Title : Small soluble α-synuclein aggregates are the toxic species in Parkinson's disease

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Abstract and major discovery :

大小、結構和形態不相同的可溶性 α-synuclein 聚集體與帕金森氏症病患的神經元凋亡具有密切關連。然而，共存且異質性的聚集體難以各自分離，因此研究這些異質性聚集體的毒性也更加困難。在本篇論文中，使用一種穩定的 non-perturbative method 來按照大小分離異質性蛋白質聚集體。作者進行體外聚集反應實驗發現，該過程中所形成之長度小於 200nm 野生型 α-synuclein 聚集體會引起發炎反應和單層微質體膜的通透化，並證實尺寸較大的聚集體毒性反而較小。於本篇論文中作者提取死後人腦中可溶性聚集體加以研究，進一步證明死後人腦中可溶性聚集體之大小、結構都與實驗室模擬聚集反應所分離出的較小尺寸聚集體相似。此外 ，作者發現與對照組大腦相比，帕金森氏症病患大腦中的可溶性聚集體尺寸較小，大部分均小於 100nm，然而其所產生的發炎反應卻較嚴重。這篇論文證明，小的非纖維狀 α-synuclein 聚集體是造成神經發炎反應和促進帕金森氏症發展的關鍵因子。

Question :

圖7 結論為與對照組相比，PD 組的 soluble protein extracts aggregates 含有較多 smaller non-fibrillar aggregates ，然而圖7 G和H 所示super-resolution images 卻與結論相違背,作者沒有對此作出解釋，且作者進一步使用AFM images 分析後，結論中仍寫道「So the AFM and super-resolution data are in closer agreement.」，我認為可能是由於 PD 組大部分brain-derived aggregate 長度為 74 nm ,因此有較大機率會取得 74 nm 的 brain-derived aggregates，並且 brain-derived aggregates 複雜程度較高也有可能導致這個結果。另外最後的可能性為作者將對照組與PD組的super-resolution images 標示相反。

Criticize and critique :

本篇研究使用 non-perturbative method 生成 Oligomers，與人腦萃取出的α-synuclein aggregates 前期產生的Oligomers 性質較為接近，比起其他研究團隊所使用的 trapped Oligomers、添加 stabilizers 或 cross-linkers 所生成的 Oligomers 以及高濃度或突變的 α-synuclein，這個方式不需要添加額外的試劑或使用突變體，受干擾的程度較小，因此更符合實際情形，並有助於了解α-synuclein 聚集過程中各個聚集體種類的毒性，也許可以進一步找出更有效的治療方法以及早期檢測方式。

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Small soluble α-synuclein aggregates are the toxic species in Parkinson's disease

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Soluble α-synuclein aggregates varying in size, structure, and morphology have been closely linked to neuronal death in Parkinson's disease. However, the heterogeneity of different co-existing aggregate species makes it hard to isolate and study their individual toxic properties. Here, we show a reliable non-perturbative method to separate a heterogeneous mixture of protein aggregates by size. We find that aggregates of wild-type α-synuclein smaller than 200 nm in length, formed during an in vitro aggregation reaction, cause inflammation and permeabilization of single-liposome membranes and that larger aggregates are less toxic. Studying soluble aggregates extracted from post-mortem human brains also reveals that these aggregates are similar in size and structure to the smaller aggregates formed in aggregation reactions in the test tube. Furthermore, we find that the soluble aggregates present in Parkinson's disease brains are smaller, largely less than 100 nm, and more inflammatory compared to the larger aggregates present in control brains. This study suggests that the small non-fibrillar α-synuclein aggregates are the critical species driving neuroinflammation and disease progression.

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer's disease, affecting up to 3% of the population over the age of 65[1]. PD is initially characterized by the irreversible damage to dopaminergic neurons in the substantia nigra that correlates with motor symptoms including bradykinesia, rigidity, and tremor; but more widespread pathology in limbic and cortical regions evolves over the disease course and is linked to a range of non-motor features[2–4]. Post-mortem brain analysis has shown the presence of proteinaceous inclusions, often referred to as Lewy bodies, which primarily contain aggregated α-synuclein[5]. Although, a recent paper identified disintegrated membranes and organelles as the main constituents of Lewy bodies rather than α-synuclein[6]. Lewy bodies are found within the substantia nigra as well as in other subcortical and cortical regions to a variable extent[7]. Their presence in limbic and cortical regions correlates with the development of PD-associated dementia[8]. During an aggregation reaction, α-synuclein monomers convert intracellularly into various sizes, structures, and morphologies over time[9–12]. All these different α-synuclein species coexist, making it challenging to identify the toxic species in complex human biofluids and tissues[13]. Previous studies have shown the small soluble prefibrillar

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