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APOE interacts with ACE2 inhibiting SARS-CoV-2 cellular entry and inflammation in COVID-19 patients

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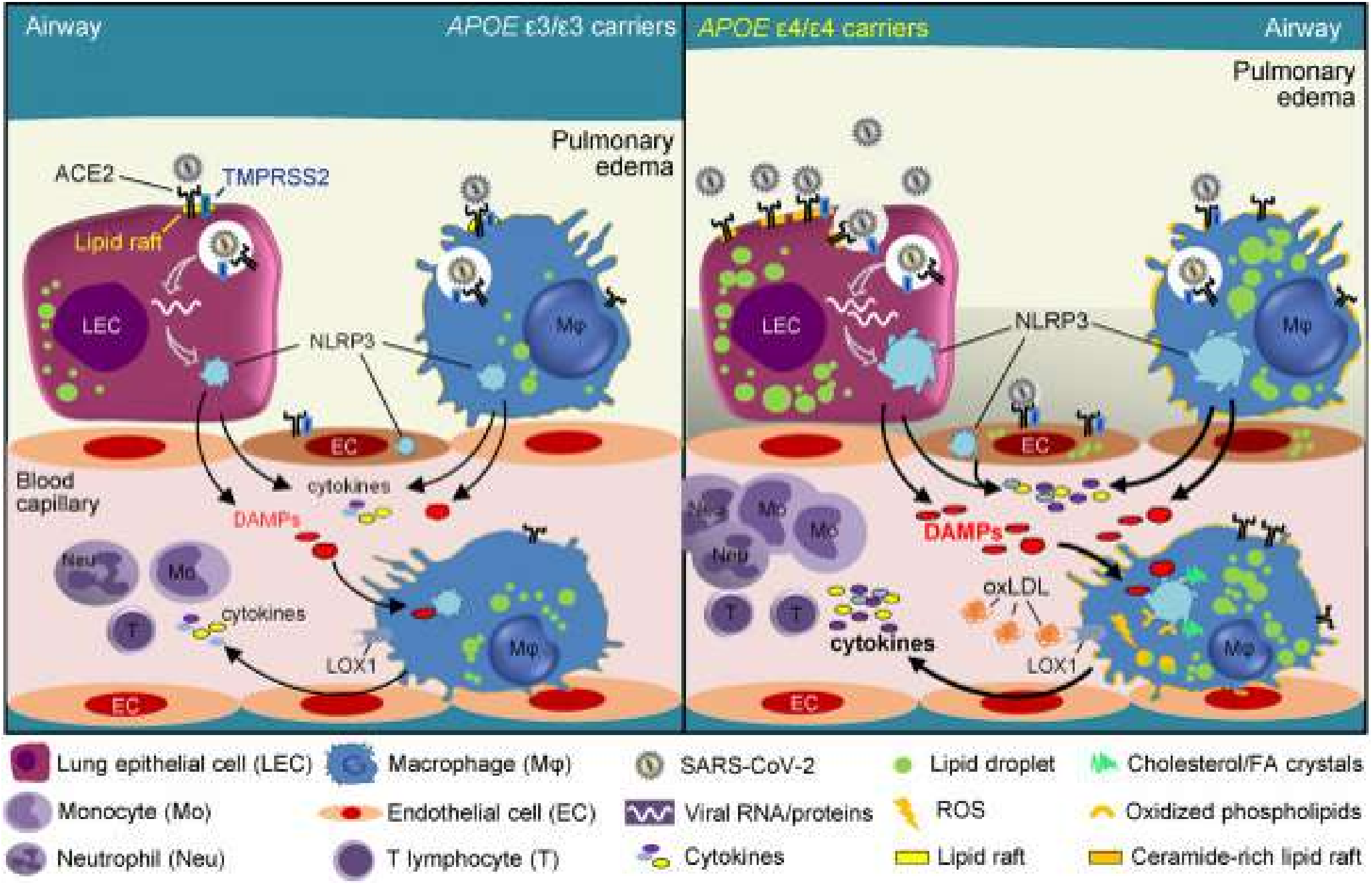
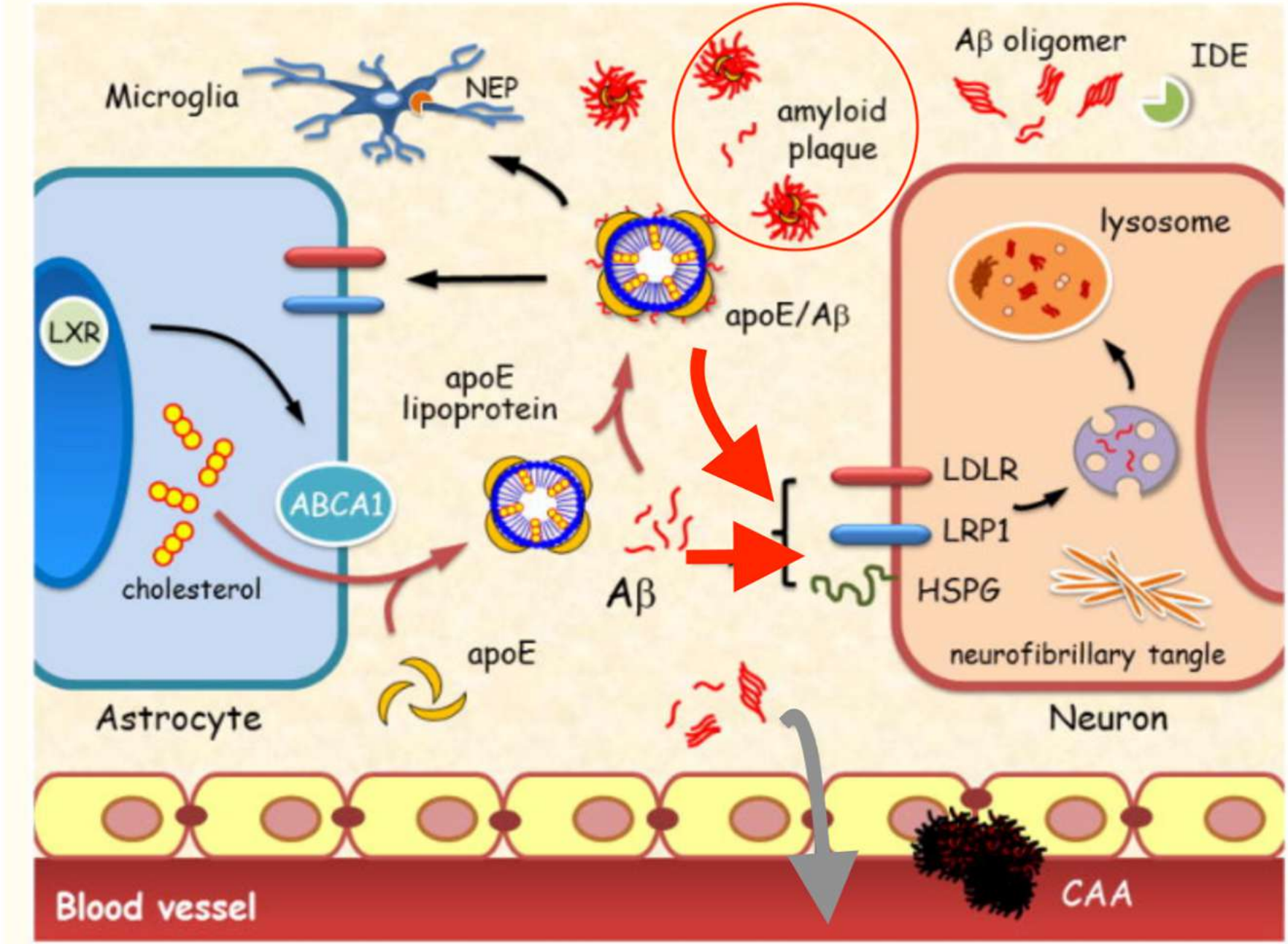
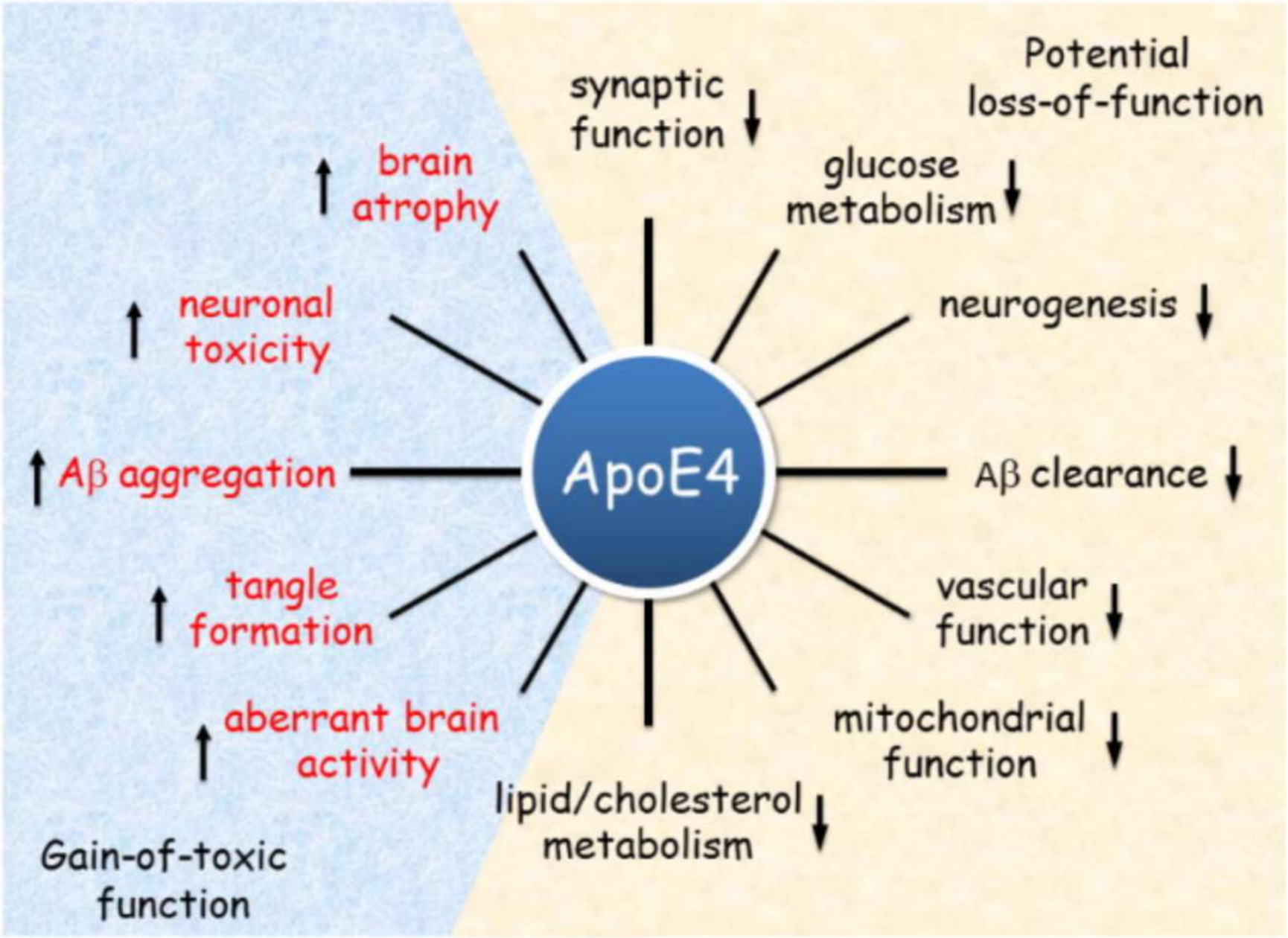
Apolipoprotein E (APOE) plays a pivotal role in lipid including cholesterol metabolism. The APOE *ε4* (APOE4) allele is a major genetic risk factor for Alzheimer's and cardiovascular diseases. Although APOE has recently been associated with increased susceptibility to infections of several viruses, whether and how APOE and its isoforms affect SARS-CoV-2 infection remains unclear. Here, we show that serum concentrations of APOE correlate inversely with levels of cytokine/chemokine in 73 COVID-19 patients. Utilizing multiple protein interaction assays, we demonstrate that APOE3 and APOE4 interact with the SARS-CoV-2 receptor ACE2; and APOE/ACE2 interactions require zinc metallopeptidase domain of ACE2, a key docking site for SARS-CoV-2 Spike protein. In addition, immuno-imaging assays using confocal, super-resolution, and transmission electron microscopies reveal that both APOE3 and APOE4 reduce ACE2/Spike-mediated viral entry into cells. Interestingly, while having a comparable binding affinity to ACE2, APOE4 inhibits viral entry to a lesser extent compared to APOE3, which is likely due to APOE4's more compact structure and smaller spatial obstacle to compete against Spike binding to ACE2. Furthermore, *APOE ε4* carriers clinically correlate with increased SARS-CoV-2 infection and elevated serum inflammatory factors in 142 COVID-19 patients assessed. Our study suggests a regulatory mechanism underlying SARS-CoV-2 infection through APOE interactions with ACE2, which may explain in part increased COVID-19 infection and disease severity in *APOE ε4* carriers.

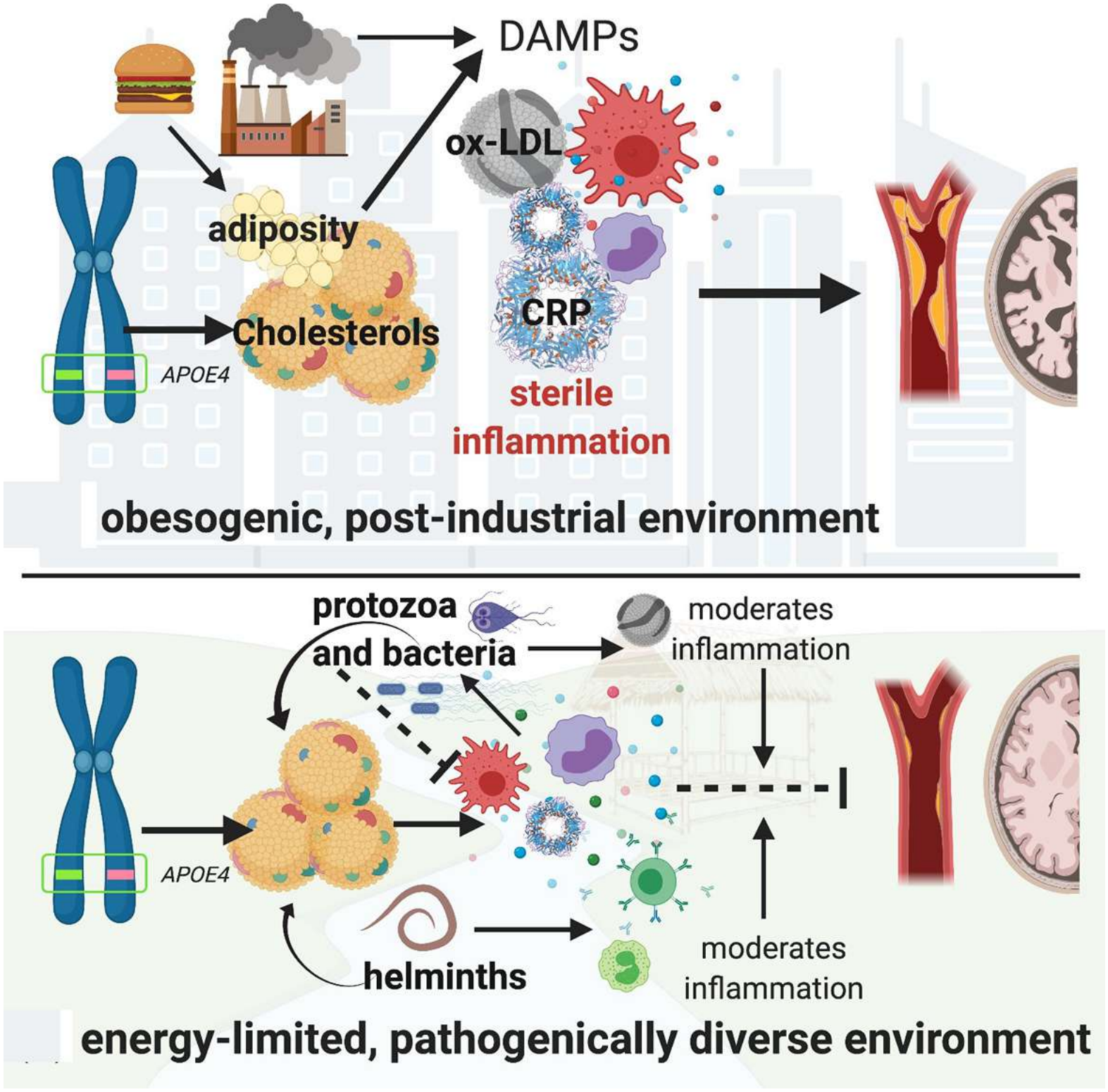

Airway
APOE ε3/ε3 carriers
APOE ε4/ε4 carriers
Airway
Pulmonary edema
Pulmonary edema
ACE2
TMPRSS2
Lipid raft
LEC
NLRP3
Mφ
EC
Blood capillary
cytokines
DAMPs
Neu
Mo
T
cytokines
LOX1
Mφ
EC
LEC
NLRP3
Mφ
EC
DAMPs
oxLDL
cytokines
LOX1
Mφ
EC
Lung epithelial cell (LEC)
Macrophage (Mφ)
SARS-CoV-2
Lipid droplet
Cholesterol/FA crystals
Monocyte (Mo)
Endothelial cell (EC)
Viral RNA/proteins
ROS
Oxidized phospholipids
Neutrophil (Neu)
T lymphocyte (T)
Cytokines
Lipid raft
Ceramide-rich lipid raft

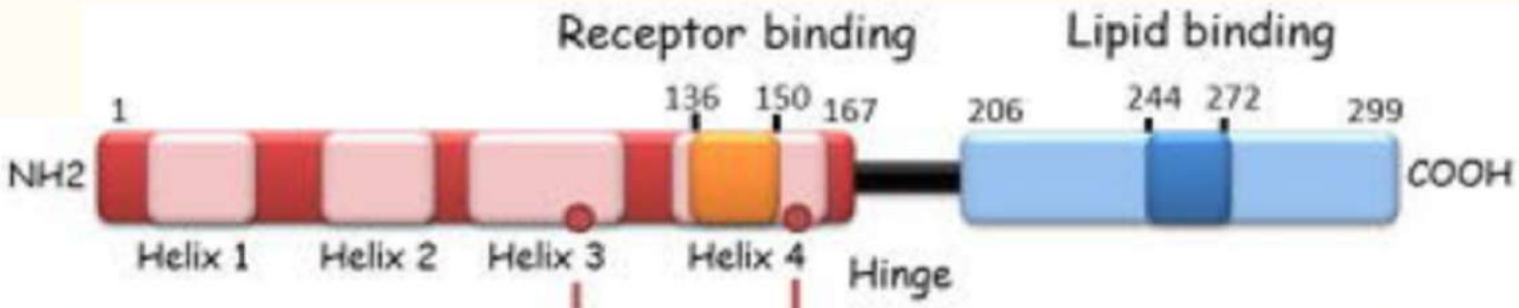


Apolipoprotein E and amyloid-β metabolism in the brain



The role of Apolipoprotein E4 in Alzheimer disease pathogenesis


DAMPs
ox-LDL
adiposity
Cholesterols
APOE4
CRP
sterile
inflammation
obesogenic, post-industrial environment
protozoa
and bacteria
moderates
inflammation
APOE4
helminths
moderates
inflammation
energy-limited, pathogenically diverse environment



	Isoform-specific amino acid difference		Allele frequency	
	112	158	General	AD
APOE2	Cys	Cys	8.4%	3.9%
APOE3	Cys	Arg	77.9%	59.4%
APOE4	Arg	Arg	13.7%	36.7%

	APOE4		
	Non-carrier	Heterozygous	Homozygous
AD frequency	20%	47%	91%
Mean age of clinical onset	84-yr	76-yr	68-yr

APOE **ε4 is a major genetic risk factor for Alzheimer disease**
(a) The ApoE2, E3, and E4 isoforms, which are encoded by the ε2, ε3 and ε4 alleles of the APOE gene, respectively, differ from one another at amino acid residues 112 and/or 158 (red circles). ApoE has two structural domains: the N-terminal domain, which contains the receptor-binding region (residues 136–150), and the C-terminal domain, which contains the lipid-binding region (residues 244–272); the two domains are joined by a hinge region. A meta-analysis demonstrated a significant association between the ε4 allele of APOE and AD.[10](b) APOE ε4 increases the risk of AD and lowers the age of disease onset in a gene-dose-dependent manner.[7, 20]