Ligands binding to the prion protein induce its proteolytic release with therapeutic potential in neurodegenerative proteinopathies

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1. 簡述論文的概要與重大發現：

   神經退化性疾病主要是因為蛋白質的錯誤摺疊、蛋白質聚集、病理傳播的機制，在普利昂蛋白中糖磷脂醯肌醇是一種重要的細胞表面受體，可以用於富含 β sheets 胜肽或蛋白質的神經毒性寡聚物，其中包含 Scrapie form prion protein（PrP^{Sc}）、amyloid β (Aβ)、tau 及 α 突觸核蛋白是神經退化性疾病中的神經元功能障礙的媒介蛋白。

   ADAM10 為一種金屬蛋白酶，負責前類澱粉蛋白(amyloid precursor protein)的非類澱粉蛋白生成(none-amyloidogenic processing)的切割。ADAM10 刺激會削弱 Aβ 與神經元的結合進而降低毒性。本篇文章作者用不同的老鼠模型去了解 ADAM10 移除對小鼠腦中 Aβ 產生斑塊的影響，以及 ADAM10 的脫落機制。實驗結果發現 ADAM10 移除後小鼠腦中的斑塊明顯較少且蛋白酶的表達與感染普利昂病毒小鼠的存活時間有關。且經由不同抗體進行治療後發現 POM2 具有神經保護作用，因 POM2 有獨特的結合特性導致 PrP^{C} 在質膜上的聚集體聚集，隨後這些聚集的細胞會吸收進行溶酶體降解。

   Shed PrP(sPrP)與普利昂病毒的轉換成負相關，在普利昂病毒沈積物或澱粉樣斑塊存在的情況下，在小鼠腦中會重新分佈，表示有隔離活性。

2. 對論文內容的提問：

   作者在結論的地方提到 sPrP 與分泌 PrP dimer 相似，透過與 PrP^{Sc} 的 seeds 結合有助於阻止 PrP^{Sc} 的累積。但這與前面轉基因小鼠的實驗結果衝突，結果表示無錨的 PrP 很容易錯誤折疊到 PrP^{Sc} 中且會先沉積為斑塊。想問生理產生出的 sPrP 容易折疊的無錨 PrP 的差別在哪裡？

3. 論文的缺點及評價：

   本篇研究探討了蛋白酶水解的脫落機制及解決 6D11 抗體治療所衍生的毒性副作用的問題，且發現透過刺激 PrP^{C} 脫落可能是神經退化性疾病的一個有前景的標靶治療點。在目前的神經退會性疾病治療方面這是一個很好的發現。

CELLULAR NEUROSCIENCE

Ligands binding to the prion protein induce its proteolytic release with therapeutic potential in neurodegenerative proteinopathies

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The prion protein (PrP^C) is a central player in neurodegenerative diseases, such as prion diseases or Alzheimer's disease. In contrast to disease-promoting cell surface PrP^C, extracellular fragments act neuroprotective by blocking neurotoxic disease-associated protein conformers. Fittingly, PrP^C release by the metalloprotease ADAM10 represents a protective mechanism. We used biochemical, cell biological, morphological, and structural methods to investigate mechanisms stimulating this proteolytic shedding. Shed PrP negatively correlates with prion conversion and is markedly redistributed in murine brain in the presence of prion deposits or amyloid plaques, indicating a sequestrating activity. PrP-directed ligands cause structural changes in PrP^C and increased shedding in cells and organotypic brain slice cultures. As an exception, some PrP-directed antibodies targeting repetitive epitopes do not cause shedding but surface clustering, endocytosis, and degradation of PrP^C. Both mechanisms may contribute to beneficial actions described for PrP-directed ligands and pave the way for new therapeutic strategies against currently incurable neurodegenerative diseases.

INTRODUCTION

Neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), as well as less frequent prion diseases, not only share mechanisms of protein misfolding, protein aggregation, and progressive spreading of pathology (*1*, *2*) but also involve common molecular players (*3*, *4*). One example is the cellular prion protein (PrP^C), a highly conserved cell surface glycoprotein with high (yet not exclusive) expression in the nervous system (*5*).

Apart from its physiological functions, PrP^C plays a key role in prion diseases of humans [e.g., Creutzfeldt-Jakob disease (CJD)] and animals (e.g., chronic wasting disease in elk and deer and bovine spongiform encephalopathy in cattle). In these transmissible diseases, PrP^C misfolds into a pathogenic and partially proteinase K (PK)–resistant conformation (PrP^{Sc}) (*6*, *7*) due to either (i) a sporadic event, (ii) mutations in the coding *Prn-p* gene (causing genetic/familial disease forms), or (iii) contact with infectious "prions" (i.e., misfolded PrP species acting as "seeds" to template further PrP^C misfolding in acquired forms). More recently, glycosylphosphatidylinositol (GPI)–anchored PrP^C has emerged as an important cell surface receptor for neurotoxic oligomers of β sheet–rich peptides/proteins (*5*, *8*–*11*) such as PrP^{Sc} itself, amyloid β (Aβ), tau, and α-synuclein, which are all mediators of neuronal dysfunction found in neurodegenerative diseases such as prion diseases, AD, tauopathies, and PD, respectively (*11*, *12*). The plasma membrane is the primary site for the detrimental interactions of such extracellular toxic conformers with the disordered N-terminal part of signaling-competent PrP^C (*13*–*15*). This binding causes synapto- and neurotoxic signaling [enabled by certain transmembrane proteins associating with PrP^C (*16*, *17*)] and, in the case of PrP^{Sc} seeds, subsequent templated misfolding of native PrP^C. In prion diseases, the survival time is inversely correlated with PrP^C expression levels (*18*, *19*). For these reasons, approaches to lower total or cell surface PrP^C levels are considered as promising therapeutic options with potential benefit also in the other abovementioned protein misfolding diseases (*20*–*25*).

Notably, surface levels of PrP^C are tightly regulated by various cellular mechanisms (*26*). Among those is the proteolytic cleavage and extracellular release (shedding) by the metalloproteinase ADAM10 (*27*–*29*). The latter is yet another example of a protein with relevance in different proteinopathies: Acting as the main "α-secretase," ADAM10 is responsible for the non-amyloidogenic processing of the Aβ precursor protein (APP), thus competing with the generation

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