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REVIEW

Role of ApoE in Conformation-Prone Diseases and Atherosclerosis

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Abstract—Three isoforms of human plasma apolipoprotein E (apoE) are ligands to lipoprotein receptors and influence in different manner the synthesis and catabolism of pro-atherogenic triglyceride-rich lipoproteins. Among three isoforms, the apoE4 isoform is associated with increased frequency of atherosclerosis and Alzheimer's disease (AD). The conformational transitions of β-amyloid (Aβ) influenced by apoE and serum amyloid P (SAP) component are key events in AD development, the accumulation of intermediate diffusible and soluble oligomers of Aβ being of particular significance. SAP and apoE, in a different manner for the three isoforms, serve as "pathological" chaperones during the aggregation of Aβ considered as a conformation-prone process. In turn, apoE consisting of two domains self-associates in solution and intermediate structures differently populated for the three isoforms exist. The different structures of the three isoforms determine their different distribution among various plasma lipoproteins. The structural and metabolic consideration of the common apoE pathway(s) in two pathologies assumes four molecular targets for AD correction: (i) inhibition of the accumulation of diffusible soluble Aβ oligomers; (ii) inhibition of apoE synthesis and secretion by astrocytes, in particular, under lipid-lowering therapy; (iii) inhibition of the binding of apoE and/or SAP to Aβ; (iv) stimulation of the expression of cholesterol transporter ABCA1.

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Key words: amyloidosis, apolipoprotein E, atherosclerosis, protein structure

Both the structural and metabolic features of the contribution of apolipoprotein E (apoE) into atherogenesis and neurodegenerative disorders on coupling of cholesterol (Ch) and amyloid-β (Aβ) metabolism will be considered, and quite new therapeutic targets will be outlined as well (Scheme).

ApoE-RELATED EVENTS IN ATHEROGENESIS

ApoE is a multifunctional protein that is synthesized by the liver and several peripheral tissues and cell types, including macrophages. ApoE and its gene are prime targets for therapeutic intervention aimed at preventing or treating atherosclerotic vascular disease. The protein is involved in the hepatic uptake of lipoprotein particles, stimulation of Ch efflux from macrophage foam cells in atherosclerotic lesions; at the same time, apoE within hypertriglyceridemic triglyceride-rich lipoproteins is thought to be a ligand for macrophage receptor(s) promoting foam cell formation [1]. In humans, apoE is polymorphic, and this genetic variation has a strong effect on its atherogenic-related characteristics. Three isoforms of apoE differ by single amino acid changes. In comparison with ε3 (corresponds to apoE3 isoform C112-R158), the ε4 allele (apoE4 isoform R112-R158) is associated with clinical and coronary disease [2] while ε2 allele (apoE2 isoform C112-C158) seems to be associated with lower Ch levels. ApoE normally self-associates in solution and consists of two N- and C-terminal domains [3-5]. ApoE folding pathway includes intermediate form(s), one [6, 7] or more [8], being important in lipid binding and differently populated among the three isoforms.

Abbreviations: AD) Alzheimer's disease; apoE) apolipoprotein E; APP) amyloid precursor protein; Aβ) amyloid-β; Ch) cholesterol; cHSA) carboxyamidomethylated human serum albumin; HSA) human serum albumin; LDL) low density lipoprotein; LDLr) LDL receptor; LRP) LDL receptor-related protein; SAP) serum amyloid P component; SR) scavenger receptor.

CONTRIBUTION OF apoE TO CONFORMATION-PRONE DISEASES

Influence of membrane Ch on Aβ synthesis. The major component of extracellular amyloid deposits in brain in Alzheimer's disease (AD) consists of the Aβ peptide of 39-43 amino acids produced by endoproteolytic cleavage of amyloid precursor protein (APP) [9, 10]. The Aβ1-42 and Aβ1-43 peptides are seen in all types of amyloid plaques in Alzheimer's disease [11]. Aβ is thought to be formed from the APP in Ch-enriched membrane domains and cellular Ch depletion decreases Aβ formation? [12]. The drop in cellular Ch induced by the expression of Ch transporter ABCA1 [13, 14] with concomitant Ch efflux by apoE-containing lipoproteins [14] decreased amyloidosis, and the same effect occurring with lipid-lowering therapy by statins [15]. The increase in membrane Ch has been suggested to result in the elevation both of β- and γ-secretase amyloidogenic activities, which localize in Ch-rich membrane domains, compared to non-amyloidogenic α-secretase [12, 16]. Indeed, the expression of ABCA1 led to both decreased β-cleavage product of APP (i.e., C99 peptide) and reduced γ-secretase cleavage of C99 peptide [17]. The amyloid deposits in the brain of ABCA1 knockout mice increased while the level of insoluble apoE did not change opposite to the decrease in soluble apoE [13]. This observation, first, confirms the amyloid-provocative action of apoE, second, implies the coupling of Ch and Aβ metabolism via apoE, and, finally, suggests ABCA1 as a therapeutic target.

Cross-β-structure and aggregation of amyloid-forming proteins. Protein self-association to amyloid fibrils and subsequent fibril aggregation into insoluble deposits are the hallmarks of AD and other neurodegenerative disorders [18], type 2 diabetes [19], and systemic amyloidosis [20]. Inhibiting fibrillogenesis is thus one approach toward therapy of these conformation-prone diseases. More than 20 proteins are able to form amyloid fibrils *in vivo* with characteristic properties of deposits [21]. Despite the large diversity in a primary structure of amyloid-forming proteins, the deposits are characterized by similar structure and morphology, i.e., by linear unbranched assemblies of precursor protein with cross-β-structure [22]. Aggregation both of extracellular amyloid [23] and intracellular unfolded τ protein [24] is induced by the conformational transition with the accumulation of an intermediate β-rich structure. Fibrillogenesis is suggested to proceed through the intermediate protofibril stage, which would be a prime target in the search of inhibitors of fibrillogenesis [25]. The fibrils are widely considered to be a major damaging structure with apoE-provoking role in fibril formation; however, neurotoxicity of the soluble Aβ oligomers has been suggested to exist [26, 27], which was inhibited by membrane Ch [27]. The particular cell surface proteins and signal transduction molecules that mediate the toxicity of soluble Aβ oligomers would be important targets for drug-based therapeutic approaches [26]. The soluble Aβ oligomers are able to accept Ch from neuronal membrane, which probably contributes to their neurotoxic effect [28]. The suggested highest cytotoxicity of intermediate instead of fibrillar form of amyloid-forming proteins results, first, in a paradoxical opinion on neuroprotective action of fibrillar structure (for instance, Lewy bodies in Parkinson's disease are suggested to be an epiphenomenon induced by neuronal death [29]) and, second, in a drastic change in target search for drug therapy. Then amyloid deposits might represent adaptive mechanisms that protect the body from soluble cytotoxic products of protein misfolding and aggregation [30].

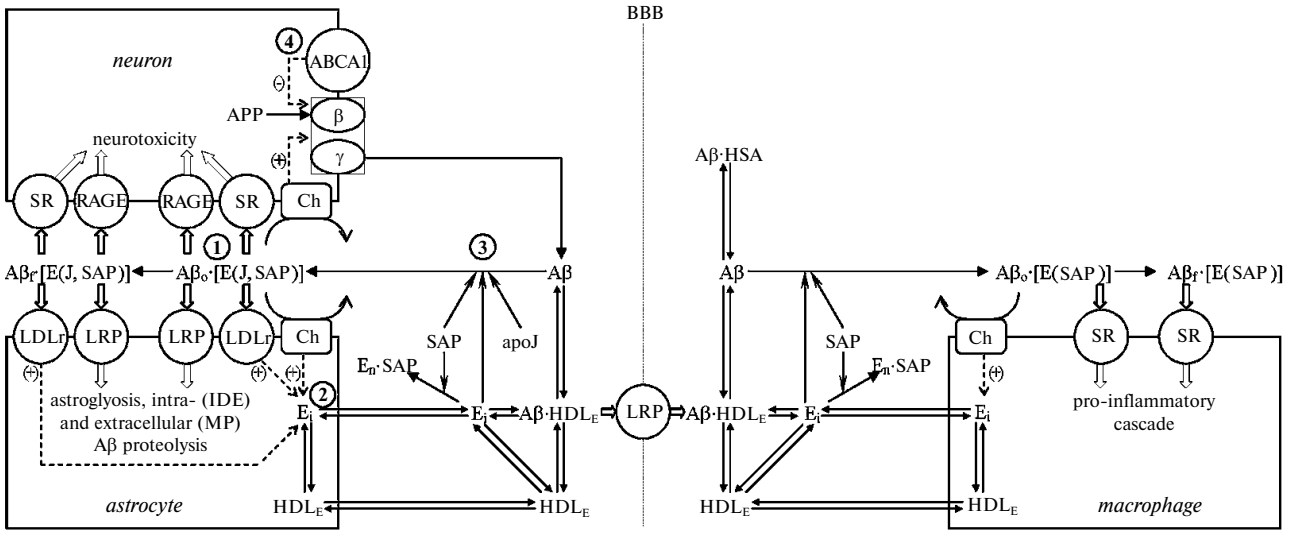
Chaperones in fibrillogenesis. Insoluble deposits include some non-fibrillar components, which influence the fibrillogenesis [31] and do not depend on the nature of the fibril-forming protein [32]; the most common are serum amyloid P (SAP) component and apoE. SAP is a Ca^{2+}-dependent glycoprotein composed of five subunits noncovalently associated into discoidal structure with A- and B-surfaces: the A-surface contains five α-helices, while the B-surface contains five Ca^{2+}-binding regions [33]. SAP aggregated on the interaction of A- and B-surfaces in a Ca^{2+}-dependent manner, while the addition of dAMP as SAP ligand induced SAP self-association into soluble decamer due to B–B interaction. The interaction of SAP with amyloid fibril and Aβ being a Ca^{2+}-dependent event [34] resulted in the increased stability of fibril structure *in vitro* [35]; however, SAP inhibited the fibril formation and increased Aβ solubility in the absence of Ca^{2+} [36]. SAP is suggested to be a chaperone during amyloid aggregation [33] and the use of inhibitors of SAP–Aβ interaction would slow AD progression [37].

The ε4 allele is associated with increased risk of developing AD [38, 39], probably due to the direct apoE–Aβ interaction [31, 40]; however, apoE-dependent involvement of low density lipoprotein (LDL) receptor-related protein (LRP) in Aβ clearance [41], which reflects Aβ transport by lipoproteins as well as albumin-bound Aβ [42], has been suggested in addition to the translation of extracellular into intracellular astrocyte response to Aβ with astrocyte activation via apoE-dependent receptors [43]. Besides, apoE is involved in proteolytic cleavage of Aβ by insulin-degrading enzyme [44]. ApoE4 bound to Aβ more efficiently compared to apoE3 [45]. ApoE has been suggested to be a "pathological" chaperone in Aβ fibril formation with the increase of aggregation/fibrillogenesis, probably due to the induction of β-structure [45-48]. However, apoE increased the lag time in the aggregation of initially soluble Aβ1-40 without any influence on aggregation kinetics of exogenous seed fibrils in the absence of Ca^{2+} [49]. The opposite views on activating [47] or inhibiting [49] role of apoE in amyloid formation result in opposite suggestions

on amyloid-provoking efficiency of the apoE4 isoform, either higher or lower, compared to apoE3. Also, the involvement of the C-terminal domain in Aβ1-40 aggregation is disclaimed [49] or postulated [50]. So apoE seems to possess a dual role in amyloidosis, i.e., the insoluble deposits are stabilized due to chaperoning effect of apoE and are decreased due to apoE-mediated clearance of Aβ. Clusterin (apoJ) may be a chaperone for diffusible and potentially more pernicious than fibrillar Aβ oligomers [26]; the toxicity of soluble oligomers seemed to require the binding to neuronal receptor for advanced glycation end products (RAGE) and scavenger receptor (SR)-like receptor [26].

ApoE–SAP competition. Carboxyamidomethylated human serum albumin (cHSA) in an intermediate highly aggregated state is suggested to be an appropriate model of amyloid-forming protein *in vitro*. This suggestion is supported by: (i) substantial increase from 0 to 20% of the β-structure in the disulfide-reduced form of bovine serum albumin [51]; (ii) accumulation of intermediate (between native and unfolded states) structure with disordered tertiary structure but with native-like secondary structure on reduction of S–S bridges in the HSA molecule [52]; (iii) appearance of fibrillar structure on the reduction of protein disulfide bonds [53, 54]. The similar complex influence of both SAP and apoE on the aggregation of amyloid-forming proteins, i.e., inhibition of formation of the initial pre-nucleation state and stabilization of the structure of growing fibrils is suggested to assume a competition between two proteins important in fibrillogenesis. Indeed, the competition between apoE and SAP for the common binding site(s) within aggregated cHSA has been observed by us [55]. The known effect of SAP as an inhibitor of clearance of amyloid deposits [35, 37, 56, 57] can also assume this competition. The competition between two chaperones, i.e., apoE and SAP if both are present, may not influence the fibrillogenesis, but the higher affinity of apoA-I to Aβ compared to apoE [58] may result in the inhibition of aggregation and cytotoxicity of Aβ that may be a new therapeutic target.

Apoproteins as amyloid-forming proteins. ApoA-I, apoA-II, apoA-IV, apoC-II, and apoE may form fibrils by themselves [59]. ApoC-II fibrils bound to scavenger



Structural and metabolic events in the coupled contribution of apoE in amyloidosis and atherosclerosis. The aggregation of amyloid-β (Aβ) peptide derived from proteolytic cleavage of amyloid precursor protein (APP) by β- and γ-secretases proceeds through the intermediate state of diffusible soluble oligomers ($Aβ_o$) followed by propagation into final fibrillar structure ($Aβ_f$). Both protease activities depend on cholesterol content in the neuronal membrane, which in turn is controlled by cholesterol transporter ABCA1. Two metabolic compartments of apoE in blood and brain that include apolipoprotein synthesis in astrocytes, macrophages, and hepatocytes are separated by the blood–brain barrier (BBB). ApoE influences both stages of fibrillogenesis and serum amyloid P (SAP) component and apoJ may compete with apoE in both stages. The main structure of apoE in solution able to interact with Aβ is suggested to be the intermediate structure E_i that exists in equilibrium with native and unfolded structures. This structure is also responsible for: (i) apolipoprotein interaction with the lipid phase and generation of apoE-containing high density lipoproteins (HDL_E) which redistribute Aβ and cholesterol; (ii) formation of apolipoprotein fibrils (E_n). The interaction of Aβ diffusible oligomers and fibrils with the astrocyte and neuronal receptors results in intracellular accumulation of Aβ and apoE and astrocyte activation (astroglyosis) and neuron degeneration, respectively. The clearance of Aβ from brain involves metalloprotease (MP) and apoE-dependent insulin-degrading enzyme (IDE) and LDL receptor-related protein (LRP) activities. A similar equilibrium between free and lipid-bound apoE exists in the plasma compartment. The Aβ fibril uptake by macrophages results in a cascade of inflammatory reactions. The amyloid-like structure of apoE in association with SAP is suggested to exist in atherosclerotic plaque. *1-4*) Probable targets for prevention and treatment of amyloidosis; (+) and (–) denote activating and inhibiting action, respectively; SR, scavenger receptor

Scheme

receptor class B CD36 in mouse macrophages that triggered the signal cascade with typical inflammatory markers (tumor necrosis factor α, reactive oxygen species, the phosphorylation of tyrosine in some proteins) which are evident in AD [60, 61]. The extracellular co-localization of apoC-II and SAP has been observed in atheromatous plaques in human coronary artery [59]. ApoE may possess similar properties. ApoE progressively accumulated extracellularly during plaque maturation, while only a few macrophages contained apolipoprotein as observed by us [62]. Stable fibrillar structure of apoE within deposits can be suggested. Indeed, the apoE detection level by specific antibodies was not changed by the prior washing of microscopic sections, opposite to the prominent decrease in apoB signal. Analogous extracellular co-localization but of apoE and Aβ in neuritic plaques in Alzheimer's brains has been observed by others [63]. The interaction of apoE with Aβ in the plaque may negatively influence the apoE expression in neighboring astrocytes, but the astroglyosis did not correlate to plaque level in ε4-bearing patients [64]. Probably the absence of apoE in astrocytes close to the plaque is related to the impaired uptake and degradation of Aβ through LDL receptor (LDLr) family [65] in astrocytes despite the increased LRP expression in Alzheimer's brains [66].

INTEGRATING ROLE OF apoE IN AMYLOIDOSIS AND ATHEROSCLEROSIS

The increased synthesis of lipid-free apolipoproteins by macrophages through LX-receptor-mediated induction of the apoE/C-I/C-IV/C-II gene cluster was observed in hypercholesterolemia [67]. Similar stages in the progression of atherosclerosis and amyloidosis can be suggested to exist with the reciprocal relations between aggregated protein matrix and chaperone, i.e., between apolipoprotein–SAP and Aβ–apoE in atherosclerosis and amyloidosis, respectively. The suggestion on the common pathway(s) in these two pathologies is strengthened by the observation of Stewart et al. [68] on the existence of cross-β-structure in oxidized LDL and on the SAP inhibition of CD36-mediated uptake of these lipoproteins by macrophages. The analysis both of structural and metabolic features of the integrating role of apoE in two pathologies (Scheme) let us accentuate four new targets for AD therapy as conformation-prone pathology: (i) inhibition of the formation of diffusible soluble Aβ oligomers; (ii) decrease in apoE synthesis and secretion by astrocytes, in particular, during lipid-lowering therapy; (iii) inhibition of apoE and/or SAP binding to Aβ; (iv) increase in the expression of cholesterol transporter ABCA1.

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REFERENCES

1. Dergunov, A. D. (2004) *Biochemistry* (Moscow), **69**, 720-737.
2. Hofman, A., Ott, A., Breteler, M. M., Bots, M. L., Slooter, A. J., van Harskamp, F., van Duijn, C. N., van Broeckhoven, C., and Grobbee, D. E. (1997) *Lancet*, **349**, 151-154.
3. Barbier, A., Clement-Collin, V., Dergunov, A. D., Visvikis, A., Siest, G., and Aggerbeck, L. P. (2006) *Biophys. Chem.*, **119**, 158-169.
4. Dergunov, A. D., Shuvaev, V. V., and Yanushevskaja, E. V. (1992) *Biol. Chem. Hoppe-Seyler*, **373**, 323-331.
5. Dergunov, A. D., Vorotnikova, Y. Y., Visvikis, S., and Siest, G. (2003) *Spectrochim. Acta Pt. A*, **59**, 1127-1137.
6. Acharya, P., Segall, M. L., Zaiou, M., Morrow, J., Weisgraber, K. H., Phillips, M. C., Lund-Katz, S., and Snow, J. (2002) *Biochim. Biophys. Acta*, **1584**, 9-19.
7. Morrow, J. A., Hatters, D. M., Lu, B., Hochtl, P., Oberg, K. A., Rupp, B., and Weisgraber, K. H. (2002) *J. Biol. Chem.*, **277**, 50380-50385.
8. Clement-Collin, V., Barbier, A., Dergunov, A. D., Visvikis, A., Siest, G., and Aggerbeck, L. P. (2006) *Biophys. Chem.*, **119**, 170-185.
9. Iwatuso, T., Odaka, A., Suzuki, N., Mizusawa, H., Nukina, N., and Ihara, Y. (1994) *Neuron*, **13**, 45-53.
10. Roher, A. E., Lowenson, J. D., Clarke, S., Woods, A. S., Cotter, R. J., Gowing, E., and Ball, M. J. (1993) *Proc. Natl. Acad. Sci. USA*, **90**, 10836-10840.
11. Gravina, S. A., Ho, L., Eckman, C. B., Long, K. E., Otvos, L., Younkin, L. H., Suzuki, N., and Younkin, S. G. (1995) *J. Biol. Chem.*, **270**, 7013-7016.
12. Wolozin, B. (2001) *Proc. Natl. Acad. Sci. USA*, **98**, 5371-5373.
13. Koldamova, R., Staufenbiel, M., and Lefterov, I. (2005) *J. Biol. Chem.*, **280**, 43224-43235.
14. Koldamova, R. P., Lefterov, I. M., Ikonomovic, M. D., Skoko, J., Lefterov, P. I., Isanski, B. A., DeKosky, S. T., and Lazo, J. S. (2003) *J. Biol. Chem.*, **278**, 13244-13256.
15. Fassbender, K., Simons, M., Bergmann, C., Stroick, M., Lutjohann, D., Keller, P., Runz, H., Kuhl, S., Bertsch, T., von Bergmann, K., Hennerici, M., Beyreuther, K., and Hartmann, T. (2001) *Proc. Natl. Acad. Sci. USA*, **98**, 5856-5861.
16. Kojro, E., Gimpl, G., Lammich, S., Marz, W., and Fahrenholz, F. (2001) *Proc. Natl. Acad. Sci. USA*, **98**, 5815-5820.
17. Sun, Y., Yao, J., Kim, T. W., and Tall, A. R. (2003) *J. Biol. Chem.*, **278**, 27688-27694.
18. Masters, C. L., Simms, G., Weinman, N. A., Multhaup, G., McDonald, B. L., and Beyreuther, K. (1985) *Proc. Natl. Acad. Sci. USA*, **82**, 4245-4249.
19. Hoppener, J. W., Ahren, B., and Lips, C. J. (2000) *N. Engl. J. Med.*, **343**, 411-419.
20. Pepys, M. B. (2001) *Philos. Trans. R. Soc. Lond. B Biol. Sci.*, **356**, 203-211.
21. Westermark, P., Benson, M. D., Buxbaum, J. N., Cohen, A. S., Frangione, B., Ikeda, S., Masters, C. L., Merlini,

G., Saraiva, M. J., and Sipe, J. D. (2002) *Amyloid*, **9**, 197-200.
22. Sunde, M., and Blake, C. C. (1998) *Q. Rev. Biophys.*, **31**, 1-39.
23. Bulone, D., Martorana, V., and San Biagio, P. L. (2001) *Biophys. Chem.*, **91**, 61-69.
24. Von Bergen, M., Barghorn, S., Biernat, J., Mandelkow, E.-M., and Mandelkow, E. (2005) *Biochim. Biophys. Acta*, **1739**, 158-166.
25. Walsh, D. M., Lomakin, A., Benedek, G. B., Condron, M. M., and Teplow, D. B. (1997) *J. Biol. Chem.*, **272**, 22364-22372.
26. Lambert, M. P., Barlow, A. K., Chromy, B. A., Edwards, C., Freed, R., Liosatos, M., Morgan, T. E., Rozovsky, I., Trommer, B., Viola, K. L., Wals, P., Zhang, C., Finch, C. E., Krafft, G. A., and Klein, W. L. (1998) *Proc. Natl. Acad. Sci. USA*, **95**, 6448-6453.
27. Sponne, I., Fifre, A., Kriem, B., Koziel, V., Bihain, B., Oster, T., Olivier, J.-L., and Pillot, T. (2004) *FASEB J.*, **18**, 836-838.
28. Michikawa, M., Gong, J. S., Fan, Q. W., Sawamura, N., and Yanagisawa, K. (2001) *J. Neurosci.*, **21**, 7226-7235.
29. Conway, K. A., Lee, S.-J., Rochet, J.-C., Ding, T. T., Williamson, R. E., and Lansbury, P. T., Jr. (2000) *Proc. Natl. Acad. Sci. USA*, **97**, 571-576.
30. Caughey, B., and Lansbury, P. T. (2003) *Annu. Rev. Neurosci.*, **26**, 267-298.
31. Golabek, A. A., Soto, C., Vogel, T., and Wisniewski, T. (1996) *J. Biol. Chem.*, **271**, 10602-10606.
32. MacRaild, C. A., Stewart, C. R., Mok, Y. F., Gunzburg, M. J., Perugini, M. A., Lawrence, L. J., Tirtaatmadja, V., Cooper-White, J. J., and Howlett, G. J. (2004) *J. Biol. Chem.*, **279**, 21038-21045.
33. Coker, A. R., Purvis, A., Baker, D., Pepys, M. B., and Wood, S. P. (2000) *FEBS Lett.*, **473**, 199-202.
34. Hamazaki, H. (1995) *J. Biol. Chem.*, **270**, 10392-10394.
35. Tennent, G. A., Lovat, L. B., and Pepys, M. B. (1995) *Proc. Natl. Acad. Sci. USA*, **92**, 4299-4303.
36. Janciauskiene, S., de Frutos, P. G., Carlemalm, E., Dahlback, B., and Eriksson, S. (1995) *J. Biol. Chem.*, **270**, 26041-26044.
37. Pepys, M. B., Herbert, J., Hutchinson, W. L., Tennent, G. A., Lachmann, H. J., Gallimore, J. R., Lovat, L. B., Bartfai, T., Alanine, A., Hertel, C., Hoffmann, T., Jakob-Roetne, R., Norcross, R. D., Kemp, J. A., Yamamura, K., Suzuki, M., Taylor, G. W., Murray, S., Thompson, D., Purvis, A., Kolstoe, S., Wood, S. P., and Hawkins, P. N. (2002) *Nature*, **417**, 254-259.
38. Corder, E. H., Saunders, A. M., Strittmatter, W. J., Schmechel, D. E., Gaskell, P. C., Small, G. W., Roses, A. D., Haines, J. L., and Pericak-Vance, M. A. (1993) *Science*, **261**, 921-923.
39. Strittmatter, W. J., Saunders, A. M., Schmechel, D., Pericak-Vance, M., Enghild, J., Salvesen, G. S., and Roses, A. D. (1993) *Proc. Natl. Acad. Sci. USA*, **90**, 1977-1981.
40. Sadowski, M., Pankiewicz, J., Scholtzova, H., Ripellino, J. A., Li, Y., Schmidt, S. D., Mathews, P. M., Fryer, J. D., Holtzman, D. M., Sigurdsson, E. M., and Wisniewski, T. (2004) *Am. J. Pathol.*, **165**, 937-948.
41. Shibata, M., Yamada, S., Kumar, S. R., Calero, M., Bading, J., Frangione, B., Holtzman, D. M., Miller, C. A., Strickland, D. K., Ghiso, J., and Zlokovic, B. V. (2000) *J. Clin. Invest.*, **106**, 1489-1499.
42. Biere, A. L., Ostaszewski, B., Stimson, E. R., Hyman, B. T., Maggio, J. E., and Selkoe, D. J. (1996) *J. Biol. Chem.*, **271**, 32916-32922.
43. LaDu, M. J., Shah, J. A., Reardon, C. A., Getz, G. S., Bu, G., Hu, J., Guo, L., and van Eldik, L. J. (2000) *J. Biol. Chem.*, **275**, 33974-33980.
44. Edland, S. D. (2004) *J. Mol. Neurosci.*, **23**, 213-217.
45. Sanan, D. A., Weisgraber, K. H., Russell, S. J., Mahley, R. W., Huang, D., Saunders, A., Schmechel, D., Wisniewski, T., Frangione, B., Roses, A. D., and Strittmatter, W. J. (1994) *J. Clin. Invest.*, **94**, 860-869.
46. Ma, J., Yee, A., Brewer, H. B., Jr., Das, S., and Potter, H. (1994) *Nature*, **372**, 92-94.
47. Wisniewski, T., and Frangione, B. (1992) *Neurosci. Lett.*, **135**, 235-238.
48. Wisniewski, T., Castano, E. M., Golabek, A. A., Vogel, T., and Frangione, B. (1994) *Am. J. Pathol.*, **145**, 1030-1035.
49. Evans, K. C., Berger, E. P., Cho, C. G., Weisgraber, K. H., and Lansbury, P. T., Jr. (1995) *Proc. Natl. Acad. Sci. USA*, **92**, 763-767.
50. Strittmatter, W. J., Weisgraber, K. H., Huang, D. Y., Dong, L. M., Salvesen, G. S., Pericak-Vance, M., Schmechel, D., Saunders, A. M., Goldgaber, D., and Roses, A. D. (1993) *Proc. Natl. Acad. Sci. USA*, **90**, 8098-8102.
51. Takeda, K., Sasa, K., Kawamoto, K., Wada, A., and Aoki, K. (1988) *J. Colloid Interface Sci.*, **124**, 284-289.
52. Lee, J. Y., and Hirose, M. (1992) *J. Biol. Chem.*, **267**, 14753-14758.
53. Goers, J., Permyakov, S. E., Permyakov, E. A., Uversky, V. N., and Fink, A. L. (2002) *Biochemistry*, **41**, 12546-12551.
54. Takase, K., Higashi, T., and Omura, T. (2002) *J. Protein Chem.*, **21**, 427-433.
55. Dergunov, A. D., and Vorotnikova, Y. Y. (1994) *Int. J. Biochem.*, **26**, 933-942.
56. Botto, M., Hawkins, P. N., Bickerstaff, M. C., Herbert, J., Bygrave, A. E., McBride, A., Hutchinson, W. L., Tennent, G. A., Walport, M. J., and Pepys, M. B. (1997) *Nat. Med.*, **3**, 855-859.
57. Togashi, S., Lim, S. K., Kawano, H., Ito, S., Ishihara, T., Okada, Y., Nakano, S., Kinoshita, T., Horie, K., Episkopou, V., Gottesman, M. E., Costantini, F., Shimada, K., and Maeda, S. (1997) *Lab. Invest.*, **77**, 525-531.
58. Koldamova, R. P., Lefterov, I. M., Lefterova, M. I., and Lazo, J. S. (2001) *Biochemistry*, **40**, 3553-3560.
59. Medeiros, L. A., Khan, T., El Khoury, J. B., Pham, C. L. L., Hatters, D. M., Howlett, G. J., Lopez, R., O'Brien, K. D., and Moore, K. J. (2004) *J. Biol. Chem.*, **279**, 10643-10648.
60. El Khoury, J. B., Moore, K. J., Means, T. K., Leung, J., Terada, K., Toft, M., Freeman, M. W., and Luster, A. D. (2003) *J. Exp. Med.*, **197**, 1657-1666.
61. Moore, K. J., El Khoury, J. B., Medeiros, L. A., Terada, K., Geula, C., Luster, A. D., and Freeman, M. W. (2002) *J. Biol. Chem.*, **277**, 47373-47379.

62. Babaev, V. R., Dergunov, A. D., Chenchik, A. A., Tararak, E. M., Yanushevskaja, E. V., Trakht, I. N., Sorg, C., and Smirnov, V. N. (1990) *Atherosclerosis*, **85**, 239-247.
63. Shao, Y., Gearing, M., and Mirra, S. S. (1997) *J. Neuropathol. Exp. Neurol.*, **56**, 376-381.
64. Overmyer, M., Helisalmi, S., Soininen, H., Laakso, M., Riekkinen, P. Sr., and Alafuzoff, I. (1999) *Dement. Geriatr. Cogn. Disord.*, **10**, 252-257.
65. Koistinaho, M., Lin, S., Wu, X., Esterman, M., Koger, D., Hanson, J., Higgs, R., Liu, F., Malkani, S., Bales, K. R., and Paul, S. M. (2004) *Nat. Med.*, **10**, 719-726.
66. Qiu, Z., Strickland, D. K., Hyman, B. T., and Rebeck, G. W. (2001) *J. Neuropathol. Exp. Neurol.*, **60**, 430-440.
67. Mak, P. A., Laffitte, B. A., Desrumaux, C., Joseph, S. B., Curtiss, L. K., Mangelsdorf, D. J., Tontonoz, P., and Edwards, P. A. (2002) *J. Biol. Chem.*, **277**, 31900-31908.
68. Stewart, C. R., Tseng, A. A., Mok, Y. F., Staples, M. K., Schiesser, C. H., Lawrence, L. J., Varghese, J. N., Moore, K. J., and Howlett, G. J. (2005) *Biochemistry*, **44**, 9108-9116.