

Pre-mci Targeting Of Amyloidβ42 Channels To Prevent Alzheimer's Disease

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Blood biomarkers developed recently to predict who will develop Alzheimer’s Disease (AD) before symptoms appear include Aβ42 oligomers and extracellular vesicles containing Aβ42/GM1 ganglioside assemblies. Targeting these assemblies may be affective in preventing farther development to AD. We have developed concentric β-barrel models of Aβ42/GM1 channels that are energetically sound and satisfy our well-established modeling criteria for membrane channels. Our models suggest numerous approaches to inhibit their pathogenic effects and they make experimentally testable predictions. Based on these models, we propose approaches to solve their 3-D structures experimentally.

INTRODUCTION

Blood biomarkers have been developed recently to predict who will develop AD before symptoms appear. Treatments are needed now to prevent farther progression. Small Aβ42 oligomers and membrane channels are present at this early pre-fibril stage. They are more toxic than Aβ fibrils, protofibrils, large oligomers, and other Aβ variants, especially when interacting GM1 gangliosides. Targeting Aβ42 channels may be complicated by polymorphism. There are several sizes, and some may be functional while other are pathogenic. To better understand their three-dimensional structures we have developed concentric β-barrel models of Aβ42 channels that are energetically sound and satisfy our well-established modeling criteria for membrane channels. They are highly restricted and may be precise enough for structure-based drug design. Our models are consistent with numerous experimental findings; e.g., single channel conductance recordings, microscopic visualization of Aβ42 channels, secondary structure measurements, NMR studies, effects of mutations, cross-linking and residue accessibility studies, effects of GM1 gangliosides and identity of residues to which they bind, and known interactions of Aβ42 with presynaptic termini and mitochondria.

METHODS

Atomic scale models were developed using in-house and the Chimera Molecular Modeling programs and were minimized using CHARMM. Molecular dynamics simulations were performed using the Amber program. Energetics were evaluated by both calculations and visual examination (high content of antiparallel β and α-helical structure, burial or lipid alkyl exposure and packing of hydrophobic side chains, hydrogen bonding, salt bridging, or solvent exposure of hydrophilic groups, and interactions among aromatic sidechains). Our models are highly constrained by well established β-barrel theories. All subunits have identical conformations in our simplest models.

B-barrel theory for S3 β-barrels of 1con models. (Left side) Flattened schematics of six subunits of 1Con Aβ42 S3 β-barrels with two possible strand tilt angles; one unit cell is shaded gray in each schematic. (Middle) Round schematics of cross-sections for β-barrels composed of six and twelve S3 strands. Green circles represent a central pore. (Right side) Parameter definitions and calculations for 1Con models of S3 β-barrels.

RESULTS

Models of soluble Aβ42 hexamers. (A-D) Smaller diameter model without GM1. (A & B) Top and side views of ribbon backbone with selected side-chains. Ribbons are rainbow colored beginning with red and ending in blue. S1 (red), S2 (yellow) and S3 β-strands are labeled. (C & D). Flattened schematics for two antiparallel subunits of the outer S1-S2 and and inner S3 barrels viewed from the outside. Larger circles represent side-chains on the outer side of the strand. Residue colors: red letter-white background = negatively charged, blue-white = positively charged, blue-gray = histidine, white-gray = small apolar, white-black = large hydrophobic. Copper ions bind to Histidine 6 and Histidine 13 and/or Histidine14. Tyrosine 10 (encircled in green) of adjacent subunits cross-link under oxidation conditions. (E-H) Larger diameter hexamer with six GM1 gangliosides (green carbon, red oxygen, blue nitrogen, white hydrogen). GM1 headgroups bind to Histidine 13 and Histidine 14, alkyl chains fill the inside of the S3 barrel.

Selected freeze-fracture images of transmembrane Aβ42 assemblies and models of transmembrane Aβ42/GM1 assemblies. (Top row) Images of putative Aβ42 hexamer TMOs clusters. (2nd row) Images of putative Aβ42 membrane channels. (3rd and 4th row) Top and side views of the ribbon backbones of channel models. S/N = 2.0 for all outer S3 β-barrels (blue). GM1 gangliosides in the bottom row have green carbons.

Cryo-electron tomography image of a fused region connecting two liposomes and model of a string of octamers consistent with the image. (A) Image of Aβ42/GM1 assemblies spanning each membrane was averaged using Photoshop (adapted from (Tian et al., 2021 (Tian et al., 2021)). The dark images of the central row correspond to the Aβ42/GM1 assemblies, the lighter top and bottom rows correspond to the inner lipid leaflets of each membrane. (B) Side view of a row of 16 octamer backbones with central GM1's (green carbons) at the same scale as the images.

CONCLUSIONS

Decades of efforts to develop inexpensive, effective, and non-toxic treatments for AD that target amyloid plaques and/or tau tangles have largely failed. Most of these treatments have been attempted only after these large assemblies have been detected. But that is likely too late; the damage and degradation process may then be irreversible. The recent development of biomarkers that identify initiation of AD before symptoms appear raise the prospect of preventing AD in its infancy before irreversible damage occurs. The main argument presented here is that Aβ42 oligomers and/or channels, especially those with associated GM1 gangliosides, constitute a wide range of potential targets present at this stage; e.g., drugs could be developed that target pathogenic Aβ42 assemblies or their precursors, mechanisms that remove excessive Aβ42 could be upregulated, initial formation of Aβ42 could be inhibited, or binding of GM1 gangliosides to Aβ42 could be blocked.

REFERENCES

Please consult our most recent publication for a long list of references.
HR GUY, Can Early Targeting of Amyloid-beta 42 Channels Stop Alzheimer's Disease Before it Starts?. **Medical Research Archives**, [S.I.], v. 14, n. 5, June 2026. ISSN 2375-1924. Available at: <<https://esmed.org/MRA/mra/article/view/7581>>. Date accessed: 12 June 2026. doi: <https://doi.org/10.18103/mra.v14i5.7581>.

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Coordinates of our models will be made freely available at ARCGUY.org.