Role of clusterin in the brain vascular clearance of amyloid-β

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Alzheimer's disease (AD) is the most common form of dementia, characterized by neurovascular dysfunction, elevated brain parenchymal and vascular amyloid-β (Aβ) levels, tau pathology, and neuronal loss (1, 2). Faulty transvascular clearance of brain Aβ across the blood–brain barrier (BBB) plays an important role in Aβ accumulation in the brain, both in human AD and animal models (1–4). Normally, transvascular brain-to-blood transport across the BBB clears most of Aβ from brain (~85%), whereas the interstitial fluid (ISF) bulk flow along perivascular spaces removes the remaining smaller fraction of ~15% of Aβ (5). The two major apolipoproteins in brain, apolipoprotein E (APOE) and apolipoprotein J (APOJ), also known as clusterin (CLU), interact with Aβ and regulate its clearance from brain (1, 2) (Fig. 1). Specifically, Aβ is cleared across the BBB as a free peptide and/or bound to apolipoproteins E2 and E3, but not E4, via endothelial low-density lipoprotein receptor-related protein 1 (LRP1), whereas CLU binds Aβ and mediates its clearance across the BBB via low-density lipoprotein-receptor-related protein 2 (LRP2; also known as megalin and gp330) (2, 4). Peripheral Aβ reenters the brain by the receptor for advanced glycation end products (RAGE) (6). In PNAS, Wojtas et al. (7) explore the effect of endogenuous murine Clu deficiency on Aβ pathology.

The CLU gene on chromosome 8p21.1 encodes a 70-kDa multifunctional CLU glycoprotein that is involved in clearance of misfolded proteins, regulation of apoptosis, inflammation, and cancer (8). Brain CLU secreted by glia binds to Aβ and plays a protective role by preventing Aβ aggregation (9–11). CLU forms a stable complex with Aβ (12–14) and promotes its clearance from brain across the BBB via LRP2 (14) (Fig. 1).

Wojtas et al. (7) used APP/PS1 mice, which carry both the amyloid precursor protein (APP) Swedish and the presenilin-1 ΔE9 mutations on a Clu\textsuperscript{+/+} and Clu\textsuperscript{−/−} background. Compared with 12-mo-old APP/PS1;Clu\textsuperscript{+/+} littermates, APP/PS1;Clu\textsuperscript{−/−} mice showed a decrease in thioflavin-S-positive Aβ plaques in brain cortex and hippocampus (7). Contrary to this, APP/PS1;Clu\textsuperscript{−/−} mice had a significant increase in thioflavin-S-positive Aβ deposits in leptomeningeal vessels and penetrating arterioles, indicative of cerebral amyloid angiopathy (CAA) (7). Additionally, Wojtas et al. (7) find that APP/PS1;Clu\textsuperscript{−/−} mice have increased Aβ40:42 ratio, which may promote the formation of CAA. This is further supported by the finding that t\textsubscript{1/2} (half-time) of Aβ\textsubscript{40} clearance from ISF as determined by in vivo microdialysis technique was significantly longer in 10-wk-old mice lacking Clu, suggesting that CLU is important for clearance of soluble Aβ from brain (7) in agreement with previous studies (14). The lack of Clu did not affect brain APP levels, APP processing, Aβ-degrading enzymes, or expression of other AD-risk genes such as Picalm and Cd33 (7). The authors conclude that

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Clu deficiency shifts brain Aβ1-42 cleavage toward the perivascular drainage pathway, thereby increasing CAA (7). Because CLU plays an important role in transvascular clearance of Aβ1-42, its absence reduces clearance across the BBB and likely increases levels of Aβ1-42 flowing along and accumulating in the perivascular drainage spaces.

Previous studies investigated the impact of the loss of Clu on Aβ accumulation in PDAPP mice homozygous for the APP1717/69 transgene driven by the platelet-derived growth factor promoter (15, 16). Similar to Wojtas et al., DeMattos et al. (15, 16) found a reduced number of thioflavin-S-positive plaques in 12-mo-old PDAPP;Clu−/− mice compared with PDAPP;Clu+/+ littermate controls. However, in contrast to Wojtas et al., they found no change in the level of total Aβ in cortex or hippocampus, nor did they identify the presence of CAA (15, 16). Contradictory to Wojtas et al. (7), DeMattos et al. (16) found that the lack of Clu in PDAPP mice may increase levels of soluble Aβ1-42 in the brain. This raises the question as to whether or not the altered levels of total Aβ and CAA observed by Wojtas et al. could be a phenomenon specific to the APP/P51 mouse model. This seems likely, as APP/P51 mice develop CAA at 6 mo of age (17), and PDAPP mice develop CAA at 24 mo of age (18).

CLU is one of the most associated late-onset AD risk genes (19, 20). The major rs11136000C SNP in the intron region of CLU is associated with reducedCLU expression and increased risk of AD (21), and the minor protective rs11136000T allele is associated with increased CLU expression in brain tissue and reduces the risk of AD (19–23). A recent study investigated the relationship of CLU SNPs with Aβ1-42 loads, as measured by PET imaging with florbetapir, and reported that individuals that carried CC allele of rs11136000 had more amyloid deposits than TC allele carriers, and TT allele individuals had the least amyloid deposits (23). Altogether, this evidence supports that increased CLU in brain may be protective in AD by preventing aggregation and increasing clearance of Aβ1-42. Development of and studies in CRISPR mice expressing human CLU SNPs in the presence of increased amyloid pathology are critical to better understand the impact of human polymorphisms in AD pathogenesis. Additionally, investigating the impact of increasing brain CLU expression in transgenic models of amyloidosis is timely and important. Based on the work of Wojtas et al., it would be interesting to determine whether therapies directed at increasing brain CLU levels can reduce CAA and behavioral deficits.

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