Misfolded amyloid-β strains and their potential roles in the clinical and pathological variability of Alzheimer’s disease

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Potential causes for the clinical and pathological variability observed in Alzheimer’s disease (AD): AD is an age-related neurodegenerative disorder characterized by the impairment of cognitive functions such as memory, learning, and reasoning. These commonly described clinical symptoms are due to particular pathological changes in the brain, including inflammation, synaptic loss, and neuronal death. These changes are a consequence of the accumulation of abnormally folded amyloid-β (Aβ) and tau proteins in specific areas of the central nervous system.

Consider the aggregating of the world’s population, the number of people affected by AD is expected to substantially and consistently increase in the coming years. This positions AD as one of the main public health challenges in the near future.

It is important to note that AD is clinically and pathologically diverse. For example, some of the clinical manifestations of the disease, such as the age of disease onset, the rate of cognitive decline, and the duration of the disease can vary among patients. Additionally, variability in AD pathology can be found in the degree of atrophy in the patients’ brains as evaluated by imaging techniques (Zhang et al., 2016), dissimilarities in plaque morphology (Thal et al., 2015), or PrPSc in susceptible mice through either intra-cerebral or peripheral routes of exposure (Morales et al., 2021) and induce pathology in mice that do not typically express amyloidosis (Morales et al., 2012). Interestingly, misfolded Aβ structures seem to be polymorphic, and hence in different conformations or “strains”. As mentioned above, this resembles the case of prion strains, which are associated with different clinical and pathological manifestations (Morales, 2017). In addition to the clinical and pathological divergence they induce, Aβ aggregates can be differentiated by their specific biochemical properties, such as resistance to proteolysis, conformational stability, seeding activity, and size distribution of aggregates, and many other features (Morales, 2017). Analogous properties have been identified for disease-associated Aβ in vitro and in vivo systems (Petkova et al., 2005; Eisenberg and Jucker, 2012; Makowski, 2020; Lau et al., 2021). However, the biological significance of these “Aβ strains” has not yet been elucidated.

Current evidence supporting the existence of pathological Aβ strains is summarized in the following section.

Conformational variation in misfolded Aβ and links with AD pathological and clinical diversity: Brain Aβ deposition is a distinctive feature of AD and it is attributed as an early change triggering tau accumulation, brain inflammation, synaptic loss, and neuronal death. As discussed above, Aβ aggregates in AD brains can be found in a variety of arrangements, including intra-cellar aggregates, diffuse plaques, vascular deposits, soluble Aβ oligomers, dense-core senile plaques, and many others (Thal et al., 2015). These different morphological deposits are reminiscent of tau inclusions seen in different tauopathies (Clavaguera et al., 2013) or PrPSc deposits induced by different prion strains (Morales, 2017). Considering this, it is plausible that the different Aβ deposits observed within and across AD patients could be composed by conformationally different misfolded Aβ aggregates.

Aβ strains can self-propagate in vitro and in vivo systems, similar to how bona fide prion strains do (Castilla et al., 2008). Early experiments by Petkova et al. (2005) that used purified/synthetic Aβ peptides were able to produce two different misfolded fibrillar polymorphs through different aggregation protocols. These misfolded Aβ aggregates, which are extensively characterized for their conformational motifs at the atomic resolution level, were the first evidence demonstrating that Aβ is able to self-propagate different disease-associated conformation.

This fact was later confirmed by several other experiments using susceptible animal models overexpressing mutated forms of the human Aβ precursor protein. Specifically, brain-derived or synthetically generated Aβ aggregates were shown to differentially propagate in susceptible animals (reviewed in Lau et al., 2021). Although these experiments confirmed the initial report using synthetic peptides (Petkova et al., 2005), they largely failed in exploring the biological significance of Aβ strains in a disease context.

More recently, some studies suggest that the conformational stability and size distribution of Aβ aggregates are responsible for rapidly progressive or slowly progressive disease phenotypes (Cohen et al., 2015). Follow-up studies by the Tycko’s group have demonstrated that amyloid deposits derived from different AD patients are associated with conformationally different Aβ fibrils (Qiang et al., 2017). Future research is needed to clarify whether conformational variants of Aβ activate specific disease pathways, and thus lead to pathologically and clinically variable AD.

A recent report from our group used AD patient brains with differing amyloid pathology to demonstrate that their misfolded Aβ seeds were able to induce diverse pathological traits in susceptible mice (Figure 1; Duran-Aniotz et al., 2021). In summary, this study included APP/PS1 transgenic mice inoculated with brain homogenates from patients diagnosed with AD dementia. However, the patients displayed a diverse array of pathological features, which may reflect clear differences in the Aβ deposits, such as the shape, distribution, reactivity to amyloid-binding dyes, and tropism to blood vessels were observed. Interestingly, these differences were reminiscent of the strain-specific pathological features observed in the brains of people affected by different strains of infectious prions. Most of the AD-brain treated APP/PS1 mice displayed significant amyloid burdens compared to control groups, however, the induced pathology was dependent on the specific inoculum used. Notably, differences seen in the same parameters listed above are still recorded in treated mice. This strongly suggests that the Aβ seeds present in the diseased individuals are responsible for the variable pathological outcomes observed between them. In turn, this may explain the clinical differences largely reported across individuals afflicted by this specific type of dementia.

Tauopathies involve conformational variants of misfolded proteins: Hyperphosphorylated-misfolded tau is an important contributing factor in AD. It is widely accepted that cognitive decline correlates more directly with tau rather than amyloid pathology. In that sense, differences at the tau level need to be considered when trying to explain clinical variation in AD.

Tau is involved in several clinically diverse diseases that are known as tauopathies. Importantly, tauopathies are associated with abnormally arranged tau that propagates disease-specific features in susceptible hosts (Clavaguera et al., 2013). These pathological differences observed across tauopathies may be due to the different tau isoforms preferentially recruited in each disease, among other factors. Recent reports show that these clinically variable tauopathies are actually linked with different structures of misfolded tau (Shi et al., 2021). These experiments demonstrate the conformational plasticity of misfolded tau.
proteins, and strongly suggest an active role of tau polymorphs across tauopathies. Whether tau conformational differences contribute to AD features needs to be evaluated in future studies.

Conclusions and perspectives: It is now widely accepted that misfolded Aβ and tau proteins spread in a manner akin to that of prions. In that sense, several properties of infectious prions have been attributed to these proteins. Among them, both disease co-occurrence and tau aggregation appear to adopt different conformations, reminiscent of prion strains in prion diseases (Morales, 2017). Considering the variable clinical manifestation observed among AD individuals, it is plausible that differences in the conformation of misfolded Aβ proteins may explain why this is occurring. There is compelling evidence suggesting that different tauopathies are associated with different conformations of the tau protein (Shi et al., 2021). Changes in Aβ conformation have also been shown between AD patients (Qiang et al., 2017). Whether clinical variation in AD is due to misfolded protein strains, and whether these differences are encoded in Aβ, tau, or both proteins, is still unknown.

Considering Aβ misfolding as one of the earliest events in AD, it is logical to think that conformational variants of this protein may differentially activate pathways leading to different clinical outcomes years later. In the same line, putative tau conformations in AD may be a result of the interaction with different Aβ strains. An intriguing case involving brain Aβ amyloidosis involves the so-called “non-demented Alzheimer’s neuropathology” individuals (Zolochevska and Taglialetela, 2016). These cognitively normal patients, displaying substantial accumulation of Aβ in their brains without clinical manifestations, are an enigma and several groups are actively working to identify what makes these patients’ brains more resilient. On one hand, several researchers support the idea that Aβ deposition is a normal event in aging with questionable relevance in pathophysiological events. This is supported by several failed clinical trials showing that amyloid reduction provides no significant improvements in cognition (Ackley et al., 2021). However, the failure of these trials may be due to several factors, including starting the treatments when extensive brain damage has already occurred. In that sense, early treatments may be key to preventing or substantially delaying brain pathology and subsequent clinical outcomes as suggested in preclinical models (Uhlmann et al., 2020). On the other hand, decades of research (not discussed here for space constraints) have strongly established a relevant (or possibly a major) role of misfolded Aβ in AD (Hardy and Higgins, 1992; Bloom, 2014). Considering the information presented above, it is plausible that specific conformations of misfolded Aβ are responsible for non-demented Alzheimer’s neuropathology. If proven, this will perfectly fit with the Aβ strain hypothesis explaining the pathological and clinical variability observed in AD.

The identification of Aβ strains may be beneficial on several fronts. Mechanistically, the identification of the most deleterious particles will provide us with better tools to pharmacologically modify this disease. In terms of diagnosis, the early identification of the Aβ strain type may allow us to provide a more accurate prognosis and better treatment plans on an individual basis. In fact, personalized medicine, targeting the patient’s most relevant Aβ strains, is envisioned if the existence and relevance of Aβ strains are finally confirmed.

We apologize for the many missing references that should also be quoted. Several review articles have been listed for further reading.

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References

Ackley SF, Zimmerman SC, Brenowitz WD, Tchetgen Tchetgen EJ, Gold AL, Manly JI, Mayeda ER, Filshein TJ, Power MC, Elahi FM, Brickman AM, Glamour MM (2021) Effect of reductions in amyloid levels on cognitive change in randomized trials: instrumental variable meta-analysis. BMJ 372:n5158.

Bloom GS (2014) Amyloid-β and tau: Jan trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol 71:505-508.

Castilla J, Morales R, Saá P, Barria M, Gambetti R, Soto C (2008) Cell-free propagation of prion strains. EMBO J 27:2557-2566.

Claveguera F, Akatsu H, Fraser G, Crowther RA, Frank S, Hensch J, Probst A, Winkler DT, Reichwald J, Staufenbiel M, Ghetti B, Goedert M, Tolnay M (2013) Brain homogenates from human tauopathies induce tau inclusions in mouse brain. Proc Natl Acad Sci U S A 110:9355-9360.

Cohen ML, Kim C, Haldiman T, ElHag M, Mehndiratta P, Picket T, Lissimore S, Shea M, Cohen Y, Chen W, Bleins J, Appleby BS, Surewicz K, Surewicz WK, Saajjavan M, Tatsukasa C, Zhang G, Patuelli M, Haines JL, et al. (2015) Rapidly progressive Alzheimer’s disease features distinct structures of amyloid-β. Brain 138:1009-1022.

Durán-Aniotz C, Moreno-González J, Gamez N, Perez-Urrutia N, Vegas-Gomez I, Soto C, Morales R (2021) Amyloid pathology arrangements in Alzheimer’s disease. Mol Psychiatry 17:1347-1353.

Eisenberg D, Jucker M (2012) The amyloid state of proteins in human diseases. Cell 148:1188-1203.

Hardy JA, Higgins GA (1992) Alzheimer’s disease: the amyloid cascade hypothesis. Science 256:184-185.

Lau HHIC, Ingelsson W, Watts JC (2021) The existence of Aβ strains and their potential for driving phenotypic heterogeneity in Alzheimer’s disease. Acta Neuropathol 142:17-39.

Makowski L (2020) The structural basis of amyloid strain in Alzheimer’s disease. ACS Biomater Sci Eng 6:2498-2505.

Morales R (2017) Prion strains in mammals: Different conformations leading to disease. PLoS Pathog 13:e1006323.

Morales R, Durán-Aniotz C, Castilla J, Estrada LD, Soto C (2021) De novo induction of amyloid-β deposition in vivo. Mol Psychiatry 17:1347-1353.

Morales R, Bravo-Alegria J, Moreno-González I, Durán-Aniotz C, Gamez N, Edwards II G, Soto C (2021) Transmission of cerebral amyloid pathology by peripheral administration of misfolded Aβ aggregates. Mol Psychiatry doi:10.1038/s41386-021-01150-4.

Petkova AT, Leopman RD, Guo Z, Yao W, WM, Mattson MP, Tycko R (2005) Self-propagating, molecular-level polymorphism in Alzheimer’s beta-amyloid fibrils. Science 307:262-265.

Qiang W, Yao WM, Lu JX, Collinge J, Tycko R (2017) Structural variation in amyloid-β fibrils from Alzheimer’s disease clinical subtypes. Nature 541:217-221.

Shi Y, Zhang W, Yang Y, Murzin AG, Falcon B, Kotecha A, van Beers M, Tarunaka H, Kakita A, Iwatsubo T, Robinson CM, Ullrich Gavilanes EM, Vidal R, Hallinan GI, Lashley T, Saito Y, Murayama S, Yoshida M, Tanaka H, Kakita A, Iwatsubo T, Robinson AC, et al. (2021) Structure-based classification of tauopathies. Nature 598:359-363.

Thal DR, Walter J, Saido TC, Fendrich M (2015) Neuropathology and biochemistry of Aβ and its aggregates in Alzheimer’s disease. Acta Neuropathol 129:167-182.

Uhlmann RE, Rother C, Rasmussen J, Schelle J, Bergmann C, Ullrich Gavilanes EM, Fritsch SK, Buehler A, Bickelmann F, Skodias A, Al-Shaana R, Besonhner N, Ye L, Kaeser SA, Ömermüller U, Christensen S, Kartberg F, Stavenshagen JB, Rahfeld JU, Cynis H, et al. (2020) Acute targeting of pre-amyloid seeds in transgenic mice reduces Alzheimer-like pathology later in life. Nat Neurosci 23:1580-1588.

Zhang X, Morimono EC, Sun N, Sperling RA, Sabuncu MR, Yeo BT (2016) Bayesian model reveals latent atlas factors with dissociable cognitive trajectories in Alzheimer’s disease. Proc Natl Acad Sci U S A 113:6635-6644.

Zolochevska O, Taglialetela G (2016) Non-demented individuals with Alzheimer’s disease neuroimaging: resistance to cognitive decline may reveal new treatment strategies. Curr Pharm Des 22:4063-4068.

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