

Previews

Flying under the radar: TMEM106B(120–254) fibrils break out in diverse neurodegenerative disorders

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Neurodegenerative diseases commonly exhibit aggregation of specific proteins that define each disease. Chang et al. (2022) establish that a C-terminal fragment of TMEM106B, a frontotemporal-lobar-degeneration risk factor, unexpectedly forms amyloid fibrils with similar structures in diverse neurodegenerative disorders. These unanticipated TMEM106B(120–254) fibrils may herald etiological shifts for several neurodegenerative diseases.

Deleterious protein aggregation is a pathological hallmark of many neurodegenerative disorders (Chuang et al., 2018). The commonly held model suggests that different disorders or classes of disorders are characterized by the aggregation of distinct proteins. For example, in TDP-43 proteinopathies, such as frontotemporal lobar degeneration (FTLD-TDP), TDP-43 forms cytoplasmic aggregates in degenerating neurons. Likewise, in synucleinopathies such as dementia with Lewy bodies (DLB), α -synuclein forms cytoplasmic inclusions, and in tauopathies such as progressive supranuclear palsy (PSP), tau forms cytoplasmic aggregates. The aberrant assembly of these proteins contributes to the respective diseases through loss- or gain-of-function toxicity, or both (Chuang et al., 2018). In this issue of *Cell*, Chang et al. unexpectedly identify a C-terminal fragment of transmembrane protein 106B (TMEM106B) that aggregates in specific TDP-43 proteinopathies, synucleinopathies, and tauopathies (Chang et al., 2022).

In search of a structural understanding of TDP-43, α -synuclein, and tau in disease aggregates, Chang et al. isolated insoluble protein fibrils from postmortem human brain tissue of FTLD-TDP, DLB, and PSP patients (Chang et al., 2022). Surprisingly, however, cryoelectron microscopy (cryo-EM) revealed a common fibril type across these disparate diseases that was not composed of TDP-43, α -synuclein, or tau. Mass spectrometry was leveraged to winnow proteins that might constitute the fibrils. By mapping the cryo-EM

density maps to these protein sequences, the fibrils were found to be formed by residues 120–254 of TMEM106B (Chang et al., 2022). Thus, rather than finding abundant TDP-43, α -synuclein, or tau fibrils as expected, TMEM106B(120–254) fibrils emerged as a major aggregated species across diverse neurodegenerative proteinopathies. Two recent *Nature* papers reinforce this surprising conclusion (Jiang et al., 2022; Schweighauser et al., 2022). Somehow, these abundant TMEM106B(120–254) fibrils had escaped notice in several devastating neurodegenerative disorders.

TMEM106B is no stranger to neurodegenerative disease and cognitive decline. Indeed, TMEM106B variants are FTLD-TDP risk factors (Van Deerlin et al., 2010). Moreover, TMEM106B risk variants are connected with neuronal loss and cognitive deficits in individuals older than 65, even in the absence of brain disease (Rhinn and Abeliovich, 2017). This finding may help explain why TMEM106B(120–254) fibrils can also be found in some older individuals without brain disease (Schweighauser et al., 2022). Nonetheless, the discovery of TMEM106B(120–254) fibrils in diverse neurodegenerative disorders now connects proteolytic processing and misfolding of TMEM106B to neurodegeneration (Chang et al., 2022; Jiang et al., 2022; Schweighauser et al., 2022).

TMEM106B is an integral type II transmembrane protein with an N-terminal cytoplasmic domain, a transmembrane domain, and a C-terminal domain in the

lysosomal lumen (Figures 1A and 1B) (Lang et al., 2012). TMEM106B localizes to late endosomes and lysosomes in neurons and is involved in several aspects of lysosomal function, including lysosomal pH and trafficking (Feng et al., 2021). Future studies in powerful model systems will help determine whether TMEM106B(120–254) fibrils elicit loss- or gain-of-function toxicity and whether TMEM106B(120–254) fibrils induce lysosomal dysfunction. Indeed, loss of TMEM106B function is anticipated to contribute to neurodegeneration (Feng et al., 2021, 2022). Future studies will help reveal whether TMEM106B(120–254) fibrilization plays a causal role in disease or whether it is a downstream consequence of disease cascades or normal aging.

Two subtypes of TMEM106B(120–254) fibrils were identified: singlets and doublets (Chang et al., 2022). Singlets contain one protofilament, whereas doublets consist of two protofilaments with 2-fold symmetry. Singlets and doublets were found in individual cases, and the predominant subtype varied. Cryo-EM density maps were constructed to high resolution for both singlet (3.0 Å) and doublet (2.7 Å) fibrils. For both subtypes, the N terminus of the protofilament resides near the center of the fibril core. The protofilament loops around, forming a three-layered fold with the C terminus near the N terminus (Figure 1C). Throughout the protofilament there are 19 β -strands, a large increase from the 8 predicted by Alpha-Fold for the native structure (Chang et al., 2022; Jumper et al., 2021).



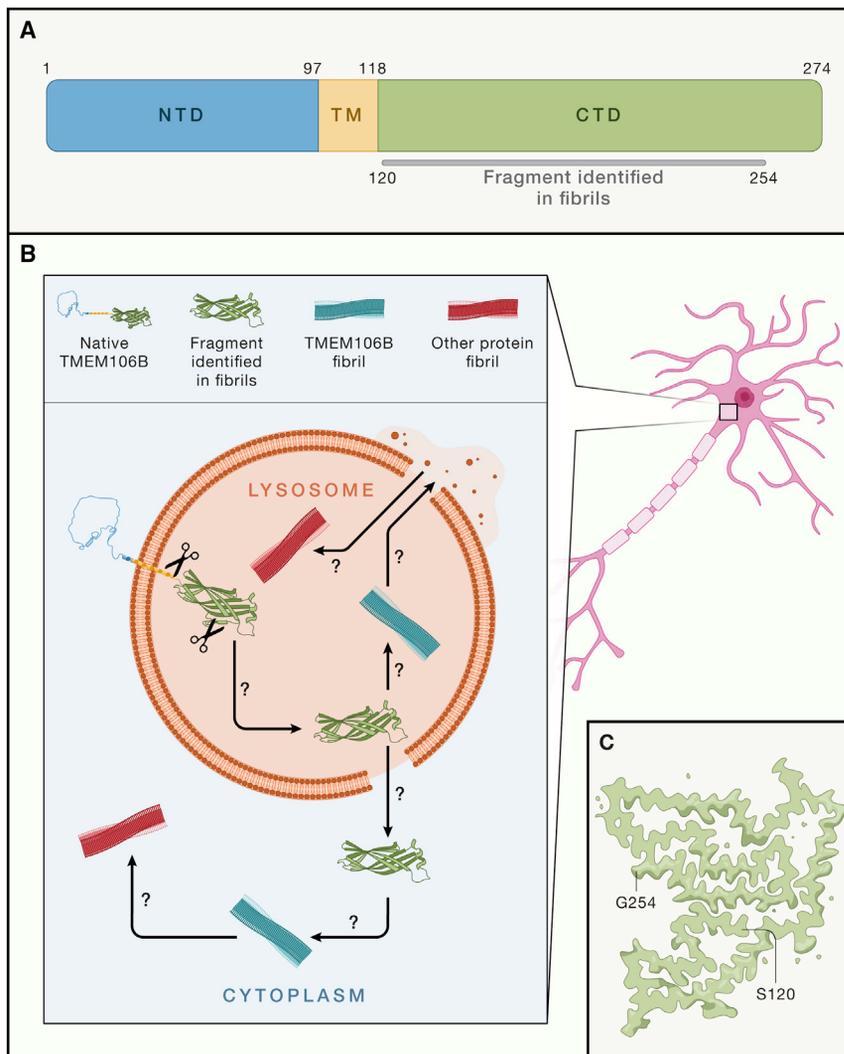


Figure 1. TMEM106B(120–254) forms amyloid fibrils in diverse neurodegenerative disorders

(A) Domain map of full-length TMEM106B. TMEM106B is composed of an N-terminal domain located in the cytoplasm (NTD; blue), a transmembrane domain (TM; yellow), and a C-terminal domain located in the lysosomal lumen (CTD; green).

(B) Hypothesized TMEM106B cleavage and downstream effects occurring within a neuron. The native TMEM106B is the predicted structure of full-length TMEM106B from Alpha-Fold (Jumper et al., 2021), colored corresponding to the domain map in (A). Native TMEM106B may be cleaved at two sites to generate TMEM106B(120–254). TMEM106B(120–254) may form fibrils within the lysosome, potentially leading to lysosomal impairment. Lysosomal impairment may also contribute to the accumulation of fibrils or aggregates of other proteins (e.g., TDP-43). TMEM106B(120–254) may leak out of the lysosome into the cytoplasm before or after forming fibrils. Cytoplasmic TMEM106B(120–254) may stimulate fibrillization of other disease-linked proteins.

(C) Cryo-EM map of TMEM106B(120–254) fibrils from FTLD-TDP patient brain tissue. The first (S120) and last (G254) residues of the protofilament are indicated. Adapted from Figure S4 from Chang et al., (2022).

Although most TMEM106B(120–254) fibrils displayed the same structure, molecular polymorphs were identified. The main alternative conformer retains similar shape, relative termini locations, and number of β -strands. However, the conformer is more twisted and compact, with alterations in β -strand alignment

and side-chain interactions (Chang et al., 2022). It will be important to determine whether TMEM106B(120–254) fibril polymorphs exert different effects on neuronal health.

Additional molecules are striking features of TMEM106B(120–254) fibril architecture (Chang et al., 2022). Asparagine

glycosylation (N-glycosylation) in the CTD of TMEM106B ensures correct localization to the lysosome (Lang et al., 2012). Based on the cryo-EM fibril structure, four sites in the CTD are N-glycosylated, indicating that TMEM106B(120–254) fibrils originate from mature protein within the endomembrane system. Another molecule of interest is an unknown cofactor that interacts with residues K178 and R180, connecting the two protofilaments of the doublet fibril (Chang et al., 2022). Identification of this cofactor may provide insight into the varied proportions of singlet versus doublet fibrils between individuals. Precisely how N-glycosylation or this cofactor might alter TMEM106B(120–254) fibrillization and structural polymorphism warrants further study.

The occurrence of TMEM106B(120–254) fibrils across diverse neurodegenerative disorders is striking. However, whether TMEM106B(120–254) fibrils are pathogenic, benign, or even protective remains unclear. Immunoblots revealed that high-molecular-weight TMEM106B species were elevated in patients versus controls (Chang et al., 2022). Thus, aberrant forms of TMEM106B may be disease linked outside of normal aging or contribute to age-dependent neurodegeneration. However, the antibody employed recognizes an epitope not specific to the fibril. Development of antibodies that recognize fibrillar TMEM106B(120–254) will be crucial to assess fibril levels in patients versus controls (Chang et al., 2022). Immunohistochemistry of brain sections with an antibody raised against residues 239–250 of human TMEM106B revealed abundant globular cytoplasmic inclusions and neuronal processes in disease cases and older individuals but not in younger individuals (Schweighauser et al., 2022). Thus, TMEM106B(120–254) inclusions can be found in the brain and are unlikely to be an artifact of the extraction process.

Numerous questions concerning TMEM106B remain to be explored. How TMEM106B is cleaved to yield the fibrillogenic fragment is unclear. Several candidate proteases have been proposed, but experimental validation is needed (Chang et al., 2022). Protease inhibition could serve as a therapeutic avenue if TMEM106B(120–254) fibrils are damaging. Likewise, it may be important to define therapeutic agents to prevent and

reverse TMEM106B(120–254) fibrillization (Chuang et al., 2018).

Finally, evaluating TMEM106B(120–254) interactions with TDP-43, tau, or α -synuclein will be intriguing (Chang et al., 2022). For example, it will be enlightening to establish whether TMEM106B(120–254) promotes TDP-43, tau, or α -synuclein fibrillization. Clearly, the precise relationship between TMEM106B, neurodegeneration and aging remains to be fully defined. Nevertheless, the emergence of TMEM106B(120–254) fibrils in diverse neurodegenerative disorders is an important finding, which may enhance our understanding of disease and empower the development of new therapeutics.

DECLARATION OF INTERESTS

K.E.C. has nothing to declare. J.S. is a consultant for Dewpoint Therapeutics, Vivid Sciences, Neumora, Korro Bio, and ADRx.

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Bacteria in tumors “hit the road” together

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Tumors contain bacteria, but the functional significance of this tumor microbiota is not appreciated. Fu et al. show that bacteria within breast tumor cells contribute to metastasis, in part, by enhancing tumor cell survival to mechanical fluid shear stress as would be found in the circulation.

Infectious agents, or associated chronic inflammatory states, are known to be associated with cancer incidence. The gut bacterial microbiome can affect cellular transformation (e.g., *Helicobacter pylori*), tumor growth, progression, and response to therapies of mostly gastrointestinal (GI) malignancies (Helmink et al., 2019). But tumors at a distance from the GI tract also contain bacteria, albeit at a very low biomass. The functional signifi-

cance of this intratumor bacteria is largely unknown. In this issue of *Cell*, Fu et al. investigate their role in the well-studied mouse spontaneous model of breast cancer: MMTV-PyMT (Fu et al., 2022). They demonstrate that breast tumor-associated bacteria are viable, distinct from breast tissue bacteria, and that the majority are in the cytosol of tumor cells. Very few tumor-associated immune cells contained bacteria. Using

multiple approaches to deplete or replete bacteria in tumors, they find that the presence of tumor bacteria positively impacts metastatic progression without affecting primary tumor growth. These exciting new functional studies beg questions regarding where, when, and how bacteria impact the metastatic process.

Cancer metastasis is, fortunately, an inefficient process (Massagué and Obenauf, 2016). Many tumor cells exit primary

