PRIONS

The fast and the furious

> initial prion conversion seems to occur first at the plasma membrane

The host cellular prion protein (PrP^{C}) can be converted into the misfolded and infectious scrapie form (PrP^{Sc}) when the two forms come into contact, causing prion diseases. By developing a new cell system, this study offers novel insights into how PrP^{C} is converted into the misfolded protein.

To study prion conversion in more detail, the authors developed PrP^{C} constructs expressing a MYC tag at the carboxyl terminus. These were transfected into a prion-susceptible mouse cell line in which endogenous PrP^{C} had been silenced (PrP-224AlaMYC cells). The MYC-tagged constructs were expressed at wild-type levels and localized normally, and exposure to prions led to robust conversion into MYC-tagged PrP^{Sc}. To confirm that the cells were producing infectious prions, extracts were used to infect mice, which subsequently developed neuropathology typical of prion disease.

Previous studies had suggested that *de novo*-synthesized PrP^{Sc} appears within 72 hours (or longer) of exposure to infectious material. Interestingly, the authors show that some PrP-224AlaMYC cells accumulated PrP^{Sc} in under 2 hours, and in fact only 1–2 minutes of exposure was enough to lead to conversion. Therefore, conversion is much faster than previously thought.

So where is PrP^{Sc} synthesized? The plasma membrane had been suggested as the site of prion conversion, and indeed, in cells exposed to infectious material for just 1 minute, PrP^{Sc} was present only on the plasma membrane. However, intracellular PrP^{Sc} was observed after 2 minutes of exposure, suggesting that it is rapidly endocytosed and trafficked into the cell. Indeed, the location of PrP^{Sc} in the cell was found to depend on the length of exposure, with PrP^{Sc} being located exclusively on the plasma membrane at the earliest time-point and distributed inside the cell later on.

To confirm that prion conversion can occur on the plasma membrane, the authors blocked endocytosis; this did not prevent PrP^{Sc} formation. Importantly, PrP^{Sc} levels were significantly reduced in PrP-224AlaMYC cells that had been treated with phosphoinositide-specific phospholipase C or with agents that disrupt lipid raft integrity. Therefore, initial prion conversion seems to occur first at the plasma membrane, perhaps in lipid rafts. However, intracellular compartments may also have a role in this, possibly by accelerating conversion after PrP^{Sc} has been endocytosed.

Together, these findings provide new insights into prion conversion by revealing the kinetics and location of PrP^{Sc} formation, and may partly explain why prion infections spread throughout the nervous system so quickly.

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ORIGINAL RESEARCH PAPER Goold, R. *et al.* Rapid cell-surface prion protein conversion revealed using a novel cell system. *Nature Commun.* 19 Apr 2011 (doi:10.1038/ncomms1282)
FURTHER READING Tuite, M. F. & Serio, T. R. The prion hypothesis: from biological anomaly to basic regulatory mechanism. *Nature Rev. Mol. Cell Biol.* **11**, 823–833 (2010)