Brain Pathology ISSN 1015-6305

MINI-SYMPOSIUM: PRION DISEASES

Recent advances on the molecular pathogenesis of prion diseases

Markus Glatzel[1] ; Christina J. Sigurdson[2]

[1] Institute of Neuropathology, University Medical Center Hamburg-Eppendorf (UKE), Hamburg, Germany.
[2] Departments of Pathology and Medicine, UC San Diego, La Jolla, CA.

Corresponding author:
Markus Glatzel, Institute of Neuropathology, University Medical Center Hamburg-Eppendorf (UKE), 20246 Hamburg, Germany (E-mail: *m.glatzel@uke.de*)

Received 17 December 2018
Accepted 18 December 2018

doi:10.1111/bpa.12693

Prion diseases continue to fascinate scientists from different disciplines since the discovery that a misfolded prion protein can act as an infectious agent. Infectious prions have caused epidemics, including kuru in humans, cervid chronic wasting disease, bovine spongiform encephalopathy (BSE) or "mad cow disease," and most recently, camel prion disease, which was identified in 2018 (1). In Kuru, spread of the disease occurred from the ingestion of prion-infected, dead relatives as part of mourning practices, whereas in chronic wasting disease, prions may be transmitted not only through ingesting prion-contaminated food, but also by exposure to a prion-contaminated environment (12, 13). In all instances, prions hold structural properties that cause different disease presentations, which can be passed on to another individuals (21). However, the most common form of human prion disease, sporadic Creutzfeldt-Jakob disease, is not caused by exposure to infectious prions but occurs as a rare disease from unknown causes (23). In all instances, prions cause a neurodegenerative disease with neuropathological and mechanistic overlap with other protein misfolding disorders, such as Alzheimer's or Parkinson's disease (9). Interestingly, a great number of neurodegenerative diseases spread through the brain as prions do, yet some obvious differences in disease characteristics have to considered (Table 1).

Although our understanding of prion disease has experienced a boost in the last 10 years, there are gaps in our understanding of the molecular basis of this complex disease (18). An incomplete list of these unchartered territories include (i) the structure of the prion aggregate and how this relates to the spread of prions within a host and also from host to host, (ii) the need to detect prions or disease biomarkers ante-mortem in order to establish and test therapies and (iii) an integrated view of the mechanisms underlying prion neurotoxicity. In this issue of Brain Pathology, we have assembled experts in the field to report on the state of the art developments in human prion diseases, animal prion diseases and on the mechanisms of prion neurotoxicity. The mini-symposium is further completed by one original article reporting on the influence of microRNAs in regulating the prion protein (17) and by one original article proposing a molecular mechanism to explain the extraordinary susceptibility of bank voles to prion infection (8).

One thing prion scientists, especially the ones involved in neuropathological characterization of the disease, are particularly proud of, is the categorization of disease subtypes based on histological, genetic and biochemical criteria. In the review by Piero Parchi and colleagues, this categorization-system is introduced, and novel aspects relevant not only to prion scientists but also to the wider neuropathological community concerning co-pathology or cross-seeding phenomena are elucidated (2).

Animal prion diseases continue to emerge, recently with variants of scrapie and BSE, a camel prion disease in Algeria (1) and chronic wasting disease in Scandinavian wild reindeer (3) and moose (19). What are the risks for animal prions infecting humans? Houston and Andreoletti summarize the history, epidemiology and pathogenesis of the animal prion diseases, and review research designed to estimate the risk of human infection (7). The authors also highlight the limitations of experimental models and consider the uncertainties for zoonotic transmission that still remain, ultimately emphasizing the importance of preventing human exposure to prions.

Table 1. Similarities and differences between bona fide prion diseases and other dementias. A, most likely incomplete and highly subjective, list of features usually attributed to prion diseases, some of which are seen in a wide range of dementias.

Disease entity		Misfolded Protein	Cell to cell spread	Strain like variants	Transmissbility with contact	Transmissbility without contact
Prion (human)	Sporadic CJD	Prion				
	Genetic CJD				(4)	
	Variant CJD					
	Inatrogenic CJD					
	Kuru					
Prion (animal)	Scrapie					
	BSE					
	CWD					
Alzheimer		ß-amyloid	(24)	(22)	(24)	
Tauopathies		Tau	(5)		(5)	
Lewy body						
Parkinson's		α-synuclein	(6)		(11)	
Huntington		huntingtin	(18)			
AA Amyloidosis		Serum AA protein	(15)		(15)	
Amyotrophic lateral sclerosis		SOD1	(14)			
		TDP43	(16)		(20)	

has been shown to occur.

no conclusive experimental evidence.

Abbreviations: CJD = Creutzfeldt-Jakob Disease; SOD1 = superoxide dismutase 1; TDP43 = Transactive response DNA binding protein 43 kDa.

The pathologic hallmarks of prion disease include spongiform degeneration, gliosis, aggregated prion protein and neuronal loss, yet we are only beginning to understand how toxic signaling through the prion protein can induce neuronal death. David Harris and colleagues note the obstacles that have hampered investigations of neurotoxicity, most notably the lack of an *in vitro* model system that recapitulates features of neuronal degeneration. They review new experimental systems used in recent years to model prion neurotoxicity in order to define the signaling pathways activated by prion aggregates (10). They also consider structural modifications in the prion protein that can trigger neurotoxic sequelae. Finally, the authors discuss missing links in the neurotoxic signaling pathway and note opportunities to identify novel drug targets to mitigate toxic signaling, which may also have relevance for other neurodegenerative diseases.

In summary, this mini-symposium is as interesting and diverse as prion diseases, and we hope the readers enjoy reading the articles as much as we have.

REFERENCES

1. Babelhadj B, Di Bari MA, Pirisinu L, Chiappini B, Gaouar SBS, Riccardi G *et al* (2018) Prion disease in dromedary camels, Algeria. *Emerg Infect Dis* **24**:1029–1036.
2. Baiardi S, Rossi M, Capellari S, Parchi P (2018) Recent advances in the histo-molecular pathology of human prion disease. *Brain Pathol* [Epub ahead of print; doi:10.1111/bpa.12695].
3. Benestad SL, Mitchell G, Simmons M, Ytrehus B, Vikoren T (2016) First case of chronic wasting disease in Europe in a Norwegian free-ranging reindeer. *Vet Res* **47**:88.
4. Cali I, Mikhail F, Qin K, Gregory C, Solanki A, Martinez MC *et al* (2018) Impaired transmissibility of atypical prions from genetic CJD(G114V). *Neurol Genet* **4**:e253.
5. Clavaguera F, Bolmont T, Crowther RA, Abramowski D, Frank S, Probst A *et al* (2009) Transmission and spreading of tauopathy in transgenic mouse brain. *Nat Cell Biol* **11**:909–913.
6. Desplats P, Lee HJ, Bae EJ, Patrick C, Rockenstein E, Crews L *et al* (2009) Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. *Proc Natl Acad Sci U S A* **106**:13010–13015.
7. Houston F, Andréoletti O (2018) Animal prion diseases: the risks to human health. *Brain Pathol* [Epub ahead of print; doi: 10.1111/bpa.12696].
8. Kobayashi A, Matsuura Y, Takeuchi A, Yamada M, Miyoshi I, Mohri S, Kitamoto T (2018) A domain responsible for spontaneous conversion of bank vole prion protein. *Brain Pathol* [Epub ahead of print; doi: 10.1111/bpa.12638].
9. Lassen LB, Reimer L, Ferreira N, Betzer C, Jensen PH (2016) Protein partners of alpha-synuclein in health and disease. *Brain Pathol* **26**:389–397.
10. Le NTT, Wu B, Harris DA (2018) Prion neurotoxicity. *Brain Pathol* [Epub ahead of print; doi: 10.1111/bpa.12694].
11. Luk KC, Kehm V, Carroll J, Zhang B, O'Brien P, Trojanowski JQ, Lee VM (2012) Pathological alpha-synuclein transmission initiates Parkinson-like neurodegeneration in nontransgenic mice. *Science* **338**:949–953.
12. Miller MW, Hobbs NT, Tavener SJ (2006) Dynamics of prion disease transmission in mule deer. *Ecol Appl* **16**:2208–2214.
13. Miller MW, Williams ES (2003) Prion disease: horizontal prion transmission in mule deer. *Nature* **425**:35–36.

14. Munch C, O'Brien J, Bertolotti A (2011) Prion-like propagation of mutant superoxide dismutase-1 misfolding in neuronal cells. *Proc Natl Acad Sci U S A* **108**:3548–3553.
15. Murakami T, Inoshima Y, Ishiguro N (2015) Systemic AA amyloidosis as a prion-like disorder. *Virus Res* **207**:76–81.
16. Nonaka T, Masuda-Suzukake M, Arai T, Hasegawa Y, Akatsu H, Obi T *et al* (2013) Prion-like properties of pathological TDP-43 aggregates from diseased brains. *Cell Rep* **4**:124–134.
17. Pease D, Scheckel C, Schaper E, Eckhardt V, Emmenegger M, Xenarios L *et al* (2018) Genome-wide identification of microRNAs regulating the human prion. *Brain Pathol* [Epub ahead of print; doi: 10.1111/bpa.12679].
18. Pecho-Vrieseling E, Rieker C, Fuchs S, Bleckmann D, Esposito MS, Botta P *et al* (2014) Transneuronal propagation of mutant huntingtin contributes to non-cell autonomous pathology in neurons. *Nat Neurosci* **17**:1064–1072.
19. Pirisinu L, Tran L, Chiappini B, Vanni I, Di Bari MA, Vaccari G *et al* (2018) Novel type of chronic wasting disease detected in moose (Alces alces), Norway. *Emerg Infect Dis* **24**:2210–2218.
20. Porta S, Xu Y, Restrepo CR, Kwong LK, Zhang B, Brown HJ *et al* (2018) Patient-derived frontotemporal lobar degeneration brain extracts induce formation and spreading of TDP-43 pathology *in vivo*. *Nat Commun* **9**:4220.
21. Ragagnin A, Ezpeleta J, Guillemain A, Boudet-Devaud F, Haeberle AM, Demais V *et al* (2018) Cerebellar compartmentation of prion pathogenesis. *Brain Pathol* **28**:240–263.
22. Rasmussen J, Mahler J, Beschorner N, Kaeser SA, Hasler LM, Baumann F *et al* (2017) Amyloid polymorphisms constitute distinct clouds of conformational variants in different etiological subtypes of Alzheimer's disease. *Proc Natl Acad Sci U S A* **114**:13018–13023.
23. Sigurdson CJ, Bartz JC, Glatzel M (2018) Cellular and molecular mechanisms of prion disease. *Annu Rev Pathol* doi: 10.1146/annurev-pathmechdis-012418-013109. [Epub ahead of print].
24. Walker LC, Schelle J, Jucker M (2016) The Prion-Like Properties of Amyloid-beta Assemblies: Implications for Alzheimer's Disease. *Cold Spring Harb Perspect Med* **6**:pii: a024398. doi: 10.1101/cshperspect.a024398.