Prion

Prions are infectious agents composed entirely of a protein material that can fold in multiple, structurally abstract ways, at least one of which is transmissible to other prion proteins, leading to disease in a manner that is epidemiologically comparable to the spread of viral infection. Prions composed of the prion protein (PrP) are believed to be the cause of transmissible spongiform encephalopathies (TSEs) among other diseases.

The absence of a human cell culture model that replicates human prions has hampered prion disease research for decades. In this paper, we show that astrocytes derived from human induced pluripotent stem cells (iPSCs) support the replication of prions from brain samples of CJD patients. For experimental exposure of astrocytes to variant CJD (vCJD), the kinetics of prion replication occur in a prion protein codon 129 genotype-dependent manner, reflecting the genotype-dependent susceptibility to clinical vCJD found in patients. Furthermore, iPSC-derived astrocytes can replicate prions associated with the major sporadic CJD strains found in human patients. Lastly, we demonstrate the subpassage of prions from infected to naive astrocyte cultures, indicating the generation of prion infectivity in vitro. Our study addresses a long-standing gap in the repertoire of human prion disease research, providing a new in vitro system for accelerated mechanistic studies and drug discovery [1)].

Neurodegeneration can be prevented by imatinib mesylate (Gleevec or STI571) that regulates c-Abl tyrosine kinases, which elicit protective effects in neurodegenerative disease models. However, the protective effect of STI571 against prion disease remains unknown. In the present study, the effect of STI571 on prion peptide-induced neuronal death was investigated. Results showed that STI571 rescued neurons from PrP106-126-induced neurotoxicity by preventing mitochondrial dysfunction. STI571-inhibited c-Abl tyrosine kinases prevented PrP106-126-induced reduction in mitochondrial potential, Bax translocation to the mitochondria and cytochrome c release. The protective effect of STI571 against mitochondrial dysfunction was related to the activation of BIM expression. This study is the first to demonstrate the protective effect of STI571 against prion-mediated neurotoxicity. Our results suggested that imatinib mesylate treatment may be a novel therapeutic strategy to treat prion-mediated neurotoxicity [2)].

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2)
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