

*Toxicity in a prion-infected brain has long been assumed to be present because of infectious prion proteins. New methods were used to test this assumption.*

Throughout its history, humanity has dealt with countless wars, pandemics, natural disasters, and other such cataclysms. In recent decades, a new challenge arose—prions. Prion proteins inhibit brain activity and aid neuron connections with their healthy form: PrP<sup>c</sup> (Prion Protein Cellular). However, a misfolding of such protein (PrP<sup>sc</sup> - Prion Protein Scrapie) leads to irreversible neurodegeneration, or continuous damage to the brain, inevitably leading to death. This infectious disease involves many types, two famous ones being Creutzfeldt-Jakob disease (CJD) and scrapie, all presenting the characteristics of brain damage and loss of neuronal cells. The mechanisms of each type are still heavily studied today; however, the cure is not yet found. It has long been assumed that the infectivity of prions is associated with neurotoxicity and is the cause of their fatality. Benilova and colleagues (2020) researched this theory using mice and new methods that allow the separation of infectivity and neurotoxicity.

In 1967, it was proposed that proteins were infectious and were involved with scrapie. Two decades later, Stanley Prusiner discovered proteins he later called “prions” from scrapie-infected hamster brains. He identified prions as infectious particles that lack nucleic acid (Prusiner, 1998). PrP<sup>c</sup> was believed to be infectious and neurotoxic, leading to its inevitable danger; however, more and more evidence suggests that that is not the case (Ma et al., 2002). Neurotoxicity refers to a negative effect on the nervous system

<sup>c</sup> concentrations (Sandberg et al., 2014), Benilova and their colleagues (2020) hypothesized that prions were not neurotoxic themselves, but it is rather the pathway switch in the second phase of prion propagation that causes this neurotoxicity. To test this hypothesis, prions of Rocky Mountain Laboratory (RML) infected mice were isolated and the infectivity was tested by the Automated

Sandberg, M. K., Al-Doujaily, H., Sharps, B., De Oliveira, M. W., Schmidt, C., Richard-Londt, A., . . . Collinge, J. (2014). Prion neuropathology follows the accumulation of alternate prion protein isoforms after infective titre has peaked. *Nature Communications* 5(1).

Schmidt, C., Fizet, J., Properzi, F., Batchelor, M., Sandberg, M. K., Edgeworth, J. A., . . . Collinge, J. (2015). A systematic investigation of production of synthetic prions from recombinant prion protein. *Open Biology* 5(12), 150165.

Spencer, P.S., and Lein, P.J. (2014) Neurotoxicity. In: *Encyclopedia of Toxicology*, P. Wexler, ed. (Elsevier Inc., Academic Press), pp. 489–500.

Thibeault, J., Patrick, J., Martin, A., Ortiz-Perez, B., Hill, S., Zhang, S., . . . Colón, W. (2019). Sarkosyl: A milder detergent than SDS for identifying proteins with moderately high hyperstability using gel electrophoresis. *Analytical Biochemistry* 571, 21-24.

Xiao, Y., Peng, Y., Wan, J., Tang, G., Chen, Y., Tang, J., . . . Shi, L. (2013). The atypical guanine nucleotide exchange factor Dock4 regulates neurite differentiation through modulation of Rac1 GTPase and actin dynamics. *Journal of Biological Chemistry* 288(27), 20034-20045.