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Prions exploit M cells in the lining of the intestine to enter Peyer's patches and establish host infection

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Prion diseases are infectious neurodegenerative disorders that affect humans and animals. Many natural prion diseases of humans and animals are considered to be acquired through oral consumption of contaminated food or pasture. A thorough understanding of the route by which prions establish host infection will help identify the important factors that influence oral prion disease susceptibility and to which intervention strategies can be developed. After exposure, the early accumulation and replication of prions within small intestinal Peyer's patches is essential for the efficient spread of disease to the brain where they ultimately cause neurodegeneration and death. To be able to replicate within Peyer's patches, the prions must first cross the gut epithelium. M cells are specialised epithelial cells within the epithelia covering Peyer's patches that transcytose particulate antigens and microorganisms from the gut lumen. M cell-development is dependent upon RANKL-RANK-signalling, and mice in which RANK is deleted only in the gut epithelium completely lack M cells. In the specific absence of M cells in these mice, the accumulation of prions within Peyer's patches and the spread of disease to the brain is blocked, demonstrating a critical role for M cells in the initial transfer of prions across the gut epithelium in order to establish host infection. Since pathogens, inflammatory stimuli and aging can modify M cell-density in the gut, we considered that these factors may also influence oral prion disease susceptibility. Mice were therefore treated with RANKL to enhance M-cell density in the gut. We show that prion uptake from the gut lumen was enhanced in RANKL-treated mice, resulting in shortened survival times and increased disease susceptibility, equivalent to a 10-fold higher infectious titre of prions. In contrast, the susceptibility of aged mice (~600 days old) to oral prion disease susceptibility is reduced and coincides with the reduced density of functional M cells in their Peyer's patches. Together these data demonstrate that M cells are the critical gatekeepers of oral prion infection, whose density in the gut epithelium directly limits or enhances disease susceptibility. Our data suggest that factors which alter M cell-density in the gut epithelium may be important risk factors which influence host susceptibility to orally acquired prion diseases.