Proteolysis and protein:protein interactions in neurodegenerative diseases

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Introduction

Alzheimer's disease (AD) is the commonest neurodegenerative disease of old age. Currently, there are no drugs available to halt or slow the progression of this devastating disease which is placing a huge burden on patients and carers. AD is characterised by the deposition in the brain of senile plaques that are composed of the amyloid-β peptide (Aβ). Through mechanisms that are poorly understood, Aβ oligomers, fibrils and/or aggregates are toxic to nerve cells. Aβ is derived from the larger transmembrane amyloid precursor protein (APP) through proteolytic cleavage by the β- and gamma-secretases (Figure 1a). The β-secretase (BACE1) cleaves within the APP sequence at the N-terminus of the Aβ peptide, with the gamma-secretase complex cleaving the resulting membrane-bound stub at the C-terminus of the Aβ sequence. Inhibition of both the β- and gamma-secretases are being considered as potential therapeutic approaches to combat AD.

The prion protein is probably best known for its role in the transmissible spongiform encephalopathies or prion diseases, such as Creutzfeldt-Jakob disease in humans and bovine spongiform encephalopathy in cattle. In these diseases the normal cellular form of the prion protein (PrPC) undergoes a conformational conversion to the infectious form, PrPSc. We have shown that PrPC inhibits the β-secretase cleavage of APP, lowering the amount of Aβ produced and, therefore, potentially protecting against AD. In both cell models and mice, reduction of PrPC levels resulted in an increase in Aβ production. BACE1 co-immunoprecipitated with PrPC from cells and brain samples, suggesting a direct interaction between the two proteins. More recently, PrPC was identified as a high affinity receptor for Aβ oligomers (Figure 1c).

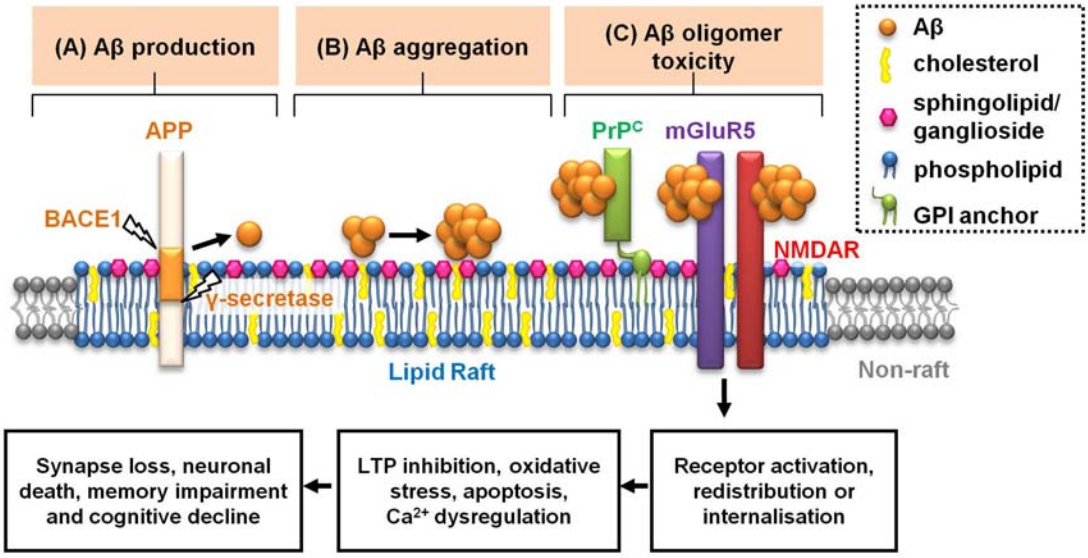

Figure 1: production, aggregation, neuronal binding and toxicity of Aβ oligomers.

Protein:protein interactions in Alzheimer's disease

Several other proteins, in addition to PrPC, have been reported to regulate the proteolytic processing of APP. For example, some proteins bind to APP and/or alter its subcellular

trafficking to modulate its proteolytic processing, including ApoER2. Thy-1, contactin and neurofascin, along with PrPC, were recently identified to interact with APP in vivo, i.e. be components of the brain interactome of APP, while other proteins have been identified through genome-wide association studies. From these studies, it is evident that APP processing and Aβ generation can be modulated by a diverse number of interacting proteins in various cellular compartments. This modulation could involve direct binding to BACE1 or APP itself, thereby influencing enzyme activities or the susceptibility of APP to cleavage. Alternatively, the mode of action may be indirect, involving the segregation of the secretases and APP into either the same or different membrane domains or cellular compartments. The molecular and cellular mechanisms underlying the modulation of APP processing in this way clearly need to be understood in order to provide a complete knowledge of AD pathogenesis. The components of the APP and BACE1 interactomes could potentially be exploited therapeutically to modulate Aβ production.

Prion protein as a receptor for Aβ oligomers

Soluble oligomers of Aβ cause neurotoxicity, synaptic dysfunction and memory impairments which underlie AD. A plethora of Aβ assemblies have been isolated from natural sources and prepared synthetically, which vary in size and morphology, although which Aβ assemblies bind to PrPC and whether these correspond to pathologically relevant Aβ oligomers that are elevated in AD brains remains unclear. Using conformation-specific antibodies, we report that fibrillar Aβ oligomers recognised by the OC antibody, that have been shown to correlate with the onset and severity of AD, bind preferentially to human neuroblastoma cells expressing PrPC. The green tea polyphenol (-)-epigallocatechin gallate (EGCG) and the red wine extract resveratrol both re-modelled the fibrillar conformation of Aβ oligomers and reduced significantly their binding to PrPC-expressing cells. Further, EGCG and resveratrol neutralised the toxicity of fibrillar Aβ oligomers towards neuroblastoma cells expressing PrPC. These data indicate that a fibrillar conformation is required for the binding of Aβ oligomers to PrPC and suggest that remodelling Aβ oligomers may prevent the neurotoxicity arising from their binding to PrPC.

Prion protein is a novel zinc transporter

Zinc is released into the synaptic cleft upon exocytotic stimuli, although the mechanism for its reuptake into neurons is unresolved. Using zinc specific fluorescent dyes we report that PrPC enhances the uptake of zinc into neuronal cells. This PrPC-mediated zinc influx was dependent on the octapeptide repeats in PrPC but did not require the endocytosis of the protein. The PrPC-mediated zinc uptake was blocked by selective antagonists of AMPA receptors and PrPC interacted with both GluA1 and GluA2 subunits. Zinc-sensitive tyrosine phosphatase activity was decreased in cells expressing PrPC and increased in the brains of PrPC null mice, providing evidence of a physiological consequence of the process. Furthermore, this PrPC-mediated zinc uptake was ablated in cells expressing a range of familial prion disease-associated mutants of PrPC and in prion-infected cells, suggesting that this loss of zinc uptake may contribute to the neurodegeneration observed in prion diseases.

Publications

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