

# Apolipoprotein A1, the neglected relative of Apolipoprotein E and its potential role in Alzheimer's disease

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Kristina Endres\*

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## Abstract

Lipoproteins are multi-molecule assemblies with the primary function of transportation and processing of lipophilic substances within aqueous bodily fluids (blood, cerebrospinal fluid). Nevertheless, they also exert other physiological functions such as immune regulation. In particular, neurons are both sensitive to uncontrolled responses of the immune system and highly dependent on a controlled and sufficient supply of lipids. For this reason, the role of certain lipoproteins and their protein-component (apolipoproteins, Apo's) in neurological diseases is perceivable. ApoE, for example, is well-accepted as one of the major risk factors for sporadic Alzheimer's disease with a protective allele variant ( $\epsilon 2$ ) and a risk-causing allele variant ( $\epsilon 4$ ). ApoA1, the major protein component of high-density lipoproteins, is responsible for transportation of excess cholesterol from peripheral tissues to the liver. The protein is synthesized in the liver and intestine but also can enter the brain via the choroid plexus and thereby might have an impact on brain lipid homeostasis. This review focuses on the role of ApoA1 in Alzheimer's disease and discusses whether its role within this neurodegenerative disorder is specific or represents a general neuroprotective mechanism.

**Key Words:** A $\beta$ ; ApoA1; cholesterol; high-density lipoproteins; lipids; lipoprotein; neurodegeneration; senile plaque

## Introduction

Alzheimer's disease (AD) is a devastating disease that is characterized by progressive loss of cognitive abilities and with it a loss of ability to cope with every day activities as well as maintaining social relationships. This places a heavy burden on patients, caregivers and relatives, requiring excessive financial, social and emotional support. The seldom-occurring familial form of the disease is clearly linked to mutations in the amyloid precursor protein and/or the presenilins (Cacace et al., 2016). However, the vast majority of cases are designated as sporadic as the underlying cause has not been resolved yet. An effort to reveal risk factors has been attempted via genome wide association studies, which clearly pointed at apolipoprotein E (ApoE) as an important risk factor (Andrews et al., 2020; Squillario et al., 2020). Additionally, various epidemiological reports indicate that diet, and especially lipid homeostasis are closely connected to pathology (Yassine and Finch, 2020). While ApoE's role in AD is undisputed, the effect of ApoA1, responsible for cholesterol efflux, is still under debate. Several investigations led to the conclusion that reduced ApoA1 CSF levels are associated with this disorder (Castano et al., 2006) but it is not clear if this observation is specific to AD or is a general effect of neurodegeneration.

ApoA1 is the core structural protein of high-density lipoproteins (HDL) that may also contain further additional proteins (ApoA-II, A-IV, C-I, C-II, C-III, and E). Besides properties in stabilizing HDL structures, ApoA1 also mediates interaction of HDL with ATP-binding cassette protein A1 (ABCA1), ABCG1,

and class B, type I scavenger receptor (SR-B1). Moreover, it is an activator of lecithin cholesterol acyltransferase. Human ApoA1 consists of 243 amino acids and is synthesized in the liver and intestine. Nascent HDL contains two anti-parallel oriented ApoA1 molecules, giving the aggregate a discoidal shape with binding capability for phospholipids (**Figure 1**). Upon maturation within blood plasma, the HDL particle adopts a more spherical appearance, which is driven by conversion of cholesterol to cholesterol esters via lecithin cholesterol acyltransferase, integration of triglycerides, and translocation of phospholipids to the surface. The mature plasma HDL particle varies in size (8.8–11 nm) and also in the amount and composition of incorporated lipids as well as in ApoA1 molecules. This might explain the immense difficulties and uncertainties in elucidation of its structure [for an elaborate comparison of different structure models see Gogonea (2016)].

Furthermore, a multitude of different proteins with a putative interaction with ApoA1 can also be found in HDL particles: a recent mass-spectrometric analysis of HDL particles from mouse plasma identified 51 different proteins, representing the four functional categories namely lipid metabolism, immune response, coagulation, and others (Zhang et al., 2019). Only 11 of these proteins were common to all HDL subclasses (small, medium and large), strongly suggesting functional subclasses. This was demonstrated for example for endothelial lipase, where the antioxidative capacity of enzyme-containing HDL was mainly determined by the

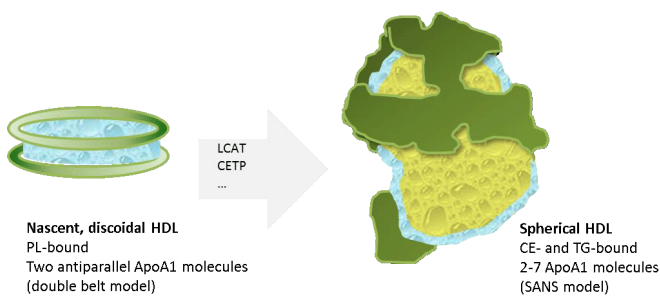
Department of Psychiatry and Psychotherapy, University Medical Center of the Johannes Gutenberg-University Mainz, Untere Zahlbacher Str. 8, 55131 Mainz, Germany

\*Correspondence to: Kristina Endres, PhD, [kristina.endres@unimedizin-mainz.de](mailto:kristina.endres@unimedizin-mainz.de).

<https://orcid.org/0000-0002-1099-8287> (Kristina Endres)

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**Figure 1 | ApoA1 exerts a highly flexible structure.**

Along the way of reverse cholesterol transport, a discoidal-shaped nascent ApoA1 dimer with bound phospholipids is transferred into the mature HDL particle, comprising a more spherical shape. Along the way, the plasma enzyme LCAT transforms free cholesterol into CE. CEs move into the core of the particle where TG join. The lipid transfer is mediated by additional plasma enzymes such as CETP. Exposure of acyl-chains of the supplanted PL leads to recruitment of additional ApoA1 molecules to shield the hydrophobic molecule moieties against the hydrophilic water-based surrounding (for example plasma). ApoA1: Apolipoprotein A1; CE: cholesterol esters; CETP: cholesteryl ester-transfer protein; HDL: high-density lipoproteins; LCAT: lecithin cholesterol acyltransferase; PL: phospholipids; TG: triglycerides. Adapted from Gogonea (2016).

resulting lipolytic products of the lipase, and not by the resulting size of the enzyme-carrying particles (Schilcher et al., 2019). The interactome and functions of the respective components (Asztalos et al., 2019) might be greatly altered in diseased states while for example transcription and protein expression may remain unaffected. The finding that small RNAs such as miRNA, tRNA, and snRNA can also be found within HDL particles (Michell and Vickers, 2016; Ben-Aicha et al., 2020) offers further intriguing functional considerations that will have to be explored in future studies.

Almost all apolipoproteins can be synthesized in the liver, while ApoA4 and ApoB48 are solely generated in the intestine. ApoA1 is derived from both liver and intestine. The intestine presents as a rather exotic milieu considering its close contact to millions of colonizing microorganisms within its lumen. Therefore, the implication of proteins generated in close proximity to this microbiota to the immune response seems plausible. For ApoA1 an immunological function has been demonstrated: HDL has been shown to decrease the amount of monocyte chemoattractant protein-1 that recruits monocytes and reactive oxygen species in vascular smooth muscle cells (Tolle et al., 2008). The lipopolysaccharide sequestering properties of ApoA1 have already been described decades ago (Levine et al., 1993). Moreover, paroxonases (PONs) that are also found to bind HDL and to correlate with HDL concentration are able to hydrolyze and thereby inactivate bacterial quorum-sensing molecules (Furlong et al., 2016). These factors produced by Gram-negative bacteria are regulators of biofilm formation and might thereby directly contribute to pro-amyloidogenic events caused by bacteria (Endres, 2020). This and many more anti-inflammatory and protective characteristics of ApoA1/HDL may allow them to be classified as ‘bug scavengers’ as has been done in a recent review by Meilhac et al. (2020).

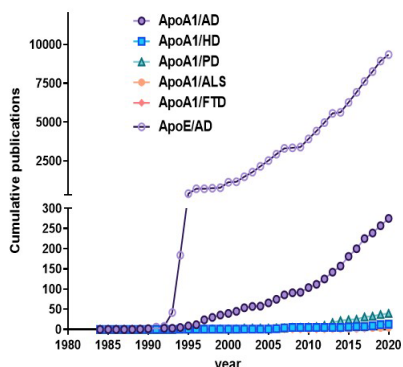
With its important role in the immune response and its major role in cholesterol efflux, ApoA1 represents a molecule that might be of high relevance in AD (for a recent meta-analysis on cholesterol and AD see Saiz-Vazquez et al. (2020)). Not least because ApoA1 is produced in the gut: the gut, its enteric nervous system, and its inhabitants, the microbiota, are currently being intensely investigated regarding their role in AD onset and disease progression (Endres and Schafer, 2018). Therefore, reviewing what is known about ApoA1s function in AD including this newly identified mechanism is important.

## Search Strategy and Selection Criteria

The articles used in this review were retrieved by an electronic search of PubMed database using the following terms: “ApoA1” OR “apolipoprotein A1” AND “Alzheimer”, “Parkinson” AND “ALS” AND “FTD”. The search was conducted on July 24, 2020. The retrieved publications were subsequently screened by title and abstract to exclude non-relevant articles and reviews. For the introduction, additional literatures (retrieved from PubMed database) on structure and function of ApoA1 were used. While literature searches for ApoE and AD result in thousands of publications, ApoA1 only gained limited interest so far (Figure 2). Altogether, some hundreds of investigations on ApoA1 have been conducted and interestingly most of them focus on AD and not on other neurodegenerative diseases such as Parkinson’s disease (PD).

## Genetic Linkage of Apolipoprotein A1 and ApoA1 Interacting Proteins with Alzheimer’s Disease

In humans, ApoA1 is encoded on the long arm of chromosome 11, closely linked to the APOC3 and APO4 gene locus. A Han Chinese population based study on 160 healthy controls and 147 AD patients, quantified mRNA and protein levels of all three apolipoproteins in serum (Lin et al., 2015): all mRNA levels decreased with Clinical Dementia Rating (CDR) score (CDR0 = healthy controls) and similar observation was made for the amount of protein detected. Comparably, HDL-cholesterol levels were also reduced. Correlation analysis with the Montgomery-Åsberg Depression Rating Scale score that reports on behavioral symptoms and with the RAND-36 score both revealed that a higher ApoA1 concentration seems to inhibit development of AD while strengthening the general health status. Several scenarios might explain decreased ApoA1 levels, ranging from a role in transcription, on epigenetic regulation or on increased rates of degradation of the resulting protein. First investigations regarding the ApoA1 gene locus had already been conducted in 2005: a cohort of English and German citizens, including 427 AD patients and 500 controls, were subjected to genotyping in regard to three ApoA1 SNPs (Vollbach et al., 2005). The two SNPs - C/T at position +83 (rs5069) and G/A at position +84 bp (rs1799837) - did not show any association with AD. The third SNP G/A at -75 bp (rs670), while also located within the promoter region, indicated an association of the A allele with an increased risk in early onset patients (aged 66 years or younger). Homozygous AA carriers had an even earlier onset (8 years) of disease compared to persons with at least one G allele. A meta-analysis with 3000 healthy persons characterized the effect of the A allele of the SNP as a statistically significant but rather mild increasing-risk factor (about 5 mg/dl; Juo et al., 1999). Furthermore, the observed impact of the allele was sex-biased with an even weaker association in females. Parameters such as gender, lifestyle or geographic location of a population might contribute to the inconsistent outcome of SNP evaluations for ApoA1. A study making use of a Tunisian population (173 AD cases and 150 healthy controls (Smach et al., 2011)), concluded that the SNP at -75 bp had no association with AD and serum protein levels were nearly unaffected. Interestingly, this study, however, revealed an association of the A allele with lower levels of CSF amyloid-beta (A $\beta$  peptides and HDL cholesterol in serum of AD patients as well as in healthy controls. Moreover, serum ApoA1 and Mini Mental State Examination (MMSE) score correlated significantly ( $r = 0.58$ ), confirming a potential, protective role of ApoA1. The analysis of three further European populations came to a similar conclusion: ApoA1 polymorphism (rs670) was not associated with the risk of AD, while the A allele was weakly associated with a lower MMSE score (Helbecque et al., 2008). A study mainly focused on cerebral amyloid angiopathy-associated intracerebral hemorrhage (CAA ICH), also including 73 AD patients, indicated a strong correlation



**Figure 2 | Research activity on ApoA1 in different neurodegenerative diseases and compared to ApoE.**

Time record of cumulative publications on the respective diseases and ApoA1 or AD and ApoE as obtained by PubMed search. The following search terms were used: "ApoA1" or "apolipoprotein A1" combined with "Alzheimer"/ "Parkinson"/ "ALS"/ "FTD", search date: 24<sup>th</sup> of July 2020; no further filtering was conducted. The search revealed no publications on the search term "multiple systems atrophy" combined with "ApoA1". Literature of the following chapters is mainly based on the findings for AD and ApoA1. AD: Alzheimer's disease; ALS: amyotrophic lateral sclerosis; ApoA: apolipoprotein A; ApoE: apolipoprotein E; FTD: frontotemporal dementia; HD: Huntington's disease.

of ApoA1 with plasma  $A\beta_{1-40}$  in CAA ICH patients but not in controls (Montanola et al., 2016). Unfortunately, no subgroup analysis of AD patients was included. No significant association could be delineated for the two SNPs of ApoA1 – rs 5069 and 670 – for any of the groups investigated and no significant association between genetic variants and plasma levels. In a Japanese population, two intronic SNPs (rs5070 and 5072) were tested for a potential association with early onset (EO) or late onset (LO) AD (154 controls, 170 EOAD, 162 LOAD (Shibata et al., 2013): no significant difference was found between frequency of alleles within controls and EOAD nor between EOAD and LOAD.

Epigenetic investigations targeting ApoA1 are scarce and only one could be identified with the applied search strategy (see legend of **Figure 2**). Analysis of two cohorts of cognitively normal older individuals from the OATS study (Older Australian Twin study, Lazarus et al., 2015) revealed no significant heritability for ApoA1 protein levels; however, a CpG methylation site (cg03010018) associated with memory performance was identified that could be replicated in the Sydney MAS study. This CpG methylation site also correlated with ApoA1 protein levels but no relation with a composite memory domain score could be demonstrated.

Besides direct genetic effects, allelic variation in encoding sequences of interaction partners of ApoA1 are also conceivable: 95–100 protein species have been found in proteomic analyses of HDL (reviewed in Wilkins and Seckler, 2019) that might all in principle be able to interact with ApoA1 and thereby determine its function and/or life time. One such example might be PON1, a protein that was shown to have a direct interaction site with ApoA1 in HDL particles (Huang et al., 2013), and *in vivo* and *in vitro* prevented accumulation of oxidized lipids in low density lipoproteins (LDL). Erlich et al. (2006) examined 29 SNPs in PON1, 2, and 3 encoding genes in 730 Caucasians and 467 African American cases and non-demented controls. An association was reported for SNP C/T at –161 bp in both ethnic groups and the deleterious effect of the T allele was assumed to be based on the affected nuclear factor-1 binding site. Another important interaction partner for ApoA 1 is its receptor ABCA1. Comparing groups of healthy individuals ( $n = 100$ ), AD ( $n = 105$ ), and PD ( $n = 116$ ) patients from northern China regarding the R219K genotype, resulted in the observation of a lower RR and RK allele frequency in both, AD and PD patients (Ya and Lu, 2017). The RR genotype

was also positively correlated with MMSE of AD and negatively with the Hoehn-Yahr scale, a read out of PD symptoms. Moreover, ABCA1 as well as ApoA1 were lowered in the serum from AD patients. However, ApoA1 levels were comparable to those of PD patients. An investigation in American caucasians (992 cases and 699 controls) identified a gender-dependency for this allelic variation, since female 219K allele carriers had a 1.75-fold increased risk of developing AD while males showed the opposite trend (Sundar et al., 2007). Importantly, this might explain why within other studies - probably due to lack of gender stratification - no effects were observed: within an Iranian population (154 sporadic AD cases and 162 control subjects) for example, no association could be found for the R219K polymorphism and AD (Khorram Khorshid et al., 2011). This was also the case within another study with an Anglo-American population (Wahrle et al., 2007). Intriguingly, a large cohort including 92,726 participants from the Copenhagen General Population Study delineated a strong association of AD with the loss-of-function N1800H mutation in ABCA1 (Nordestgaard et al., 2015), underpinning the immense importance of a functional cholesterol efflux for the disease.

## Apolipoprotein A1 as an Amyloid-Promoting Agent

Recent reviews highlight the interaction of the  $A\beta$  peptide, one of the hallmarks of AD, with other amyloidogenic proteins and peptides of human or even non-human origin (Endres, 2019; Ciccone et al., 2020). In this regard, it is important to acknowledge that ApoA1 itself can also form protein aggregates (Cottini et al., 2019; Colombat et al., 2020). No ApoA1 reactivity could be found in for example primary and secondary cutaneous amyloidosis (Chang et al., 2001), but 43 out of 48 formalin-fixed heart-specimen with different kinds of systemic amyloidosis reacted with an anti-ApoA1 antibody (Sakata et al., 2005). The amyloidogenic property of the apolipoprotein is mediated by mutations such as the Iowa mutation (G26R) and seems to depend on cell surface heparin sulfates (Kuwabara et al., 2015). In addition to this self-aggregation, in 1995, ApoA1 was already found in senile plaques of six AD cases and four Down syndrome cases (Wisniewski et al., 1995), which led the authors to suggest a conformational mimicry of ApoA1 that could augment or even initiate fibril formation of  $A\beta$  in AD. Shortly thereafter, a first publication described binding of apolipoproteins to immobilized  $A\beta_{40}$ , with hydrophobic forces as a main driver for ApoA1- $A\beta$  interaction (Shuvaev and Siest, 1996). A KD of 25 nM was found; however, in these experimental conditions, ApoA1 must have been predominantly provided as a monomer which does not represent its major form in biological systems. The relevance of the ApoA1 conformation might also be concluded from the fact that ApoA1 alone had no protective effect on MCF5 cells, while HDL or ApoA1 in combination with alpha-tocopherol shielded cells against  $A\beta$ -induced toxicity (Maezawa et al., 2004). These neuronal cells produce the C-terminal part of the amyloid precursor protein (APP) - a prerequisite for  $A\beta$  synthesis - after tetracycline removal, and thereby induce autotoxicity if no protective agents are administered. Further investigations followed that confirmed the finding of a saturable, specific and reversible binding between ApoA1 and  $A\beta$  with an even higher affinity than ApoE (Koldamova et al., 2001). This binding prevented  $\beta$ -sheet formation and was initially reported to lower Thioflavin T (ThT)-derived fluorescence in *in vitro* assays respectively. However, Paula-Lima et al. (2019) who once more confirmed the neuro-protective function of ApoA1 against  $A\beta$  revealed that this lowering of ThT fluorescence signal only occurred with a low molar ratio of ApoA1 (20:1  $A\beta$  to ApoA1), while higher ratios (2:1) resulted in elevated ThT binding and fluorescence. The ThT signal reduction could be also obtained by a ratio of 10:1 (Stoye et al., 2020a). The binding

of ApoA1 to A $\beta$  was accompanied by generation of smaller A $\beta$  aggregates with shorter, curvilinear and thinner structures (Paula-Lima et al., 2009). Interestingly, A $\beta$ /ApoA1 complexes could be also identified in AD CSF. Furthermore, the binding site of A $\beta$  could be narrowed down by biopanning against fibrillar A $\beta$  to the following stretch in the N-terminal domain of ApoA1: namely  $_{42}$ LNLKLLD $_{48}$ . This peptide stretch is located directly N-terminal to the first class A amphipathic helix of ApoA1 (Segrest et al., 1992). The 4F peptides, mimics of these structural domains of apolipoproteins that do not necessarily share sequence homology to the naturally occurring proteins, have been analyzed for their potential to bind A $\beta$ : electrostatic interaction with A $\beta_{42}$  has been reported (Sahoo et al., 2020) which subsequently caused peptide unfolding. The resulting heteromers, however, induced neurotoxicity. Nevertheless, these peptide mimetics have been already tested as therapeutics: for instance, they have been found to elevate ApoE secretion and lipidation in murine and human astrocytes by positively influencing protein transport (Chernick et al., 2018). The more stable D-enantiomer has been used in combination with pravastatin in the APP/PS1 AD mouse model and evoked improved learning and memory formation as well as a reduction of A $\beta$  load by exerting anti-inflammatory actions after oral application (Handattu et al., 2009). While these peptides also showed beneficial effects for other inflammatory diseases than AD (Meriwether et al., 2019; McGrath et al., 2020; Oehler et al., 2020), they might not fully substitute the full spectrum of HDL functionality as has been shown for anti-atherogenic effects and protection of endothelial cells (Xu et al., 2019). Presumably, the structure of such applied HDL-derived therapeutics might play a role: discoidal HDL displayed a superior capability to promote efflux of A $\beta$  *in vitro* through an artificial blood-brain barrier in comparison to spherical HDL particles, which also led to destabilization of fibrils (Dal Magro et al., 2019).

### Apolipoprotein A1's Role in Alzheimer's Disease: Observations from Mouse Models

As soon as ApoA1 was identified as part of senile plaques of AD patients' brains, the question arose whether ApoA1 might contribute to amyloidogenic processes itself, and preclinical attempts to answer this were conducted. In an early attempt, mutant C57BL/6J mice that lacked ApoA1 were analyzed concerning secondary induced amyloidosis. Here, no changes in splenic anti-amyloidogenic immunoreactivity were assessed (Elliott-Bryant and Cathcart, 1997). Subsequently, analyses in AD mouse models were conducted that are based on heterologous APP and presenilin (PS1/2) expression. The first investigation of a direct effect on AD-like pathology in PDAPP mice revealed the expected effects on plasma and brain cholesterol; however, no alteration of A $\beta$  amount or A $\beta$  deposits were found in the hippocampus (Fagan et al., 2002; Fagan et al., 2004). In these publications, no analysis of amyloids in the vasculature was reported. However, two following publications suggested that ApoA1 does not seem to influence parenchymal amyloids but angiopathic events. Knock-out of ApoA1 in APP/PS1D9 mice increased cerebral amyloid angiopathy (Lefterov et al., 2010), while a two-fold elevation of ApoA1 by overexpression reduced it and moreover also reduced glial inflammation (Lewis et al., 2010). Interestingly, two recent reports came to opposing results with the same ApoA1 knock-out mouse cross-bred with two AD mouse model lines. Button et al. (2019) described that 12 month old APP/PS1 mice showed increased cortical and vascular plaque burden with reduced ApoA1 amount and increased phospho-Tau in dependency of ApoA1 reduction. These animals revealed no behavioral changes (contextual and cued fear conditioning). The same time, Contu et al. (2019) described that in 12–13 month old Tg2576 mice a knock-out of ApoA1 resulted in diminished parenchymal and vascular

amyloid pathology. The contradictory outcome might be based on the fact that AD models differed. Endogenous regulation due to the genotype of the respective models might have affected ApoA1 levels and led to an adaptive response. The Tg2576 mice for example showed reduced ApoA1 levels in the brain as compared to wild type controls (Contu et al., 2019). An investigation of the proteome after intracerebroventricular injection of A $\beta$  in wild type rats described elevated amounts of ApoA1 in hippocampus 40 days after establishing the spontaneous model (Zali et al., 2015). This indicates that precising timing and expression levels of A $\beta$  might lead to differential regulation of endogenous ApoA1.

The promoter for neurodegenerative disease-inducing transgenes such as APP or PS1 in rodent models is most often neuron-specific such as a deleted Thy1-promoter variant. In this regard, it is important to know that the intestine provides its own nervous system – the enteric nervous system (ENS) – and heterologous expression of A $\beta$  in AD models – driven by the Thy1 promoter – has been described not only in brain, but also in the neurons of the ENS (Brandscheid et al., 2017). Therefore, the reaction of the intestinal neurons to overexpression of neurotoxic A $\beta$  peptides might be of higher relevance regarding ApoA1 as secondary effects occurring in cortical neurons. Recently, age-dependent regulation of ApoA1 in the colon of 5xFAD model mice was described: at an age of 1 or 2 months ApoA1 was reduced while with a higher age and progression of pathology, a strong increase in its amounts was assessed (Stoye et al., 2020a). Interestingly, ApoA1 also exerted a protective effect against A $\beta$  on enteric neurons as has been shown before in endothelial cells (Fernandez-de Retana et al., 2017) or neurons of different origins (Paula-Lima et al., 2009).

Evidence for significant mRNA levels of ApoA1 has not been described in the human brain and it is assumed that ApoA1 may enter CSF via the choroid plexus (Elliott et al., 2010). ApoA1 mRNA levels were for example found to be at only 0.3–0.7% of the mean levels found in within different gut sections of C57Bl6/J mice (own unpublished results). Entry of peripheral ApoA1 into the brain has been doubted: while a chronic intravenous application of recombinant human ApoA1 was able to decrease cerebral A $\beta$  and inflammatory markers in APP23 mice, it could not be detected within brain tissue (Fernandez-de Retana et al., 2017). However, Alexa Fluor 647-labeled recombinant ApoA1 could be demonstrated in the choroid plexus after intravenous injection in mice (Stukas et al., 2014). More recently, bolus injection of radioiodinated ApoA1 in wild type rats revealed transportation across the blood-brain barrier (permeability–surface area product of hippocampus and cerebellum: 0.36 and 0.76 mL/g per second  $\times 10^{-6}$ ) (Zhou et al., 2019)).

It has been suggested that ApoA1 imported into the brain elicits neuroprotection via promoting efflux of the neurotoxic A $\beta$  peptide. In a combinatory knock-out of Abca1 and ApoA1 in AD model mice, a delayed export of A $\beta$  from the brain has been described (Fitz et al., 2015). Therefore, the effect of ApoA1 might affect the soluble pool of A $\beta$ : soluble brain A $\beta_{40}$  and A $\beta_{42}$  levels were significantly reduced via acute administration of reconstituted HDL from human serum in APP/PS1 mice (Robert et al., 2016), while chronic administration over 4 weeks failed to do this. Lack of reduction of soluble brain A $\beta_{40}$  and A $\beta_{42}$  levels with prolonged treatment might rely on the elimination of rHDL, due to the fact that the investigation was performed 7 days after the final dose.

Approaches to regulate endogenous ApoA1 levels have been successfully conducted, as for example the *Lavendula angustifolia* extract was able to counterbalance an A $\beta$ -evoked increase in ApoA1 in intracerebroventricular injected rats (Zali et al., 2015). *Ganoderma lucidum* preparations increased brain ApoA1 protein concentration and also improved

learning and memory in APP/PS1 mice (Qin et al., 2017). Moreover, as the intestine presents one of the major sites of ApoA1 production, its regulation by pro- or prebiotics might be assumed. For example, reduced expression of ApoA1 was found to be associated with alterations in Firmicutes specific for Crohn's disease (Haberman et al., 2014). Rescue of such dysbioses that are also assumed for AD might also result in beneficial effects by reconstituting an optimal ApoA1 level.

## Human Studies on Peripheral and Central Apolipoprotein A1 Levels in Cognitive Impairment and Alzheimer's Disease

In human patients, the majority of investigations regarding ApoA1 is based on plasma or serum samples (**Table 1**). These mainly report a reduction of the protein or related structures

and binding partners (e.g. PON-arylesterase; Romani et al., 2020). Besides reduced protein concentrations, single reports also suggest a correlation with other disease hallmarks such as CSF Tau (Romani et al., 2020), brain atrophy (Choi et al., 2016; Liu et al., 2019) or MMSE score (Uchida et al., 2015). This is substantiated by other reports describing significant association of plasma ApoA1 with mild cognitive impairment (MCI) to AD conversion (Westwood et al., 2018). In the Amsterdam dementia cohort, one standard deviation increase of CSF ApoA1 was associated with a 30% increased risk of clinical progression in non-demented persons with subjective cognitive decline (effect attributable to ApoEε4 carriers; Slot et al., 2017). This might point to ApoA1 as being involved in the earliest stages of AD. Moreover, ApoA1 was also shown to decrease from mid-life onwards [1.21 µg/mL per decade (Muenchhoff et al., 2017)] even if a significant correlation

**Table 1 | Analysis of ApoA1 levels in patients-derived samples**

Biomaterials	Investigated cohorts	Observation	References
Plasma/serum	MCI vs. HC	ApoA1↓	Yang et al. (2020)
	Early AD vs. HC (postmenopausal women)	HDL-Chol↓	Li et al. (2020)
	AD and VD vs. HC	PON-arylesterase↓ ApoA1 positively correlated with CSF total and P-Tau	Romani et al. (2020)
	Meta-analysis, AD vs. HC	ApoA1↓	Rehiman et al. (2020)
	AD and MCI vs. HC	ApoA1↓ (MCI vs. HC) Serum levels of ApoA1 negatively correlated with atrophy in medial temporal structure	Liu et al. (2019)
	AD vs. HC	ApoA1↓	Kim et al. (2018)
	Mild AD vs. HC	ApoA1↓	Kitamura et al. (2017)
	AD vs. HC (with or without family history of AD)	ApoA1↓ AD vs. ND (without family history of AD)	Shih et al. (2014)
	AD (with or without cardiovascular comorbidity and risk factors)	HDL↓ in AD (with cardiovascular comorbidity and risk factors) vs. HC	Dias et al. (2014)
	Population-based cohort	ApoA1↓ MCI vs. HC Lower ApoA1 levels increased risk of cognitive decline	Song et al. (2013)
	AD vs. HC	ApoA1↓	Liu et al. (2006)
	AD vs. HC	ApoA1↓ Highly correlated with MMSE scores	Merched et al. (2000)
	AD vs. HC	ApoA1↓ (ApoE3/3 or ApoE3/4 carriers)	Kawano et al. (1995)
	LOAD and VD vs. HC	ApoA1↓	Kuriyama et al. (1994)
	Individuals that developed dementia in a follow-up vs. HC	ApoA1 not related to dementia risk, HDL-ApoA1 not associated with baseline cognition or dementia development	Koch et al. (2020)
	AD and idiopathic normal pressure hydrocephalus vs. HC	ApoA1-	Fania et al. (2017)
	Population-based cohorts	Deviating proteoform patterns in AD vs. both other groups ApoA1 not associated with future dementia or AD	Tynkynen et al. (2016)
	AD and amnesic/non-amnesic MCI vs. HC	ApoA1↑ AD vs. HC ApoA1↓ amnesic MCI vs. HC ApoA1- non-amnesic MCI vs. HC	Song et al. (2014)
	AD and MCI vs. HC	Small sized HDL particles ↑ (MCI vs. HC)	Ohtani et al. (2018)
	CSF	AD vs. HC	ApoA1↑ AD vs. HC
AD vs. other psychiatric diseases (e.g. PD)		ApoA1-	Stoye et al. (2020b)
AD and non-AD demented vs. HC		ApoA1-	Marchi et al. (2019)
AD vs. HC		ApoA1-	Wang et al. (2010)
AD (LOAD and EOAD) vs. HC		ApoA1-	Song et al. (1997)
AD and idiopathic normal pressure hydrocephalus vs. HC		ApoA1↓ (AD vs. idiopathic normal pressure hydrocephalus) Deviating proteoform patterns in AD vs. both other groups	Fania et al. (2017)
AD vs. HC		ApoA1↓ Correlated positively with MMSE score and negatively with CSF p-Tau	Johansson et al. (2017)
AD and non-AD demented vs. HC		ApoA1↓ AD vs. HC	Roher et al. (2009)
AD vs. HC		ApoA1↓	Castano et al. (2006)
AD vs. HC		ApoA1↓ (two isoforms)	Puchades et al. (2003)
Brain tissue	AD vs. HC (ventricular fluid of autopsy cases)	ApoA1↓ (general reduction in apolipoproteins)	Montine et al. (1997)
	AD vs. HC (frontal lobe)	ApoA1-	Harr et al. (1996)

"-" Unchanged; AD: Alzheimer's disease; ApoA1: apolipoprotein A1; Chol: cholesterol; CSF: cerebrospinal fluid; EOAD: early onset AD; HC: healthy control; HDL: high-density lipoprotein; LOAD: late onset AD; MCI: mild cognitive impairment; ND: non-demented; VD: vascular dementia.

## Review

with frailty or cognition could not be identified. As one of the major risk factors for at least sporadic AD is age, this might underline the importance of ApoA1 in pathogenesis.

Nevertheless, there are also individual reports on reduced ApoA1 or HDL particles associated with AD. Besides the mere reduction of the protein in blood-based samples, qualitative differences have also been observed: for instance, Fania and colleagues described that while ApoA1 levels were comparable between AD cases, idiopathic hydrocephalus patients with normal pressure and healthy controls, proteoform patterns of AD cases differed as compared to both other groups (Fania et al., 2017). This might explain why some reports conclude that ApoA1 decreases in AD, whilst others not, depending on the methods used to detect comparable proteoforms. Another investigation in a Taiwanese AD population found elevated Nε(carboxyethyl)lysine adducts of serum ApoA1, accompanied by increased amounts of autoantibodies against these modifications (Lin et al., 2018) while in CSF carbonylation status was not found to differ between AD cases and healthy controls (Korolainen et al., 2007).

Interestingly, even if the number of publications is still low (**Figure 2**), there are at least some reports on other neurodegenerative diseases in the context of ApoA1: for example, ApoA1 was also reduced in serum samples from patients with general paresis (late form of neurosyphilis) while syphilitic patients without neurosyphilis were comparable to healthy controls (Jiang et al., 2016). Moreover, there was a significant positive correlation between increased ApoA1 level and MMSE score after treatment with antibiotics. Also a decline in CSF ApoA1 was reported for PD patients (Maarouf et al., 2013) and a reduced plasma level in a behavioral variant of FTD (Kim et al., 2018).

## Conclusion

In summary, the majority of publications involving patient studies demonstrate a reduction of ApoA1 in peripheral biomaterials such as serum or plasma in AD patients or prodromal stages. For CSF and brain material, data are less clear-cut, as half of the publications show reduced levels, while the other half reports no changes. This inconsistency is mirrored in preclinical studies using AD mouse models: even knock-out of ApoA1 led to contradictory results in terms of pathological hallmarks. Interestingly, there are hardly any data on the expression of ApoA1 in its tissues of origin - the intestine or liver - for AD. However, with an increasingly systemic view of the disease, data on this will undoubtedly emerge over the coming years. The inclusion of the gut-brain axis or the gut-liver axis could provide valuable insights into disease pathogenesis. In particular, the importance of the gut microbiome and its possible influence on ApoA1 should be further explored in the future. The fact that ApoA1, in addition to its well-known role in cholesterol regulation, is also an important component of the immune system, allows speculation about the influence of the microbiome on host ApoA1 levels and vice versa. Significantly, ApoA1 is found, for example, in direct contact with myeloperoxidase (Huang et al., 2013), an enzyme that plays a crucial role in antimicrobial defense starting from neutrophil granulocytes. Altered MPO levels have already been described in AD patients and the influence of the enzyme on disease progression has recently been demonstrated in a mouse model (Volkman et al., 2019). Perhaps, therefore, it would be more fruitful to consider ApoA1 not in isolation but in its interplay with other binding partners to elucidate its role in AD and related diseases in the future.

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## References

- Andrews SJ, Fulton-Howard B, Goate A (2020) Interpretation of risk loci from genome-wide association studies of Alzheimer's disease. *Lancet Neurol* 19:326-335.
- Asztalos BF, Niisuke K, Horvath KV (2019) High-density lipoprotein: our elusive friend. *Curr Opin Lipidol* 30:314-319.
- Ben-Aicha S, Badimon L, Vilahur G (2020) Advances in HDL: much more than lipid transporters. *Int J Mol Sci* 21.
- Brandscheid C, Schuck F, Reinhardt S, Schafer KH, Pietrzik CU, Grimm M, Hartmann T, Schwierz A, Endres K (2017) Altered gut microbiome composition and tryptic activity of the 5xFAD Alzheimer's mouse model. *J Alzheimers Dis* 56:775-788.
- Button EB, Boyce GK, Wilkinson A, Stukas S, Hayat A, Fan J, Wadsworth BJ, Robert J, Martens KM, Wellington CL (2019) ApoA-I deficiency increases cortical amyloid deposition, cerebral amyloid angiopathy, cortical and hippocampal astrogliosis, and amyloid-associated astrocyte reactivity in APP/PS1 mice. *Alzheimers Res Ther* 11:44.
- Cacace R, Slegers K, Van Broeckhoven C (2016) Molecular genetics of early-onset Alzheimer's disease revisited. *Alzheimers Dement* 12:733-748.
- Castano EM, Roher AE, Esh CL, Kokjohn TA, Beach T (2006) Comparative proteomics of cerebrospinal fluid in neuropathologically-confirmed Alzheimer's disease and non-demented elderly subjects. *Neurol Res* 28:155-163.
- Chang YT, Tsai SF, Wang WJ, Hong CJ, Huang CY, Wong CK (2001) A study of apolipoproteins E and A-I in cutaneous amyloids. *Br J Dermatol* 145:422-427.
- Chernick D, Ortiz-Valle S, Jeong A, Swaminathan SK, Kandimalla KK, Rebeck GW, Li L (2018) High-density lipoprotein mimetic peptide 4F mitigates amyloid-beta-induced inhibition of apolipoprotein E secretion and lipidation in primary astrocytes and microglia. *J Neurochem* 147:647-662.
- Choi HJ, Seo EH, Yi D, Sohn BK, Choe YM, Byun MS, Lee JM, Woo JI, Lee DY (2016) Amyloid-independent amnesic mild cognitive impairment and serum apolipoprotein A1 levels. *Am J Geriatr Psychiatry* 24:144-153.
- Cicone L, Shi C, di Lorenzo D, Van Baelen AC, Tonali N (2020) The positive side of the Alzheimer's disease amyloid cross-interactions: the case of the abeta 1-42 peptide with Tau, TTR, CysC, and ApoA1. *Molecules* 25:2439.
- Colombat M, Aldigier JC, Rothschild PR, Javaugue V, Desport E, Frouget T, Goujon JM, Rioux-Leclercq N, Quillard N, Rerolle JP, Paraf F, Beugnet C, Tiple A, Durrbach A, Samuel D, Brezin A, Bridoux F, Valleix S (2020) New clinical forms of hereditary apoA-I amyloidosis entail both glomerular and retinal amyloidosis. *Kidney Int* 98:195-208.
- Contu L, Carare RO, Hawkes CA (2019) Knockout of apolipoprotein A-I decreases parenchymal and vascular beta-amyloid pathology in the Tg2576 mouse model of Alzheimer's disease. *Neuropathol Appl Neurobiol* 45:698-714.
- Cottini F, Bott C, Nadasdy T, Brodsky SV, Benson D (2019) A novel APOA1 mutation in a patient with renal amyloidosis: unveiling amyloid by next-generation sequencing. *Amyloid* 26:253-254.
- Dal Magro R, Simonelli S, Cox A, Formicola B, Corti R, Cassina V, Nardo L, Mantegazza F, Salerno D, Grasso G, Deriu MA, Danani A, Calabresi L, Re F (2019) The extent of human apolipoprotein a-i lipidation strongly affects the beta-amyloid efflux across the blood-brain barrier in vitro. *Front Neurosci* 13:419.
- Dias IH, Polidori MC, Griffiths HR (2014) Hypercholesterolaemia-induced oxidative stress at the blood-brain barrier. *Biochem Soc Trans* 42:1001-1005.
- Elliott-Bryant R, Cathcart ES (1997) Apolipoprotein E and apolipoprotein A-1 knock-out mice readily develop amyloid A protein amyloidosis. *Clin Immunol Immunopathol* 85:104-108.
- Elliott DA, Weickert CS, Garner B (2010) Apolipoproteins in the brain: implications for neurological and psychiatric disorders. *Clin Lipidol* 51:555-573.
- Endres K (2019) Retinoic acid and the gut microbiota in Alzheimer's disease: fighting back-to-back? *Curr Alzheimer Res* 16:405-417.
- Endres K (2020) Amyloidogenic peptides in human neuro-degenerative diseases and in microorganisms: a sorrow shared is a sorrow halved? *Molecules* 25: 925.
- Endres K, Schafer KH (2018) Influence of commensal microbiota on the enteric nervous system and its role in neurodegenerative diseases. *J Innate Immun* 10:172-180.
- Erlich PM, Lunetta KL, Cupples LA, Huyck M, Green RC, Baldwin CT, Farrer LA, Group MS (2006) Polymorphisms in the PON gene cluster are associated with Alzheimer disease. *Hum Mol Genet* 15:77-85.

- Fagan AM, Watson M, Parsadanian M, Bales KR, Paul SM, Holtzman DM (2002) Human and murine ApoE markedly alters A beta metabolism before and after plaque formation in a mouse model of Alzheimer's disease. *Neurobiol Dis* 9:305-318.
- Fagan AM, Christopher E, Taylor JW, Parsadanian M, Spinner M, Watson M, Fryer JD, Wahrle S, Bales KR, Paul SM, Holtzman DM (2004) ApoA1 deficiency results in marked reductions in plasma cholesterol but no alterations in amyloid-beta pathology in a mouse model of Alzheimer's disease-like cerebral amyloidosis. *Am J Pathol* 165:1413-1422.
- Fania C, Arosio B, Capitanio D, Torretta E, Gussago C, Ferri E, Mari D, Gelfi C (2017) Protein signature in cerebrospinal fluid and serum of Alzheimer's disease patients: the case of apolipoprotein A-1 proteoforms. *PLoS One* 12:e0179280.
- Fernandez-de Retana S, Montanola A, Marazuela P, De La Cuesta M, Batlle A, Fatar M, Grudzenski S, Montaner J, Hernandez-Guillamon M (2017) Intravenous treatment with human recombinant ApoA-I Milano reduces beta amyloid cerebral deposition in the APP23-transgenic mouse model of Alzheimer's disease. *Neurobiol Aging* 60:116-128.
- Fitz NF, Tapias V, Cronican AA, Castranio EL, Saleem M, Carter AY, Lefterova M, Lefterov I, Koldamova R (2015) Opposing effects of ApoE/Apoa1 double deletion on amyloid-beta pathology and cognitive performance in APP mice. *Brain* 138:3699-3715.
- Furlong CE, Marsillach J, Jarvik GP, Costa LG (2016) Paraoxonases-1,-2 and -3: What are their functions? *Chem Biol Interact* 259:51-62.
- Gogonea V (2016) Structural insights into high density lipoprotein: old models and new facts. *Front Pharmacol* 6:318.
- Haberman Y, Tickle TL, Dexheimer PJ, Kim MO, Tang D, Karns R, Baldassano RN, Noe JD, Rosh J, Markowitz J, Heyman MB, Griffiths AM, Crandall WV, Mack DR, Baker SS, Huttenhower C, Keljo DJ, Hyams JS, Kugathasan S, Walters TD, et al. (2014) Pediatric Crohn disease patients exhibit specific ileal transcriptome and microbiome signature. *J Clin Invest* 124:3617-3633.
- Handattu SP, Garber DW, Monroe CE, van Groen T, Kadish I, Nayyar G, Cao D, Palgunachari MN, Li L, Anantharamaiah GM (2009) Oral apolipoprotein A-I mimetic peptide improves cognitive function and reduces amyloid burden in a mouse model of Alzheimer's disease. *Neurobiol Dis* 34:525-534.
- Harr SD, Uint L, Hollister R, Hyman BT, Mendez AJ (1996) Brain expression of apolipoproteins E, J, and A-I in Alzheimer's disease. *J Neurochem* 66:2429-2435.
- Helbecque N, Codron V, Cottel D, Amouyel P (2008) An apolipoprotein A-I gene promoter polymorphism associated with cognitive decline, but not with Alzheimer's disease. *Dement Geriatr Cogn Disord* 25:97-102.
- Huang Y, Wu Z, Riwanto M, Gao S, Levison BS, Gu X, Fu X, Wagner MA, Besler C, Gerstenecker G, Zhang R, Li XM, DiDonato AJ, Gogonea V, Tang WH, Smith JD, Plow EF, Fox PL, Shih DM, Lusic AJ, et al. (2013) Myeloperoxidase, paraoxonase-1, and HDL form a functional ternary complex. *J Clin Invest* 123:3815-3828.
- Jiang Y, Zhang YF, Liu M, Ma LL, Peng FH, Huang QL, Ma XM, Chen XH (2016) Syphilitic dementia and lipid metabolism. *Eur J Neurol* 23:1541-1547.
- Johansson P, Almqvist EG, Björke M, Wallin A, Johansson JO, Andreasson U, Blennow K, Zetterberg H, Svensson J (2017) Reduced cerebrospinal fluid concentration of apolipoprotein A-I in patients with Alzheimer's disease. *J Alzheimers Dis* 59:1017-1026.
- Juo SH, Wyszynski DF, Beaty TH, Huang HY, Bailey-Wilson JE (1999) Mild association between the A/G polymorphism in the promoter of the apolipoprotein A-I gene and apolipoprotein A-I levels: a meta-analysis. *Am J Med Genet* 82:235-241.
- Kawano M, Kawakami M, Otsuka M, Yashima H, Yaginuma T, Ueki A (1995) Marked decrease of plasma apolipoprotein AI and AII in Japanese patients with late-onset non-familial Alzheimer's disease. *Clin Chim Acta* 239:209-211.
- Khorram Khorshid HR, Gozalpour E, Kamali K, Ohadi M, Karimloo M, Shahhosseini MH (2011) The association between sporadic Alzheimer's disease and the human ABCA1 and APOE gene polymorphisms in iranian population. *Iran Red Crescent Med J* 13:256-262.
- Kim WS, He Y, Phan K, Ahmed RM, Rye KA, Piguet O, Hodges JR, Halliday GM (2018) Altered high density lipoprotein composition in behavioral variant frontotemporal dementia. *Front Neurosci* 12:847.
- Kitamura Y, Usami R, Ichihara S, Kida H, Satoh M, Tomimoto H, Murata M, Oikawa S (2017) Plasma protein profiling for potential biomarkers in the early diagnosis of Alzheimer's disease. *Neuro Res* 39:231-238.
- Koch M, DeKosky ST, Goodman M, Sun J, Furtado JD, Fitzpatrick AL, Mackey RH, Cai T, Lopez OL, Kuller LH, Mukamal KJ, Jensen MK (2020) Association of apolipoprotein E in lipoprotein subspecies with risk of dementia. *JAMA Netw Open* 3:e209250.
- Koldamova RP, Lefterov IM, Lefterova MI, Lazo JS (2001) Apolipoprotein A-I directly interacts with amyloid precursor protein and inhibits A beta aggregation and toxicity. *Biochemistry-US* 40:3553-3560.
- Korolainen MA, Nyman TA, Nyyssonen P, Hartikainen ES, Pirttila T (2007) Multiplexed proteomic analysis of oxidation and concentrations of cerebrospinal fluid proteins in Alzheimer disease. *Clin Chem* 53:657-665.
- Kuriyama M, Takahashi K, Yamano T, Hokezu Y, Togo S, Osame M, Igakura T (1994) Low levels of serum apolipoprotein A I and A II in senile dementia. *Jpn J Psychiatry Neurol* 48:589-593.
- Kuwabara K, Nishitsuji K, Uchimura K, Hung SC, Mizuguchi M, Nakajima H, Mikawa S, Kobayashi N, Saito H, Sakashita N (2015) Cellular interaction and cytotoxicity of the iowa mutation of apolipoprotein A-I (ApoA-IIowa) amyloid mediated by sulfate moieties of heparan sulfate. *J Biol Chem* 290:24210-24221.
- Lazarus J, Mather KA, Armstrong NJ, Song F, Poljak A, Thalamuthu A, Lee T, Kochan NA, Brodaty H, Wright MJ, Ames D, Sachdev PS, Kwok JB (2015) DNA methylation in the apolipoprotein-A1 gene is associated with episodic memory performance in healthy older individuals. *J Alzheimers Dis* 44:175-182.
- Lefterov I, Fitz NF, Cronican AA, Fogg A, Lefterov P, Kodali R, Wetzel R, Koldamova R (2010) Apolipoprotein A-I deficiency increases cerebral amyloid angiopathy and cognitive deficits in APP/PS1DeltaE9 mice. *J Biol Chem* 285:36945-36957.
- Levine DM, Parker TS, Donnelly TM, Walsh A, Rubin AL (1993) In vivo protection against endotoxin by plasma high density lipoprotein. *Proc Natl Acad Sci U S A* 90:12040-12044.
- Lewis TL, Cao D, Lu H, Mans RA, Su YR, Jungbauer L, Linton MF, Fazio S, LaDu MJ, Li L (2010) Overexpression of human apolipoprotein A-I preserves cognitive function and attenuates neuroinflammation and cerebral amyloid angiopathy in a mouse model of Alzheimer disease. *J Biol Chem* 285:36958-36968.
- Li N, Xu X, Mao S, Jiang Y, Hu Y, Xing R, Chen Y, Ye J, Ling L, Zeng X, Han G (2020) Association of dyslipidaemia with Alzheimer's disease in a cohort of postmenopausal women. *J Int Med Res* 48:300060520926020.
- Lin CY, Sheu JJ, Tsai IS, Wang ST, Yang LY, Hsu IU, Chang HW, Lee HM, Kao SH, Lee CK, Chen CH, Lin YF (2018) Elevated IgM against nepsilon-(carboxyethyl)lysine-modified apolipoprotein A1 peptide 141-147 in taiwanese with Alzheimer's disease. *Clin Biochem* 56:75-82.
- Lin Q, Cao YP, Gao J (2015) Decreased expression of the APOA1-APOC3-APOA4 gene cluster is associated with risk of Alzheimer's disease. *Drug Des Dev Ther* 9:5421-5431.
- Liu HC, Hu CJ, Chang JG, Sung SM, Lee LS, Yuan RY, Leu SJ (2006) Proteomic identification of lower apolipoprotein A-I in Alzheimer's disease. *Dement Geriatr Cogn Disord* 21:155-161.
- Liu S, Suzuki H, Ito H, Korenaga T, Akatsu H, Meno K, Uchida K (2019) Serum levels of proteins involved in amyloid-beta clearance are related to cognitive decline and neuroimaging changes in mild cognitive impairment. *Alzheimers Dement (Amst)* 11:85-97.
- Maarouf CL, Beach TG, Adler CH, Malek-Ahmadi M, Kokjohn TA, Dugger BN, Walker DG, Shill HA, Jacobson SA, Sabbagh MN, Roher AE, Arizona Parkinson's Disease C (2013) Quantitative appraisal of ventricular cerebrospinal fluid biomarkers in neuropathologically diagnosed Parkinson's disease cases lacking Alzheimer's disease pathology. *Biomark Insights* 8:19-28.
- Maewawa I, Jin LW, Woltjer RL, Maeda N, Martin GM, Montine TJ, Montine KS (2004) Apolipoprotein E isoforms and apolipoprotein AI protect from amyloid precursor protein carboxy terminal fragment-associated cytotoxicity. *J Neurochem* 91:1312-1321.
- Marchi C, Adorni MP, Caffarra P, Ronda N, Spallazzi M, Barocco F, Galimberti D, Bernini F, Zimetti F (2019) ABCA1- and ABCG1-mediated cholesterol efflux capacity of cerebrospinal fluid is impaired in Alzheimer's disease. *J Lipid Res* 60:1449-1456.
- Marksteiner J, Jmarhiagbe D, DeFrancesco M, Deisenhammer EA, Kemmler G, Humpel C (2014) Analysis of 27 vascular-related proteins reveals that NT-proBNP is a potential biomarker for Alzheimer's disease and mild cognitive impairment: a pilot-study. *Exp Gerontol* 50:114-121.
- McGrath KC, Li X, Twigg SM, Heather AK (2020) Apolipoprotein-AI mimetic peptides D-4F and L-5F decrease hepatic inflammation and increase insulin sensitivity in C57BL/6 mice. *PLoS One* 15:e0226931.
- Meilhac O, Tanaka S, Couret D (2020) High-density lipoproteins are bug scavengers. *Biomolecules* 10:598.
- Merched A, Xia Y, Visvikis S, Serot JM, Siest G (2000) Decreased high-density lipoprotein cholesterol and serum apolipoprotein AI concentrations are highly correlated with the severity of Alzheimer's disease. *Neurobiol Aging* 21:27-30.
- Meriwether D, Sulaiman D, Volpe C, Dorfman A, Grijalva V, Dorreh N, Solorzano-Vargas RS, Wang J, O'Connor E, Papesh J, Larauche M, Trost H, Palgunachari MN, Anantharamaiah GM, Herschman HR, Martin MG, Fogelman AM, Reddy ST (2019) Apolipoprotein A-I mimetics mitigate intestinal inflammation in COX2-dependent inflammatory bowel disease model. *J Clin Invest* 129:3670-3685.
- Michell DL, Vickers KC (2016) Lipoprotein carriers of microRNAs. *Biochim Biophys Acta* 1861:2069-2074.
- Montanola A, de Retana SF, Lopez-Rueda A, Merino-Zamorano C, Penalba A, Fernandez-Alvarez P, Rodriguez-Luna D, Malagelada A, Pujadas F, Montaner J, Hernandez-Guillamon M (2016) ApoA1, ApoJ and ApoE plasma levels and genotype frequencies in cerebral amyloid angiopathy. *Neuromolecular Med* 18:99-108.
- Montine TJ, Montine KS, Swift LL (1997) Central nervous system lipoproteins in Alzheimer's disease. *Am J Pathol* 151:1571-1575.
- Muenchhoff J, Song F, Poljak A, Crawford JD, Mather KA, Kochan NA, Yang Z, Trollor JN, Reppermund S, Maston K, Theobald A, Kirchner-Adelhardt S, Kwok JB, Richmond RL, McEvoy M, Attia J, Schofield PW, Brodaty H, Sachdev PS (2017) Plasma apolipoproteins and physical and cognitive health in very old individuals. *Neurobiol Aging* 55:49-60.

- Nordestgaard LT, Tybjaerg-Hansen A, Nordestgaard BG, Frikke-Schmidt R (2015) Loss-of-function mutation in ABCA1 and risk of Alzheimer's disease and cerebrovascular disease. *Alzheimers Dement* 11:1430-1438.
- Oehler B, Klocka J, Mohammadi M, Ben-Kraiem A, Rittner HL (2020) D-4F, an ApoA-I mimetic peptide ameliorating TRPA1-mediated nocifensive behaviour in a model of neurogenic inflammation. *Mol Pain* 16:1744806920903848.
- Ohtani R, Nirengi S, Nakamura M, Murase N, Sainouchi M, Kuwata Y, Takata M, Masuda Y, Kotani K, Sakane N (2018) High-density lipoprotein subclasses and mild cognitive impairment: Study of Outcome and aPolipoproteins in Dementia (STOP-Dementia)1. *J Alzheimers Dis* 66:289-296.
- Paula-Lima AC, Tricerri MA, Brito-Moreira J, Bomfim TR, Oliveira FF, Magdesian MH, Grinberg LT, Panizzutti R, Ferreira ST (2009) Human apolipoprotein A-I binds amyloid-beta and prevents A beta-induced neurotoxicity. *Int J Biochem Cell B* 41:1361-1370.
- Puchades M, Hansson SF, Nilsson CL, Andreassen N, Blennow K, Davidsson P (2003) Proteomic studies of potential cerebrospinal fluid protein markers for Alzheimer's disease. *Brain Res Mol Brain Res* 118:140-146.
- Qin C, Wu S, Chen B, Wu X, Qu K, Liu J, Zhang G, Xu Y, Shu S, Sun L, Li Y, Zhu H, Huang L, Ma C, Xu Y, Han Y, Lu Y (2017) Effect of ganoderma lucidum preparation on the behavior, biochemistry, and autoimmune parameters of mouse models of APP/PS1 double transgenic Alzheimer's disease. *Zhongguo Yi Xue Ke Xue Yuan Xue Bao* 39:330-335.
- Rehman SH, Lim SM, Neoh CF, Majeed ABA, Chin AV, Tan MP, Kamaruzzaman SB, Ramasamy K (2020) Proteomics as a reliable approach for discovery of blood-based Alzheimer's disease biomarkers: a systematic review and meta-analysis. *Ageing Res Rev* 60:101066.
- Robert J, Stukas S, Button E, Cheng WH, Lee M, Fan J, Wilkinson A, Kulic I, Wright SD, Wellington CL (2016) Reconstituted high-density lipoproteins acutely reduce soluble brain Abeta levels in symptomatic APP/PS1 mice. *Biochim Biophys Acta* 1862:1027-1036.
- Roher AE, Maarouf CL, Sue LI, Hu Y, Wilson J, Beach TG (2009) Proteomics-derived cerebrospinal fluid markers of autopsy-confirmed Alzheimer's disease. *Biomarkers* 14:493-501.
- Romani A, Trentini A, Flier WMV, Bellini T, Zuliani G, Cervellati C, Teunissen CE (2020) Arylesterase Activity of paraoxonase-1 in serum and cerebrospinal fluid of patients with Alzheimer's disease and vascular dementia. *Antioxidants (Basel)* 9.
- Sahoo BR, Bekier ME, 2nd, Liu Z, Kocman V, Stoddard AK, Anantharamaiah GM, Nowick J, Fierke CA, Wang Y, Ramamoorthy A (2020) Structural interaction of apolipoprotein A-I mimetic peptide with amyloid-beta generates toxic hetero-oligomers. *J Mol Biol* 432:1020-1034.
- Saiz-Vazquez O, Puente-Martinez A, Ubillos-Landa S, Pacheco-Bonrostro J, Santabarbara J (2020) Cholesterol and Alzheimer's disease risk: a meta-meta-analysis. *Brain Sci* 10:386.
- Sakata N, Hoshii Y, Nakamura T, Kiyama M, Arai H, Omoto M, Morimatsu M, Ishihara T (2005) Colocalization of apolipoprotein AI in various kinds of systemic amyloidosis. *J Histochem Cytochem* 53:237-242.
- Schlicher I, Ledinski G, Radulovic S, Hallstrom S, Eichmann T, Madl T, Zhang F, Leitinger G, Kolb-Lenz D, Darnhofer B, Birner-Gruenberger R, Wadsack C, Kratky D, Marsche G, Frank S, Cvirn G (2019) Endothelial lipase increases antioxidative capacity of high-density lipoprotein. *Biochim Biophys Acta Mol Cell Biol Lipids* 1864:1363-1374.
- Segrest JP, Jones MK, Deloof H, Brouillette CG, Venkatachalapathi YV, Anantharamaiah GM (1992) The amphipathic helix in the exchangeable apolipoproteins - a review of secondary structure and function. *J Lipid Res* 33:141-166.
- Shibata N, Nagata T, Shinagawa S, Ohnuma T, Shimazaki H, Komatsu M, Kuerban B, Tomson K, Nakayama K, Yamada H, Arai H (2013) Genetic association between APOA1 and APOD polymorphisms and Alzheimer's disease in a Japanese population. *J Neural Transm (Vienna)* 120:1599-1603.
- Shih YH, Tsai KJ, Lee CW, Shiesh SC, Chen WT, Pai MC, Kuo YM (2014) Apolipoprotein C-III is an amyloid-beta-binding protein and an early marker for Alzheimer's disease. *J Alzheimers Dis* 41:855-865.
- Shuvaev VV, Siest GR (1996) Interaction between human amphipathic apolipoproteins and amyloid beta-peptide: Surface plasmon resonance studies. *FEBS Lett* 383:9-12.
- Slot RE, Van Harten AC, Kester MI, Jongbloed W, Bouwman FH, Teunissen CE, Scheltens P, Veerhuis R, van der Flier WM (2017) Apolipoprotein A1 in cerebrospinal fluid and plasma and progression to alzheimer's disease in non-demented elderly. *J Alzheimers Dis* 56:687-697.
- Smach MA, Edziri H, Charfeddine B, Ben Othman L, Lammouchi T, Ltaief A, Nafati S, Dridi H, Bennamou S, Limem K (2011) Polymorphism in apoA1 influences high-density lipoprotein cholesterol levels but is not a major risk factor of alzheimer's disease. *Dement Geriatr Cogn Dis Extra* 1:249-257.
- Song F, Poljak A, Kochan NA, Rafferty M, Brodaty H, Smythe GA, Sachdev PS (2014) Plasma protein profiling of mild cognitive impairment and Alzheimer's disease using iTRAQ quantitative proteomics. *Proteome Sci* 12:5.
- Song H, Saito K, Seishima M, Noma A, Urakami K, Nakashima K (1997) Cerebrospinal fluid apo E and apo A-I concentrations in early- and late-onset Alzheimer's disease. *Neurosci Lett* 231:175-178.
- Song X, Mitnitski A, Zhang N, Chen W, Rockwood K, Alzheimer's Disease Neuroimaging I (2013) Dynamics of brain structure and cognitive function in the Alzheimer's disease neuroimaging initiative. *J Neurol Neurosurg Psychiatry* 84:71-78.
- Squillario M, Abate G, Tomasi F, Tozzo V, Barla A, Uberti D, Alzheimer's Disease Neuroimaging I (2020) A telescope GWAS analysis strategy, based on SNPs-genes-pathways ensemble and on multivariate algorithms, to characterize late onset Alzheimer's disease. *Sci Rep* 10:12063.
- Stoye NM, Dos Santos Guilherme M, Endres K (2020a) Alzheimer's disease in the gut-Major changes in the gut of 5xFAD model mice with ApoA1 as potential key player. *FASEB J* 34:11883-11899.
- Stoye NM, Jung P, Guilherme MDS, Lotz J, Fellgiebel A, Endres K (2020b) Apolipoprotein A1 in cerebrospinal fluid is insufficient to distinguish alzheimer's disease from other dementias in a naturalistic, clinical setting. *J Alzheimers Dis Rep* 4:15-19.
- Stukas S, Robert J, Lee M, Kulic I, Carr M, Tourigny K, Fan J, Namjoshi D, Lemke K, DeValle N, Chan J, Wilson T, Wilkinson A, Chapanian R, Kizhakkedathu JN, Cirrito JR, Oda MN, Wellington CL (2014) Intravenously injected human apolipoprotein A-I rapidly enters the central nervous system via the choroid plexus. *J Am Heart Assoc* 3:e001156.
- Sundar PD, Feingold E, Minster RL, DeKosky ST, Kamboh MI (2007) Gender-specific association of ATP-binding cassette transporter 1 (ABCA1) polymorphisms with the risk of late-onset Alzheimer's disease. *Neurobiol Aging* 28:856-862.
- Tolle M, Pawlak A, Schuchardt M, Kawamura A, Tietge UJ, Lorkowski S, Keul P, Assmann G, Chun J, Levkau B, van der Giet M, Nofer JR (2008) HDL-associated lysosphingolipids inhibit NAD(P)H oxidase-dependent monocyte chemoattractant protein-1 production. *Arterioscler Thromb Vasc Biol* 28:1542-1548.
- Tynkynen J, Hernesniemi JA, Laatikainen T, Havulinna AS, Sundvall J, Leiviska J, Salo P, Salomaa V (2016) Apolipoproteins and HDL cholesterol do not associate with the risk of future dementia and Alzheimer's disease: the National Finnish population study (FINRISK). *Age (Dordr)* 38:465-473.
- Uchida K, Shan L, Suzuki H, Tabuse Y, Nishimura Y, Hirokawa Y, Mizukami K, Akatsu H, Meno K, Asada T (2015) Amyloid-beta sequester proteins as blood-based biomarkers of cognitive decline. *Alzheimers Dement (Amst)* 1:270-280.
- Volkman R, Ben-Zur T, Kahana A, Garty BZ, Offen D (2019) Myeloperoxidase deficiency inhibits cognitive decline in the 5XFAD mouse model of Alzheimer's disease. *Front Neurosci* 13:990.
- Vollbach H, Heun R, Morris CM, Edwardson JA, McKeith IG, Jessen F, Schulz A, Maier W, Kolsch H (2005) APOA1 polymorphism influences risk for early-onset nonfamilial AD. *Ann Neurol* 58:436-441.
- Wahrle SE, Shah AR, Fagan AM, Smemo S, Kauwe JS, Grupe A, Hinrichs A, Mayo K, Jiang H, Thal LJ, Goate AM, Holtzman DM (2007) Apolipoprotein E levels in cerebrospinal fluid and the effects of ABCA1 polymorphisms. *Mol Neurodegener* 2:7.
- Wang ES, Sun Y, Guo JG, Gao X, Hu JW, Zhou L, Hu J, Jiang CC (2010) Tetraacetin and apolipoprotein A-I in cerebrospinal fluid as potential biomarkers for Parkinson's disease. *Acta Neurol Scand* 122:350-359.
- Westwood S, Baird AL, Hye A, Ashton NJ, Nevado-Holgado AJ, Anand SN, Liu B, Newby D, Bazenot C, Kiddle SJ, Ward M, Newton B, Desai K, Tan Hehir C, Zanette M, Galimberti D, Parnetti L, Lleó A, Baker S, Narayan VA, et al. (2018) Plasma protein biomarkers for the prediction of csf amyloid and tau and [<sup>18</sup>F]-flutemetamol PET scan result. *Front Aging Neurosci* 10:409.
- Wilkins JT, Seckler HS (2019) HDL modification: recent developments and their relevance to atherosclerotic cardiovascular disease. *Curr Opin Lipidol* 30:24-29.
- Wisniewski T, Lalowski M, Golabek A, Vogel T, Frangione B (1995) Is Alzheimer's disease an apolipoprotein E amyloidosis? *Lancet* 345:956-958.
- Xu WQ, Qian MM, Huang CH, Cui PF, Li W, Du Q, Yi SH, Shi XH, Guo YS, Zheng JL, Liu DH, Lin DH (2019) Comparison of mechanisms of endothelial cell protections between high-density lipoprotein and apolipoprotein A-I mimetic peptide. *Front Pharmacol* 10.
- Ya L, Lu Z (2017) Differences in ABCA1 R219K Polymorphisms and serum indexes in Alzheimer and Parkinson diseases in northern China. *Med Sci Monit* 23:4591-4600.
- Yang H, Gu S, Wu Y, Jiang Y, Zhao J, Cheng Z (2020) Plasma protein panels for mild cognitive impairment among elderly chinese individuals with different educational backgrounds. *J Mol Neurosci* 70:1629-1638.
- Yassine HN, Finch CE (2020) APOE alleles and diet in brain aging and Alzheimer's disease. *Front Aging Neurosci* 12:150.
- Zali H, Zamanian-Azodi M, Rezaei Tavirani M, Akbar-Zadeh Baghban A (2015) Protein drug targets of *lavandula angustifolia* on treatment of rat Alzheimer's disease. *Iran J Pharm Res* 14:291-302.
- Zhang Y, Gordon SM, Xi H, Choi S, Paz MA, Sun R, Yang W, Saredy J, Khan M, Remaley AT, Wang JF, Yang X, Wang H (2019) HDL subclass proteomic analysis and functional implication of protein dynamic change during HDL maturation. *Redox Biol* 24:101222.
- Zhou AL, Swaminathan SK, Curran GL, Poduslo JF, Lowe VJ, Li L, Kandimalla KK (2019) Apolipoprotein A-I crosses the blood-brain barrier through clathrin-independent and cholesterol-mediated endocytosis. *J Pharmacol Exp Ther* 369:481-488.

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