Molecular Therapy
Nucleic Acids
Review

Apolipoprotein E and viral infection: Risks and Mechanisms

Feng Chen,[1,3] Qiongwei Ke,[1,3] Wenyan Wei,[2] Lili Cui,[1] and Yan Wang[1]

[1]Guangdong Key Laboratory of Age-Related Cardiac and Cerebral Diseases, Affiliated Hospital of Guangdong Medical University, Zhanjiang 524000, China; [2]Department of Gerontology, Affiliated Hospital of Guangdong Medical University, Zhanjiang 524000, China

Apolipoprotein E (ApoE) is a multifunctional protein critical for lipid metabolism and cholesterol homeostasis. In addition to being a well known genetic determinant of both neurodegenerative and cardiovascular diseases, ApoE is frequently involved in various viral infection-related diseases. Human ApoE protein is functionally polymorphic with three isoforms, namely, ApoE2, ApoE3, and ApoE4, with markedly altered protein structures and functions. ApoE4 is associated with increased susceptibility to infection with herpes simplex virus type-1 and HIV. Conversely, ApoE4 protects against hepatitis C virus and hepatitis B virus infection. With the outbreak of coronavirus disease 2019, ApoE4 has been shown to determine the incidence and progression of severe acute respiratory syndrome coronavirus 2 infection. These findings clearly indicate the critical role of ApoE in viral infection. Furthermore, *ApoE* polymorphism has various or even opposite effects in these infection processes, which are partly related to the structural features that distinguish the different ApoE statuses. In the current review, we summarize the emerging relationship between ApoE and viral infection, discuss the potential mechanisms, and identify future directions that may help to advance our understanding of the link between ApoE and viral infection.

INTRODUCTION

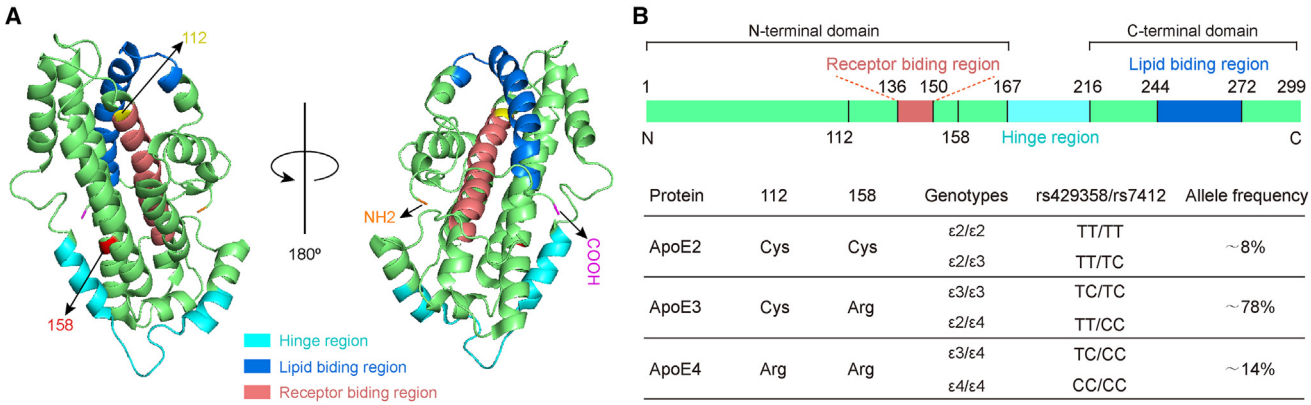
Apolipoprotein E (ApoE) is a multifunctional glycoprotein with the most well known roles in lipid transport and metabolism by serving as a ligand for cellular receptors such as low-density lipoprotein receptors (LDLRs) and heparan sulfate proteoglycans (HSPGs).[1] ApoE is produced primarily by hepatocytes and macrophages in peripheral tissues[2] and by astrocytes in the central nervous system (CNS).[3] ApoE has two structural and functional regions, the nitrogen-terminal domain (NTD) (amino acids 1–167) and the carbon-terminal domain (CTD) (amino acids 206–299), separated by a hinge domain (amino acids 168–205) (Figure 1A).[4] The NTD is arranged in a bundle of four antiparallel helices, contains the receptor-binding region (residues 136–150) and the HSPG-binding region (residues 142–150), and exhibits a weak interaction with lipids.[5] Human ApoE is functionally polymorphic with three isoforms, namely, ApoE2 (Cys112 and Cys158), ApoE3 (Cys112 and Arg158), and ApoE4 (Arg112 and Arg158), arising from allelic variants of *ε2*, *ε3*, and *ε4*, respectively (Figure 1B).[6] These amino acid polymorphisms profoundly alter the conformation, stability, and function of the ApoE protein.[4,7] In ApoE4, Arg-112 directs the side chain of Arg-61 to the aqueous environment, where it can interact with Glu-255, strengthening the N/CTD interaction, whereas Arg-61 is unable to interact with Glu-255 in ApoE3, leading to the more compact structure of ApoE4 compared with that of ApoE3.[8] Because of their different conformations, the three ApoE isoforms have different receptor-binding abilities and lipoprotein-binding preferences. The single residue substitution of Arg with Cys at position 158, which is apparently distant from the LDLR-binding site, critically disrupts the interactions between ApoE2 and LDLR.[9] ApoE isoforms also differentially regulate its lipidation with a potency rank order of ApoE4 < ApoE3 < ApoE2,[10,11] which has been reported to impact the receptor binding capacity, molecular stability, and function. Apart from modulating receptor binding, ApoE4 exhibits reduced stability and the lowest plasma ApoE protein levels compared with other ApoE isoforms.[12,13]

ApoE has been most extensively studied as a potent genetic risk modifier in Alzheimer disease (AD), and hetero and homozygosity for the *ε4* allele increasing AD risk by approximately 3-fold and 12-fold, respectively, compared with that of individuals harboring *ε3* homozygosity.[14] Conversely, *ApoE2* is considered protective,[15] whereas *ApoE3* is considered risk neutral because it is the most common isoform in the general population. In addition to AD, ApoE also impacts several other neurological diseases, such as Parkinson disease,[16] frontotemporal dementia,[17] and dementia with Lewy bodies.[18] ApoE is also important for cardiovascular disease. To date, the $ApoE^{-/-}$ mouse remains the most popular animal model in atherosclerosis research.[19] Apart from the pathologies of the above-mentioned neurological and cardiovascular diseases, ApoE has been shown to be dramatically involved in the life cycle and pathogenesis of viral infections, such as chronic hepatitis C virus (HCV), hepatitis B virus (HBV), herpes simplex virus type-1 (HSV-1), and HIV infections.

https://doi.org/10.1016/j.omtn.2023.07.031.

[3]These authors contributed equally

Correspondence: Yan Wang, Guangdong Key Laboratory of Age-Related Cardiac and Cerebral Diseases, Affiliated Hospital of Guangdong Medical University, Zhanjiang 524000, China.
E-mail: jwangyan@gdmu.edu.cn
Correspondence: Lili Cui, Guangdong Key Laboratory of Age-Related Cardiac and Cerebral Diseases, Affiliated Hospital of Guangdong Medical University, Zhanjiang 524000, China.
E-mail: cuilili@gdmu.edu.cn



Protein	112	158	Genotypes	rs429358/rs7412	Allele frequency
ApoE2	Cys	Cys	ε2/ε2	TT/TT	~8%
			ε2/ε3	TT/TC	
ApoE3	Cys	Arg	ε3/ε3	TC/TC	~78%
			ε2/ε4	TT/CC	
ApoE4	Arg	Arg	ε3/ε4	TC/CC	~14%
			ε4/ε4	CC/CC	

Figure 1. Structural model of human ApoE protein

(A) Three-dimensional structure of the ApoE protein (PDB: 2l7b). The human ApoE protein contains three main domains, the NTD (1–167) and the CTD (206–299), which are joined by a flexible hinge region (167–206). The NTD harbors four α-helices and contains the receptor-binding region (brown), and the CTD contains the lipid-binding domain (deep blue).

(B) Linear form of the ApoE peptide. The three ApoE isoforms differ at positions 112 and 158. ApoE2 (Cys112, Cys158) is encoded by the *ε2/ε2* (rs429358 TT/rs7412 TT) and *ε2/ε3* (rs429358 TT/rs7412 TC) alleles, with an allele frequency of approximately 8%; ApoE3 (Cys112, Arg158) is encoded by the *ε3/ε3* (rs429358 TT/rs7412 CC) and *ε2/ε4* (rs429358 TC/rs7412 TC) alleles, with an allele frequency of approximately 78%; and ApoE4 (Arg112, Arg158) is encoded by the *ε3/ε4* (rs429358 TC/rs7412 CC) and *ε4/ε4* (rs429358 CC/rs7412 CC) alleles, with an allele frequency of approximately 14%.

With the coronavirus disease 2019 (COVID-19) outbreak, emerging evidence demonstrates that *ApoE* is a vital genetic factor that determines host responses to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[20–22] Notably, ApoE plays different or even opposite roles in the process of viral infection. ApoE4 has been reported to be associated with increased susceptibility to infection with HSV-1[23] and HIV.[24] Conversely, ApoE4 protects against HCV and HBV infection.[25] Therefore, it is necessary to comprehensively summarize the role of ApoE and different ApoE isoforms in the process of viral infection.

Here, we systematically describe the emerging link between ApoE and viral infection with a focus on HCV, HBV, HIV, HSV-1, and, most recently, SARS-CoV-2 infections (Table 1). We further discuss the potential underlying mechanisms by which different ApoE isoforms contribute to or counteract these viral infections and further indicate future directions.

ApoE4 IS A MAJOR GENETIC RISK FACTOR FOR SARS-CoV-2 INFECTION

The COVID-19 pandemic, which was caused by the recently emerged SARS-CoV-2, caused more than 761 million cases and more than 6 million deaths worldwide as of 20 March 2023 (https//covid19.who.int). The spike protein located on the viral surface is the critical antigen of SARS-CoV-2. The spike protein has two subunits, and S1 contains a receptor-binding domain (RBD) that enables SARS-CoV-2 to interact with the angiotensin-converting enzyme 2 (ACE2) receptor to invade host cells.[48] It is well established that genetic backgrounds play an essential role in determining the clinical manifestations of COVID-19. Shortly after the discovery of SARS-CoV-2, researchers began to pay attention to the association between *ApoE* gene polymorphism and SARS-CoV-2 infection, because ApoE reportedly plays an important role in the process of viral infection, such as infection with HCV, HBV, HSV-1, and HIV. Kuo et al.[26] observed that in individuals registered in the United Kingdom Biobank, *ε4/ε4* homozygotes for the *ApoE* gene had a 2 times greater risk of SARS-CoV-2 (odds ratio [OR], 2.31; 95% confidence interval [CI], 1.65–3.24), even after adjusting for *ApoE4*-associated comorbidities, including dementia, coronary artery disease, hypertension and type 2 diabetes,[26] and a four times higher risk of death from COVID-19 (OR, 4.29; 95% CI, 2.38–7.72) than *ε3/ε3* homozygotes.[27] The correlation between ApoE4 and the risk and symptoms of COVID-19 was also independently detected by several other research teams.[21,49,50] For example, one study of Finnish individuals suggested that ApoE4 is associated with an enhanced incidence of severe COVID-19 and post-COVID mental fatigue. Some of these effects might be attributed to increased cerebrovascular damage.[51] In addition, ApoE4 is reportedly associated with an increased risk of delirium during COVID-19-related hospitalizations[52] and cognitive loss and dementia in long COVID-19.[53] More studies are needed to determine the ApoE isoform-related symptoms and pathological consequences in COVID-19 patients.

Why ApoE4 increases susceptibility to COVID-19 and disease severity is currently being explored (Figure 2). A recent *in vitro* study discovered that human-induced pluripotent stem cell-derived ApoE4 astrocytes and neurons are more susceptible to SARS-CoV-2 infection than cells expressing the nonpathogenic isoform ApoE3 and that ApoE4 astrocytes infected with coronavirus exert a stronger cytopathogenic effect than ApoE3 astrocytes.[54] Notably, a recent study reported that mice bearing the ApoE4 variant exhibited accelerated COVID-19 development and worse survival outcomes, which may be attributed to enhanced viral infection and dampened adaptive antiviral immunity.[20] As mentioned in the above section, ApoE performs its biological function partly by binding to receptors or proteins. Does

Table 1. Association between *ApoE* gene polymorphism and virus infection

Viruses/ ApoE4-related effects	SARS-CoV-2	HSV-1	HIV	HCV	HBV
Main findings	ApoE4 increases the risk and severity of COVID-19[26,27]	HSV-1 together with ApoE4 increase the risk of AD[23,28,29]	ApoE4 enhances HIV-1 infection and disease progression[24,30]	ApoE4 protects against HCV infection and liver fibrosis[31–33]	ApoE4 protects against liver cirrhosis caused by HBV[34,35]
Mechanisms	due to the tight structure of ApoE4 protein, the ability to inhibit the binding of Spik to ACE2 is weaker[22]	ApoE4 is more capable of promoting HSV-1 colonization into the brain than ApoE3 by interacting with HSPGs[36,37]	ApoE4 is less effective than other ApoE isoforms in competing with Tat for LRP1 binding[38]	the lower LDLR concentration in ApoE4 individuals may prevent HCV entry[32,39]	the mechanisms may be similar to those of ApoE in HCV infection and needs to be verified by experimental studies
	ApoE4 exhibits the lowest plasma ApoE concentration; thus, the effect on viral attachment is weaker[40]	—	the higher receptor-binding ability of ApoE4 facilitates contact between the virus and target cells[39]	the protein concentration of ApoE is reduced by *ApoE4*, which limits the role of ApoE in viral infection[40]	—
	ApoE4 is related to BBB leakage[41,42] and concomitant diseases[43,44]	—	ApoE4 is associated with higher immune reactivity and a stronger inflammatory response[45]	ApoE4-induced hyperbetalipoproteinemia influences LDLR-mediated viral uptake[46]	—
	ApoE4 is related to dysregulation of inflammation and the immune response[45]	—	ApoE4 is less efficient than ApoE3 in promoting cholesterol outflow from cells[47]	—	—

ApoE interact with the spike protein or ACE2 to affect viral infection? By using multiple protein interaction approaches, Xu et al. revealed that ApoE4 mildly impedes the docking of the spike protein to the ACE2 receptor at the host cell surface relative to ApoE3, which may be attributed to the more compact structure of ApoE4 compared with that of ApoE3, leading to a lesser reduction in spike/ACE2-mediated SARS-CoV-2 pseudovirus infection.[22] More specifically, the zinc domain, which has been demonstrated to be responsible for spike-ACE2 binding, is needed for the interaction between ACE2 and ApoE. Furthermore, the authors detected a significant inverse correlation between the serum ApoE levels and the concentrations of cytokines and chemokines in COVID-19 patients, suggesting that high levels of ApoE may inhibit the inflammatory response triggered by SARS-CoV-2. Thus, the lowest plasma levels of ApoE4 among all *ApoE* genotypes[40] may correspond with a higher inflammatory response in COVID-19 patients, which may be one of the potential reasons why ApoE4 accelerates COVID-19 progression.

Notably, a recent molecular dynamics simulation study observed that the CTD of serum ApoE may interact with the RBD of the spike protein, which may result in noticeable structural changes in ApoE and thereby to activation of the metabolic pathway of ApoE and to facilitation of viral infection.[55] Because *ApoE* gene polymorphisms may affect the binding of ApoE to receptors, it is reasonable to postulate that the binding ability to the spike protein varies between different ApoE isoforms, which leads to ApoE4 increasing the susceptibility to SARS-CoV-2 infection. However, using a biolayer interferometry binding assay, a recent study found that ApoE interacts with the RBD of the spike protein in an isoform-independent manner.[56] However, whether the interactions could affect the affinity between ACE2 and the spike protein and subsequently SARS-CoV-2 infection is unknown. In contrast, an *in vitro* study reported an inhibiting effect of ApoE on SARS-CoV-2 infection.[57]

Several other potential reported mechanisms are as follows. It has been reported that HSPGs, such as syndecan, may represent a potential process through which SARS-CoV-2 enters cells.[58,59] Some researchers speculate that the higher binding affinity between ApoE4 and HSPGs may promote viral infection, bridging the virus to the ACE2 receptor on the cell membrane and facilitating coronavirus spread through tissues.[60] In addition, ApoE4 has been reported to be associated with the incidence of neurodegenerative diseases,[43] diabetes,[44] and cardiovascular diseases.[44] The incidence and progression of COVID-19 may be impacted by these pre-existing comorbidities. Thus, although ApoE may have an independent effect on COVID-19, it is also important to consider ApoE4-related concomitant diseases. Additionally, ApoE4 is a risk factor for increased BBB leakage, thereby allowing coronavirus entry into the brain, where the virus can induce neuroinflammation, which may cause neurodegeneration.[41,42] Notably, in addition to acting as a major receptor of SARS-CoV-2, ACE2 was originally referred to as an antagonist of the renin-angiotensin system by catalyzing the conversion of angiotensin II to Ang 1–7; thus, ACE2 exerts multiple protective effects in several diseases, including heart failure, hypertension, myocardial infarction, AD, diabetes, and acute lung injury.[61–64] Accordingly, SARS-CoV-2 not only uses ACE2 to attach to cells, but also downregulates ACE2 protein expression,[65,66] which in turn leads to disruption of the protective effect of ACE2. ApoE4 has been reported to be associated with

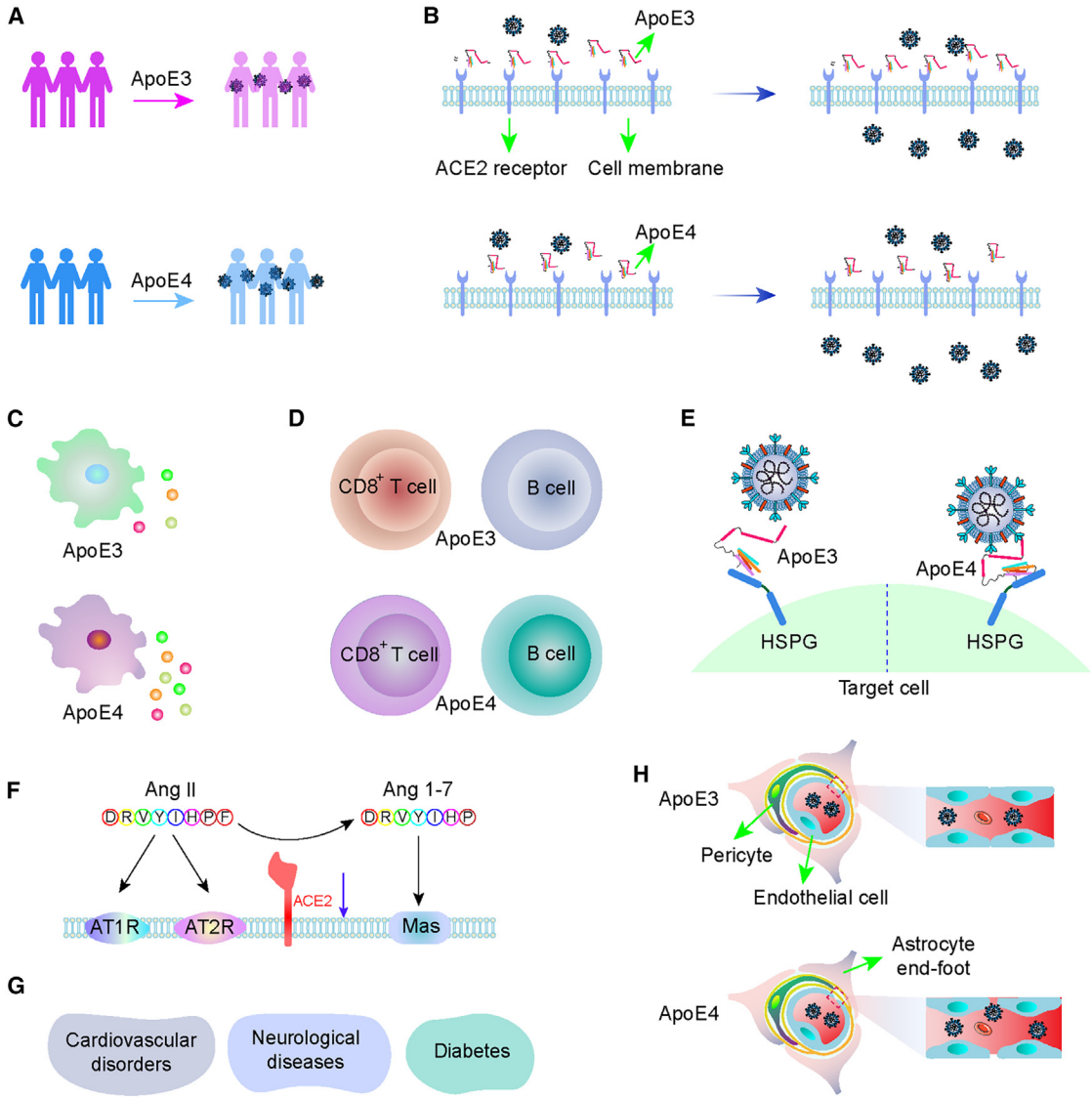


Figure 2. *ApoE4* is a genetic risk factor for COVID-19

(A) Individuals with the *ApoE4* genotype are more prone to COVID-19 infection and develop severe symptoms.

(B) On the one hand, because of the tight structure of the ApoE4 protein, the ability to inhibit the binding of the spike protein to the ACE2 receptor is weaker. On the other hand, ApoE4 exhibits the lowest plasma ApoE concentration, conferring weaker impeding effects on viral attachment.

(C) ApoE4 mediates increased inflammatory responses responsible for severe COVID-19 infection.

(D) *ApoE4* mice show dampened adaptive immune responses related to T and B cell activation at the early stage of SARS-CoV-2 infection and generate elevated antiviral $CD8^+$ T cell responses at the later stage of virus infection.

(E) ApoE4 is more capable of binding to HSPGs, which may strengthen viral infection.

(F) Downregulation of ACE2 by ApoE4 reduces the ability of ACE2 to hydrolyze Ang II to Ang 1–7, resulting in dysregulation of renin-angiotensin system and aggravation of tissue damage.

(G) ApoE4 is associated with susceptibility to several concomitant diseases, such as cardiovascular diseases, neurodegenerative diseases, and diabetes, which can increase the risk of acquisition and faster progression of COVID-19.

(H) ApoE4 has been linked to blood-brain barrier disruption, which may increase the risk of viral infection.

significant inhibition of ACE2 expression,[67] which may also be one of the reasons for the severity of COVID-19 caused by ApoE4.[56] The increased risk of COVID-19 infection with ApoE4 may partly explain why Black Africans suffer a higher possibility of COVID-19 severity and mortality; the prevalence of the *ε4*/*ε4* allele is more common in black African individuals (population frequency, 30%–40%) than in Caucasian and Asian individuals (population frequency, 7%–20% and 5%–15%, respectively).[68,69]

In summary, the potential mechanisms responsible for ApoE4-mediated SARS-CoV-2 infection and disease severity need to be further confirmed by more experimental studies. Moreover, whether *ApoE* gene polymorphisms affect the life cycle of SARS-CoV-2 is currently unknown and needs to be investigated.

ApoE IN COMBINATION WITH HSV-1 CONFERS A HIGH RISK OF AD

HSV-1 is highly prevalent as a latent form in the brains of both normal individuals and AD patients.[70] The latent form can be reactivated by various stimuli, such as stress, inflammation, and other factors, triggering a productive infection and consequent damage.[71] AD, the most common cause of dementia, is defined by the aberrant accumulation of β-amyloid (Aβ) plaques, neurofibrillary tangle deposits, and the progression of cognitive impairment.[72] There are many hypotheses regarding the etiology of AD, such as the tau hypothesis,[73] Aβ cascade hypothesis,[74] oxidative stress hypothesis,[75] ApoE cascade hypothesis,[7] and others. Accumulating epidemiologic and experimental evidence of the infectious etiology of AD[76,77] has sparked a paradigm shift from the prevailing hypothesis to the pathogen infection and antimicrobial protection hypothesis.[78] In particular, HSV-1 has gained greater attention because of its ability to cause recurrent, lifetime infection.[79] Infection with HSV-1 could trigger similar molecular hallmark features observed in AD, such as neuroinflammation, Aβ production, and the accumulation of phosphorylated tau.[76] In fact, numerous autopsy studies have confirmed the presence of HSV-1 DNA in the brain tissues of AD patients.[80] HSV-1 has been recognized as a causative agent of AD for more than 40 years, when Ball[81] noted similarities between HSV-1 encephalitis and AD in terms of affected brain regions and resulting memory deficits.

Nevertheless, the "infection theory" of AD failed to receive substantial attention and was largely ignored by AD researchers for a long time. A growing number of discoveries, however, have reignited interest in the infectious theory. HSV-1 DNA is present at greater frequency in the brains of AD patients than in those of healthy controls,[82] and viral DNA is especially prominent adjacent to Aβ plaques.[83] A recent retrospective cohort study examined a decade-long incidence of dementia in 8,362 subjects with HSV-1 or HSV-2 infection and in 25,086 matched controls without previous HSV infection and revealed that individuals diagnosed with HSV infections may have a 2.56-fold greater risk (95% CI, 2.351–2.795) of developing dementia, including AD.[84] Most provocatively, for the first time, the authors observed that anti-herpetic medication treatment significantly attenuated the incidence (reduced nearly 91%) of dementia in HSV-positive patients. The study provides important evidence supporting the hypothesis that reactivation and replication of viruses in the brain may increase the risk of developing dementia, including AD.

Nevertheless, HSV-1-infected individuals do not generally develop AD, and the existence of environmental or genetic predisposing factors seems to be necessary for this theory to be valid. Recent evidence has indicated that HSV-1 together with the *ε4* allele of the *ApoE* gene contributes to a strong risk of developing AD. Researchers have reported that subjects with HSV-1 DNA present in the brain and those carrying the *ApoE4* allele are at quite a high risk of developing AD relative to those harboring only one of these factors.[28] Additionally, two recent studies detected anti-HSV-1 immunoglobulins in aged participants, providing strong evidence that the cooperativity between *ApoE-ε4* and HSV-1 could contribute to the heightened risk of AD.[23,29] Among *ApoE4*-positive individuals, those who are more likely to exhibit HSV-1 reactivation, that is, IgM positivity or elevated IgG levels, had a 3.68- and 3.28-fold higher risk of AD, respectively. However, there was no significant correlation observed in non-*ApoE4* carriers. Moreover, in a large population-based cohort study, both cross-sectional and longitudinal data supported a close link between HSV infection and memory decline, especially among *ApoE ε4*-positive subjects.[85] In murine studies, *ApoE4* transgenic mice have higher expression of HSV-1, suggesting that ApoE4 may cause an increased risk of HSV-1 infection.[36,86,87] HSV-1 seropositive patients harboring the *ε4* allele of the *ApoE* gene have a higher possibility of developing symptomatic oral herpetic lesions (labialis) than *ε4*-negative carriers, with a relative ratio of 4.64.[88] The *ε4* allele is also reportedly a hazardous factor for cold sores (herpes labialis) caused by HSV-1.[28] Available evidence has indicated that the ApoE4 isoform can facilitate HSV-1 particles into cells.[89] ApoE and HSV-1 accumulate after entering a cell via an HSPG receptor.[90] During acute infection, ApoE4 is more capable of promoting HSV-1 colonization into the brain than ApoE3 by interacting with HSPGs and accelerates neurodegenerative processes related to ApoE4.[36,37]

In conclusion, the collaboration between ApoE4 and HSV-1 modifiers in the occurrence and development of AD has gained increasing attention and recognition in recent years. Although numerous clinical association studies have highlighted the close link between HSV-1 infection and AD occurrence, it remains challenging to determine the causative relationship between HSV-1 infection and AD. Moreover, how the *ε4* allele endows carriers with increased susceptibility to HSV-1 infection and ultimately the development of AD remains unclear.

ApoE4 ACCELERATES HIV INFECTION

HIV infection and the development of acquired immunodeficiency syndrome (AIDS) remain a serious global burden.[91] More than 38 million people are living with HIV worldwide in 2021, and 1.7 million people are newly infected yearly. Advances in effective antiretroviral therapy over the past decades have prolonged the lives of individuals infected with HIV. However, there is no cure for HIV; thus, pathogenic mechanisms need to be further explored. Because cholesterol is an important component of the HIV envelope, is tightly linked to multiple stages of the HIV life ,cycle and plays an important role in cholesterol transport, mounting evidence highlights the association between ApoE and HIV infection.

Proteomic analysis has revealed that ApoE protein can be detected in virus particles derived from HIV-1-infected monocyte-derived macrophages (MDMs).[92] HIV-1 infection specifically increases endogenous ApoE protein expression in human primary MDMs, which in

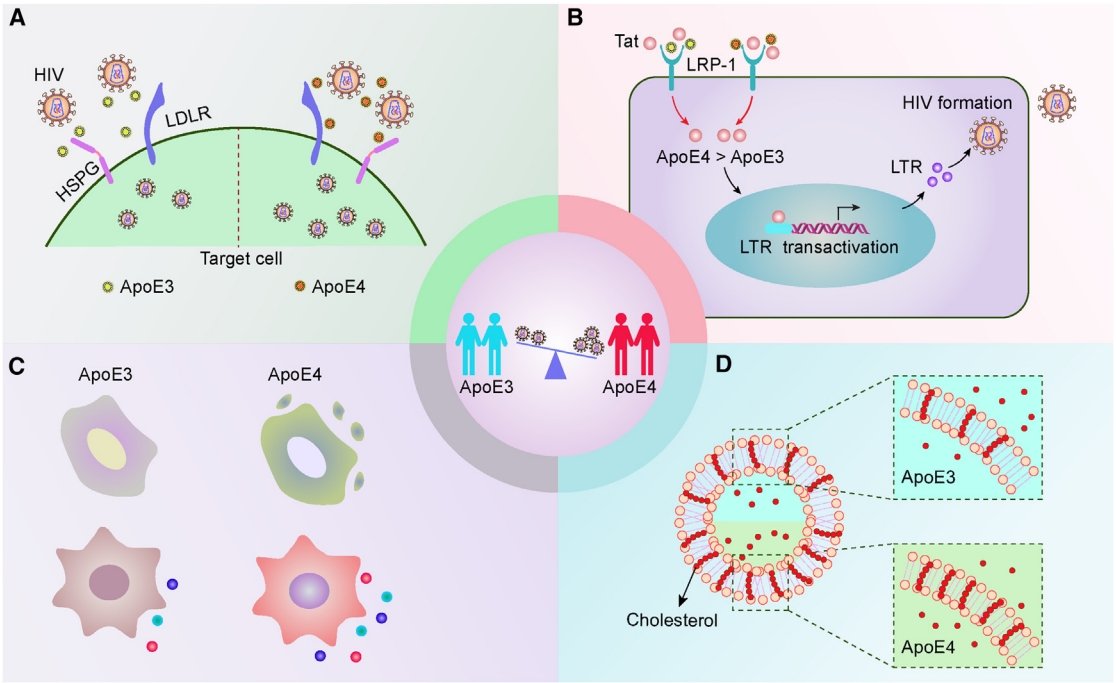


Figure 3. ApoE4 accelerates HIV infection

(A) The isoform-specific interaction between ApoE and its receptor (such as HSPGs and LDLR) may accelerate the contact between HIV and cell membranes, which facilitates virus cell entry.

(B) ApoE4 is less effective than ApoE3 in restricting Tat-mediated long terminal repeat (LTR) transactivation, a viral protein that is necessary for HIV-1 replication.

(C) ApoE4 is associated with higher immune reactivity and inflammatory responses, which may accelerate disease progression.

(D) ApoE4 is less able to promote cholesterol efflux than ApoE3, resulting in intracellular and plasma membrane raft-associated cholesterol accumulation, which is beneficial for the HIV infectious cycle.

turn impedes HIV-1 production and infectivity by inhibiting HIV-1 envelope glycoprotein production.[93] This study suggests that ApoE is a potential inhibitor of HIV-1-inducible viral production and infectivity. The authors further revealed that the decrease in viral infectivity induced by ApoE seems to be associated with lysosomal degradation of the HIV-1 envelope, which is critical for HIV-1 to enter target cells through the intracellular connection between ApoE and the HIV-1 envelope.[93]

Regarding ApoE isoforms, studies have reported that ApoE4 is associated with enhanced HIV-1 infection, disease progression, and an increased incidence of developing HIV-associated neurocognitive disorder (HAND) (Figure 3). Although the authors did not detect a positive correlation between the ApoE genotype and the incidence of acquiring HIV, they found that, compared with the *ε3*/*ε3* genotype, *ε4*/*ε4* homozygosity accelerates disease progression in a large group of European and African American individuals.[24] Consistent with the observed genotype-phenotype correlations, the *in vitro* results suggest that purified recombinant ApoE4 protein promotes HIV infection by elevating viral attachment and fusion. In addition, HIV-positive patients with *ε4* allele carriers have 2-fold higher rates of dementia (30% vs. 15%) and peripheral neuropathy (70% vs. 39%) than non-*ε4* allele carriers.[30] Similarly, ApoE4 is reportedly associated with worse cognitive performance in HIV-infected individuals.[94–97] However, based on neuropsychological assessments, several studies have failed to confirm the correlation between *ε4* alleles and HAND or *ε4* alleles and dementia with relatively large sample sizes and well-characterized HIV-infected patients.[98–101] These seemingly contradictory results regarding the effects of ApoE4 on cognitive performance in these HIV infections may be attributed, at least in part, to an age-dependent ApoE4 effect.

Several possibilities may underlie how ApoE isoforms differentially regulate HIV-AIDS pathogenesis. Transactivation of transcription protein (Tat) is a viral protein that is essential for HIV-1 replication and serves as a ligand of LRP1. A recent study found that ApoE4 is less effective than other ApoE isoforms in competing with Tat for LRP1 binding, impeding the internalization of Tat and Tat-mediated long terminal repeat transactivation.[38] Thus, the ApoE mimetic peptide might be a potential therapeutic candidate against HIV-1 infection. In addition, differential effects of ApoE isoforms may be exerted at the level of attachment to HSPGs, a rate-limiting step in HIV infection. The ApoE region harboring the heparin-binding domain (amino acids 142–147) has antiviral activity against HIV infection, which may be due to the inhibition of HIV attachment to HSPGs.[89] Compared with other isoforms, the

relatively lower HSPG-mediated very low-density lipoprotein in ApoE4-expressing cells[90] suggests that in *ApoE4* individuals, lower competition seems to be involved in promoting HSPG-mediated viral cell entry. Additionally, ApoE present on the viral envelope may promote the entry of viruses by targeting HIV particles to the LDLR.[92] The moderately higher receptor-binding ability of ApoE4 may facilitate contact between the virus and the target cells and, thus, increase the entry of HIV cells and subsequently disease progression.[39] Furthermore, ApoE4 is less efficient than ApoE3 in promoting cholesterol outflow from cells.[47] This different effect of ApoE isoforms on cellular cholesterol mobilization may support the accumulation of plasma membrane raft-associated cholesterol in *ApoE4* homozygotes, thus enhancing the viral infection cycle, including HIV fusion, entry, assembly, and release.[102] Moreover, because immune dysfunction is a prominent pathological feature of AIDS, the isoform-specific immunoregulation of ApoE may, therefore, accelerate disease progression.[45]

In summary, the influence of the *ApoE* phenotype on the pathogenesis of HIV infection is controversial, and the reason for this discrepancy is not yet clear. Further studies with longitudinal follow-up and larger sample sizes are warranted to clarify the isoform-dependent effect. In addition, the association between *ApoE* gene polymorphisms and the different subtypes of HIV-1 should be established in the future. Currently, the association between ApoE and HIV is still focused on the clinical correlation. More studies are clearly needed to reveal the mechanisms by which *ApoE* subtypes convey contrasting effects on HIV attachment and fusion.

ApoE4 PROTECTS AGAINST HCV INFECTION

HCV is a hepatotropic enveloped virus in the *Flaviviridae* family.[103] HCV infection remains one of the primary causes of liver damage, affecting more than 185 million individuals globally.[104] HCV infection of human hepatocytes is a multistep process that includes attachment, entry, uncoating, translation, replication, assembly, maturation, and release.[105] These infection processes are strongly associated with host lipid biology.[106] In the early stages of infection, HCV particles are captured by HSPGs and enter the cytoplasm through clathrin-mediated endocytosis upon interaction with various cellular membrane molecules, such as scavenger receptor BI, CD81, occludin, and claudin-1.[107] The hallmark of HCV is its existence in the sera of infected patients together with lipoproteins that form viral hybrid particles termed lipoviroparticles.[108] ApoE is enriched in HCV particles, suggesting that ApoE is possibly associated with the assembly and infectivity modification of HCV particles.[109,110]

As an important component of lipoproteins, ApoE exerts its major biological function of lipid metabolism, mainly by serving as a ligand that binds to specific cell-surface receptors, such as LDL receptor (LDLR), ApoE receptor 2, VLDL receptor, LRP1, and HSPG.[2,111] Some of these receptors, such as LDLR and HSPGs, are often involved in HCV entry. Indeed, several independent studies have indicated that ApoE participates in the entry, replication, assembly, and release of HCV and may be a potential therapeutic candidate to control HCV infection (Figure 4). ApoE facilitates HCV attachment through specific interactions with HSPGs,[112–114] and, among these, syndecan-1 and syndecan-4 are the main HSPGs that mediate viral attachment.[115,116] In addition, ApoE enhances HCV entry by interacting with LDLR and SR-B1 expressed on the surface of hepatocytes.[117–119] Additionally, some studies have shown that ApoE facilitates the assembly and production of HCV particles via a specific interaction with nonstructural protein 5A (NS5A);[120–122] specifically, the C-terminal α-helix domain (amino acids 205–280) of ApoE is responsible for the ApoE-NS5A interaction. However, other researchers have argued that the interaction involves the HCV envelope glycoprotein E2.[123] Depletion of *ApoE* decreases the formation of extracellular HCV particles without affecting the amount of intracellular viral nucleocapsids or viral envelopment,[123,124] indicating that ApoE is likely involved in the late assembly step of HCV, such as particle maturation. Nevertheless, a direct interaction between ApoE and E2 glycoproteins of HCV is detectable in the endoplasmic reticulum,[125] indicating that the association of ApoE with HCV also occurs at the early stage of assembly.

In an HCV cell culture system, downregulating ApoE by small interfering RNA remarkably suppresses the production of HCV particles, which can be restored by exogenously expressing the C-terminal construct of ApoE, suggesting the essential role of ApoE in HCV production.[120,122,126,127] In addition, ectopic expression of ApoE protein is also capable of increasing the low amounts of HCV particles released from mouse hepatoma cells, supporting the notion of ApoE as a limiting factor for HCV assembly in mouse cells.[128] More important, a recent study found that secreted ApoE is able to incorporate into secreted HCV particles, thus elevating viral infectivity, which is likely due to enhanced particle-HSPG interactions.[129] The incorporation of ApoE and virus also endows the virus with the ability to escape antibodies and, therefore, provides important guidance for the development of prophylactic hepatitis C vaccines. Together, these findings highlight the close relationship between ApoE and the life cycle of HCV both inside and outside infected cells.

The *ApoE* polymorphism is closely associated with HCV infection and is potentially an important tool for monitoring liver damage in patients harboring HCV. Studies have reported a significantly low frequency of the *ε4* allele in patients with HCV infections, and, compared with the *ε3* allele, the *ε4* allele exerts a protective effect against HCV infection and slows the progression of liver fibrosis caused by HCV.[31–33] The *ApoE4* allele has also been reported to have a protective effect on inflammatory progression in HCV-induced liver injury before and after liver transplantation.[130] In addition, the *ApoE4* allele is significantly under-represented in patients with chronic HCV infection, but over-represented in patients with spontaneously cleared HCV infection.[131] Moreover, in a cohort of HCV-infected Egyptian subjects, *ε4* allele carriers were found to be more prone to viral clearance and recovery after they received combined therapy, whereas *ε3* allele carriers are considered to have a high frequency of developing chronic infection and resistance to therapy.[132] These studies indicate that the ApoE4 status is closely involved in not only HCV infection, but also the disease treatment response.

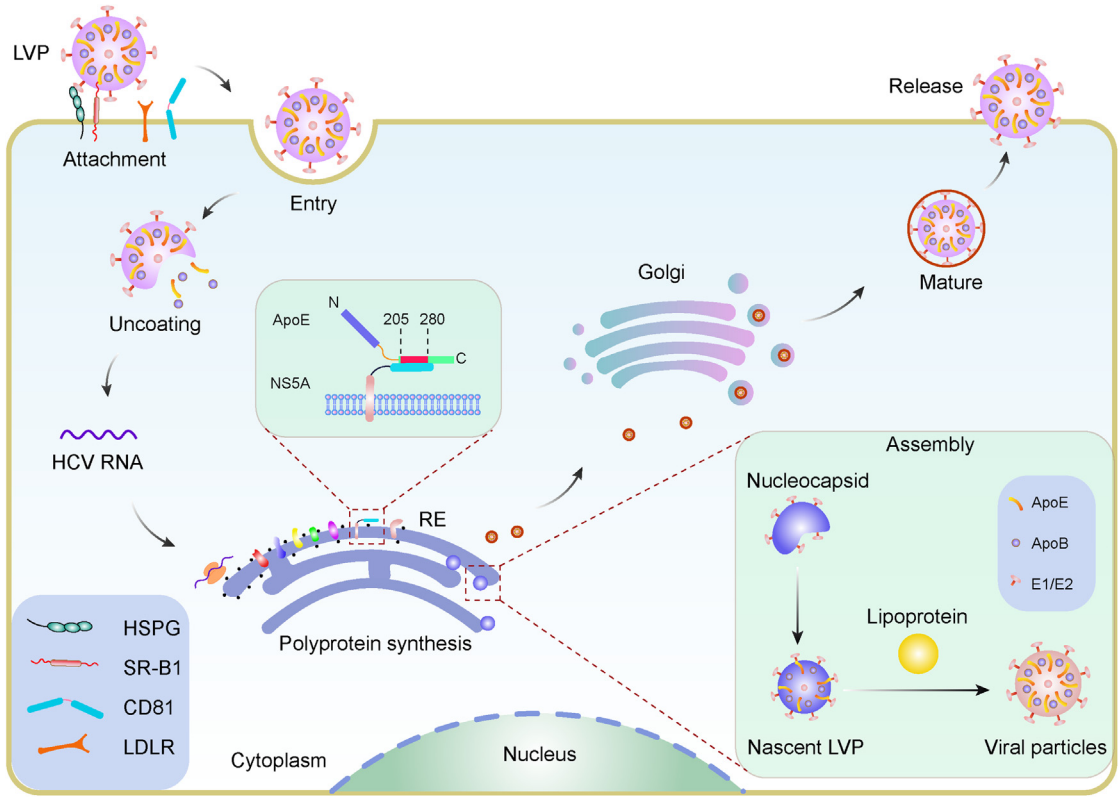


Figure 4. Involvement of ApoE in the HCV lifecycle

HCV infection is initiated by binding of the envelope glycoprotein E2 to CD81, occludin, claudin-1, and other entry factors expressed on the membrane of hepatocytes. High amounts of ApoE on the surface of HCV particles enable interactions with receptors, such as HSPGs, SR-B1, and LDLR, which may facilitate virus entry. After internalization into the cytoplasm, the viral genome is released, and viral RNA is then translated into a precursor polyprotein, which subsequently generates structural (core, E1, and E2) and nonstructural (p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B) proteins by protease processing. In the endoplasmic reticulum (ER), the E1 and E2 envelopes associate with ApoE and initiate lipoviroparticle (LVP) formation. At the same time, the nonstructural NS5A protein is involved in HCV replication and assembly and interacts with ApoE, especially the CTD of ApoE (amino acids at positions 205–280), which is responsible for the ApoE-NS5A interaction. Subsequently, the nascent LVP, together with lipoprotein, participates in viral particle formation in the lumen of the ER. The release of mature viral particles is thought to occur via the Golgi apparatus. The viral particles secreted from cells can also combine with ApoE in then circulation and thus participate in virus infection and virus escape from antibody-mediated neutralization.

Infectious viruses from cultured cells display similar characteristics to those observed in HCV patients. In an *in vitro* culture system, different subtypes of secreted ApoE in the cell culture medium can change the infectivity of HCV. For example, secreted ApoE4 decreases the infectivity of HCV, which is consistent with clinical findings, indicating that ApoE4 is related to a certain degree of HCV infection resistance.

How might ApoE4 protect against HCV infection and disease pathology? First, hyperbetalipoproteinemia, which is induced by ApoE4, has the ability to influence LDLR-mediated viral uptake because of the competitive binding between free betalipoproteins and virus-lipoprotein particles for free LDLR sites.[46] In addition, a lower LDLR concentration in *ApoE4* individuals may prevent or decrease HCV entry and spread between hepatocytes.[32,39] Moreover, it has been recognized that the protein stability and plasma concentration of ApoE are reduced by *ApoE4*,[40] which potentially limits the role of ApoE in viral infection.

In summary, as a part of the viral particle, ApoE is involved not only in the attachment and entry of HCV on the cell surface, but also in the assembly and release process of HCV viral particles from infected cells. Although ApoE4 tends to be resistant to chronic HCV infection, the detailed mechanism remains unclear. A better understanding of the life cycle of HCV and establishing an appropriate *in vitro* model to simulate the complex molecular network of HCV entry into cells will help researchers obtain deeper insight into the role of ApoE and the ApoE status in HCV infection.

ApoE IS IMPORTANT FOR HBV INFECTION AND PRODUCTION

HBV is a DNA virus that is transmitted through contact with infected blood and body secretions, specifically infects hepatocytes, and results in serious liver diseases such as chronic hepatitis, cirrhosis, and liver cancer.[133] Chronic HBV infection results in more than 257 million cases globally.[134] Currently, antiviral drugs against HBV can only

inhibit viral replication, but cannot eradicate the virus. Therefore, it is important to explore new mechanisms of HBV infection.

Recent studies have revealed that ApoE plays important roles in determining HBV infection. ApoE enrichment has been detected in purified HBV, and ApoE is incorporated into the viral envelope and promotes the infection, production and secretion of HBV.[135] Sodium taurocholate cotransporting polypeptide, LDLR, epidermal growth factor receptor, and HSPGs are important for HBV infection, likely by serving as virus attachment receptors.[136–138] Both LDLR family proteins and HSPGs are recognized as important ApoE-binding proteins.[139] Therefore, similar to the mechanism of HCV infection, ApoE probably promotes HBV infection by binding to LDLR and HSPGs, as evidenced by the fact that HBV infection is potently inhibited by the removal of HSPGs[137,140] or blockade of LDLR expression.[136] An *in vitro* pull-down assay using an ApoE-specific monoclonal antibody showed that ApoE is incorporated into the HBV envelope.[135] In addition, the serum ApoE concentrations in patients with HBV-related liver cirrhosis and hepatocellular carcinoma are obviously elevated relative to those in healthy controls.[141]

Landmark progress has been made regarding the role of ApoE in HBV infection in recent years, partly because of advances in *in vitro* culture cell lines that support HBV infection, replication, and morphogenesis.[142] Notably, antibody-specific targeting of the ApoE protein can be used to not only capture HBV, but also to effectively neutralize viral infectivity (>90%). Importantly, inhibiting ApoE protein expression or depleting *ApoE* by CRISPR/Cas9 gene editing technology gives rise to a more than 90% decrease in HBV infection and a greater than 80% decrease in HBV production, and these effects could be potently restored by ectopic expression of ApoE.[135] However, silencing the expression of other apolipoprotein members, such as ApoB, has no profound effect on HBV infection, suggesting the specific needs of ApoE for HBV infection. It is also important to note that silencing or knocking out the *ApoE* gene impacts viral DNA replication and nonenveloped capsid protein production in HBV-producing HepAD38 cells,[135] indicating that ApoE is specifically critical for HBV infection and production and is not essential for HBV protein expression or DNA replication.

Several studies have attempted to unravel the relationship between HBV infection and the ApoE status and have shown that *ApoE3* allele carriers are more likely to develop HBV-related cirrhosis,[34,141] and that *ApoE4* alleles have a protective effect on the development of liver cirrhosis.[34,35] However, all of these genetic association studies were based on a relatively small number of patients, especially when the subgroup analysis was stratified by ApoE isoforms and disease status. Further studies are, therefore, warranted to replicate these findings in larger participant cohorts to determine the association between the ApoE4 genotype and HBV infection, as well as disease progression.

In summary, significant progress has been made regarding the critical role and therapeutic potential of ApoE in HBV infection in recent years. The underlying mechanism may be similar to that of ApoE in HCV infection and needs to be verified by experimental studies, which will soon be performed because an *in vitro* cell culture system for HBV infection was established in recent years.

OTHER VIRUSES

In addition to the above mentioned viruses, there are several other viruses worth mentioning. *ApoE* was recently identified as an antiviral gene that restricts influenza A virus (IAV) infection by inhibiting IAV attachment to viral receptors, which attributes to the dysregulation of cellular cholesterol homeostasis.[57] Because the cholesterol levels are higher in obese individuals, the antiviral effect of ApoE by downregulating cellular cholesterol provides a reasonable explanation for the tendency of obese patients to develop severe disease after influenza infection. In addition, atherosclerotic plaques contain high cholesterol levels, which are more conducive to the invasion of viruses, leading to the aggravation of cardiovascular disease and hospitalization. Thus, these findings also explain the significant increase in hospital admissions caused by exacerbations of atherosclerotic cardiovascular illness during the influenza season. However, differences in IAV infection among ApoE subtypes were not analyzed in this study; thus, and these need to be addressed in follow-up studies, especially considering the significant differences in lipid metabolism among ApoE subtypes. In addition, the presence of *ApoE ε4* carriers is related to significantly higher levels of serum cytomegalovirus (CMV) IgG antibody.[143] CMV is known to infect the CNS, and the proinflammatory response to CMV infection confers a risk of chronic neurodegenerative diseases such as AD. Moreover, ApoE3 and ApoE4 are significantly linked to protection against hepatitis E virus infection.[144] These studies provide important supplementary information on the role of ApoE in viral infection, and the association and precise mechanisms connecting the relationships between ApoE and these viruses should be investigated in the future.

CONCLUSIONS AND PERSPECTIVES

The profound impact of ApoE on infectious diseases has been gradually recognized, especially in recent years. Here, we summarize the emerging correlation and mechanisms between ApoE and viral infection. During this process, several interesting issues arose and are worth discussing. First, what could be the main biological basis for the finding ApoE4 accelerates the infection of some viruses, such as HIV and SARS-CoV-2, but protects against others, such as HCV? On the one hand, the mechanisms underlying these viruses infecting host cells vary. The specific manifestation is that the receptors of virus-infected organisms are different, and the binding ability of ApoE4 to these receptors is different. After binding to these receptors, ApoE4 promotes or inhibits viral infection. On the other hand, ApoE is an essential component of viruses, such as HCV and HBV. Thus, ApoE is necessary for the reproduction of some viruses but may not have such a role with other viruses. Notably, the mechanism of ApoE4 in these viral infections is not fully understood and needs further exploration. Second, the liver is an important target of SARS-CoV-2 because of the expression of the ACE2 receptor in hepatocytes. In this case, ApoE4 is a protective factor for HCV and a risk factor for SARS-CoV-2; thus, to better understand the relationship among ApoE4, HCV, and

COVID-19, it would be interesting to examine whether HCV-infected patients carrying the *ApoE4* gene have an increased or decreased risk for SARS-CoV-2 infection. In addition, because the onset of the COVID-19 pandemic was far more recent, it is unclear whether the mechanism of ApoE in other viral infections is also suitable for SARS-CoV-2. For example, whether ApoE4 enhances the risk of COVID-19 infection through the HSPG receptor needs further experimental verification. In addition, whether ApoE has the ability to regulate the life cycle of SARS CoV-2 as it affects HBV and HCV remains unknown. In particular, a recent study found that ApoE affects influenza virus infection by affecting the cholesterol levels.[57] Does ApoE affect SARS-CoV-2 infection through the same mechanisms? Considering the isoform-related impact of ApoE in viral infections, it is important to assess the vaccination efficacy of these viruses in subjects with distinct ApoE genotypes. Moreover, two copies of the *ApoE3* Christchurch (R136S) mutation seem to decrease the risk of suffering AD, and the beneficial effect is likely due to the disrupted binding affinity between ApoE and its receptor, such as HSPG and LDLR.[145] It is reasonable to speculate that the R136S mutation may impact ApoE-related viral infection because these receptors are important for viral cellular entry. Notably, ApoE-based AD therapies have been studied extensively in the past two decades. Whether these approaches, such as converting ApoE4 to an "ApoE3-like" molecule, could be used to prevent ApoE isoform-relevant viral infection is worth exploring.

In conclusion, the critical role of ApoE in the process of viral infection has attracted increasing attention in recent years. Although much progress has been made, how single amino acid alterations dramatically influence the process of viral infection remains an open question. Summarizing the key role of ApoE in the process of viral infection will aid the development of effective strategies against the virus and directions for further research. It is anticipated that, with rapid advances in biological methods such as pseudoviruses, *in vitro* robust cell culture models of viral infection and propagation will be greatly promoted to reveal the process of viral infection and the role of ApoE in this process. Additionally, because of the enormous variability of viral genomic sequences, detecting the effect of ApoE on viral infections should be a long-term process.

ACKNOWLEDGMENTS

This work was supported by the National Nature Science Foundation of China (81671181 and 82101269), a project funded by the China Postdoctoral Science Foundation (2022M710848) and the Natural Science Foundation of Guangdong Province (2023A1515010179). The authors are grateful to American Journal Experts for providing professional language editing of the manuscript.

AUTHOR CONTRIBUTIONS

F.C. drafted the manuscript and designed the figures. Q.K. and W.W. reviewed the manuscript and revised it critically for important intellectual content. Y.W. and L.C. designed and reviewed the manuscript. All authors approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare that they have no competing interests.

REFERENCES

1. Getz, G.S., and Reardon, C.A. (2009). Apoprotein E as a lipid transport and signaling protein in the blood, liver, and artery wall. J. Lipid Res. *50*, S156–S161.
2. Mahley, R.W. (1988). Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. Science *240*, 622–630.
3. Xu, Q., Bernardo, A., Walker, D., Kanegawa, T., Mahley, R.W., and Huang, Y. (2006). Profile and regulation of apolipoprotein E (ApoE) expression in the CNS in mice with targeting of green fluorescent protein gene to the ApoE locus. J. Neurosci. *26*, 4985–4994.
4. Chen, Y., Strickland, M.R., Soranno, A., and Holtzman, D.M. (2021). Apolipoprotein E, structural insights and links to Alzheimer disease pathogenesis. Neuron *109*, 205–221.
5. Wilson, C., Wardell, M.R., Weisgraber, K.H., Mahley, R.W., and Agard, D.A. (1991). Three-dimensional structure of the LDL receptor-binding domain of human apolipoprotein E. Science *252*, 1817–1822.
6. Weisgraber, K.H. (1994). Apolipoprotein E: structure-function relationships. Adv. Protein Chem. *45*, 249–302.
7. Martens, Y.A., Zhao, N., Liu, C.C., Kanekiyo, T., Yang, A.J., Goate, A.M., Holtzman, D.M., and Bu, G. (2022). ApoE Cascade Hypothesis in the pathogenesis of Alzheimer's disease and related dementias. Neuron *110*, 1304–1317.
8. Mahley, R.W., Weisgraber, K.H., and Huang, Y. (2009). Apolipoprotein E: structure determines function, from atherosclerosis to Alzheimer's disease to AIDS. J. Lipid Res. *50*, S183–S188.
9. Weisgraber, K.H., Innerarity, T.L., and Mahley, R.W. (1982). Abnormal lipoprotein receptor-binding activity of the human E apoprotein due to cysteine-arginine interchange at a single site. J. Biol. Chem. *257*, 2518–2521.
10. Hubin, E., Verghese, P.B., van Nuland, N., and Broersen, K. (2019). Apolipoprotein E associated with reconstituted high-density lipoprotein-like particles is protected from aggregation. FEBS Lett. *593*, 1144–1153.
11. Morrow, J.A., Segall, M.L., Lund-Katz, S., Phillips, M.C., Knapp, M., Rupp, B., and Weisgraber, K.H. (2000). Differences in stability among the human apolipoprotein E isoforms determined by the amino-terminal domain. Biochemistry *39*, 11657–11666.
12. Gregg, R.E., Zech, L.A., Schaefer, E.J., Stark, D., Wilson, D., and Brewer, H.B., Jr. (1986). Abnormal *in vivo* metabolism of apolipoprotein E4 in humans. J. Clin. Invest. *78*, 815–821.
13. Huynh, T.P.V., Wang, C., Tran, A.C., Tabor, G.T., Mahan, T.E., Francis, C.M., Finn, M.B., Spellman, R., Manis, M., Tanzi, R.E., et al. (2019). Lack of hepatic apoE does not influence early Abeta deposition: observations from a new APOE knock-in model. Mol. Neurodegener. *14*, 37.
14. Roses, A.D. (1996). Apolipoprotein E alleles as risk factors in Alzheimer's disease. Annu. Rev. Med. *47*, 387–400.
15. Li, Z., Shue, F., Zhao, N., Shinohara, M., and Bu, G. (2020). APOE2: protective mechanism and therapeutic implications for Alzheimer's disease. Mol. Neurodegener. *15*, 63.
16. Fyfe, I. (2021). APOE epsilon4 influences Parkinson disease progression. Nat. Rev. Neurol. *17*, 726.
17. Mishra, A., Ferrari, R., Heutink, P., Hardy, J., Pijnenburg, Y., and Posthuma, D.; International FTD-Genomics Consortium (2017). Gene-based association studies report genetic links for clinical subtypes of frontotemporal dementia. Brain *140*, 1437–1446.
18. Jin, Y., Li, F., Sonoustoun, B., Kondru, N.C., Martens, Y.A., Qiao, W., Heckman, M.G., Ikezu, T.C., Li, Z., Burgess, J.D., et al. (2022). APOE4 exacerbates alpha-synuclein seeding activity and contributes to neurotoxicity in Alzheimer's disease with Lewy body pathology. Acta Neuropathol. *143*, 641–662.
19. Ilyas, I., Little, P.J., Liu, Z., Xu, Y., Kamato, D., Berk, B.C., Weng, J., and Xu, S. (2022). Mouse models of atherosclerosis in translational research. Trends Pharmacol. Sci. *43*, 920–939.

20. Ostendorf, B.N., Patel, M.A., Bilanovic, J., Hoffmann, H.H., Carrasco, S.E., Rice, C.M., and Tavazoie, S.F. (2022). Common human genetic variants of APOE impact murine COVID-19 mortality. Nature *611*, 346–351.

21. Chen, F., Chen, Y., Wang, Y., Ke, Q., and Cui, L. (2022). The COVID-19 pandemic and Alzheimer's disease: mutual risks and mechanisms. Transl. Neurodegener. *11*, 40.

22. Zhang, H., Shao, L., Lin, Z., Long, Q.X., Yuan, H., Cai, L., Jiang, G., Guo, X., Yang, R., Zhang, Z., et al. (2022). APOE interacts with ACE2 inhibiting SARS-CoV-2 cellular entry and inflammation in COVID-19 patients. Signal Transduct. Target. Ther. *7*, 261.

23. Linard, M., Letenneur, L., Garrigue, I., Doize, A., Dartigues, J.F., and Helmer, C. (2020). Interaction between APOE4 and herpes simplex virus type 1 in Alzheimer's disease. Alzheimers Dement. *16*, 200–208.

24. Burt, T.D., Agan, B.K., Marconi, V.C., He, W., Kulkarni, H., Mold, J.E., Cavrois, M., Huang, Y., Mahley, R.W., Dolan, M.J., et al. (2008). Apolipoprotein (apo) E4 enhances HIV-1 cell entry *in vitro*, and the APOE epsilon4/epsilon4 genotype accelerates HIV disease progression. Proc. Natl. Acad. Sci. USA *105*, 8718–8723.

25. Tréguier, Y., Bull-Maurer, A., and Roingeard, P. (2022). Apolipoprotein E, a crucial cellular protein in the lifecycle of hepatitis viruses. Int. J. Mol. Sci. *23*, 3676.

26. Kuo, C.L., Pilling, L.C., Atkins, J.L., Masoli, J.A.H., Delgado, J., Kuchel, G.A., and Melzer, D. (2020). APOE e4 genotype predicts severe COVID-19 in the UK biobank community cohort. J. Gerontol. A Biol. Sci. Med. Sci. *75*, 2231–2232.

27. Kuo, C.L., Pilling, L.C., Atkins, J.L., Masoli, J.A.H., Delgado, J., Kuchel, G.A., and Melzer, D. (2020). ApoE e4e4 genotype and mortality with COVID-19 in UK biobank. J. Gerontol. A Biol. Sci. Med. Sci. *75*, 1801–1803.

28. Itzhaki, R.F., Lin, W.R., Shang, D., Wilcock, G.K., Faragher, B., and Jamieson, G.A. (1997). Herpes simplex virus type 1 in brain and risk of Alzheimer's disease. Lancet *349*, 241–244.

29. Lopatko Lindman, K., Weidung, B., Olsson, J., Josefsson, M., Kok, E., Johansson, A., Eriksson, S., Hallmans, G., Elgh, F., and Lövheim, H. (2019). A genetic signature including apolipoprotein Eepsilon4 potentiates the risk of herpes simplex-associated Alzheimer's disease. Alzheimers Dement. *5*, 697–704.

30. Corder, E.H., Robertson, K., Lannfelt, L., Bogdanovic, N., Eggertsen, G., Wilkins, J., and Hall, C. (1998). HIV-infected subjects with the E4 allele for APOE have excess dementia and peripheral neuropathy. Nat. Med. *4*, 1182–1184.

31. Mueller, T., Gessner, R., Sarrazin, C., Graf, C., Halangk, J., Witt, H., Köttgen, E., Wiedenmann, B., and Berg, T. (2003). Apolipoprotein E4 allele is associated with poor treatment response in hepatitis C virus (HCV) genotype 1. Hepatology *38*, 1592. author reply 1592-1593.

32. Nascimento, J.C.R., Matos, G.A., Pereira, L.C., Mourão, A.E.C.C.B., Sampaio, A.M., Oriá, R.B., and Toniutto, P. (2020). Impact of apolipoprotein E genetic polymorphisms on liver disease: An essential review. Ann. Hepatol. *19*, 24–30.

33. Wozniak, M.A., Itzhaki, R.F., Faragher, E.B., James, M.W., Ryder, S.D., and Irving, W.L.; Trent HCV Study Group (2002). Apolipoprotein E-epsilon 4 protects against severe liver disease caused by hepatitis C virus. Hepatology *36*, 456–463.

34. Ahn, S.J., Kim, D.K., Kim, S.S., Bae, C.B., Cho, H.J., Kim, H.G., Kim, Y.J., Lee, J.H., Lee, H.J., Lee, M.Y., et al. (2012). Association between apolipoprotein E genotype, chronic liver disease, and hepatitis B virus. Clin. Mol. Hepatol. *18*, 295–301.

35. Toniutto, P., Fattovich, G., Fabris, C., Minisini, R., Burlone, M., Pravadelli, C., Peraro, L., Falleti, E., Caldera, F., and Bitetto, D. (2010). Genetic polymorphism at the apolipoprotein E locus affects the outcome of chronic hepatitis B. J. Med. Virol. *82*, 224–331.

36. Burgos, J.S., Ramirez, C., Sastre, I., Bullido, M.J., and Valdivieso, F. (2003). ApoE4 is more efficient than E3 in brain access by herpes simplex virus type 1. Neuroreport *14*, 1825–1827.

37. Appleby, B.S., Nacopoulos, D., Milano, N., Zhong, K., and Cummings, J.L. (2013). A review: treatment of Alzheimer's disease discovered in repurposed agents. Dement. Geriatr. Cogn. Disord *35*, 1–22.

38. Khan, N., Datta, G., Geiger, J.D., and Chen, X. (2018). Apolipoprotein E isoform dependently affects Tat-mediated HIV-1 LTR transactivation. J. Neuroinflammation *15*, 91.

39. Kuhlmann, I., Minihane, A.M., Huebbe, P., Nebel, A., and Rimbach, G. (2010). Apolipoprotein E genotype and hepatitis C, HIV and herpes simplex disease risk: a literature review. Lipids Health Dis. *9*, 8.

40. Rasmussen, K.L., Tybjærg-Hansen, A., Nordestgaard, B.G., and Frikke-Schmidt, R. (2019). Plasma levels of apolipoprotein E, APOE genotype, and all-cause and cause-specific mortality in 105 949 individuals from a white general population cohort. Eur. Heart J. *40*, 2813–2824.

41. Montagne, A., Nation, D.A., Sagare, A.P., Barisano, G., Sweeney, M.D., Chakhoyan, A., Pachicano, M., Joe, E., Nelson, A.R., D'Orazio, L.M., et al. (2020). APOE4 leads to blood-brain barrier dysfunction predicting cognitive decline. Nature *581*, 71–76.

42. Zhang, L., Zhou, L., Bao, L., Liu, J., Zhu, H., Lv, Q., Liu, R., Chen, W., Tong, W., Wei, Q., et al. (2021). SARS-CoV-2 crosses the blood-brain barrier accompanied with basement membrane disruption without tight junctions alteration. Signal Transduct. Target. Ther. *6*, 337.

43. Yamazaki, Y., Zhao, N., Caulfield, T.R., Liu, C.C., and Bu, G. (2019). Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat. Rev. Neurol. *15*, 501–518.

44. El-Lebedy, D., Raslan, H.M., and Mohammed, A.M. (2016). Apolipoprotein E gene polymorphism and risk of type 2 diabetes and cardiovascular disease. Cardiovasc. Diabetol. *15*, 12.

45. Lin, Y.T., Seo, J., Gao, F., Feldman, H.M., Wen, H.L., Penney, J., Cam, H.P., Gjoneska, E., Raja, W.K., Cheng, J., et al. (2018). APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. Neuron *98*, 1141–1154.e47.

46. Monazahian, M., Böhme, I., Bonk, S., Koch, A., Scholz, C., Grethe, S., and Thomssen, R. (1999). Low density lipoprotein receptor as a candidate receptor for hepatitis C virus. J. Med. Virol. *57*, 223–229.

47. Okoro, E.U., Zhao, Y., Guo, Z., Zhou, L., Lin, X., and Yang, H. (2012). Apolipoprotein E4 is deficient in inducing macrophage ABCA1 expression and stimulating the Sp1 signaling pathway. PLoS One *7*, e44430.

48. Clausen, T.M., Sandoval, D.R., Spliid, C.B., Pihl, J., Perrett, H.R., Painter, C.D., Narayanan, A., Majowicz, S.A., Kwong, E.M., McVicar, R.N., et al. (2020). SARS-CoV-2 infection depends on cellular heparan sulfate and ACE2. Cell *183*, 1043–1057.e15.

49. Hubacek, J.A., Dlouha, L., Dusek, L., Majek, O., and Adamkova, V. (2021). Apolipoprotein E4 allele in subjects with COVID-19. Gerontology *67*, 320–322.

50. Del Ser, T., Fernández-Blázquez, M.A., Valentí, M., Zea-Sevilla, M.A., Frades, B., Alfayate, E., Saiz, L., Calero, O., García-López, F.J., Rábano, A., et al. (2021). Residence, clinical features, and genetic risk factors associated with symptoms of COVID-19 in a cohort of older people in Madrid. Gerontology *67*, 281–289.

51. Kurki, S.N., Kantonen, J., Kaivola, K., Hokkanen, L., Mäyränpää, M.I., Puttonen, H., Finn, G., Martola, J., Pöyhönen, M., Kero, M., et al. (2021). APOE epsilon4 associates with increased risk of severe COVID-19, cerebral microhaemorrhages and post-COVID mental fatigue: a Finnish biobank, autopsy and clinical study. Acta Neuropathol. Commun. *9*, 199.

52. Kuo, C.L., Pilling, L.C., Atkins, J.L., Fortinsky, R.H., Kuchel, G.A., and Melzer, D. (2022). APOE e4 genotypes increase risk of delirium during COVID-19-related hospitalizations: evidence from a large UK Cohort. J. Gerontol. A Biol. Sci. Med. Sci. *77*, 879–880.

53. Maiese, K. (2022). Apolipoprotein-epsilon4 allele (APOE-epsilon4) as a mediator of cognitive loss and dementia in long COVID-19. Curr. Neurovasc. Res. *19*, 435–439.

54. Wang, C., Zhang, M., Garcia, G., Jr., Tian, E., Cui, Q., Chen, X., Sun, G., Wang, J., Arumugaswami, V., and Shi, Y. (2021). ApoE-Isoform-dependent SARS-CoV-2 neurotropism and cellular response. Cell Stem Cell *28*, 331–342.e5.

55. Yin, Y.W., Sheng, Y.J., Wang, M., Ma, Y.Q., and Ding, H.M. (2021). Interaction of serum proteins with SARS-CoV-2 RBD. Nanoscale *13*, 12865–12873.

56. Chen, F., Chen, Y., Ke, Q., Wang, Y., Gong, Z., Chen, X., Cai, Y., Li, S., Sun, Y., Peng, X., et al. (2023). ApoE4 associated with severe COVID-19 outcomes via downregulation of ACE2 and imbalanced RAS pathway. J. Transl. Med. *21*, 103.

57. Gao, P., Ji, M., Liu, X., Chen, X., Liu, H., Li, S., Jia, B., Li, C., Ren, L., Zhao, X., et al. (2022). Apolipoprotein E mediates cell resistance to influenza virus infection. Sci. Adv. *8*, eabm6668.

58. Hudák, A., Letoha, A., Szilák, L., and Letoha, T. (2021). Contribution of syndecans to the cellular entry of SARS-CoV-2. Int. J. Mol. Sci. *22*, 5336.

59. Kulminski, A.M., Raghavachari, N., Arbeev, K.G., Culminskaya, I., Arbeeva, L., Wu, D., Ukraintseva, S.V., Christensen, K., and Yashin, A.I. (2016). Protective role of the apolipoprotein E2 allele in age-related disease traits and survival: evidence from the long life family study. Biogerontology *17*, 893–905.

60. Lima, F.B., Bezerra, K.C., Nascimento, J.C.R., Meneses, G.C., and Oriá, R.B. (2022). Risk factors for severe COVID-19 and Hepatitis C infections: the dual role of apolipoprotein E4. Front. Immunol. *13*, 721793.

61. Hamming, I., Cooper, M.E., Haagmans, B.L., Hooper, N.M., Korstanje, R., Osterhaus, A.D.M.E., Timens, W., Turner, A.J., Navis, G., and van Goor, H. (2007). The emerging role of ACE2 in physiology and disease. J. Pathol. *212*, 1–11.

62. Patel, V.B., Zhong, J.C., Grant, M.B., and Oudit, G.Y. (2016). Role of the ACE2/Angiotensin 1-7 axis of the renin-angiotensin system in heart failure. Circ. Res. *118*, 1313–1326.

63. Lim, S., Bae, J.H., Kwon, H.S., and Nauck, M.A. (2021). COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat. Rev. Endocrinol. *17*, 11–30.

64. Evans, C.E., Miners, J.S., Piva, G., Willis, C.L., Heard, D.M., Kidd, E.J., Good, M.A., and Kehoe, P.G. (2020). ACE2 activation protects against cognitive decline and reduces amyloid pathology in the Tg2576 mouse model of Alzheimer's disease. Acta Neuropathol. *139*, 485–502.

65. Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., Yang, P., Zhang, Y., Deng, W., et al. (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat. Med. *11*, 875–879.

66. Lei, Y., Zhang, J., Schiavon, C.R., He, M., Chen, L., Shen, H., Zhang, Y., Yin, Q., Cho, Y., Andrade, L., et al. (2021). SARS-CoV-2 spike protein impairs endothelial function via downregulation of ACE 2. Circ. Res. *128*, 1323–1326.

67. Kehoe, P.G., Wong, S., Al Mulhim, N., Palmer, L.E., and Miners, J.S. (2016). Angiotensin-converting enzyme 2 is reduced in Alzheimer's disease in association with increasing amyloid-beta and tau pathology. Alzheimer's Res. Ther. *8*, 50.

68. Abondio, P., Sazzini, M., Garagnani, P., Boattini, A., Monti, D., Franceschi, C., Luiselli, D., and Giuliani, C. (2019). The genetic variability of APOE in different human populations and its implications for longevity. Genes *10*, 222.

69. Holmes, L., Jr., Enwere, M., Williams, J., Ogundele, B., Chavan, P., Piccoli, T., Chinacherem, C., Comeaux, C., Pelaez, L., Okundaye, O., et al. (2020). Black-white risk differentials in COVID-19 (SARS-COV2) transmission, mortality and case fatality in the United States: translational epidemiologic perspective and challenges. Int. J. Environ. Res. Public Health *17*, 4322.

70. Jamieson, G.A., Maitland, N.J., Wilcock, G.K., Craske, J., and Itzhaki, R.F. (1991). Latent herpes simplex virus type 1 in normal and Alzheimer's disease brains. J. Med. Virol. *33*, 224–227.

71. Marcocci, M.E., Napoletani, G., Protto, V., Kolesova, O., Piacentini, R., Li Puma, D.D., Lomonte, P., Grassi, C., Palamara, A.T., and De Chiara, G. (2020). Herpes Simplex Virus-1 in the brain: the dark side of a sneaky infection. Trends Microbiol. *28*, 808–820.

72. Scheltens, P., De Strooper, B., Kivipelto, M., Holstege, H., Chételat, G., Teunissen, C.E., Cummings, J., and van der Flier, W.M. (2021). Alzheimer's disease. Lancet *397*, 1577–1590.

73. Congdon, E.E., and Sigurdsson, E.M. (2018). Tau-targeting therapies for Alzheimer disease. Nat. Rev. Neurol. *14*, 399–415.

74. Frisoni, G.B., Altomare, D., Thal, D.R., Ribaldi, F., van der Kant, R., Ossenkoppele, R., Blennow, K., Cummings, J., van Duijn, C., Nilsson, P.M., et al. (2022). The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. Nat. Rev. Neurosci. *23*, 53–66.

75. Butterfield, D.A., and Halliwell, B. (2019). Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. Nat. Rev. Neurosci. *20*, 148–160.

76. Fülöp, T., Itzhaki, R.F., Balin, B.J., Miklossy, J., and Barron, A.E. (2018). Role of microbes in the development of Alzheimer's disease: state of the art - an international symposium presented at the 2017 IAGG congress in San Francisco. Front. Genet. *9*, 362.

77. Itzhaki, R.F., Lathe, R., Balin, B.J., Ball, M.J., Bearer, E.L., Braak, H., Bullido, M.J., Carter, C., Clerici, M., Cosby, S.L., et al. (2016). Microbes and Alzheimer's disease. J. Alzheimers Dis. *51*, 979–984.

78. Haas, J.G., and Lathe, R. (2018). Microbes and Alzheimer's disease: new findings call for a paradigm change. Trends Neurosci. *41*, 570–573.

79. Ikeda, T., and Tsuboya, T. (2020). Letter to the editor Re: author's response to letter to the editor. Arch. Phys. Med. Rehabil. *101*, 1096–1097.

80. Steel, A.J., and Eslick, G.D. (2015). Herpes viruses increase the risk of Alzheimer's disease: a meta-analysis. J. Alzheimers Dis. *47*, 351–364.

81. Ball, M.J. (1982). Limbic predilection in Alzheimer dementia: is reactivated herpesvirus involved? Can. J. Neurol. Sci. *9*, 303–306.

82. Itzhaki, R.F. (2018). Corroboration of a major role for Herpes Simplex Virus type 1 in Alzheimer's disease. Front. Aging Neurosci. *10*, 324.

83. Wozniak, M.A., Mee, A.P., and Itzhaki, R.F. (2009). Herpes simplex virus type 1 DNA is located within Alzheimer's disease amyloid plaques. J. Pathol. *217*, 131–138.

84. Tzeng, N.S., Chung, C.H., Lin, F.H., Chiang, C.P., Yeh, C.B., Huang, S.Y., Lu, R.B., Chang, H.A., Kao, Y.C., Yeh, H.W., et al. (2018). Anti-herpetic medications and reduced risk of dementia in patients with herpes simplex virus infections-a nationwide, population-based cohort study in Taiwan. Neurotherapeutics *15*, 417–429.

85. Lövheim, H., Norman, T., Weidung, B., Olsson, J., Josefsson, M., Adolfsson, R., Nyberg, L., and Elgh, F. (2019). Herpes Simplex Virus, APOEvarepsilon4, and cognitive decline in old age: results from the Betula Cohort study. J. Alzheimers Dis. *67*, 211–220.

86. Burgos, J.S., Ramirez, C., Sastre, I., and Valdivieso, F. (2006). Effect of apolipoprotein E on the cerebral load of latent herpes simplex virus type 1 DNA. J. Virol. *80*, 5383–5387.

87. Bhattacharjee, P.S., Neumann, D.M., Foster, T.P., Bouhanik, S., Clement, C., Vinay, D., Thompson, H.W., and Hill, J.M. (2008). Effect of human apolipoprotein E genotype on the pathogenesis of experimental ocular HSV-1. Exp. Eye Res. *87*, 122–130.

88. Koelle, D.M., Magaret, A., Warren, T., Schellenberg, G.D., and Wald, A. (2010). APOE genotype is associated with oral herpetic lesions but not genital or oral herpes simplex virus shedding. Sex. Transm. Infect. *86*, 202–206.

89. Dobson, C.B., Sales, S.D., Hoggard, P., Wozniak, M.A., and Crutcher, K.A. (2006). The receptor-binding region of human apolipoprotein E has direct anti-infective activity. J. Infect. Dis. *193*, 442–450.

90. Ji, Z.S., Pitas, R.E., and Mahley, R.W. (1998). Differential cellular accumulation/retention of apolipoprotein E mediated by cell surface heparan sulfate proteoglycans. Apolipoproteins E3 and E2 greater than e4. J. Biol. Chem. *273*, 13452–13460.

91. Holmes, C.B., Kilonzo, N., Zhao, J., Johnson, L.F., Kalua, T., Hasen, N., Morrison, M., Marston, M., Smith, T., Benech, I., et al. (2021). Strengthening measurement and performance of HIV prevention programmes. Lancet. HIV *8*, e306–e310.

92. Chertova, E., Chertov, O., Coren, L.V., Roser, J.D., Trubey, C.M., Bess, J.W., Jr., Sowder, R.C., 2nd, Barsov, E., Hood, B.L., Fisher, R.J., et al. (2006). Proteomic and biochemical analysis of purified human immunodeficiency virus type 1 produced from infected monocyte-derived macrophages. J. Virol. *80*, 9039–9052.

93. Siddiqui, R., Suzu, S., Ueno, M., Nasser, H., Koba, R., Bhuyan, F., Noyori, O., Hamidi, S., Sheng, G., Yasuda-Inoue, M., et al. (2018). Apolipoprotein E is an HIV-1-inducible inhibitor of viral production and infectivity in macrophages. PLoS Pathog. *14*, e1007372.

94. Chang, L., Andres, M., Sadino, J., Jiang, C.S., Nakama, H., Miller, E., and Ernst, T. (2011). Impact of apolipoprotein E epsilon4 and HIV on cognition and brain atrophy: antagonistic pleiotropy and premature brain aging. Neuroimage *58*, 1017–1027.

95. Andres, M.A., Feger, U., Nath, A., Munsaka, S., Jiang, C.S., and Chang, L. (2011). APOE epsilon 4 allele and CSF APOE on cognition in HIV-infected subjects. J. Neuroimmune Pharmacol. *6*, 389–398.

96. Mukerji, S.S., Locascio, J.J., Misra, V., Lorenz, D.R., Holman, A., Dutta, A., Penugonda, S., Wolinsky, S.M., and Gabuzda, D. (2016). Lipid profiles and APOE4 allele impact midlife cognitive decline in HIV-infected men on antiretroviral therapy. Clin. Infect. Dis. *63*, 1130–1139.

97. Mu, T., Wei, J., Sun, J., Jin, J., Zhang, T., Wu, H., and Su, B. (2022). Association of apolipoprotein E epsilon 4 and cognitive impairment in adults living with human immunodeficiency virus: a meta-analysis. Chin. Med. J. *135*, 2677–2686.

98. Becker, J.T., Martinson, J.J., Penugonda, S., Kingsley, L., Molsberry, S., Reynolds, S., Aronow, A., Goodkin, K., Levine, A., Martin, E., et al. (2015). No association between Apoepsilon4 alleles, HIV infection, age, neuropsychological outcome, or death. J. Neurovirol. *21*, 24–31.

99. Morgan, E.E., Woods, S.P., Letendre, S.L., Franklin, D.R., Bloss, C., Goate, A., Heaton, R.K., Collier, A.C., Marra, C.M., Gelman, B.B., et al. (2013). Apolipoprotein E4 genotype does not increase risk of HIV-associated neurocognitive disorders. J. Neurovirol. *19*, 150–156.

100. Joska, J.A., Combrinck, M., Valcour, V.G., Hoare, J., Leisegang, F., Mahne, A.C., Myer, L., and Stein, D.J. (2010). Association between apolipoprotein E4 genotype and human immunodeficiency virus-associated dementia in younger adults starting antiretroviral therapy in South Africa. J. Neurovirol. *16*, 377–383.

101. Cooley, S.A., Paul, R.H., Fennema-Notestine, C., Morgan, E.E., Vaida, F., Deng, Q., Chen, J.A., Letendre, S., Ellis, R., Clifford, D.B., et al. (2016). Apolipoprotein E epsilon4 genotype status is not associated with neuroimaging outcomes in a large cohort of HIV+ individuals. J. Neurovirol. *22*, 607–614.

102. Burt, T.D., Agan, B.K., Marconi, V.C., He, W., Kulkarni, H., Mold, J.E., Cavrois, M., Huang, Y., Mahley, R.W., Dolan, M.J., et al. (2008). Apolipoprotein (apo) E4 enhances HIV-1 cell entry *in vitro*, and the APOE epsilon4/epsilon4 genotype accelerates HIV disease progression. Proc. Natl. Acad. Sci. USA *105*, 8718–8723.

103. Pietschmann, T., and Brown, R.J.P. (2019). Hepatitis C virus. Trends Microbiol. *27*, 379–380.

104. GBD 2016 Causes of Death Collaborators (2017). Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet *390*, 1151–1210.

105. Bukh, J. (2016). The history of hepatitis C virus (HCV): Basic research reveals unique features in phylogeny, evolution and the viral life cycle with new perspectives for epidemic control. J. Hepatol. *65*, S2–S21.

106. Bassendine, M.F., Sheridan, D.A., Bridge, S.H., Felmlee, D.J., and Neely, R.D.G. (2013). Lipids and HCV. Semin. Immunopathol. *35*, 87–100.

107. Douam, F., Lavillette, D., and Cosset, F.L. (2015). The mechanism of HCV entry into host cells. Prog. Mol. Biol. Transl. Sci. *129*, 63–107.

108. André, P., Komurian-Pradel, F., Deforges, S., Perret, M., Berland, J.L., Sodoyer, M., Pol, S., Bréchot, C., Paranhos-Baccalà, G., and Lotteau, V. (2002). Characterization of low- and very-low-density hepatitis C virus RNA-containing particles. J. Virol. *76*, 6919–6928.

109. Huang, H., Sun, F., Owen, D.M., Li, W., Chen, Y., Gale, M., Jr., and Ye, J. (2007). Hepatitis C virus production by human hepatocytes dependent on assembly and secretion of very low-density lipoproteins. Proc. Natl. Acad. Sci. USA *104*, 5848–5853.

110. Catanese, M.T., Uryu, K., Kopp, M., Edwards, T.J., Andrus, L., Rice, W.J., Silvestry, M., Kuhn, R.J., and Rice, C.M. (2013). Ultrastructural analysis of hepatitis C virus particles. Proc. Natl. Acad. Sci. USA *110*, 9505–9510.

111. Huang, Y., and Mahley, R.W. (2014). Apolipoprotein E: structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. Neurobiol. Dis. *72*, 3–12.

112. Jiang, J., Wu, X., Tang, H., and Luo, G. (2013). Apolipoprotein E mediates attachment of clinical hepatitis C virus to hepatocytes by binding to cell surface heparan sulfate proteoglycan receptors. PLoS One *8*, e67982.

113. Xu, Y., Martinez, P., Séron, K., Luo, G., Allain, F., Dubuisson, J., and Belouzard, S. (2015). Characterization of hepatitis C virus interaction with heparan sulfate proteoglycans. J. Virol. *89*, 3846–3858.

114. Jiang, J., Cun, W., Wu, X., Shi, Q., Tang, H., and Luo, G. (2012). Hepatitis C virus attachment mediated by apolipoprotein E binding to cell surface heparan sulfate. J. Virol. *86*, 7256–7267.

115. Lefèvre, M., Felmlee, D.J., Parnot, M., Baumert, T.F., and Schuster, C. (2014). Syndecan 4 is involved in mediating HCV entry through interaction with lipoviral particle-associated apolipoprotein E. PLoS One *9*, e95550.

116. Shi, Q., Jiang, J., and Luo, G. (2013). Syndecan-1 serves as the major receptor for attachment of hepatitis C virus to the surfaces of hepatocytes. J. Virol. *87*, 6866–6875.

117. Owen, D.M., Huang, H., Ye, J., and Gale, M., Jr. (2009). Apolipoprotein E on hepatitis C virion facilitates infection through interaction with low-density lipoprotein receptor. Virology *394*, 99–108.

118. Mazumdar, B., Banerjee, A., Meyer, K., and Ray, R. (2011). Hepatitis C virus E1 envelope glycoprotein interacts with apolipoproteins in facilitating entry into hepatocytes. Hepatology *54*, 1149–1156.

119. Dao Thi, V.L., Granier, C., Zeisel, M.B., Guérin, M., Mancip, J., Granio, O., Penin, F., Lavillette, D., Bartenschlager, R., Baumert, T.F., et al. (2012). Characterization of hepatitis C virus particle subpopulations reveals multiple usage of the scavenger receptor BI for entry steps. J. Biol. Chem. *287*, 31242–31257.

120. Jiang, J., and Luo, G. (2009). Apolipoprotein E but not B is required for the formation of infectious hepatitis C virus particles. J. Virol. *83*, 12680–12691.

121. Benga, W.J.A., Krieger, S.E., Dimitrova, M., Zeisel, M.B., Parnot, M., Lupberger, J., Hildt, E., Luo, G., McLauchlan, J., Baumert, T.F., et al. (2010). Apolipoprotein E interacts with hepatitis C virus nonstructural protein 5A and determines assembly of infectious particles. Hepatology *51*, 43–53.

122. Cun, W., Jiang, J., and Luo, G. (2010). The C-terminal alpha-helix domain of apolipoprotein E is required for interaction with nonstructural protein 5A and assembly of hepatitis C virus. J. Virol. *84*, 11532–11541.

123. Lee, J.Y., Acosta, E.G., Stoeck, I.K., Long, G., Hiet, M.S., Mueller, B., Fackler, O.T., Kallis, S., and Bartenschlager, R. (2014). Apolipoprotein E likely contributes to a maturation step of infectious hepatitis C virus particles and interacts with viral envelope glycoproteins. J. Virol. *88*, 12422–12437.

124. Hueging, K., Doepke, M., Vieyres, G., Bankwitz, D., Frentzen, A., Doerrbecker, J., Gumz, F., Haid, S., Wölk, B., Kaderali, L., et al. (2014). Apolipoprotein E codetermines tissue tropism of hepatitis C virus and is crucial for viral cell-to-cell transmission by contributing to a postenvelopment step of assembly. J. Virol. *88*, 1433–1446.

125. Boyer, A., Dumans, A., Beaumont, E., Etienne, L., Roingeard, P., and Meunier, J.C. (2014). The association of hepatitis C virus glycoproteins with apolipoproteins E and B early in assembly is conserved in lipoviral particles. J. Biol. Chem. *289*, 18904–18913.

126. Hishiki, T., Shimizu, Y., Tobita, R., Sugiyama, K., Ogawa, K., Funami, K., Ohsaki, Y., Fujimoto, T., Takaku, H., Wakita, T., et al. (2010). Infectivity of hepatitis C virus is influenced by association with apolipoprotein E isoforms. J. Virol. *84*, 12048–12057.

127. Chang, K.S., Jiang, J., Cai, Z., and Luo, G. (2007). Human apolipoprotein e is required for infectivity and production of hepatitis C virus in cell culture. J. Virol. *81*, 13783–13793.

128. Long, G., Hiet, M.S., Windisch, M.P., Lee, J.Y., Lohmann, V., and Bartenschlager, R. (2011). Mouse hepatic cells support assembly of infectious hepatitis C virus particles. Gastroenterology *141*, 1057–1066.

129. Bankwitz, D., Doepke, M., Hueging, K., Weller, R., Bruening, J., Behrendt, P., Lee, J.Y., Vondran, F.W.R., Manns, M.P., Bartenschlager, R., et al. (2017). Maturation of secreted HCV particles by incorporation of secreted ApoE protects from antibodies by enhancing infectivity. J. Hepatol. *67*, 480–489.

130. Nascimento, J.C.R., Pereira, L.C., Rêgo, J.M.C., Dias, R.P., Silva, P.G.B., Sobrinho, S.A.C., Coelho, G.R., Brasil, I.R.C., Oliveira-Filho, E.F., Owen, J.S., et al. (2021). Apolipoprotein E polymorphism influences orthotopic liver transplantation outcomes in patients with hepatitis C virus-induced liver cirrhosis. World J. Gastroenterol. *27*, 1064–1075.

131. Mueller, T., Fischer, J., Gessner, R., Rosendahl, J., Böhm, S., van Bömmel, F., Knop, V., Sarrazin, C., Witt, H., Marques, A.M., et al. (2016). Apolipoprotein E allele frequencies in chronic and self-limited hepatitis C suggest a protective effect of APOE4 in the course of hepatitis C virus infection. Liver Int. *36*, 1267–1274.

132. Gomaa, H.E., Mahmoud, M., Saad, N.E., Saad-Hussein, A., Ismail, S., Thabet, E.H., Farouk, H., Kandil, D., Heiba, A., and Hafez, W. (2018). Impact of Apo E gene polymorphism on HCV therapy related outcome in a cohort of HCV Egyptian patients. J. Genet. Eng. Biotechnol. *16*, 47–51.

133. Nguyen, M.H., Wong, G., Gane, E., Kao, J.H., and Dusheiko, G. (2020). Hepatitis B Virus: Advances in Prevention, Diagnosis, and Therapy. Clin. Microbiol. Rev. *33*, e00046-19.

134. Asrani, S.K., Devarbhavi, H., Eaton, J., and Kamath, P.S. (2019). Burden of liver diseases in the world. J. Hepatol. *70*, 151–171.

135. Qiao, L., and Luo, G.G. (2019). Human apolipoprotein E promotes hepatitis B virus infection and production. PLoS Pathog. *15*, e1007874.

136. Li, Y., and Luo, G. (2021). Human low-density lipoprotein receptor plays an important role in hepatitis B virus infection. PLoS Pathog. *17*, e1009722.

137. Leistner, C.M., Gruen-Bernhard, S., and Glebe, D. (2008). Role of glycosaminoglycans for binding and infection of hepatitis B virus. Cell Microbiol. *10*, 122–133.

138. Yan, H., Zhong, G., Xu, G., He, W., Jing, Z., Gao, Z., Huang, Y., Qi, Y., Peng, B., Wang, H., et al. (2012). Sodium taurocholate cotransporting polypeptide is a functional receptor for human hepatitis B and D virus. Elife *1*, e00049.

139. Mahley, R.W., and Ji, Z.S. (1999). Remnant lipoprotein metabolism: key pathways involving cell-surface heparan sulfate proteoglycans and apolipoprotein E. J. Lipid Res. *40*, 1–16.

140. Schulze, A., Gripon, P., and Urban, S. (2007). Hepatitis B virus infection initiates with a large surface protein-dependent binding to heparan sulfate proteoglycans. Hepatology *46*, 1759–1768.

141. Shen, Y., Li, M., Ye, X., and Bi, Q. (2015). Association of apolipoprotein E with the progression of hepatitis B virus-related liver disease. Int. J. Clin. Exp. Pathol. *8*, 14749–14756.

142. Qiao, L., Sui, J., and Luo, G. (2018). Robust human and murine hepatocyte culture models of hepatitis B virus infection and replication. J. Virol. *92*, e01255-18.

143. Aiello, A.E., Nguyen, H.O.T., and Haan, M.N. (2008). C-reactive protein mediates the effect of apolipoprotein E on cytomegalovirus infection. J. Infect. Dis. *197*, 34–41.

144. Zhang, L., Yesupriya, A., Chang, M.H., Teshale, E., and Teo, C.G. (2015). Apolipoprotein E and protection against hepatitis E viral infection in American non-Hispanic blacks. Hepatology *62*, 1346–1352.

145. Wardell, M.R., Brennan, S.O., Janus, E.D., Fraser, R., and Carrell, R.W. (1987). Apolipoprotein E2-Christchurch (136 Arg——Ser). New variant of human apolipoprotein E in a patient with type III hyperlipoproteinemia. J. Clin. Invest. *80*, 483–490.