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Prion protein and Alzheimer disease

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Abbreviations: Aβ, amyloid-β peptide; AD, Alzheimer disease; AICD, amyloid intracellular domain; APP, amyloid precursor protein; BACE1, β-site APP cleaving enzyme-1; CJD, Creutzfeldt-Jakob disease; LTP, long-term potentiation; PrP^C, cellular form of the prion protein; PrP^{Sc}, infectious form of the prion protein; sAPPβ, soluble ectodomain fragment of APP after cleavage by β-secretase; TSE, transmissible spongiform encephalopathy

Alzheimer and prion diseases are neurodegenerative disorders characterised by the abnormal processing of amyloid-β (Aβ) peptide and prion protein (PrP^C), respectively. Recent evidence indicates that PrP^C may play a critical role in the pathogenesis of Alzheimer disease. PrP^C interacts with and inhibits the β-secretase BACE1, the rate-limiting enzyme in the production of Aβ. More recently PrP^C was identified as a receptor for Aβ oligomers and the expression of PrP^C appears to be controlled by the amyloid intracellular domain (AICD). Here we review these observations and propose a feedback loop in the normal brain where PrP^C exerts an inhibitory effect on BACE1 to decrease both Aβ and AICD production. In turn, the AICD upregulates PrP^C expression, thus maintaining the inhibitory effect of PrP^C on BACE1. In Alzheimer disease, this feedback loop is disrupted, and the increased level of Aβ oligomers bind to PrP^C and prevent it from regulating BACE1 activity.

Introduction

Alzheimer disease (AD) is the most common form of dementia which currently affects more than 37 million people worldwide.[1,2] The prevalence of AD will increase further with an aging population, bringing wide social and economic demands for the care and treatment of AD patients. AD is characterized pathologically by the formation of senile plaques composed of the amyloid-β (Aβ) peptide and neurofibrillary tangles composed of hyperphosphorylated Tau.[3] However, it is the accumulation of Aβ in the brain that appears to be critical for the pathogenesis of AD.

The prion protein (PrP) is involved in neurodegeneration via its conversion from the normal cellular form, PrP^C, to the infectious form, PrP^{Sc}, which is the causative agent of the transmissible spongiform encephalopathies (TSEs) including Creutzfeldt-Jakob disease (CJD).[4] While there is an established role for PrP^C in TSEs, the physiological role of PrP^C has still not been fully established; roles in metal homeostasis, neuroprotective signalling, lymphocyte activation, neurite growth, synaptogenesis, cellular signalling, cell viability and in the cellular response to oxidative stress have all been proposed (reviewed in ref. 5).

There are a number of neuropathological similarities and genetic links between AD and prion diseases. The coexistence of AD pathology in CJD has been reported[6] and PrP^C has been shown to co-localise with Aβ in plaques.[7] These compound PrP^C-Aβ plaques were shown to be present in most CJD patients with associated AD-type pathology[8] and it has been proposed that PrP^C may promote Aβ plaque formation.[9] A genetic correlation between PrP^C and AD has also been reported. A systematic meta-analysis of AD genetic association studies revealed that the gene encoding PrP^C (*PRNP*) is a potential AD susceptibility gene[10] and the Met/Val 129 polymorphism in *PRNP* has been reported to be a risk factor for early-onset AD.[8,11,12]

Until recently, although such pathological and genetic links between AD and PrP^C had been identified, there was no evidence of an interaction between the proteins involved in these diseases. However, in 2007 we reported an interaction between PrP^C and the rate-limiting enzyme in the production of Aβ, the β-secretase BACE1,[13] and more recently, two further studies have also found direct links; PrP^C has been reported to be a receptor for Aβ oligomers[14] and the expression of PrP^C is controlled by the amyloid intracellular domain (AICD).[15] In this review, we discuss these molecular and cellular links between AD and PrP^C and propose a model to encompass these recent findings.

Proteolytic Production and Degradation of Amyloid-β

Aβ is formed by the proteolytic processing of the amyloid precursor protein (APP) (**Fig. 1**).[16] The amyloidogenic pathway of APP processing involves the initial cleavage of APP by the β-secretase (BACE1; β-site APP cleaving enzyme-1), to release a soluble N-terminal fragment, sAPPβ. The residual short membrane-bound C-terminal fragment of APP (C99) is subsequently cleaved by the presenilin-containing γ-secretase complex to form Aβ and the amyloid intracellular domain (AICD). The amyloidogenic cleavage of APP results in a number of Aβ isoforms from 39–43 amino acids in length. Of these isoforms, $Aβ_{40}$ and $Aβ_{42}$ are the most commonly found. $Aβ_{42}$ is the more amyloidogenic isoform as it aggregates more readily and it is this isoform that is predominantly found in senile plaques. Aβ peptides can self-assemble into

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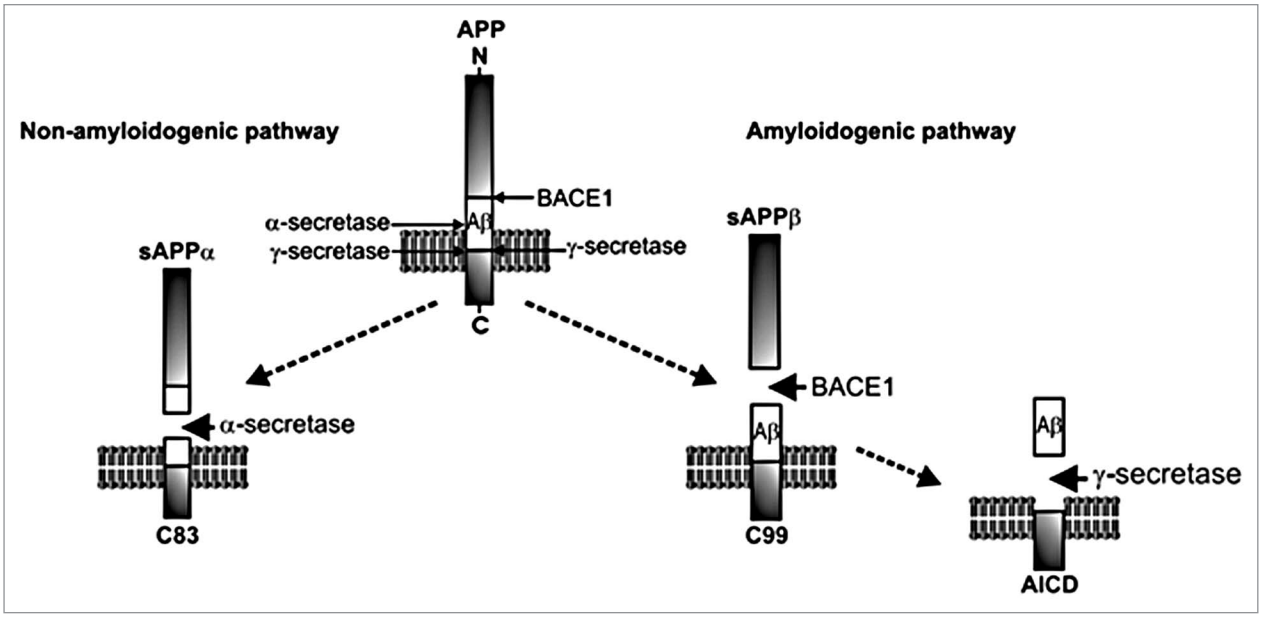

Figure 1. Proteolytic processing of APP. The amyloidogenic pathway involves the sequential cleavage of APP first by BACE1, producing sAPPβ and C99, and then by γ-secretase to release the amyloidogenic Aβ and the AICD. In the non-amyloidogenic pathway, α-secretase cleaves within the Aβ fragment, preventing the formation of Aβ peptides.

small soluble oligomers or larger protofibrils and fibrils. While monomeric Aβ is generally non-toxic, there is growing evidence that Aβ oligomers are responsible for the synaptic dysfunction that occurs in AD.[17-19] APP can alternatively be processed via the non-amyloidogenic pathway (**Fig. 1**) where the initial cleavage is by α-secretase, members of the ADAM (a disintegrin and metalloprotease) family.[16] This α-cleavage occurs within the Aβ region, thus precluding the formation of the Aβ peptide.

The amyloid cascade hypothesis, formulated in 1991,[20] implies that amyloid deposition is the central event in the progression of AD and therefore indicates that an understanding of the mechanisms involved in Aβ generation, degradation and clearance are critical to understanding the development of the disease. In normal brains, Aβ is degraded by multiple peptidases, including neprilysin, endothelin-converting enzyme and insulin-degrading enzyme.[21] While Aβ is commonly thought of as the main toxic agent in AD, there is emerging evidence of a normal physiological role for the peptide in the regulation of neuronal calcium and potassium channel currents.[22,23] This, therefore, indicates that Aβ should only be considered as a toxic agent when levels increase as a result of an imbalance in its production and degradation/clearance, such as occurs in AD.

In late-onset, sporadic AD the amyloidogenic processing of APP is increased as a result of increased BACE1 activity and protein levels.[24-26] As BACE1 is the rate-limiting step in Aβ production, an increase in the expression and activity of this protein will have a significant effect on Aβ levels. More recently, it has also been shown that γ-secretase activity may be enhanced in AD as presenilin-1 mRNA levels have been shown to be increased in AD brains.[27] In addition to increased Aβ production, the degradation of Aβ is decreased due a reduction in the levels of the Aβ-degrading enzymes. For example, insulin-degrading enzyme is decreased in the brains of AD patients[28] and more specifically in the hippocampus, an area primarily affected in AD[29] and neprilysin levels decline in brain areas affected by AD.[30]

PrP^C Regulates the β-Secretase Cleavage of APP

In 2007, we reported that PrP^C decreased the amyloidogenic processing of APP thereby decreasing Aβ levels.[13] Overexpression of PrP^C in a human neuroblastoma cell line decreased both sAPPβ and Aβ levels, while PrP^C depletion by siRNA in a murine neuroblastoma (N2a) cell line or by genetic knockout in mice resulted in increased Aβ levels. As the effect of PrP^C on APP processing was seen at the level of β-secretase cleavage, indicated by the change in sAPPβ levels, it was concluded that PrP^C mediates its effect on Aβ levels by decreasing the cleavage of APP by BACE1. We went on to investigate the mechanism involved in PrP^C inhibition of BACE1, and were able to determine that the interaction between PrP^C and BACE1 required localisation of PrP^C to cholesterol-rich lipid rafts, where BACE1 cleavage of APP preferentially occurs,[31,32] and found that the polybasic region at the extreme N-terminus of mature PrP^C possibly through interactions with glycosaminoglycans is critical for the interaction with BACE1. To study the effect of the Met/Val129 polymorphism in human *PRNP* on Aβ production, we utilized mice whose endogenous *Prnp* gene was replaced with the human *PRNP* harboring either the MM or VV 129 genotypes.[33] Interestingly, we found that there was a significant increase in the amount of $A\beta_{40}$ in the brains of the MM mice compared to the VV mice.[13] Further studies are required to determine whether a similar increase in Aβ occurs in humans homozygous for Met129 and if the polymorphism contributes to an increased risk of early onset AD.[12] Together our results indicated that PrP^C

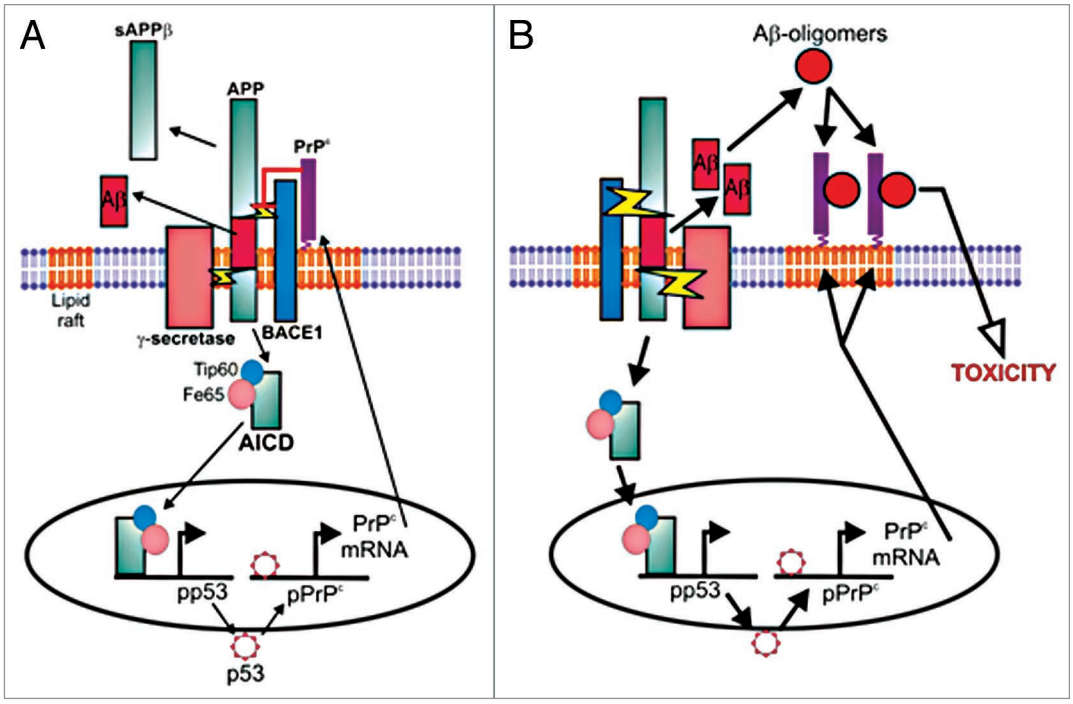

Figure 2. A model for the regulation of APP processing by PrP^C. (A) Aβ levels are kept in balance under physiological conditions via inhibition of BACE1 by PrP^C and regulation of PrP^C levels via AICD. (B) In AD, Aβ levels are increased as a result of increased production and/or decreased degradation and clearance resulting in the increased formation of Aβ-oligomers which are toxic via their interaction with PrP^C. The binding of the Aβ-oligomers to PrP^C may disrupt its regulation of BACE1, thereby further increasing APP processing and Aβ levels.

has a regulatory role in mediating Aβ production and suggested that PrP^C is protective against AD.[34]

p53-Dependent Transcriptional Control of PrP^C by Presenilins

Vincent et al.[15] recently reported a link between PrP^C expression and regulation by the presenilins, the catalytic subunits of the γ-secretase complex. The study revealed a direct link between γ-secretase activity and PrP^C mRNA levels and protein expression. The authors determined that the AICD, resulting from the γ-secretase cleavage of APP (**Fig. 1**), plays a role in the regulation of PrP^C expression. The mechanism proposed by the authors is that the AICD, in association with Tip60 and Fe65, translocates to the nucleus and acts as a transcription factor to regulate p53 expression. p53 was shown to regulate PrP^C at the transcriptional level by interacting with its promoter, resulting in changes in PrP^C mRNA and protein expression. Previous work by the same authors[35] and others[36] has reported that the AICD acts as a transcription factor and that one of its target genes is the Aβ-degrading enzyme neprilysin.

A Model for the Regulation of APP Processing by PrP^C—A Feedback Loop

Our work showing that PrP^C inhibits the β-secretase cleavage of APP and hence reduces Aβ production, along with the recent observation that the AICD from the γ-secretase cleavage of APP upregulates PrP^C expression, suggests that there might be a potential feedback loop to control Aβ production (**Fig. 2A**). PrP^C exerts an inhibitory effect on BACE1 to decrease the amyloidogenic processing of APP hence controlling both Aβ and AICD production. In turn, the amount of APP processing regulates the inhibitory effect of PrP^C on BACE1 via the AICD regulating PrP^C expression. Such a feedback loop would control Aβ production to maintain the balance between its production and degradation, so ensuring that there is adequate Aβ to maintain its normal physiological roles while preventing the toxicity that results from excessive Aβ. If the inhibitory effect of PrP^C on BACE1 is reduced, resulting in higher Aβ and AICD levels, the increased AICD would lead to increased expression of PrP^C, thus restoring the inhibition of BACE1 and lowering Aβ and AICD levels.

PrP^C Mediates Impairment of Synaptic Plasticity by Aβ Oligomers

Lauren et al.[14] recently reported the results from an expression cloning screen to identify potential binding sites for $A\beta_{42}$-oligomers. Two-independent positive clones isolated from a total of 225,000 clones revealed that the $A\beta_{42}$-oligomers bound to full-length PrP^C and further investigation indicated that PrP^C has high affinity and high selectivity for $A\beta_{42}$-oligomers. Purified recombinant PrP^C was shown to interact directly with $A\beta_{42}$-oligomers in a pull-down assay and the binding of synthetic $A\beta_{42}$-oligomers to neurons was shown to be decreased in PrP^C-null mice, suggesting

that PrP^C acts as a receptor for $A\beta_{42}$-oligomers. To determine the region of PrP^C involved in the interaction, several mutated forms of PrP^C were generated lacking specific domains; the results identified that a specific charge cluster region (amino acids 95–110) within the unstructured central region of PrP^C was the principal site for $A\beta_{42}$-oligomer binding. The critical role of this charge cluster region in binding $A\beta_{42}$-oligomers was confirmed using antibodies against specific epitopes of PrP^C. The authors also examined the effects of the interaction between PrP^C and $A\beta_{42}$-oligomers on long-term potentiation (LTP) using hippocampal slices from wild-type and PrP^C-null mice. Soluble $A\beta_{42}$-oligomers reduced LTP in the wild-type mice but not in the PrP^C-null mice, indicating that PrP^C is required to mediate one of the toxic effects of Aβ. This study concluded that there is a direct interaction between PrP^C and $A\beta_{42}$-oligomers and that this interaction affects synaptic plasticity. This suggests, therefore, that PrP^C mediates a toxic effect of the $A\beta_{42}$-oligomers and thereby plays an important role in the neurodegeneration associated with AD. The implication from this is that higher levels of PrP^C would be detrimental in AD as they would allow for further $A\beta_{42}$-oligomer interaction and thus greater neuronal toxicity, while a reduction in PrP^C levels would be protective.

Disruption in AD of the Feedback Loop by which PrP^C Regulates APP Processing

With the observation that PrP^C exerts a regulatory effect on Aβ production, it is perhaps surprising that it also may be a mediator of neuronal toxicity by acting as a receptor for $A\beta_{42}$-oligomers. So, does PrP^C have a protective role in AD or does it mediate the neuronal toxicity of Aβ? The identification of PrP^C as a regulator of BACE1 activity may reflect a physiological role for PrP^C to control Aβ generation in the 'normal' brain. The binding of $A\beta_{42}$-oligomers to PrP^C may be more reflective of the later stages of AD when Aβ levels are elevated in the brain.

As discussed above, in AD Aβ levels increase above that seen in age-matched normal brains, and specifically, $A\beta_{42}$ levels have been shown to increase in AD patients[37] which may result in an increased pool of $A\beta_{42}$ which can then aggregate to form toxic oligomers. These oligomers then mediate their toxic effects in part via PrP^C. In addition, the increased proteolytic cleavage of APP would also increase AICD generation which would further increase PrP^C levels providing more receptors for the $A\beta_{42}$-oligomers resulting in further cell toxicity (**Fig. 2B**). But why can't the increased level of PrP^C regulate the BACE1 cleavage of APP? One possibility is that binding of the $A\beta_{42}$-oligomers to PrP^C sterically prevents it from interacting with BACE1. Alternatively, binding of $A\beta_{42}$-oligomers may, for example, result in the removal of PrP^C from lipid rafts, through enhancing its endocytosis, thus preventing PrP^C from interacting with BACE1. The other possibility is that in the AD brain there is a disruption in the feedback loop by which the AICD normally upregulates PrP^C expression. In support of this latter possibility is the observation that the amount of PrP^C in the brains of AD patients was significantly lower than in age-matched controls.[38] (Whitehouse and Hooper NM, unpublished). A recent brief report[39] that showed a decrease of PrP^C in the hippocampus, frontal cortex and temporal cortex in AD would also appear to support this. However, the number of cases (two AD and three controls) was too small for statistical analysis and whether the AD cases were sporadic and appropriately age matched with the controls not reported. Like many biological changes that occur as a consequence of the pathologic cascade in AD, this reduction in PrP^C could simply be explained by downstream events associated with the neurodegeneration and further studies are required to clarify this.

Conclusions

The recent data reviewed here hints at two potential roles for PrP^C in AD: first, a role in the physiological regulation of APP processing via its interaction with BACE1; and second, a role in the pathological progression of AD by mediating Aβ toxicity by binding $A\beta_{42}$-oligomers. The feedback loop between PrP^C, BACE1, APP and AICD described here provides a model linking these recent observations. However, several questions remain to be answered, including what effect does $A\beta_{42}$-oligomer binding have on the functions of PrP^C, how do the levels of PrP^C compare in the brains of AD patients and age-matched controls, and what is the effect of altering PrP^C levels in mouse models of AD. Clearly understanding the molecular and cellular mechanisms involved in the interactions between PrP^C and APP/Aβ is crucial to our understanding of AD pathogenesis and warrants urgent further investigation.

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