Protein Cell 2010, 1(4): 312–314
DOI 10.1007/s13238-010-0046-6

Protein & Cell

PERSPECTIVE

Amyloid and Alzheimer's disease

Hongxing Lei ✉

Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing 100029, China
✉ Correspondence: leihx@big.ac.cn

A CLASSICAL HISTOPATHOLOGICAL HALLMARK

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease afflicting over 30 million patients worldwide. The typical symptoms of AD include memory loss and impairment of cognitive function, and currently, there is no available approach to cure the disease. The projected fast increase of the senior population is a growing burden for the international society in terms of both medical cost and patient care. Since the first case examination in1907, amyloid has been associated with the disease named after its pioneer Dr. Alois Alzheimer. A classical histopathological hallmark for AD is the extracellular deposition of amyloid plaques found in the postmortem brain of AD patients, along with the intracellular neurofibrillary tangles (NFT). It is widely believed that amyloid is the cause of all the symptoms and the eventual death of AD patients. This so called "amyloid hypothesis" is dominant in the field of AD research, and a good portion of the work in this field has been devoted to the mechanism and pathological effect of amyloid formation.

A CHALLENGING PROTEIN FOLDING PROBLEM

Structure characterization has revealed that amyloid is a fibril structure consisting of several protofibrils, each of which is formed by the stacking of two or more prolonged β-sheets. The hydrogen bonding within a β-sheet is along the fibril axis while each β strand is perpendicular to the fibril axis, forming the so called "cross-β" architecture. The building block of this esthetically pleasing architecture is the Aβ protein. Unlike most proteins featuring a stable globular structure, Aβ protein is unstructured in the cytosol under physiologic condition. The exact mechanism by which this unstructured entity forms fibril has been pursued by experimentalists and theoreticians for many years.

From structural studies by solid-state NMR (nuclear magnetic resonance) (Petkova et al., 2002), site-directed spin-labeling EPR (electron paramagnetic resonance) (Török et al., 2002), and hydrogen/deuterium-exchange (HX) (Lührs et al., 2005), it was revealed that Aβ can form a protofibril structure by stacking hairpin-like building blocks and forming a two-layered β-sheet (Fig. 1). Although it greatly enhanced our understanding of the amyloid structure at atomic level, the dynamic process by which Aβ monomers form amyloid fibril is still unclear. At the beginning of this process, Aβ monomers need to adapt an amyloid-ready conformational state, which may or may not be one of the states in the unstructured ensemble. In the next step, it will need two monomers in the same conformational state to form the dimer with a pair of β-sheets. Then, the protofibril can grow upon this dimer by continuously adding monomers or stacking dimers in the hydrogen bonding direction. This whole process is accompanied by significant loss of entropy, which must be compensated by the gain of enthalpy from main chain hydrogen bonding and side chain interactions.

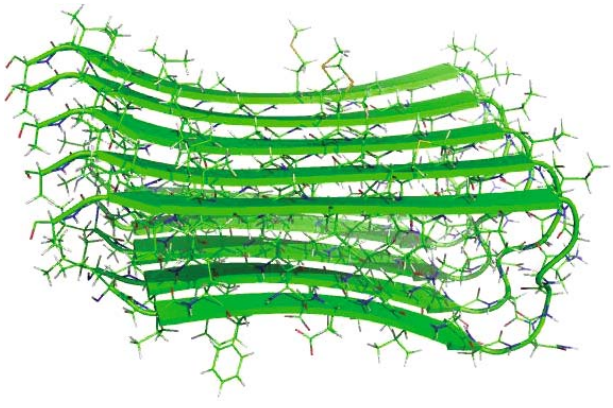

Figure 1. 3D Structure of Alzheimer's Abeta(1–42) fibrils (PDB code 2BEG). Only residues 17–42 are shown, the 16 N-terminal residues are unstructured. This figure is generated by Pymol software.

The mechanism of amyloid formation presents a new challenge to the protein folding society. It has been examined

© Higher Education Press and Springer-Verlag Berlin Heidelberg 2010

by almost every imaginable techniques for structural characterization (Langkilde and Vestergaard, 2009; Tompa, 2009), including circular dichroism (CD), fluorescence, Fourier-transform infrared spectroscopy (FTIR), X-ray crystallography, small angle X-ray scattering (SAXS), NMR, solid-state NMR, cryo-EM (electron microscopy), STEM (scanning tunneling EM) and AFM (atomic force microscopy). Nevertheless, due to the dynamic nature of the oligomerization process, information gathered from experiments regarding the initial stage of oligomerization has been scarce to date. In the mean time, molecular modeling and simulation has provided some insight about the oligomerization process at atomic level (Lei et al., 2006). However, the inaccuracy in the modeling and simulation tools has severely hampered the understanding of the kinetics and thermodynamics and further dissection of energetic and entropic contributions.

To make things even more complicated, it has been recently discovered that amyloid has structural polymorphism (Fändrich et al., 2009). Many fibril species may coexist for the same amyloidogenic protein/peptide and different physico-chemical environment can result in the shift of the equilibrium. These fibril species differ in the number of protofibrils, arrangement of protofibrils in amyloid fibril, and the polypeptide conformation within protofibrils. This phenomenon adds another level of complexity that has yet to be understood quantitatively. Nevertheless, the strong interest from diverse fields such as basic science, drug development and materials design will continue to drive the research forward.

A PLETHORA OF INVOLVED CELLULAR PATHWAYS

Adding to the complexity at the structural level is the existence of a plethora of cellular pathways that amyloid is involved in. Aβ is generated from amyloid precursor protein (APP) by subsequent cleavage by β and γ secretases, while α secretase cuts in the middle of Aβ thereby preventing Aβ aggregation. Aβ mainly exist in two forms: Aβ42 and Aβ40. From genetic association studies, it has been found that all familiar form of AD are associated with mutations in either APP or two of the subunits in γ secretase (PS1 and PS2), while sporadic AD is mainly associated with apolipoprotein E (ApoE), a protein involved in the transport of cholesterol, lipoproteins and fat-soluble vitamins.

The processing and metabolism of APP can be regulated by extracellular stimuli or the binding of adaptor proteins to the YENPTY motif of its intracellular domain (Jacobsen and Iverfeldt, 2009). APP intracellular domain (AICD) possesses transcriptional regulatory activity and alters signaling pathways (Pimplikar, 2009). Aβ has been implicated in the regulation of lipid metabolism, demonstrating inhibition against hydroxymethylglutaryl-CoA reductase (HMGR) and activation of sphingomyelinases (SMases) (Normando et al., 2009). Aβ can disrupt calcium homeostasis by forming channel with oligomers in the membrane (Kawahara et al., 2009), it can also disrupt iron homeostasis through MAPK (mitogen activated protein kinase) cascade (Cahill et al., 2009). Aβ can increase the production of ROS (reactive oxygen species) in mitochondrion and nucleus which lead to apoptosis of neurons (Kaminsky et al., 2010). The induced neural cell death by Aβ can also be achieved by the activation of nicotinic acetylcholine receptors with the involvement of ERK/MAPK pathway, JNK pathway, PI3K/AKT pathway and JAK-2/STAT-3 pathway (Buckingham et al., 2009).

In a proposed positive feedback loop, Aβ can have signaling effect on the transcription of BACE1, a candidate β secretase (Tabaton et al., 2010). This can be achieved by the activation of G-protein coupled receptors (GPCR) or calcium ion channels, or the inhibition of insulin receptors. It can also be achieved by the interaction with ER (endoplasmic reticulum). This signaling may involve the JNK and ERK/Akt pathways and eventually lead to the transcriptional activation of BACE1 by transcription factor AP1, which result in more production of Aβ and complete the positive feed back loop. The binding of Aβ to RAGE (receptor for advanced glycation end products) can also activate the MAPK signaling pathway and activation of transcription factor NF-κB through Ras-ERK1/2 pathway, Cdc42/Rac pathway, p38 and JNK pathways (Origlia et al., 2009).

AN ATTRACTIVE THERAPEUTIC TARGET

Due to the proposed central role of amyloid in AD development, it has enjoyed great attention from the pharmaceutical industry as well as the academic society (Amijee and Scopes, 2009). Currently, FDA and EMEA approved drugs for AD are all symptomatic, including four acetylcholinesterase inhibitors and one NMDA-antagonist. These drugs can only alleviate the symptoms and cannot cure the disease. To find disease-modifying treatments, many people have turned to the amyloid formation process. The basic idea is to develop drugs that reduce the load of amyloid plaques by shifting the equilibrium toward the non-toxic Aβ monomer. This can be accomplished by binding preferentially to the Aβ monomer or oligomers therefore inhibiting the fibrilization process. It can also be achieved by disrupting the fibrils, protofibrils and oligomers. The involvement of zinc and copper ions in the fibrilization process has also been investigated. Based on this idea, many chemical compounds and peptide analogs have been discovered and/or developed, some of which target specific region of Aβ such as HHQK(13–16) and KLVFF (16–20). Encouraging results has been observed in mouse models and clinical trials, including the reduction of amyloid plaques and improvement of the symptoms. Unfortunately, most of them have been withdrawn at one stage or another due to various concerns and none has reached the market.

Another strategy is the reduction of Aβ production by modifying the proteolytic activity or expression level of the

© Higher Education Press and Springer-Verlag Berlin Heidelberg 2010

secretases involved in the cleavage of APP and production of Aβ. However, these secretases also participate in many other cellular pathways, some known and some unknown, raising serious concern and driving many people away from further pursuing in this direction. Yet another strategy is the facilitated clearance of amyloid from the central nervous system (CNS). A hot topic along this line is the development of antibodies to stimulate the immune system to accomplish this mission (Pahnke et al., 2009). One caveat of this strategy is that most antibodies can only be developed against the mature amyloid fibril with well-formed structure while the toxic oligomers are difficult to be targeted. Another hurdle is the blood brain barrier (BBB) which may limit the transport of the amyloid and liberated toxic oligomers away from the CNS and lead to increase in severity of cerebral amyloid angiopathy (CAA).

A LONG-STANDING CONTROVERSY

Ever since the inception of the "amyloid hypothesis", the controversy has always been around it (Pimplikar, 2009). Many evidences have been presented to support this hypothesis, but on the other hand, many evidences against this hypothesis also exist. Another histopathological hallmark of AD is the taupathy caused by NFT, which originated from the aggregation of hyperphosphorylated tau, another natively unstructured protein. It has been observed that the severity of AD symptoms has better correlation with the load of NFT than that of amyloid plaques, and amyloid plaques have also been found in cognitively normal people. In addition, the Aβ42/Aβ40 ratio has been found to have good correlation with the severity of the disease. It has also been found that some oligomer species, including dimer, trimer and dodecamer are much more toxic than amyloid fibrils. In summary, some doubts have been raised regarding the central role of amyloid from pathology, cell biology, animal models and genetics studies. The original theme of amyloid fibril standing alone at the top of the hierarchy has been modified to include other Aβ species during amyloid formation. Furthermore, increasing evidences have suggested that the disruption of other cellular pathways independent of amyloid formation may also act as the source of AD development. After more than 100 years since the discovery of AD, enormous hurdles are still ahead of us before we can reach a clear understanding and eventual cure of the disease.

ACKNOWLEDGMENTS

This work was supported by research grants from National Natural Science Foundation of China (Grant No. 30870474) and SRF for ROCS, SEM.

REFERENCES

Amijee, H., and Scopes, D.I.C. (2009). The quest for small molecules as amyloid inhibiting therapies for Alzheimer's disease. J Alzheimers Dis 17, 33–47.

Buckingham, S.D., Jones, A.K., Brown, L.A., and Sattelle, D.B. (2009). Nicotinic acetylcholine receptor signalling: roles in Alzheimer's disease and amyloid neuroprotection. Pharmacol Rev 61, 39–61.

Cahill, C.M., Lahiri, D.K., Huang, X.D., and Rogers, J.T. (2009). Amyloid precursor protein and alpha synuclein translation, implications for iron and inflammation in neurodegenerative diseases. Biochimica Et Biophysica Acta-General Subjects 1790, 615–628.

Fändrich, M., Meinhardt, J., and Grigorieff, N. (2009). Structural polymorphism of Alzheimer Abeta and other amyloid fibrils. Prion 3, 89–93.

Jacobsen, K.T., and Iverfeldt, K. (2009). Amyloid precursor protein and its homologues: a family of proteolysis-dependent receptors. Cell Mol Life Sci 66, 2299–2318.

Kaminsky, Y.G., Marlatt, M.W., Smith, M.A., and Kosenko, E.A. (2010). Subcellular and metabolic examination of amyloid-beta peptides in Alzheimer disease pathogenesis: evidence for Abeta (25–35). Exp Neurol 221, 26–37.

Kawahara, M., Negishi-Kato, M., and Sadakane, Y. (2009). Calcium dyshomeostasis and neurotoxicity of Alzheimer's beta-amyloid protein. Expert Rev Neurother 9, 681–693.

Langkilde, A.E., and Vestergaard, B. (2009). Methods for structural characterization of prefibrillar intermediates and amyloid fibrils. FEBS Lett 583, 2600–2609.

Lei, H., Wu, C., Wang, Z., and Duan, Y. (2006). Molecular dynamics simulations and free energy analyses on the dimer formation of an amyloidogenic heptapeptide from human beta2-microglobulin: implication for the protofibril structure. J Mol Biol 356, 1049–1063.

Lührs, T., Ritter, C., Adrian, M., Riek-Loher, D., Bohrmann, B., Döbeli, H., Schubert, D., and Riek, R. (2005). 3D structure of Alzheimer's amyloid-beta(1–42) fibrils. Proc Natl Acad Sci U S A 102, 17342–17347.

Normando, E.M., Coxon, K.M., Guo, L., and Cordeiro, M.F. (2009). Focus on: amyloid beta. Exp Eye Res 89, 446–447.

Origlia, N., Arancio, O., Domenici, L., and Yan, S.S. (2009). MAPK, beta-amyloid and synaptic dysfunction: the role of RAGE. Expert Rev Neurother 9, 1635–1645.

Pahnke, J., Walker, L.C., Scheffler, K., and Krohn, M. (2009). Alzheimer's disease and blood-brain barrier function-Why have anti-beta-amyloid therapies failed to prevent dementia progression? Neurosci Biobehav Rev 33, 1099–1108.

Petkova, A.T., Ishii, Y., Balbach, J.J., Antzutkin, O.N., Leapman, R.D., Delaglio, F., and Tycko, R. (2002). A structural model for Alzheimer's beta-amyloid fibrils based on experimental constraints from solid state NMR. Proc Natl Acad Sci USA 99, 16742–16747.

Pimplikar, S.W. (2009). Reassessing the amyloid cascade hypothesis of Alzheimer's disease. Int J Biochem Cell Biol 41, 1261–1268.

Tabaton, M., Zhu, X.W., Perry, G., Smith, M.A., and Giliberto, L. (2010). Signaling effect of amyloid-beta(42) on the processing of AbetaPP. Exp Neurol 221, 18–25.

Tompa, P. (2009). Structural disorder in amyloid fibrils: its implication in dynamic interactions of proteins. FEBS J 276, 5406–5415.

Török, M., Milton, S., Kayed, R., Wu, P., McIntire, T., Glabe, C.G., and Langen, R. (2002). Structural and dynamic features of Alzheimer's Abeta peptide in amyloid fibrils studied by site-directed spin labeling. J Biol Chem 277, 40810–40815.

 © Higher Education Press and Springer-Verlag Berlin Heidelberg 2010