Low-density Lipoprotein Receptor: A Promising Therapeutic Target to Promote Cerebral Beta-amyloid Clearance?

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In 1985, the Nobel Prize in Physiology or Medicine was awarded jointly to Michael S. Brown and Joseph L. Goldstein for their discoveries on regulation of cholesterol metabolism. Among their findings, they determined that familial hypercholesterolemia (FH) is caused by genetic defects in the low-density lipoprotein receptor (LDLR). FH heterozygotes (1:500) exhibit a 50% deficiency in LDLR expression, which leads to a twofold increase in the number of LDL particles in the blood from birth and an increased risk of cardiovascular disease. This prevalence is sufficiently high to warrant the diagnosis and treatment of FH at primary health care by the World Health Organization.

Given its pivotal role in the metabolism of apolipoprotein B-100-containing LDL particles, a great deal of attention has been devoted to understanding the role of the LDLR in the pathogenesis of atherosclerosis and coronary heart disease. In contrast, the physiological and pathological roles of LDLR in the brain are only beginning to be revealed. In this regard, Daniel Zambón and colleagues [1] recently reported that middle-aged patients with FH exhibit a particularly high incidence of mild cognitive impairment (MCI), a transitional state between the cognitive decline observed in the elderly and proper dementia. Of note, Ramirez and colleagues [2] and we [3] corroborated this observation in ApoB100/LDLr^{-/-} and LDLr^{-/-} experimental mouse models of FH, respectively. Specifically, we found that middle-aged LDLr^{-/-} mice exhibited working, spatial reference, and procedural memory impairments without alterations in exploratory activities and anxiety-related responses. Moreover, we did not observe signs of stroke-related features in middle-aged LDLr^{-/-} mice [3]. This latter observation agrees with previous clinical data reported by Zambón and colleagues [1]

regarding the observation of MCI without cerebrovascular disease in FH patients.

Currently, significant research efforts are attempting to investigate the role of LDLR in the development of Alzheimer's disease (AD)-like pathology. Notably, a series of elegant studies have shown that LDLR plays an important role in pathways that modulate amyloid- β (A β) metabolism. On one hand, Katsouri and Georgopoulos [4] reported that a lack of LDLR aggravated amyloid deposition in a transgenic mouse model of AD. Conversely, Kim and colleagues [5] demonstrated a marked reduction of amyloid plaque formation in the brains of amyloid precursor protein (APP) transgenic mice that overexpress LDLR. Accordingly, Basak and colleagues [6] demonstrated that modulation of the LDLR levels altered both A β uptake and degradation by astrocytes. Deletion of LDLR caused a decrease in A β uptake, whereas increased LDLR expression significantly enhanced both A β uptake and clearance [6]. Taken together, all of these findings clearly indicate that LDLR can regulate A β levels. Nonetheless, it is important to note that in a study by Fryer and colleagues [7], LDLR deletion had no effect on amyloid deposition in huAPP transgenic mice.

To date, the mechanism by which LDLR modulates A β metabolism has remained unclear. It is known that the ϵ 4 allele of the apolipoprotein E (APOE) gene accelerates cerebral amyloid deposition as well as progression from MCI to dementia. Conversely, ApoE deletion in most mouse models of AD was found to significantly inhibit amyloid plaque formation. Although LDLR was shown to regulate ApoE levels in the brain, suggesting that ApoE is a potential key mediator of the LDLR effects on amyloid deposition, Katsouri and Georgopoulos [4] generated 5XFAD/ApoE^{-/-}LDLr^{-/-} mice and compared amyloid deposition in these

mice to that in 5XFAD/ApoE^{-/-} mice. Notably, these researchers found that LDLR might be involved in a mechanism affecting amyloid deposition, whereas ApoE was not involved. Moreover, Basak and colleagues [6] found that LDLR is capable of promoting the uptake of A β into primary astrocytes even in ApoE^{-/-} cells. Katsouri and Georgopoulos [4] also found that LDLR deletion had no impact on APP processing and production of α and β carboxy terminal fragments in the mouse brain.

In their study, Basak and colleagues [6] provided evidence that A β can directly bind to LDLR, suggesting that an interaction between LDLR and A β could be responsible for LDLR-mediated A β uptake. Specifically, the authors showed via immunoprecipitation and surface plasmon resonance that both A β ₄₀ and A β ₄₂ could bind to the extracellular domain of LDLR with K_D values of 47.4 and 37.4 nM, respectively [6]. Kim and colleagues [5] demonstrated that LDLR overexpression decreases amyloid deposition by altering the steady-state concentration of A β in the brain interstitial fluid (ISF). Notably, Castellano and colleagues [8] used a brain efflux index method to demonstrate a unique role for LDLR in the blood–brain barrier (BBB)-mediated A β clearance. Specifically, these authors found that LDLR overexpression significantly increased the appearance rate of endogenously produced human A β (from the brain) in the blood. As a result, one could conclude that LDLR affects A β metabolism by promoting its clearance from the brain into blood [8].

It is worth noting that the continuous removal of A β species from the brain into the blood is important for preventing potentially neurotoxic accumulations in ISF. Consequently, one might also expect increased susceptibility to A β -induced neurotoxicity in the case of LDLR dysfunction because A β uptake and clearance might be impaired in this context. In this regard, we recently

observed that the absence of LDLR potentiated the A β -induced neurotoxic effects in mice [9]. Specifically, LDLR^{-/-} mice treated with A β _{1–40} peptide via acute intracerebroventricular injection presented with increased astrogliosis, oxidative stress, and cell permeability within the hippocampus in comparison with identically treated wild-type C57Bl/6 mice.

Taken together, these studies have identified LDLR as a pathway for mediating the cellular regulation of A β levels and provided evidence that increasing LDLR levels may promote A β degradation within the brain. In this context, some compounds, including tamoxifen, statins, and gemfibrozil [10], have been found to increase the hepatic LDLR levels; therefore, the use of such compounds is incumbent upon novel investigations on their therapeutic potentials in experimental models of amyloidosis. Furthermore, increasing the glial levels of LDLR may be a feasible therapeutic strategy for promoting A β clearance from the extracellular space.

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Conflict of Interest

The authors declare no conflict of interest.

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