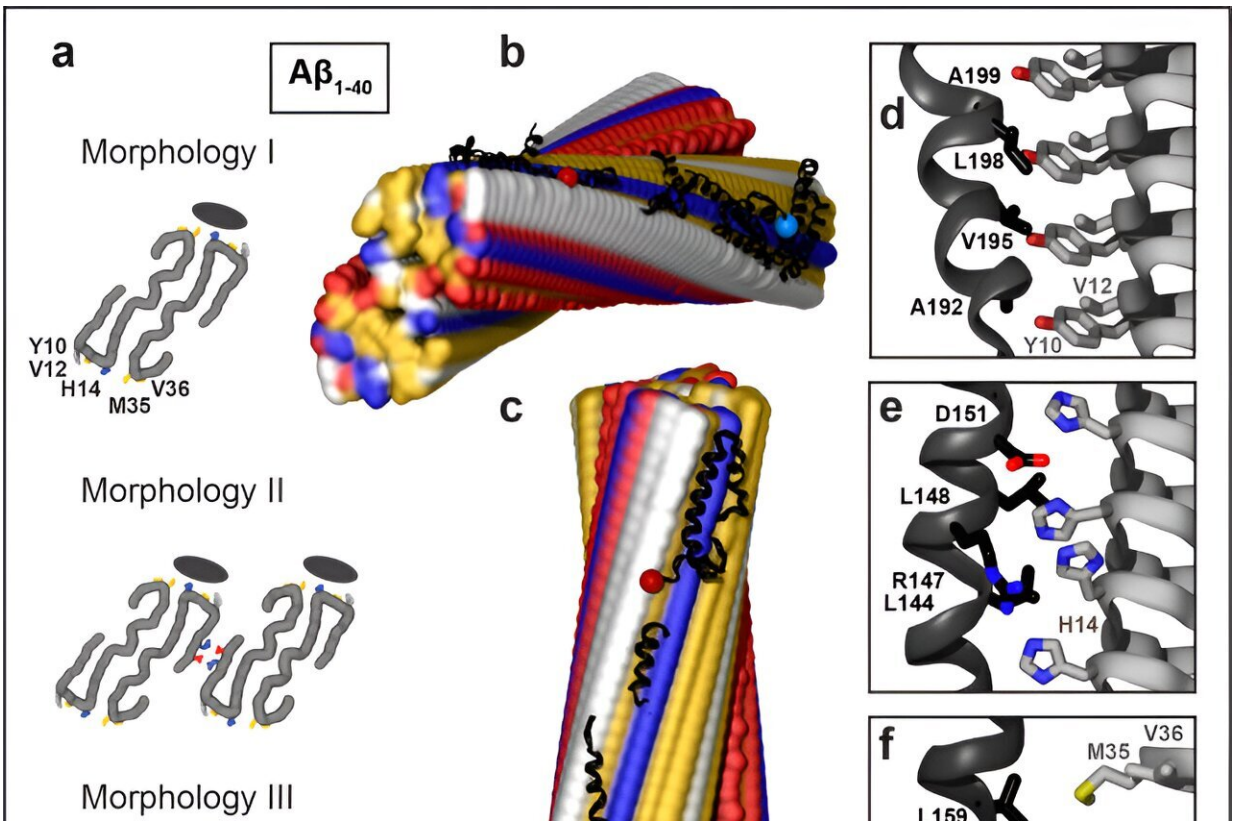
Researchers determine the structural basis for ApoE-Aβ interactions

December 7 2023



Structural model of apoE docked onto $A\beta_{1–40}$ fibril from AD vasculature. The model was obtained by using apoE segments shown in supplemental Fig. 2d–h and the fibril structure (PDB ID: 6SHS). Segment positions are compatible with full-length apoE. (**a**) Fibril morphologies I-III containing one to three paired protofilaments (main chain in gray, view down the fibril axis). Morphology I was used for docking. Black ovals mark the apoE docking position at one of two predicted sites per paired protofilament. ApoE-coordinating residues Y10, V12, H14 from molecule 1 and M35, V36 from molecule 2 of $A\beta_{1–40}$ protofilament

are indicated. In morphologies II and III, residue pairs E3 and R5 that form salt bridges between adjacent protofilaments [63] are shown. (**b, c**) Top and side views of the docking model show apoE alongside $A\beta_{1–40}$ protofilament. In this and other figures of apolipoprotein-amyloid complexes, apolipoprotein main chains are in black ribbons; blue and red dots mark N- and C-termini. Amyloid fibrils are in a surface representation: yellow – hydrophobic, white – polar, red – acidic, blue – basic (including His). Panels d-g show apoE-amyloid contacts within ~5Å in selected regions (apoE – black, Aβ – gray). (**d**) $A\beta_{1–40}$ residue ladder Y10, V12 forms hydrophobic interactions with apoE residues; A192, V195, L198, A199 from the apoE hinge region are shown. (**e**) H14 of $A\beta_{1–40}$ forms mixed (polar/hydrophobic) interactions with apoE residues; R147, L144, L148, D151 from helix 4 are shown. (**f**) R158 in apoE3/E4, which flanks the hydrophobic face of helix 4, interacts unfavorably with M35 of $A\beta_{1–40}$. (**g**) Hydrophobic residues of apoE helix 3 interact with residue ladders of V12 and H14 in $A\beta_{1–40}$. Residue 112 (R112 in apoE4) points away from amyloid. Credit: *Cellular and Molecular Life Sciences* (2023). DOI: 10.1007/s00018-023-05026-w

Alzheimer's disease (AD) is a debilitating incurable disease that affects millions of patients worldwide. Deposits of amyloid beta (Aβ) amyloid in the brain is key to AD pathology at early stages. Apolipoprotein E (apoE) interacts with Aβ and can influence this pathologic process. Although apoE-Aβ interactions have been extensively studied and have been proposed as a therapeutic target in AD, results of prior studies are confusing. Some report that apoE promotes Aβ amyloid formation while others report that apoE blocks this pathological process.

A new biophysical study from researchers at Boston University Chobanian & Avedisian School of Medicine explains why apoE and other apolipoproteins co-deposit with amyloids and provides a structural basis for understanding how apolipoproteins modulate amyloid growth and proliferation in the body.

"Our analysis of four different amyloid fibrils shows that apoE-amyloid interactions depend on the exact amyloid structure, termed polymorph. Amyloid polymorphs are disease- and tissue-specific and can differ in different experiments, which explains discrepancies among prior studies. Understanding such disease-specific factors is essential for harnessing apoE-Aβ interactions for therapeutic targeting," explains first author Emily Lewkowicz, a Ph.D. candidate in biophysics at the school.

The researchers used four different structures of Aβ fibrils from the brains of patients with Alzheimer's and other neurodegenerative diseases . To build models of apoE in complexes with different fibrils, they performed protein docking (the prediction of the structure of the complex based on the structures of the individual proteins) using computer modeling, followed by molecular dynamics simulations to test the stability of the complex.

The computational results, taken together with prior experimental data, revealed the driving forces and the molecular mechanisms for apolipoprotein binding to amyloid fibrils.

According to the researchers, apolipoproteins such as apoE are "amyloid signature proteins" that are found in amyloid deposits and probably influence their formation. "Our work shows how these proteins can interact directly with various amyloids and thereby promote or block their growth and proliferation by binding alongside fibrils or at their ends," adds corresponding author Olga Gursky, Ph.D., professor of pharmacology, physiology & biophysics at the school.

Besides Aβ, nearly 40 other proteins form pathologic amyloids in various human diseases, including Parkinson's disease, chronic traumatic encephalopathy, light chain amyloidosis, and many other life-threatening disorders. Apolipoproteins such as apoE are found in all these amyloid deposits. This work shows how these proteins can interact directly with

amyloids and thereby influence their physical and biological properties.

These findings appear online in *Cellular and Molecular Life Sciences*.

More information: Emily Lewkowicz et al, Molecular modeling of apoE in complexes with Alzheimer's amyloid-β fibrils from human brain suggests a structural basis for apolipoprotein co-deposition with amyloids, *Cellular and Molecular Life Sciences* (2023). DOI: 10.1007/s00018-023-05026-w

Provided by Boston University School of Medicine

Citation: Researchers determine the structural basis for ApoE-Aβ interactions (2023, December 7) retrieved 8 May 2024 from https://medicalxpress.com/news/2023-12-basis-apoe-a-interactions.html

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