Title : Age-dependent formation of TMEM106B amyloid filaments in human Brains

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Abstract and major discovery :

許多年齡依賴性神經退化性疾病都具有富含的澱粉樣細絲內涵物的特性,像是阿茲海默症及帕金森氏症,絲狀內涵物以tau蛋白、β-澱粉樣蛋白、α 突觸核蛋白和反式反應 DNA 結合蛋白（TARDBP；也稱為TDP-43）最為常見。在本文，我們透過低溫電子顯微鏡進行結構測定以呈現出溶酶體第II 型跨膜蛋白106B (TMEM106B)之第120-254個氨基酸也會在人腦中形成澱粉樣蛋白絲。藉由22名具有豐富澱粉樣蛋白沉積物之個體的多個腦區，包括由散發性和遺傳性tau蛋白疾病、澱粉樣蛋白-β澱粉樣蛋白疾病、突觸核蛋白疾病和TDP-43蛋白疾病引起的個體，以及3名神經功能正常且沒有或僅有少量澱粉樣蛋白沉積物之個體的額葉皮層確定了TMEM106B細絲的結構。本文觀察到TMEM106B具有三種折疊態樣，折疊態樣與疾病之間沒有明確的關係。透過抗體對TMEM106B的羧基末端區域具有特異性所檢測到的結果表明，TMEM106B細絲與29-kDa肌氨酸不溶性片段和球狀細胞質內涵物之存在具有相關性。在年齡較年長而非年輕且其神經功能正常之個體大腦中進行TMEM106B細絲鑑定，結果表明細絲以年齡依賴性方式形成。

Question :

文獻中表一所統計之TMEM106B細絲百分比僅為TMEM106B細絲預測,無法證實是否為腦內真實狀態，此外，圖二中神經功能異常之個體經由immunoblotting後雖發現15歲之個體不存在TMEM106B細絲但是其他年齡之個體均有該細絲，因此應無法直接表明TMEM106B細絲之堆積必然不會導致其他蛋白質堆積進而產生疾病,縱使在神經正常之年老個體腦內發現TMEM106B細絲存在亦有可能是尚未產生其他蛋白質沉澱之前驅時期。

Criticize and critique :

由圖二可知神經功能正常且幾乎無其他蛋白質堆積之46歲以上個案大腦內TMEM106B細絲堆積情形隨年齡增長而有增加之趨勢，可以證明年齡增加與TMEM106B細絲之堆積有正向關係。間接表明TMEM106B之堆積與神經退化性疾病之間的關聯性仍有待確定。

Article

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Many age-dependent neurodegenerative diseases, such as Alzheimer's and Parkinson's, are characterized by abundant inclusions of amyloid filaments. Filamentous inclusions of the proteins tau, amyloid-β, α-synuclein and transactive response DNA-binding protein (TARDBP; also known as TDP-43) are the most common[1,2]. Here we used structure determination by cryogenic electron microscopy to show that residues 120–254 of the lysosomal type II transmembrane protein 106B (TMEM106B) also form amyloid filaments in human brains. We determined the structures of TMEM106B filaments from a number of brain regions of 22 individuals with abundant amyloid deposits, including those resulting from sporadic and inherited tauopathies, amyloid-β amyloidoses, synucleinopathies and TDP-43 proteinopathies, as well as from the frontal cortex of 3 individuals with normal neurology and no or only a few amyloid deposits. We observed three TMEM106B folds, with no clear relationships between folds and diseases. TMEM106B filaments correlated with the presence of a 29-kDa sarkosyl-insoluble fragment and globular cytoplasmic inclusions, as detected by an antibody specific to the carboxy-terminal region of TMEM106B. The identification of TMEM106B filaments in the brains of older, but not younger, individuals with normal neurology indicates that they form in an age-dependent manner.

TMEM106B is a type II transmembrane protein of 274 residues that localizes to late endosomes and lysosomes[3,4]. It is expressed ubiquitously, with the highest levels in the brain, heart, thyroid, adrenal and testis[5] (https://www.proteinatlas.org). Reminiscent of the amyloid precursor protein APP, TMEM106B is sequentially processed through ectodomain shedding, followed by intramembrane proteolysis, with possible variability in the intramembrane cleavage site. Lysosomal proteases have been implicated in the cleavage of TMEM106B in the C-terminal luminal domain, but no specific enzymes have been identified. Although the cleavage site is unknown, it has been shown indirectly to be at a position close to G127. The resulting C-terminal fragment contains five glycosylation sites at N145, N151, N164, N183 and N256. Following shedding of the ectodomain, the N-terminal fragment is cleaved by signal peptide peptidase-like 2a (SPPL2a), possibly at two different sites around residue 106 (ref. [6]).

Genetic variation at the *TMEM106B* locus has been identified as a risk factor for frontotemporal lobar degeneration with TDP-43 inclusions (FTLD-TDP), especially for individuals with granulin (*GRN*) gene mutations[7]. The change of T185 to serine (encoded by rs3173615) has been suggested to protect against FTLD-TDP (ref. [8]), possibly because the protein with a serine is more rapidly degraded[9]. In addition, the protective effects of the noncoding variant rs1990622 have been attributed to reduced expression of TMEM106B (refs. [7,8]). Levels of TMEM106B are elevated in FTLD-TDP (ref. [10]). TMEM106B has also been reported to be involved in other diseases[3,4]. Genome-wide association studies have also implicated *TMEM106B* in age-associated phenotypes in the

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