Prion devoid of prpc do not show neurodegeneration

Prion diseases can occur spontaneously, byinfection, or by hereditary mutations, but the common connection between allprion diseases is the misfolded state of prion (Cohen andPrusiner, 1998; Collinge, 2001; Aguzzi et al., 2008a). A large number of prion diseasecases appear spontaneously (? 85 %), or are transmitted from individualsinfected with prion diseases (? 5%). Nevertheless, a significant number (? 10%) of hereditary (familial) forms of prion diseases, due to specific mutationsin the Prnp gene, have been reportedin humans and other mammals (Mead, 2006). Mutations inthe Prnp gene that are associatedwith prion diseases can be broadly divided into two categories: mutations thatcause changes in the protein and induce prion diseases, and mutations thatprevent prion disease propagation (Jones et al.

, 2006; Aguzzi et al., 2008a; Van der Kamp and Daggett, 2009; Coleman et al., 2014; Asante et al., 2015; Singh andUdgaonkar, 2015; Sabareesanand Udgaonkar, 2016; Sabareesan and Udgaonkar, 2017). Despite the fact that pathogenicmutations show different effects on PrP, it is very unlikely that TSEs are induced by the loss of functional PrPCdue its misfolding, because mice devoid of PrPC do not showneurodegeneration (Büeler et al., 1993). Hence, it ispossible that TSEs are caused by a gain of toxic function due to the formationof PrPSc. In some, but not all, prion diseases, the formation and accumulation of the pathological form of the prion protein, PrPSc is seen (Collinge, 2001; Aguzzi andPolymenidou, 2004; Aguzzi et al.

, 2008a). The progressive accumulation ofPrPSc in certain prion diseases is known to correlate with theextent of severity of the disease (Prusiner et al., 1983; Caughey et al.

, 2009; Laurén et al., 2009). It appears that there is a strongcorrelation between prion protein misfolding and TSEs. However, increasing evidence suggests that misfoldingand aggregation of PrP is an important, but not a sufficient factor in prion diseaseaetiology.

Although PrPSc is well established as the infectiousform, it might not be the direct cause of neurodegeneration, at least in someprion diseases. Several disease-linked mutations inanimals do not result in any accumulation of such amyloid plaques (Nitrini et al., 1997; Hegde et al., 1998; Coleman et al., 2014). For example, it has been reportedthat the A116V mutation facilitates the formation of a transmembrane form ofPrP, which leads to neurodegeneration without any detectable accumulation ofPrPSc (Hegde et al., 1998).

Despitethe clear understanding about the presence of these two species, PrPCand misfolded prion protein, the mechanism of conformational conversion, aswell as the final structure of the misfolded prion protein remain unclear. Althoughthe structure of PrPC is well known, the structure of PrPScremains poorly defined. A detailed structural understanding of the misfolded, aggregated, protease-resistant PrPSc is therefore essential.

In vitro studies of prion proteinmisfolding and aggregation invariably utilize recombinant PrP (PrP).