierre and Marie Curie University Paris 6.

**References**