3.1. Introduction

While a great deal of research has been done during the last years to elucidate modes and spread of prion infection, and significant advances have been achieved in those fields, the way how prions harm the central nervous system still remains enigmatic. The clinical picture in prion diseases is dominated by central neurological symptoms, which are presently believed to be due to an early synaptic dysfunction and, at later stages, neuronal loss. What we do not know is, how are neurons actually affected by the disease? Why are some neurons more readily destroyed than others? What is the role of the cellular prion protein, PrP\textsubscript{C}, in the whole process? And how does the pathological prion protein, PrP\textsubscript{Sc}, contribute?

Historically, there were two major approaches to prion pathogenesis: once, the so-called “gain of function-hypothesis”, which put forward a possible neurotoxic effect of an abnormally folded, not further degradable protein that is deposited in considerable amounts in the brains of affected individuals. On the other hand, one could argue, that the continuous conversion of PrP\textsubscript{C} to PrP\textsubscript{Sc} might lead to decreased availability and/or functional impairment of the former, so that its assumed neuroprotective effects are lost. This was central to the “loss of function-hypothesis”. Both theories had their advocates. Although none of them has definitely proven right or wrong, the situation is certainly much too complex to be satisfyingly explained by one simple model.

What seems now clear is the incapacity of PrP\textsubscript{Sc} accumulation alone for causing symptomatic disease\textsuperscript{2,3}. PrP deficient mice are generally
resistant to scrapie. When PrP<sub>Sc</sub> deposition is induced in such animals by grafting neural tissue overexpressing PrP<sup>C</sup> into their brains and intracerebrally inoculating them with scrapie prions, the grafts accumulate PrP<sub>Sc</sub>, which also spills over to the host brain. But while the grafts develop severe, scrapie-like neurodegeneration, the brain tissue devoid of PrP<sup>C</sup> shows no damage at all. Furthermore, if neuronal PrP<sup>C</sup> is depleted in mice with ongoing neuroinvasive prion infection, non-neural replication and accumulation of prion infectivity continues, but early cerebral histopathological changes are reversed, and neuronal loss and progression to clinical disease are prevented. Thus, expression of the normal prion protein must play a crucial role in the development of neurodegeneration after prion infection. This knowledge implies another question: must PrP<sup>C</sup> necessarily be present on all types of brain cells (i.e. neurons, astrocytes, and oligodendrocytes) to confer 1. susceptibility to clinical prion disease, 2. formation of PrP<sub>Sc</sub>, and 3. transmission of infectivity and disease?

To address this issue, several transgenic mouse models have been generated expressing PrP<sup>C</sup> selectively in neurons, astrocytes, and oligodendrocytes, respectively. Subsequent inoculation and transmission experiments revealed that mere neuron-specific expression of hamster PrP<sup>C</sup> suffices to support prion infection and disease development, while restriction of murine PrP<sup>C</sup> to oligodendrocytes does not. The role and impact of astrocyte-specific PrP<sup>C</sup> expression is discussed controversially. Raeber and colleagues reported that transgenic mice expressing hamster PrP<sup>C</sup> selectively in astrocytes are susceptible to prion infection. On the ultrastructural level, brains of these mice show TSE-typical neuronal lesions despite lack of neuronal PrP<sup>C</sup>, suggesting that deposition of PrP<sub>Sc</sub> in intimate proximity to neurons and their processes is sufficient to induce TSE pathology. However, the studies mentioned before, although using a different approach (neuroectodermal grafting or postnatal neuron-specific downregulation of PrP<sup>C</sup> expression) argue against this hypothesis, since close proximity of PrP<sub>Sc</sub> to the neuronal cell surface in these models did not induce obvious morphological alterations, neuronal loss, or clinical disease. Whether these differences reflect distinct pathogenic mechanisms determined by neuronal and astrocytic PrP<sup>C</sup> expression or certain strain properties (hamster 263K versus mouse RML), or if they rely on varying expression levels of astrocytic prion protein in the mouse models used (or on other still unknown factors), is presently not clear.

Finally, it is important to note that mice with selective genetic elimination of the prion protein gene (Prnp) open reading frame (ORF) within the borders of exon 3 (leaving the splice acceptor site of exon 3