

S003 Proteolytic processing of the prion protein and amyloid precursor protein

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The Alzheimer's amyloid precursor protein (APP) is proteolytically processed by the β - and γ -secretases to release the amyloid- β (A β) peptide that is neurotoxic and aggregates in the brain of Alzheimer's patients. β -secretase is a membrane-bound aspartic protease that appears to cleave APP within cholesterol-rich lipid rafts. Targeting β -secretase to lipid rafts by replacing its transmembrane and cytosolic domains with a GPI anchor increased the production of A β providing evidence that localisation in lipid rafts modulates the processing of APP. The prion protein (PrP), the causative agent of the transmissible spongiform encephalopathies such as Creutzfeldt-Jakob disease in humans, is also subject to multiple proteolytic processing events. The cellular form of the prion protein (PrP^C) undergoes reactive oxygen species-mediated β -cleavage within the copper-binding octapeptide repeats, α -cleavage possibly mediated by ADAMs within the central neurotoxic domain, calpain-dependent cleavage of the infectious form (PrP^{Sc}), and shedding from the membrane by zinc metalloproteases. The shedding of PrP^C bears remarkable similarities to the α -secretase mediated non-amyloidogenic cleavage of APP. The roles of these various proteolytic events in the processing of APP and PrP will be discussed.