Distinct disease phenotypes produced by a de novo generated synthetic prion strain: Conformational instability before adaptation

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increased in wild-type (wt) MoPrP. To test these mutants in vitro, we produced recombinant proteins and carried out a fibrilization assay and compared the lag phases duration among different constructs. The results clearly show that the constructs with tyrosine (H95Y, H110Y, or H95,110Y) required shorter lag phases to aggregate compared to wt MoPrP. Based on these data, we could conclude that substitution of histidine by tyrosine residues at non-OR region can enhance PrP^{C}-PrP^{Sc} conversion process, and that the non-OR copper-binding site may possess a critical role in this process.

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Prions are infectious proteins that possess multiple self-propagating structures, which define different strains. The structural information for strain diversity is contained in the folding of the pathological isoform, PrP^{Sc}. Following an *in vitro* protocol, recombinant mouse PrP (recMoPrP) was converted to ultrastructurally different amyloid fibrils without any seeding factor. One of these preparations (recMoPrP#4) efficiently propagated in PMCA using the brains of mice overexpressing PrP^{C} (Tga20) as substrate. RecMoPrP#4 was able to infect either GT1 or N2a cell lines causing the conversion of endogenous PrP^{C} to PK-resistant forms. We next assessed the ability of recMoPrP#4 to propagate *in vivo* after intracerebral inoculation in CD1 mice. The animals did not show any evident prion-like pathology and were culled at the end of their lifespan. The brain of these mice was either used for (i) a second passage transmission or (ii) analyzed by PMCA. The latter revealed the presence of PK-resistant PrP with an uncommon biochemical profile when compared to that of known murine prion strains. This amplified isolate was intracerebrally injected in CD1 mice, which developed disease after a relative short incubation time (~160 days). Immunohistochemical and biochemical analysis revealed the presence of three different PK-resistant prion isolates able to produce a subset of completely different pathologies. The biochemical profiles of the isolates that accumulated in the CNS of these animals were distinct from that of the original amyloid used as inoculum. These results indicate that synthetic prions can assume multiple intermediate conformations before adapting and converging to stable strains.

P.125: Distinct strains of Aβ prions implicated in rapidly progressive Alzheimer disease

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Because over 75% of phenotypic variance of late onset Alzheimer disease (AD) remains unexplained by currently identified risk genes, we aimed to investigate the prion paradigm of AD, specifically the role of structure of the brain amyloid β (Aβ) in remarkably variable rates of clinical decline. Using a tandem of novel biophysical methods, we inventoried and analyzed conformational structural characteristics of Aβ in the cortex of 48 cases of sporadic AD with distinctly different disease durations, and correlated the data with clinical profiles