Alzheimer’s and prion diseases: distinct pathologies, common proteolytic denominators

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Alzheimer’s and prion pathologies are often seen as distinct neurodegenerative diseases, particularly because the infectious character of some prion-associated pathology makes this stand apart from classical neurodegenerative, age-related syndromes. Are there specific common denominators that could link the two diseases? It appears that βAPP (β-amyloid precursor protein) and PrPc (cellular prion protein), the ‘guilty’ proteins involved in these pathologies, undergo protein-kinase-C-regulated proteolysis by identical proteases of the disintegrin family. This cleavage occurs in an analogous way, in the middle of the ‘toxic’ Aβ and PrPc106–126 domains of βAPP and PrPc, respectively. As these two sequences trigger similar caspase-dependent and -independent cascades, this proteolytic attack could be seen as an inactivating process aimed at clearing these endogenous ‘toxins’ and, thus, preventing the associated proteinaceous accumulation usually detected in affected brains. It is our opinion that targeting these disintegrins with specific ‘activators’ could be a suitable strategy to slow down, or even arrest, βAPP and PrPc-related aggregation and toxicity.

Alzheimer’s and prion pathologies are two lethal neurodegenerative diseases, characterized at the immunohistochemical level by extracellular lesions corresponding to proteinaceous deposits [1–5]. Both diseases can be either sporadic or of genetic origin [2,6–9]. In familial cases of Alzheimer’s disease, mutations in the genes encoding three distinct proteins – β-amyloid precursor protein (βAPP) [10–12] and presenilins 1 and 2 [13–15] – have been shown to lead to overproduction of β-amyloid peptides. These two parent peptides, of 40 to 42 amino acids, accumulate as the disease progresses and correspond to the main component of brain senile plaques [16,17]. Prion diseases are often (but not always) characterized by brain deposition of the prion protein (PrP) [18–20].

At first sight, Alzheimer’s and prion pathologies appear entirely distinct. Unlike Alzheimer’s disease, prion diseases can also be of infectious etiology [2], explaining the characteristically different frequencies with which these diseases occur. Whereas Alzheimer’s disease is the most common age-related syndrome, with about one in four people in their eighties being affected, cases of prion diseases remain extremely rare [4]. A second criterion that clearly distinguishes the two diseases is that the two major current hypotheses concerning their etiology and, in the case of prion diseases, mode of transmission. The ‘amyloidogenic’ hypothesis of Alzheimer’s disease states that initiation of the degenerative process is related to exacerbated production of the β-amyloid peptide [21]. This fragment is produced physiologically and its concentration is tightly controlled by biosynthesis and catabolism rates [16,22–24]. At equilibrium, the peptide is likely to remain below its threshold of solubility but mutations, certain environmental conditions or other effectors could alter this steady-state level of circulating peptide. This abnormal increase in the concentration of β-amyloid probably contributes to, at least, the initiation of the aggregation and degeneration process. In prion disease, it is thought that the pathogenic process is entirely related to transformation of the normal cellular prion protein (PrPc) into a protease-resistant and readily aggregated isoform, called PrPsc (scrapie prion protein) that could serve as a ‘matrix’ for further biophysical transformation [1,25].

Besides the drastic differences characterizing these diseases already discussed, close examination of the molecular events associated with βAPP and PrPc proteins allows striking analogies to be identified. First, both βAPP and PrPc are complex multi-domain proteins (Fig. 1) that bear potential toxic sequences (Aβ and PrPc106–126, respectively) [26,27]. Interestingly, Aβ and PrPc106–126 trigger similar macroscopic deleterious apoptotic phenotypes that seem to be associated with identical molecular pathways. Second, the ‘toxic domains’ of both βAPP and PrPc undergo a series of proteolytic attacks that are triggered by identical proteolytic activities and that are similarly regulated.

β-Amyloid peptide and 106–126-containing PrP fragments: common toxic mechanisms?

Several initial reports suggested that the Aβ [28–30] and PrPc106–126 [27,31] peptides could both trigger neurotoxicity and, later, be associated with apoptotic responses [32–34]. Before considering the putative mechanisms accounting for such phenotypes, some questions could legitimately be raised about the relevance of the PrPc106–126 peptide as a probe with which to delineate PrP-associated molecular dysfunction. Unlike Aβ, the PrPc106–126 fragment is never detectable in any physiological or pathological situations per se. However, a recent interesting paper showed that C-terminal PrP fragments that bear part or all the PrPc106–126 sequence at their N-terminus have different effects on intrinsic neurotoxicity in cultured neurons, indicating that PrPc106–126 could modulate PrP-related phenotypes even when embedded in its precursor, the PrPc protein [35].
Several reports indicate that both A\(\beta\) and PrP\(^{106-126}\) peptides could trigger not only caspase-dependent, but also caspase-independent, cell responses, and that the caspase-dependent activation could be dissociated from neurotoxic effects [36,37,39]. This suggests that both of these peptides might elicit an acute toxic response or, alternatively, modulate long-term caspase-dependent proapoaptotic phenotypes, which would be in agreement with the slowly progressing nature of their diseases.

Our aim here is not to provide an extensive review of the numerous studies concerning the cellular responses and dysfunctions elicited by the A\(\beta\) and PrP-related fragments. The preceding few statements merely point out the striking similarities between some of the caspase-associated cellular responses triggered by these peptides. It is, therefore, interesting to think that common proteolytic pathways could control A\(\beta\) and PrP\(^{106-126}\)-associated phenotypes. Two main proteolytic routes appear common to the two proteins. First, A\(\beta\) and PrP are both targeted by the proteasome for final clearance [45–47] (although the endosomal–lysosomal pathway remains the main catabolic routes of these proteins). This is probably the easiest way to rid the cells of putative toxicity associated with the A\(\beta\) and 106–126 domains. Second, any specific cleavage taking place within A\(\beta\) and PrP\(^{106-126}\) could be seen as an ‘inactivating’ proteolytic event. Here again, such breakdowns occur for both proteins and, in addition to being regulated by identical mechanisms, are performed by identical enzymes.

**Processing of A\(\beta\) and PrP: common alternative nonamyloidogenic pathways?**

Because autosomal mutations in the genes encoding two distinct types of protein, A\(\beta\) and the presenilins, exacerbated A\(\beta\) production in an identical way [16,17], the major contribution of this peptide to Alzheimer’s disease etiology seems more than likely. As a corollary, strategies aimed at slowing A\(\beta\) formation naturally led to the search for the proteases (\(\beta\)- and \(\gamma\)-secretases) responsible for the proteolytic attacks on A\(\beta\) that result in A\(\beta\) [48]. Hopefully, this should help in the design of highly specific and potent, biologically available inhibitors that could be used as therapeutic probes [49–52]. An alternative approach, that seems to have been underestimated, would be to target \(\alpha\)-secretase [53], another enzyme that acts on the middle of the A\(\beta\) domain of A\(\beta\) (Fig. 2). This enzyme is physiologically important, not only because it inhibits endogenous production of A\(\beta\), but also because it yields sAPP\(\alpha\), a naturally secreted product of A\(\beta\) (Fig. 2) that displays a large spectrum of beneficial biological functions [54,55]. Therefore, another tactic in the fight against Alzheimer’s pathology could be the activation of \(\alpha\)-secretase.

Interestingly, nature has developed endogenous mechanisms aimed at upregulating the \(\alpha\)-secretase pathway. Levels of sAPP\(\alpha\) are increased by phorbol...
ADAM (‘a disintegrin and metalloprotease’)10 appears to be involved mainly in the constitutive production of sAPPα [60–63], although it also participates in the regulated α-secretase pathway along with another disintegrin, ADAM17 (also called tumor-necrosis-factor α-converting enzyme) [61,64]. Prohormone convertase 7 (PC7), an intracellular activity involved in processing of polyprotein precursors [65], also appears to contribute to the constitutive α-secretase pathway, although probably upstream of the disintegrin activities. For example, PC7 could be involved in the maturation of ADAM10 [62], as indicated by our recent data showing that expression of PC7 does not increase sAPPα levels in ADAM10-deficient fibroblasts (F. Chedeville and B. Vincent, unpublished).

PrP is also processed in the normal brain and in cells in vitro [66–70]. The ‘normal’ cleavage of PrPc occurs inside the 106–126 ‘toxic’ core of the protein, leading to the formation of a 11–12 kDa product referred to as N1 (Fig. 2). This constitutive cleavage also has a regulated counterpart, as N1 formation can be increased upon treatment of various cell systems with agonists of the PKC pathway [69]. Of most interest, we have established that overexpression or deletion of the gene encoding ADAM10 increases or decreases the production of N1, respectively [71]. Furthermore, similar transfection and knock-out approaches has demonstrated that ADAM17 fully contributes to the PKC-mediated production of N1 [71]. Thus, both jAPP and PrP undergo a cleavage inside their ‘toxic’ domains in a constitutive and PKC-regulated manner, and in both cases, ADAM10 and ADAM17 appear to be involved in the constitutive and regulated pathways, respectively.

The participation of disintegrins in the processing of PrP is unexpected because ADAM proteases are ectoenzymes (i.e. transmembrane activities, displaying their catalytic site facing the extracellular space). Substrates of disintegrins are generally transmembrane proteins (e.g. jAPP; Fig. 1); PrPc is, to our knowledge, the first example of a glycosylphosphatidylinositol (GPI)-anchored protein that behaves as a substrate of ADAM10 and ADAM17 [59]. This is probably explained by the very loose specificity of these α-secretases [72], as also illustrated by the apparent lack of a linear motif in the targeted sequences of jAPP and PrPc (Fig. 3).

The interesting common feature is that cleavage by ADAM10 and ADAM17 takes place inside the ‘toxic’ domain of PrP and jAPP and, therefore, ADAM10 and ADAM17 could be seen as ‘nactivating’ enzymes. This hypothesis would imply that disintegrins act on PrP before its pathogenic conversion because such a biotransformation prior to catalysis would probably render PrP resistant to disintegrins and prevent the possibility of targeting these enzymes as a therapeutic strategy.

It is noticeable that in pathological conditions, both jAPP and PrP undergo exacerbated alternative cleavages upstream of the jβ or PrPc.
Prion protein (PrPC), respectively. The schematic representation of PrPC 106–126-associated deleterious phenotype, that these proteases could become the centre of a unifying theory [78], stating that all diseases linked to protein misfolding could be due to the inherent toxicity associated with protein aggregates [79].That protein aggregates could inhibit the proteasomal machinery responsible for final clearance per se [80] might be seen as a molecular dysfunction that could explain why the neurodegeneration is always an irreversible process that feeds itself. It is interesting to note that upstream of these events, common pathways can also be delineated for two apparently distinct diseases. That βAPP and PrP can be processed by identical proteases, in the same PKC-regulated manner, is unlikely to be coincidental. It is also a striking feature that these cleavage events occur in the middle of the ‘pathogenic cores’ of these proteins, thereby inactivating their ‘toxic potential’. One should not underestimate the potential side effects associated with inhibition of disintegrins but, although optimistic, the possibility that these proteases could become the centre of a strategy in which their activation lowers levels of Aβ and 106–126-PrP-containing peptides is far from being purely a dream.

Questions remain concerning the further parallel between βAPP and PrP processing events. First, both βAPP and prion proteins appear to interact with Cu²⁺, and this cation has recently been shown to affect α-secretase-mediated cleavage of βAPP [76]. It would be interesting to examine whether Cu²⁺ also modulates prion hydrolysis. Second, it would be interesting to examine whether, by analogy with the βAPP–β-secretase pathway, neuronal BACE1 [77] has something to do with the alternative ‘pathogenic’ cleavage of PrP. Third, does N1 have a biological function? More precisely, does it have a cytoprotective or neurotrophic sAPPα-like function? In other words, could disintegrins be seen as proteases that mediate maturation of PrP, the cleavage of which would liberate biologically active products as was demonstrated for production of sAPPα from βAPP?

Conclusion
Recent reports have suggested that some of the major neurodegenerative pathologies could be gathered under a unifying theory [78], stating that all diseases linked to protein misfolding could be due to the inherent toxicity associated with protein aggregates [79]. That protein aggregates could inhibit the proteasomal machinery responsible for final clearance per se [80] might be seen as a molecular dysfunction that could explain why the neurodegeneration is always an irreversible process that feeds itself. It is interesting to note that upstream of these events, common pathways can also be delineated for two apparently distinct diseases. That βAPP and PrP can be processed by identical proteases, in the same PKC-regulated manner, is unlikely to be coincidental. It is also a striking feature that these cleavage events occur in the middle of the ‘pathogenic cores’ of these proteins, thereby inactivating their ‘toxic potential’. One should not underestimate the potential side effects associated with inhibition of disintegrins but, although optimistic, the possibility that these proteases could become the centre of a strategy in which their activation lowers levels of Aβ and 106–126-PrP-containing peptides is far from being purely a dream.

References
Opinion


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