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Review

Protein aggregation and prionopathies

Agrégation de protéines et prionopathies

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ABSTRACT

Prion protein and prion-like proteins share a number of characteristics. From the molecular point of view, they are constitutive proteins that aggregate following conformational changes into insoluble particles. These particles escape the cellular clearance machinery and amplify by recruiting the soluble for of their constituting proteins. The resulting protein aggregates are responsible for a number of neurodegenerative diseases such as Creutzfeldt-Jacob, Alzheimer, Parkinson and Huntington diseases. In addition, there are increasing evidences supporting the inter-cellular trafficking of these aggregates, meaning that they are "transmissible" between cells. There are also evidences that brain homogenates from individuals developing Alzheimer and Parkinson diseases propagate the disease in recipient model animals in a manner similar to brain extracts of patients developing Creutzfeldt-Jacob's disease. Thus, the propagation of protein aggregates from cell to cell may be a generic phenomenon that contributes to the evolution of neurodegenerative diseases, which has important consequences on human health issues. Moreover, although the distribution of protein aggregates is characteristic for each disease, new evidences indicate the possibility of overlaps and crosstalk between the different disorders. Despite the increasing evidences that support prion or prion-like propagation of protein aggregates, there are many unanswered questions regarding the mechanisms of toxicity and this is a field of intensive research nowadays.

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RÉSUMÉ

La protéine prion et les protéines qui ont des propriétés de type prion partagent un certain nombre de caractéristiques. Du point de vue moléculaire, ces protéines constitutives s'assemblent en particules protéiques insolubles qui échappent à la machinerie cellulaire de dégradation des protéines à la suite de changements conformationnels. Ces particules s'amplifient par le recrutement de la forme soluble des protéines qui les constituent. Ces agrégats protéiques sont responsables d'un certain nombre de maladies neurodégénératives comme les maladies de Creutzfeldt-Jacob, d'Alzheimer, de Parkinson et de Huntington. De nombreuses évidences soutiennent la propagation de ces agrégats protéiques et suggèrent qu'ils sont « transmissibles » entre cellules. Il existe aussi des données qui montrent que des homogénats de cerveaux d'individus développant les maladies d'Alzheimer ou de Parkinson propagent ces maladies dans des animaux modèles tout comme les homogénats de cerveaux de patients développant la maladie de Creutzfeldt-Jacob. De ce fait, la propagation des agrégats protéiques de cellule à cellule pourrait être un phénomène générique qui contribue à l'évolution des maladies neurodégénératives ce qui pourrait avoir des conséquences importantes dans ces maladies. De plus, alors que la distribution des agrégats protéiques est caractéristique pour chaque maladie, de nouvelles évidences suggèrent un chevauchement/interférence de ces agrégats protéiques dans les différents désordres neurologiques. Malgré les nombreuses évidences qui soulignent l'importance de la propagation de type prion des agrégats protéiques impliqués dans les maladies neurodégénératives, il persiste de nombreuses questions sans réponses concernant les mécanismes à l'origine la toxicité de ces particules qui constitue à présent un domaine de recherche intense.

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1. Introduction

Several progressive neurodegenerative disorders are the consequence of protein misfolding and aggregation (reviewed in [1–3]). Indeed, Creutzfeldt-Jacob (CJD), Alzheimer (AD), Parkinson (PD) and Huntington diseases are associated with the aggregation of aberrantly folded proteins or imperfectly degraded peptides into insoluble amyloid polymers, which are highly ordered fibrilar aggregates with elevated β-sheet content. In a first step, these proteins aggregate into oligomers that are diffusible and non-fibrillar in nature. Further aggregation leads to larger polymers that compose the inclusion bodies or extracellular deposits (plaques) that characterize these disorders [4]. More importantly, once aggregated these proteins can grow and amplify by recruitment of their soluble counterparts [3–5]. According to the nucleated polymerization model, seeds composed of abnormally folded proteins template the conformational transition of soluble cognate proteins. This seeding capacity, together with the ability to grow indefinitely and the resistance to degradation, confer to amyloid fibrils the capacity to propagate and is central to the infectious protein (prion) concept.

The correlation between protein aggregation and pathology is undeniable. Even if the mechanisms through which these aggregates damage cells remain elusive, the pathologies are most likely due to a gain of toxic properties associated to misfolding [6,7]. The production of these aberrant protein conformers is favoured by chemical or environmental stress and countered by molecular chaperones and cellular proteolytic activities (reviewed in [8,9]). The age-related decline in protein homeostasis challenges the capacity of cells to counteract the accumulation of misfolded proteins. This may explain in part the late onset of amyloidosis [9]. The continued accumulation of misfolded proteins probably defies the capacity of the lysosomal and proteasomal clearance systems, promoting further protein accumulation and the development of a self-propagating cycle [10].

It is not clear whether fibrils and plaques are the toxic species in all neurodegenerative diseases or if they result from a defensive response aimed at protecting cells from more toxic oligomeric species. Even if the aggregation is common to several neurodegenerative diseases, the different proteins involved and their subcellular location probably leads to differences in the toxicity of the different aggregated forms. Notably, some large-order aggregates are extracellular (plaques in AD) and some others, intracellular (inclusion bodies in PD). Intracellular aggregates could be more toxic because of their ability to:

- sequester essential cellular components, in particular molecular chaperones;
- generate oxidative species;
- inhibit proteasomal activity [11].

The polypeptides responsible for AD, PD or Huntinton's disease are well known. Despite the differences between these polypeptides in terms of sequence and biosynthesis, the three diseases share surprisingly similar pathological pathways. In particular, neuronal degeneration spreads through interconnected brain regions [5,12–15]. This feature is compatible with a model where the misfolded proteins might spread from a site of onset to adjacent cells, recruiting their endogenously expressed counterparts to induce pathology throughout the nervous system [16]. The seeding of intracellular proteins assemblies requires seed export from affected cells and import by healthy cells. A few years back the idea that protein aggregates could penetrate inside cells was probably as heretic as the prion concept once was. However, there are increasing evidences that misfolded proteins are released in the extracellular medium and that they can enter cells (Table 1). Cells can release aggregates either by exocytic process or passively, either by local rupture of the membrane or after cell lysis [3]. Internalization mechanisms probably differ depending on the size and structure of the protein aggregate and on the cell-type. Tunnelling nanotubes (50–200 nm diameter hollow filaments linking cells) also constitute a passage route for protein aggregates [17,18].

The similarities between prions and other misfolded proteins responsible for neurodegenerative diseases make it tempting to consider all these proteins as prions. However, there is one crucial difference between prions and all other amyloids: prions are infectious agents that are transmissible between individuals. Other self-aggregating proteins have not been so far shown to propagate within communities and to cause macroepidemics such as Kuru and bovine spongiform encephalopathy. This is why they have been called "prionoids" [16] or prion-like [2,3,19] so far.

2. Prion diseases

Prion diseases, also called transmissible spongiform encephalopathies, are rare fatal neurodegenerative diseases with genetic, sporadic and acquired forms. They include bovine encephalopathy, scrapie and Creutzfeldt – Jakob disease in humans. These diseases are characterized by neuronal loss, gliosis and spongiform changes in the brain leading to dementia and ataxia (reviewed in [20–22]).

Prionopathies are tightly associated to the aggregation of a 23 kDa constitutive protein with unknown function named PrP. The key causative event in neurodegeneration is the conversion of the normal prion protein PrP^{C} into a disease-associated form that resists limited proteolysis, PrP^{Res}. The conversion process is thought to be autocatalytic and implies refolding and aggregation of PrP^{C} to form PrP^{Res} and/or the failure of quality control mechanisms for PrP^{Res} suppression or degradation [20]. This conversion, which is rare and certainly stochastic, takes place at the plasma membrane. After formation, PrP^{Res} is rapidly internalized [23] and either recycled to the plasma membrane or transported to the Golgi apparatus. During the early stages of prion infection PrP^{Res} is mostly cleared within the lysosomes [23]. The fraction of PrP^{Res} that escapes clearance persists in cells and templates PrP^{C} polymerization into amyloid fibrils and coalescence into plaques [20–24].

Prion diseases can be genetic, sporadic or infectious. Sporadic and genetic forms develop endogenously following the spontaneous

Table 1
Propagation of misfolded proteins associated with neurodegenerative diseases.

Pathology	Main implicated protein	Deposits	Localization of deposits	Trancellular propagation?	*In vivo* propagation?
Prion diseases	PrP^{res}	Amyloids	Extracellular	Yes [17,26,27]	Yes [19,20]
Parkinson disease	α-synuclein	Lewy bodies	Intracellular	Yes [38,41,45,49]	Yes [38,39,41]
Alzheimer disease	Amyloid β peptide	Amyloid plaques	Extracellular	Yes [72]	Yes [66,67,69–71]
Tauopathies	Tau	Neurofibrillary tangles	Intracellular	Yes [76,80]	Yes [78,79]
Amyotrophic lateral sclerosis	SOD1	Inclusion bodies	Intracellular	Yes [86]	Not reported
Huntinton disease	Htt with polyglutamine expansion	Inclusion bodies	Intracellular	Yes [93]	Not reported