Nature Reviews Microbiology | AOP, published online 10 July 2006; doi:10.1038/nrmicro1481

PRION DISEASE

Partners in crime

DOI:
10.1038/nrmicro1481

URLs

Entrez Genome
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome

HIV-1
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genome&cmd=Retrieve&dopt=Overview&list_uids=12171

Although there is much evidence to suggest that PrP^{Sc}, a misfolded form of the cellular prion protein PrP^{c}, is the infectious agent of prion diseases, the mechanism of PrP^{Sc} transmission and the factors that affect its spread remain unknown. Pascal Leblanc *et al.* now show that the release of PrP^{Sc} from scrapie-infected cells is markedly enhanced by retroviral infection, implicating retroviruses in the spread of prion diseases and providing mechanistic insights into prion transmission.

PrP^{c} is found in sections of the plasma membrane known as detergent-resistant microdomains (DRMs) and in endosomal compartments. Retroviruses such as moloney murine leukemia virus (MoMuLV) and HIV-1 also associate with both DRMs and endosomes, where they assemble new virions, incorporating host membrane proteins into the viral envelope. Because the intracellular paths of prion proteins and retroviruses coincide, the authors proposed that retroviruses might 'pick up' prion proteins during assembly and budding, thereby contributing to prion protein release and spread.

To investigate this further, Leblanc and colleagues subjected scrapie-infected mouse cell lines that had been coinfected with MoMuLV to subcellular fractionation, separating out the different cellular membrane compartments. Immunoanalysis of the separated fractions revealed that MoMuLV Gag and Env colocalized with PrP^{c} and PrP^{Sc} in DRMs and in soluble fractions, suggesting that PrP^{c} and PrP^{Sc} were incorporated into virions during assembly and budding. Although only small amounts of prion proteins were found in the supernatant of cells infected with scrapie alone, coinfection with MoMuLV markedly increased the release of PrP^{Sc} in association with MoMuLV virions and exosomes and, importantly, the released PrP^{Sc} infected target cells in a coculture assay.

The link between retrovirus infection and prion infectivity is an important one, as small ruminant lentiviruses are endemic in many sheep flocks and goat herds. In 2005, a paper from the Aguzzi laboratory reported the detection of PrP^{Sc} in the mammary glands of sheep with mastitis, a pathology that is often associated with retroviral infection. Together, these findings point to retroviruses as crucial cofactors involved in prion propagation. It remains to be seen if other enveloped viruses are also implicated in the spread of the pathological prion agent.

Shannon Amoils

ORIGINAL RESEARCH PAPER Leblanc, P. *et al.* Retrovirus infection strongly enhances scrapie infectivity release in cell culture. *EMBO J.* **25**, 2674–2685 (2006)